1 Monoterpenes and Related Compounds from the Medicinal Plants of Africa

Michel Kenne Tchimene[a], *Christopher O. Okunji*[a,c], *Maurice Mmaduakolam Iwu*[a] *and Victor Kuete*[b]

[a]International Centre for Ethnomedicine and Drug Development, Nsukka, Nigeria, [b]Department of Biochemistry, University of Dschang, Dschang, Cameroon, [c]USP Headquarter, Rockville, MD

1.1 Introduction

Monoterpenes are a class of terpenes that consist of two isoprene units and have the molecular formula $C_{10}H_{16}$. They are predominantly products of the secondary metabolism of plants, although specialized classes occur in some animals and microorganisms, and are usually isolated from the oils obtained by steam distillation or solvent extraction of leaves, fruits, some heartwoods, and, rarely, roots, and bark [1]. In favorable cases they occur to the extent of several percent of the wet weight of the tissue. Conjugated nondistillable forms, e.g., terpene-β-D-glucoside, are also frequently found, especially in the floral organs. They are the most representative molecules, constituting 90% of the essential oils, and have a great variety of structures. Monoterpenes may be linear (acyclic) or they may contain rings. Biochemical modifications such as oxidation or rearrangement produce the related monoterpenoids. They are known for their many biological activities such as antimicrobial, hypotensive, antiinflammatory, antipruritic, antigerminative, antiplasmodial, antiesophageal cancer, and anticandidal. The compounds are inexpensive and have been widely used in flavoring and fragrances since the beginning of the nineteenth century. More recently, they have played a great role in the pharmaceutical industry because of their potential. Monoterpenes are also included in the category of nutraceuticals, which represent an industry in excess of US$75.5 billion with prospects of growing to US$167 billion by 2010 [1].

1.2 Biosynthesis and Structural Diversity

Modern methods of separation and structure determination, as well as the advent of radioisotope techniques, have led to a very rapid advance in knowledge of the route of biosynthesis of this class and the other types of terpenoids over the last 30 years.

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Several reviews, of differing completeness, have outlined the routes to terpenoids and steroids [2–8] in general and monoterpenes in particular [9,10]. One important conclusion that emerges is the accuracy with which chemical theory can predict the course of the biochemical processes. Enzymes exploit the innate reactivity of their substances, and the biosynthetic routes can be dissected into unit steps such as elimination, electrophilic addition, and Wagner–Meerwein rearrangement that are controlled by the stereoelectronic factor known to operate in nonbiological systems. Even the reactivity of apparently nonactivated atoms can usually be rationalized in terms of conformational and electronic changes imposed by postulated substrate–enzyme or substrate–cofactor linkages. The well-established patterns found can be used to asses feasible structures for novel terpenoids and to design biogenetic-type synthesis.

1.2.1 Biosynthetic Pathways

1.2.1.1 Isoprene Rule

The earliest attempt to rationalize the pattern of structures of the monoterpenes was the rule proposed by Wallach in 1887, who envisaged such compounds as being constructed from an isoprene unit (**1**) (Figure 1.1). Thirty years later, Robinson extended this isoprene rule by pointing out that in monoterpenes, and such higher terpenes as were then known, the units were almost invariably linked in a head-to-tail fashion, as shown for limone (**2**) and camphor (**3**). However, many higher terpenes and a few monoterpenes were later found not to obey this amended rule, and Ruzicka and his collaborators [11,12] proposed a biogenetic isoprene rule. This generalization, which is now universally accepted, states that naturally occurring terpenoids are derived either directly or by way of predictable stereospecific cyclization, rearrangement, and dimerizations form acyclic C-10, C-15, C-20, and C-30 precursors geraniol, farnesol, geranylgeraniol, and squalene, respectively. This rule implies a common pathway of biosynthesis for the whole family and any proposal for irregular biogenetic routes must be treated with reservations.

Although isoprene has been formed on pyrolytic decomposition of some monoterpenes, it is not found in plants, and much speculation has occurred around the nature of the active isoprene of the condensing unit, ranging from apiose to tiglic acid. The C-5 unit was also postulated to arise from degradation of carbohydrates, proteins, amino acids, and many other classes of plant metabolites or by elaboration of acetic acid, ethyl acetoacetate, or acetone. These early views have been well

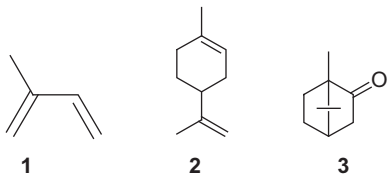


Figure 1.1 Chemical structure of isoprene unit (**1**), limone (**2**), and camphor (**3**).

summarized [13,14]. Many C-10 compounds have been implicated as progenitors of monoterpenes including citral [15], geraniol [16], nerol [17], limonene [18], linalool [19], ocimene [20], and others [21–24]. None of these speculations were backed by experimental evidence of any kind.

1.2.1.2 Acyclic Compounds and Cyclohexane Derivatives

1.2.1.2.1 Hypotheses

The proposals of Ruzicka and his coworkers [11] for the pattern of monoterpene biogenesis are outlined in Figure 1.2. Several of the intermediates are formally represented as carbonium ions, but structurally equivalent species such as alcohols, phosphate esters, terpene glycosides, or sulfonium salts, either free or bonded to proteins, may be the reactants *in vivo*. The scheme is extremely attractive; the formation

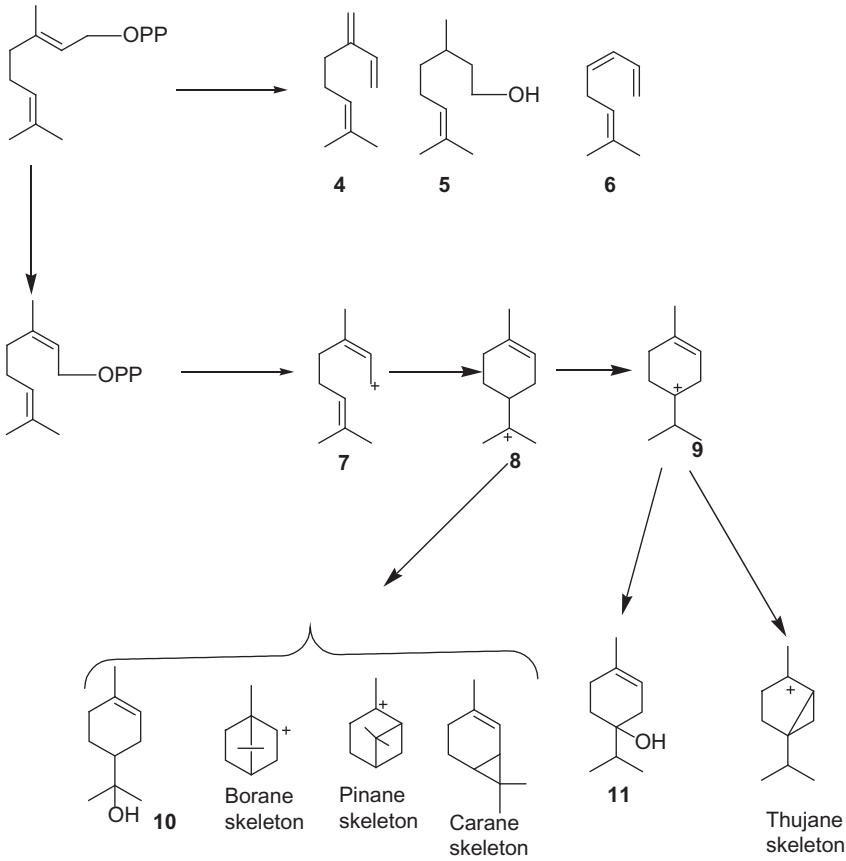
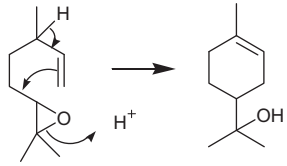
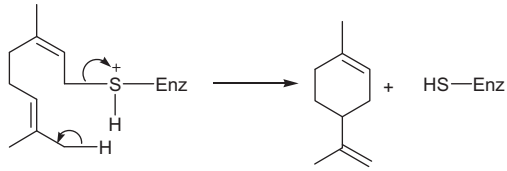


Figure 1.2 Formation of acyclic monoterpene: myrcene (**4**), ctronellol (**5**), *cis*-ocimene (**6**), α-terpineol (**10**), and terpinen-4-ol (**11**).

of acyclics such as myrcene (**4**), citronellol (**5**), or *cis*-ocimene (**6**) from geranyl pyrophosphate (GPP) has many *in vitro* analogies, and monocyclization of the ion (**7**) formed from neryl pyrophosphate (NPP) to give α-terpineol (**10**), or terpinen-4-ol (**11**) is also chemically reasonable, although the biochemical details are open to conjecture. For the latter process, either epoxides (which have been isolated from several essential oils) [25] or sulfonium compounds formed with a thiol group of an enzyme [26] may be involved as outlined in Eq. (1.1) and (1.2). Both of these types of intermediates are known to be implicated in the formation of rings in higher terpenoids, and interesting model systems for the synthesis of monoterpenes *in vitro* using sulfonium ylides have been developed; the elucidation of the importance (if any) of such routes in the plant must await the advent of suitable cell-free systems.



(1.1)



(1.2)

Bicyclic skeletons of the pinane and borane series are (according to Ruzicka's scheme) derived by internal additions of positive centers to double bonds within monocyclic frameworks in a direction governed either by electronic factors (Markovnikov addition) or by steric factors. Hydride shift within the ion (**8**) followed by cyclization of **9** gives rise to the thujane skeleton, and that of the caranes arises from an internal electrophilic substitution at the allylic position of the former carbonium ion. This latter reaction, as given, is biochemically improbable, and an internal displacement (Figure 1.3) in an intermediate such as **12** (X = ester) or the intermediary of a nonclassical ion (**13**) has been suggested [27], but both proposals beg the question. A study of the mechanism of decomposition of certain unsaturated epoxides suggests that Eq. (1.3)

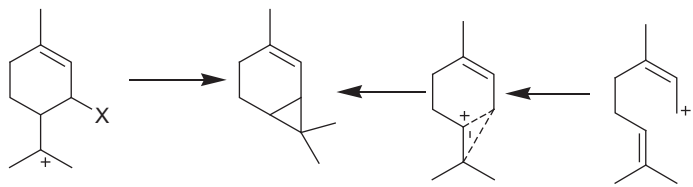
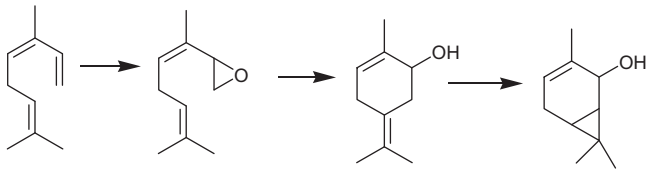
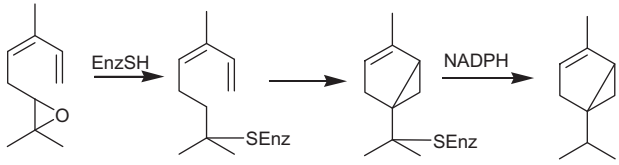


Figure 1.3 Suggested internal displacement in an intermediate in monocyclic monoterpenes.

is feasible and the mechanism could be modified to form other bicyclic monoterpenes directly from acyclic precursors; *cf.* Eq. (1.4). The generation of the intermediate



(1.3)



(1.4)

carbenes, or their formal equivalents, may be possible at the enzyme surface where water and other potential scavengers may be locally excluded. No evidence is available to assess these hypotheses.

1.2.1.3 Cyclopentane Derivatives

1.2.1.3.1 General

Iridoids (Figure 1.4) are a family of compounds based on carbon skeleton (**14**) that can be regarded as being formed by cyclization of **15**. They were originally isolated from the defensive secretions of *Iridomyrmex*, a genus of ant [28,29], but are now known to be widely distributed in higher plants, usually, but not invariably, as the

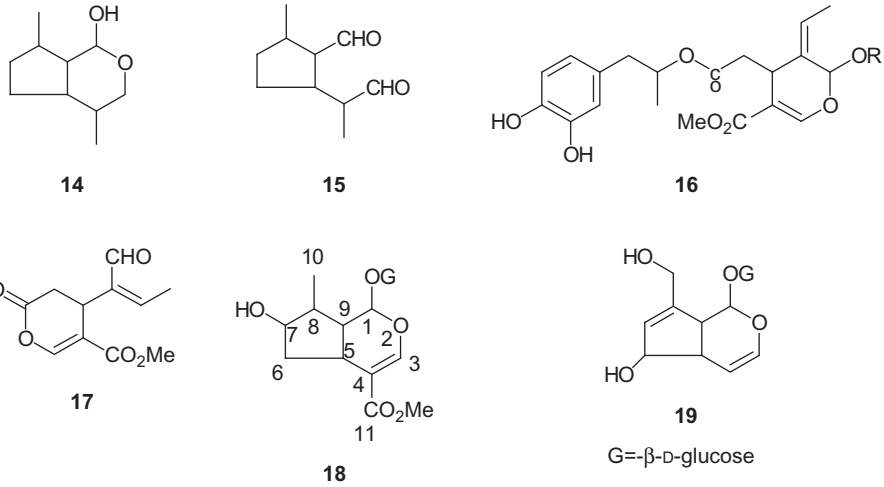


Figure 1.4 Structure of some iridoids.

β-D-glucosides. Several hundred iridoids and related compounds have been isolated from leaf, seed, fruit, bark, and root tissue of dicotyledons. This widespread distribution in plant tissues may be a consequence of the water solubility endowed by the sugar residue, and contrasts with the storage and retention in specialized oil glands of the largely water-insoluble monoterpenes of the types considered previously. Few systematic studies of chemotaxonomy have been made [30], although a simple field test is available to detect iridoids.

A decade ago it was suggested [31,32] that tetrahydropyranmethycyclopentane monoterpenes of this then unusual type were possible biogenetic precursors of the indole alkaloids; similar proposals were made for the formation of oleuropeine (**16**) and elenolide (**17**). More recent work has amply confirmed these speculations, and there is little doubt that loganin, or a close-related compound, does fulfill these roles. Most of the biosynthetic studies on the iridoids have been concerned with their function as intermediates en route to indole alkaloids, and it is only recently that these monoterpenes have begun to be studied in their own right.

Loganin is also an intermediate in the biosynthesis of other iridoids and of secoiridoids formed by rearrangement and functionalization of the skeleton (**14**) [33,34]. Its aglucone is unstable and the sugar moiety may play a solubilizing, transport-facilitating, and, very importantly, protective role; in particular, it may protect the C_1-linked hydroxyl group (for numbering of the ring see **18**; alternative systems are sometimes used) from oxidation until the appropriate stage in the biosynthetic scheme, when the sugar residue is cleaved off.

The fused bicyclic system of loganin accounts for 8 of the 10 carbon atoms derived from the acyclic monoterpene precursor. One of the remaining carbon is absent in some compounds that cooccur with, and are undoubtedly related to, the iridoids, although there is no formal biosynthetic demonstration for these relationships saved in the case of aucubin (**19**) [35]. Unedoside (**20**) (Figure 1.5) [36] is the only compound so far characterized that has lost both peripheral carbons; none have been reported which have lost the C_{10} methyl group but not the C_{11} carboxyl group, whereas in contrast several families of compounds have lost the latter group but retained the former, e.g., aucubin (**19**) and catalposide (**21**); R = *p*-hydroxybenzol) [37,38]. Secoiridoids such as gentiopicroside (**22**) [39] may be derived from loganin or a close-related compound by cleavage of the C7−C8 bond yielding initially, in the case of loganin itself [40], secologanin (**23**) [41]. The isolation of compounds such as foliamenthin (**24**) [42], sweroside (**25**) [43], and ipecoside (**26**) [44], as well as biosynthetic studies, provide further evidence that these groups of compounds are biogenetically related. Other relatives are the alkaloids β-skytanthine (**27**) [45] and actinidine (**28**) [46]; most of these compounds occur as their glucosides, but in addition to those described, genipin (**29**) and a few others appear to be presenting plant tissues as their aglycones. A diglucoside and a thioester are among interesting iridoids that have recently been characterized.

All the biosynthetic studies on this group of compounds have depended on investigation of the fate in intact plant tissue of specifically labeled and carefully chosen precursors, and these have often been supplemented by the isolation of suspected intermediates from the tissue. Only a few plant species have been investigated, especially young shoots of *Vinca rosea* or *Catharanthus roseus*.

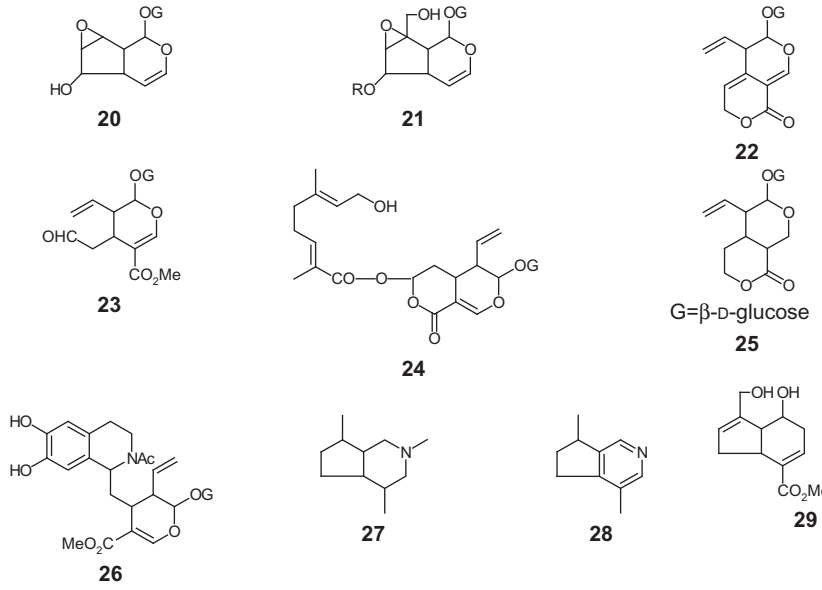


Figure 1.5 Chemical structure of unedoside (**20**), captaposide (**21**), gentiopicroside (**22**), secologanin (**23**), foliamenthin (**24**), sweroside (**25**), ipecoside **(26)**, β-skytanthine (**27**), actinidine (**28**), and genipin (**29**).

Whereas the broad outlines of the biosynthetic pathways have undoubtedly been unveiled, some of the minor details may be species or even tissue specific. For example, differences in labeling patterns between the same compound found in the leaves and flowers may occur. Generally the influence of this, and of other physiological parameters, on biosynthetic routes has been ignored, but studies on the formation of verbenalin (**30**) (Figure 1.6), β-skytanthine (**27**), and nepetalactone (**31**) have demonstrated the critical importance of these factors may have on labeling patterns. The same substrate may also be an effective precursor of a particular iridoid in one plant species but not in another; for example, whole and sliced rhizomes of *Menyanthes trifoliata* did not incorporate [2-^{14}C]MVA into loganin, whereas in *V. rosea* the additive was an efficient and specific precursor [47]. Data based on several different experimental approaches or procedures are thus desirable for investigation of any one species.

Experiments using the 4*R* and 4*S* isomers of [2-^{14}C, 4-^{3}H$_1$]MVA have confirmed that the stereospecificity of formation of the two double bonds of geraniol used in loganin formation is similar to that found in terpene synthesis in general, and that direct condensation of isopentenyl pyrophosphate (IPP) with dimethyl allyl pyrophosphate (DMAPP) to give nerol rather than geraniol directly also does not occur in this class of compounds. Geraniol, GPP, or some other derivative such as the enzyme-bound intermediate previously discussed, appears to be an obligatory precursor. The use of (1*R*)- and (1*S*)-[2-^{14}C,1-^{3}H$_1$]GPP has demonstrated that conversion of the C_1 carbon into an aldehydic or equivalent oxidation level is also stereospecific, and the hydrogens at rogens at C_2 and C_6 geraniol are retained during its transformation into

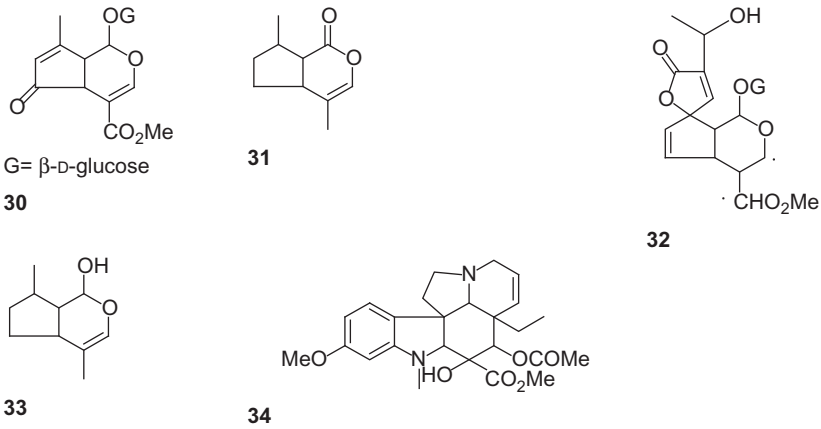


Figure 1.6 Chemical structure of verbenalin (**30**), nepetalactone (**31**), plumieride (**32**), iridodial (**33**), and loganin (**34**).

loganin. However, if saturation of the C_2/C_3 double bond of geraniol is a prerequisite for the formation of loganin, then both reduction and subsequent removal of the added proton occur in a stereospecific fashion [48,49].

The occurrence of foliamenthin (**24**) and related compounds also suggests that oxidation of the isopropylidene group in geraniol is essential for its conversion into loganin. However, evidence from the incorporation of doubly labeled mevalonic acid (MVA) into indole alkaloids suggests that incorporation of the intact propylidene unit of geraniol takes place. Such findings are now reconciled by our knowledge that oxidation occurs at both C_9 and C_{10} of geraniol (Figure 1.7) and that equilibration of these two carbons of geraniol occurs during the biosynthesis of loganin and related compounds from geraniol. Thus early studies [50] on the biosynthesis of plumieride (**32**) [51] proved that during its formation from geraniol the C_9 and C_{10} atoms of the latter became biosynthetically equivalent, for 25% of the label present was located at the starred atoms in **32** when [2-^{14}C]MVA was used as a precursor. A similar pattern in loganin (**18**) was obtained with the same precursor and with [3-^{14}C]MVA, and analogous results have been reported for all the iridoids, secoiridoids, and indole alkaloids that have been studied. To account for the pattern in plumieride, iridodial (or irodial) (**33**) was proposed as an intermediate, but this compound is not a precursor of loganin or vindoline (**34**) in *V. rosea* [52]. The equilibration of carbon atoms equivalent to C_9 and C_{10} of geraniol may, however, not always be complete and can vary with the physiological condition of the plant used. However, the point was made that asymmetric labeling of the part of the molecule derived from IPP, common for the monoterpenes described in the previous section, is not as widespread a phenomenon for these cyclopentane derivatives. 10-Hydroxygeraniol (**35**) and 10-hydroxynerol (**36**) (using the accepted numbering) have recently been shown to be precursors of loganin and of the indole alkaloid, and a reasonable route for loganin biosynthesis can be summarized in Figure 1.7. Complete randomization of ^{14}C label from C_9 and C_{10} of **35** was observed. Several related monoterpenes—linalool,

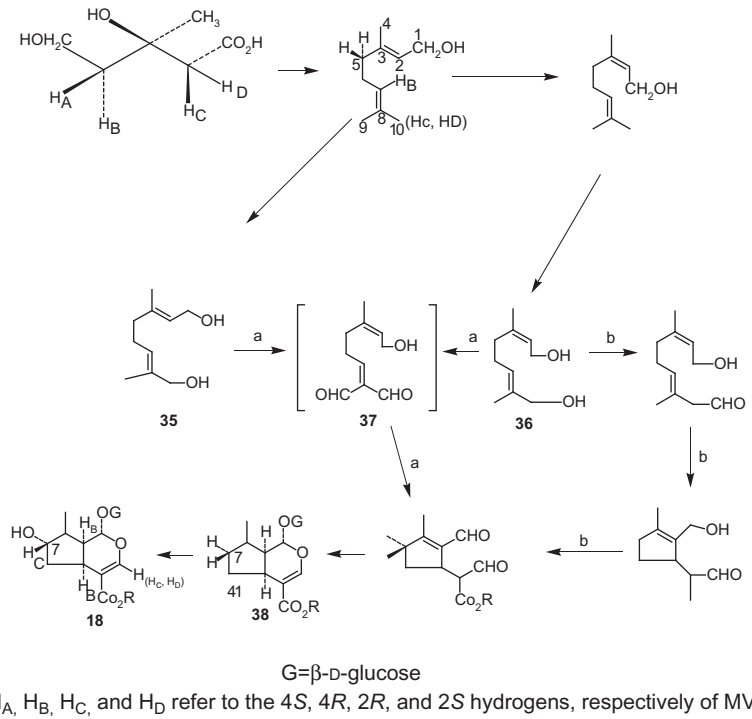


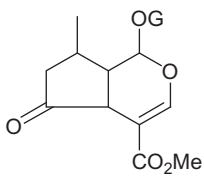
Figure 1.7 Formation of cyclopentane derivatives.

citronellol, and citral—were not significantly incorporated. These results suggest that a further step after **35** and **36** in the biosynthesis of iridoids involves attack on C_9 of **35** or **36** (or of the corresponding aldehydes) to give a hypothetical species such as **37** (route a, Figure 1.7). It is not known whether C_5 or C_{10} is oxidized first, or if indeed there is a specific order. 10-Hydroxynerol was a more efficient precursor than its isomer, and this suggests that the immediate precursors of the iridoids and indole alkaloids [53] have the *cis* double bond at C_2 and C_3 that is expected on stereochemical grounds. The rate of isomerization of this double bond may play an important role in diverting GPP from its alternative function as a precursor of higher terpenoids. It is also possible that cyclization may proceed prior to further oxidation at C_9 of 10-hydroxynerol (route b, Figure 1.7). The only other intermediates that have been demonstrated between geraniol and loganin or loganic acid are deoxyloganin and deoxyloganic acid, respectively ((**38**), R = Me, H), and both have been shown to be specific precursors of loganin [54]. Deoxyloganin occurs together with loganin in *V. rosea* and *Strychnos nux-vomica* [55]. Neither the aglucone of deoxyloganin nor the isomers with the double bonds at the C_6/C_7 or C_7/C_8 positions were incorporated into the final product. The final stage of loganin [56] biosynthesis is therefore envisaged as hydroxylation of deoxyloganin at C_7, which data on loganic acid biosynthesis suggest is stereospecific, like other biological hydroxylations. Both

deoxyloganin and loganic acid occur in *V. rosea*, and a cell-free system from this plant can convert the acid into loganin; thus a dual pathway is suggested in which methylation can occur at different points (Figure 1.8). Similar and more complicated metabolic grids have been observed in the biosynthesis of other terpenoids, especially carotenoids, and others will be mentioned shortly.

Recent work on loganic acid and gentiopicroside [57–59] biosynthesized from ^{14}C and ^{3}H doubly labeled isomers of MVA and geraniol has confirmed the formation of geraniol and hence of the cyclopentane derivatives from MVA. The stoichiometry of both the decarboxylation of MVAPP to give IPP and of the addition of IPP to DMAPP to give GPP is similar to that reported previously for other terpenoids and steroids. Deviations from the expected $^{14}C/^{3}H$ ratio of activities of C_7 of loganic acid were found that were similar to those reported in steroid synthesis. Such results have been accounted for by the relatively slow rate of removal of DMAPP by prenyl transferase as compared to the rate of establishing the equilibrium between IPP and DMAPP by IPP isomerase. Conversion of DMAPP into IPP in the latter equilibration would result in a partial loss of asymmetry of the $^{3}H/^{1}H$ pair at C_2 of IPP.

No preferential labeling of the two isoprene units of loganic acid was observed. However, such patterns can occur at the monoterpene level; formation of menthiafolin, a hydroxylated isomer of **24**, from [2-^{14}C]geraniol gave a product in which the two C-10 moieties were labeled in the ratio of 3:1. This finding suggests that either the monoterpene or its constituent units may be synthesized in different pools, which may correspond to intra- and extrachloroplastic sites of synthesis (both of which sites contain terpene synthesizing enzymes). The pools may be connected at the monoterpene-glucoside level as these compounds are water soluble. However, the stage at which glucose is coupled to a monoterpene remains unknown; present evidence suggests that it is not the final step in loganin or iridoid biosynthesis. The earlier findings indicate that iridoids may pass through several intra- and extracellular compartments during biosynthesis, and the distribution of iridoids in all types of plant tissues may provide further evidence for such tortuous pathways. The changes in labeling pattern at C_3 and C_{11} of certain iridoids and related compounds dependent on the age of the plant material may also be related to the need for the biosynthetic scheme to occur at several distinct sites. Indeed, the observed $^{14}C/^{3}H$ isotope ratios of activities of C_7 of loganic acid biosynthesized from 4*R* and 4*S* isomers of [2-^{14}C,-4-$^{3}H_1$]MVA that have been discussed earlier may be the result of incomplete randomization at the two positions, since the



G=β-D-glucose

41

Figure 1.8 Chemical structure of loganin derivative.

expected isotope ratios were calculated on the assumption of the complete biosynthetic equivalence of these two positions. However, the pattern of randomization between C_3 and C_{11} of loganic acid formed from [2-^{14}C]MVA did not vary with the age of the *V. rosea* specimen that was used.

1.2.1.3.2 Other Iridoids and Related Compounds

The biosynthesis of some members of one family of iridoids, most of which have been mentioned in the preceding discussion, is outlined in Figure 1.9. Deoxyloganic acid (**38**) (R = H) is an efficient precursor for asperuloside (**39**) [60], aucubin (**29**), and verbenalin (**40**), as well as loganin. Early work showed that [2-^{14}C]MVA was a specific precursor of verbenalin in *Verbena officinalis* but not of aucubin in *Verbascum thapsus*. The incorporation of tracer into the latter was very low and was randomly distributed, with appreciable radioactivity appearing in the glucose moiety. Similar labeling of the sugar occurred on biosynthesis of plumieride from [2-^{14}C]MVA and of loganic acid from HMG, and such observations emphasize the imperative need for determination of specific labeling patterns when presumed precursors are fed and compounds possibly derived from them are isolated. Verbenalin may be biosynthesized directly from 7-deoxyloganin, but it is usually found that **41** or a close relative is a parent of both verbenalin and aucubin, as shown in Figure 1.9, although the biochemical details are wanting. [2-^{14}C]MVA was found to be a specific precursor of verbenalin in *V. officinalis*, and differences occurred in the labeling of the product after feeding 1−2- or 4-month-old plants; in the young plants, complete randomization of label between C_3 and C_{11} had occurred (27% of total in C_3 and 23% in C_{11} of the expected total in these two positions of 50% of that incorporated). In older plants, little randomization took place (42% in C_3 and 8% in C_{11}). These differences, as mentioned before, have implications for all work on terpene biosynthesis and may either reflect differences in pool sizes or may indicate that the actual pathway of biosynthesis varies with age. The actual patterns of randomization here, and in similar experiments on the formation of β-skytanthine, although varying in extent, are similar to those found in the biosynthesis of loganin and indole alkaloids from [2-^{14}C]MVA.

Another pattern of biosynthesis is shown in Figure 1.5. MVA, deoxyloganin, and both loganin and loganic acid are precursors of the secoiridoid gentiopicroside (**22**), which may be more immediately derived from secologanin (**23**). Sweroside (**25**) is also a known precursor of gentiopicroside, as detailed by feeding experiments, and is itself probably formed from secologanin by an intramolecular transesterification either before or after reduction of the aldehyde group. Further work on the biosynthesis of ipecoside (**26**) demonstrated that cleavage of loganin (**19**) to secologanin (**23**) occurs via a mechanism which leaves the proton at C_9 unaffected. As expected, disacetyl ipecoside (but not its isomer), the condensation product of dopamine with secologanin, is also a precursor of ipecoside.

The biosynthesis of β-skytanthine (**27**) from MVA has been studied in detail, and it was confirmed that this compound is biogenetically related to the iridoids, as is also the pyridine alkaloid actinidine (**28**). The labeling pattern of nepetalactone (**31**) biosynthesized from [2-^{14}C]MVA by *Nepeta cataria* suggests that some randomization of label occurs at the C-5 (IPP-DMAPP) as well as at the C-10 (monoterpene) stage of

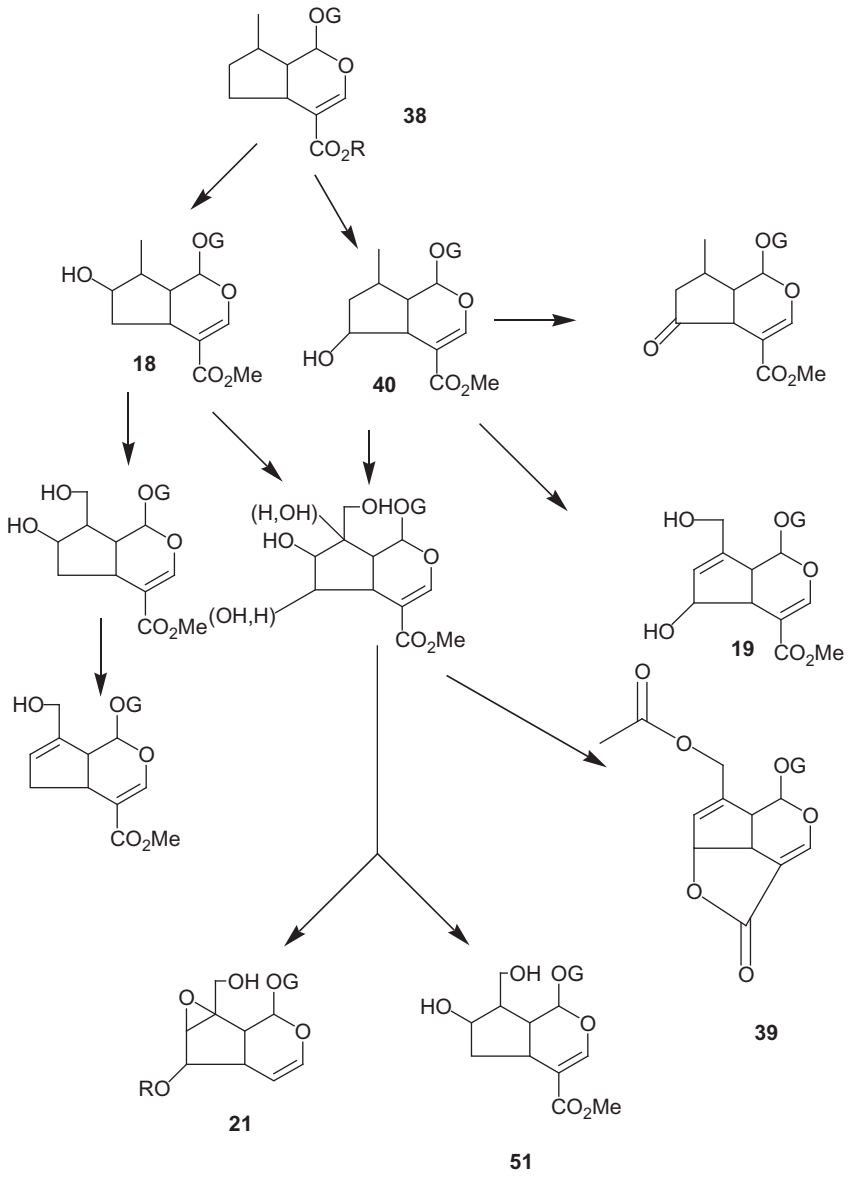


Figure 1.9 Formation of catalposide (**21**), deoxyloganic acid (**38**), and asperuloside (**39**).

biosynthesis. The work confirms the suggested monoterpene nature of the compound, which was indicated by preliminary tracer studies [61]. The observed labeling pattern would not be in accord with the proposed mechanism of IPP isomerase, which certainly applies in the biosynthesis of loganin and loganic acid. Evidence for the catabolism of MVA was obtained in these experiments on *N. cataria*, and the observed randomization

of label may result from this effect, which was probably brought into prominence by the prolonged periods of incubation that were used in the feeding procedures.

Various biogenetic schemes for β-skytanthine, actinidine, and nepetalactone have been outlined and pathways to other iridoids have been proposed. In all these schemes, iridodial is thought to be a key intermediate, but the recent demonstration that the C_8 and C_{10} atoms of nerol must be oxidized at an early stage en route to these compounds may rule this out. Furthermore, iridodial is not a precursor for loganin or vindoline.

Figure 1.10, which is based on recent detailed discussions, summarizes most of the speculations made in this section and includes many steps for which there is evidence from feeding experiments. The major problems of the mechanism of the closure of the cyclopentane ring and of the order in which the oxidation steps occur are still uncertain.

1.2.1.3.3 Indole Alkaloid

Figure 1.11 summarizes our present knowledge of the formation of the indole alkaloids from loganin and later precursors. The terpenoid moieties in the alkaloids are outlined with heavier lines. The indole part of these compounds was shown to be derived from tryptophan or tryptamine [62–65]; first experiments designed to confirm the suggestion that the remaining 9 or 10 carbon atoms were of terpenoid origin were inconclusive. However, recent work has clearly that ^{14}C-labeled MVA, geraniol, and loganin are efficient precursors of the nontryptophan part of the molecule in many members of this class. As with the iridoids, current ideas on the routes involved are based almost entirely on experiments which trace the metabolic fate of added presumed precursors. In most cases, the postulated intermediate has also been isolated from the plants under investigation. The presence of structurally related compounds such as ipecoside (**26**), foliamenthin (**25**), vincoside (**42**), and its isomer isovincoside (or strictoside) derivatives of secamine and many others provide indirect evidence for the accepted pathways, although the secamines may be artifacts of isolation [66].

The nature of the postulated monoterpenoid precursor was demonstrated by the incorporation of 0-[^{3}H]methylloganin into representatives of the three main structural types of indole alkaloids: ajmalicine (**44**) and corynantheine (**43**) (Corynantheine type), catharanthine (**49**) (Figure 1.12) (Iboga type), and vindoline (**34**) (Aspidosperma type). The related iridoids monotropeine methyl ester (**51**), verbenalin (**29**), and genipin (**28**) were not incorporated. The incorporation results with loganin could not, therefore, be attributed to transfer of the *O*-methyl group. [8-^{14}C]- or [2-^{14}C]loganin, as well as various tritiated forms of this compound, was also specifically incorporated.

The next established precursor of the class was secologanin (**24**). The route of formation of this compound from loganin is at present obscure, although it is generally believed that 10-hydroxyloganin may be an intermediate as outlined in Figure 1.11 the isolation of many 10-hydroxylated compounds such as genipin (**28**) demonstrates that the C_{10} methyl group can be hydroxylated *in vivo* 10-Hydroxyloganin should readily be cleaved to secologanin, particularly if the exocyclic hydroxyl was

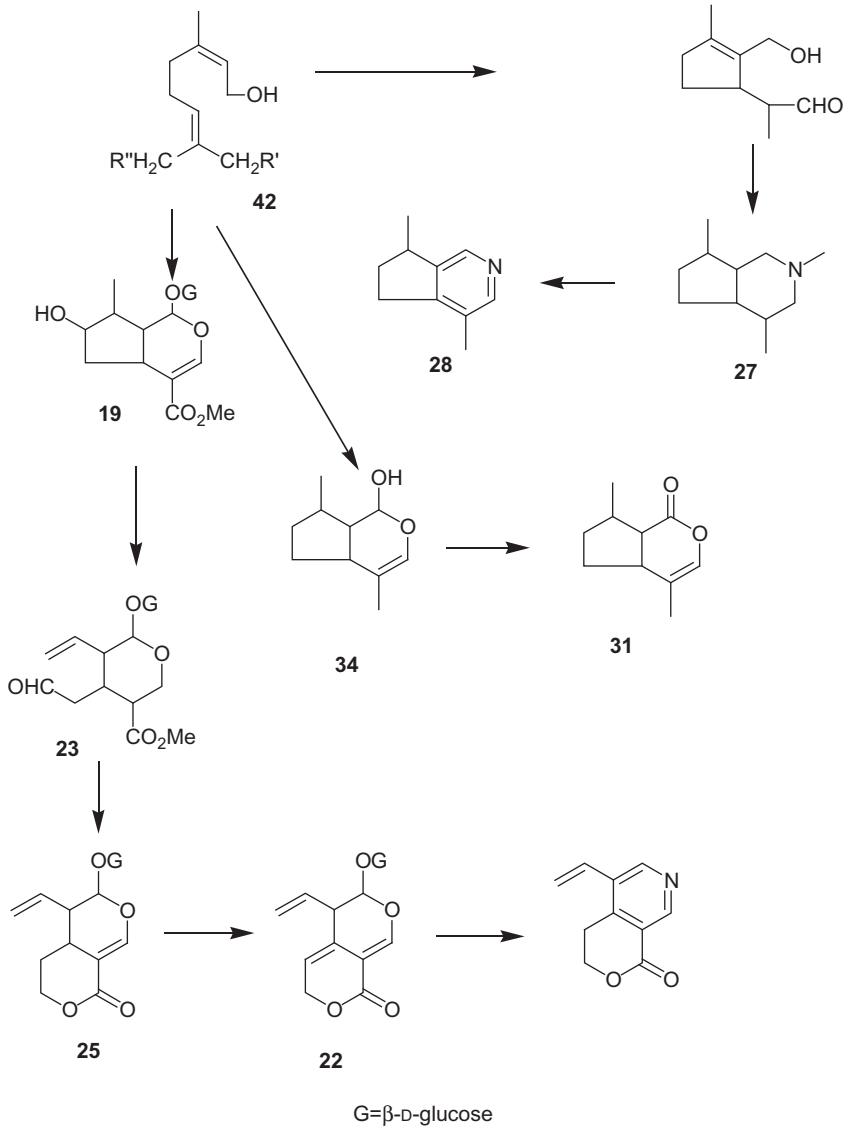


Figure 1.10 Formation of gentiopicroside (**22**), secologanin (**23**), sweroside (**25**), ipecoside (**26**), β-skytanthine (**27**), actinidine (**28**), nepetalactone (**31**), loganin (**34**), and vincoside (**42**).

first converted into a good leaving group such as phosphate or pyrophosphate. Secologanin has been shown to condense *in vitro* with tryptamine to form vincoside (**42**) and isomeric compounds, and the reaction also occurs *in vivo* [67].

Sweroside (**25**), which is closely related to secologanin, is also an excellent precursor of vindoline and is incorporated in 11% yield, but recent evidence

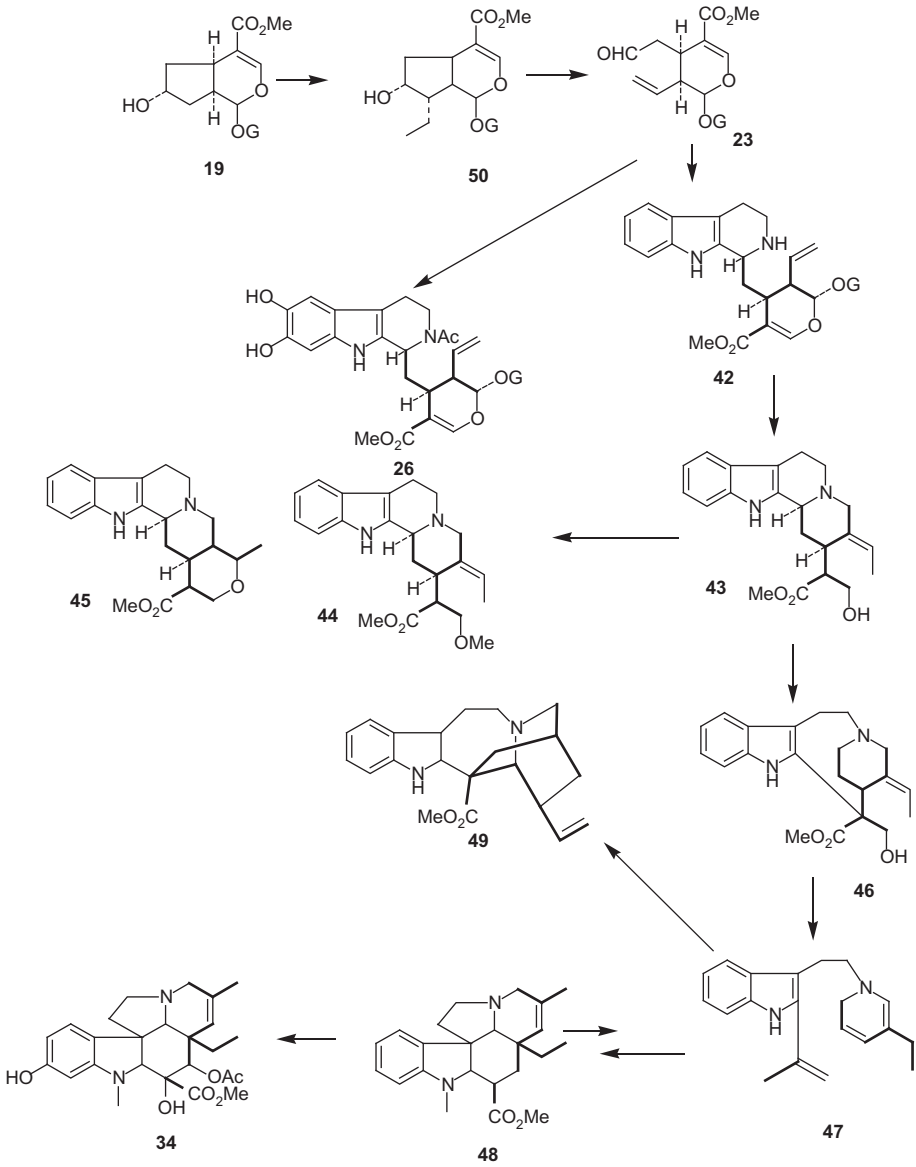


Figure 1.11 Formation of secologanin (**23**), loganin (**34**), ajmalicine (**44**), stemmadenine (**46**), and catharanthine (**49**). Note: G = glucose.

suggests that this and its hydroxy derivative swertiamarin are probably on a branch of the biosynthetic pathway leading from secologanin but not proceeding directly to the indole alkaloids. Gentiopicroside cannot be a direct precursor of the indole alkaloids since it loses a C_5 hydrogen when biosynthesized from loganin, whereas

the indole alkaloids lose a C_5 hydrogen. Vincoside (**42**) seems to be the precursor of most indole alkaloids, being initially converted into geissoschizine (**41**) and corynantheine aldehyde (**42**), and present evidence suggests that the rearrangement of the 2−10 monoterpene skeleton to give the three classes of indole alkaloids takes place after formation of this parent compound. Isovincoside does not appear to be a natural precursor [68].

Current investigation suggests that the three main classes of indole alkaloid are formed in the order: Corynantheine, Aspidosperma, and Iboga types. A novel approach to the problem has been introduced by following the formation of different alkaloids during the germination of seeds of *V. rosea.* Saturation of the nonindolic bond of vincoside destroyed its ability to act as a precursor of the class; furthermore the hydrogen at C_5 of vincoside is retained in all three classes of alkaloid. Geissoschizine may also be a precursor of all classes and has been isolated from *V. rosea*, whereas corynantheine aldehyde is not, and is only a precursor compound of its own class, e.g., corynantheine (**42**). In feeding experiments, geissoschizine is specifically incorporated into catharanthine (**47**), coronaridine (a dihydro derivative of **47**, vindoline (**34**), and also the strychnos group alkaloid akuammicine. An isomer of stemmadenine (**46**) was also isolated, which was converted by base into akuammicine [69].

Stemmadenine (**46**) may be related to the intermediates, the secamines (**47**), and tabersonine (**48**), which rearrange to give Iboga- and Aspidosperma-type compounds. 16, 17-Dihydrosecodin-17-01 that is isolated from *Rhazya orientalis*, similar secodines, and also an alkaloid isolated from *Tabernamontana cumminsii* may also be related to this intermediate. In *V. rosea*, tabersonine (**48**) is a precursor of catharanthine (**49**) and vindoline (**34**) [70].

Further evidence for the pathway in Figure 1.11 is provided by the location in the alkaloids of the tritium from C_7 of loganin (**18**), which is incorporated without loss. No migration of hydrogen occurs from the carbon corresponding to Ci of loganin and Cs of vincoside (**42**)—the C_3 of the alkaloids—during all the subsequent rearrangements.

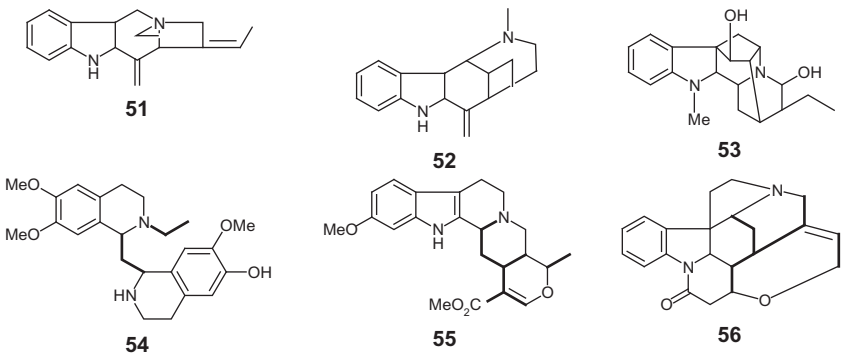


Figure 1.12 Chemical structure of appraising (**51**), uleine (**52**), and related compounds (**53**–**56**).

These last steps in the biosynthesis (Figure 1.6) are supported by the reported conversions *in vitro* of the Aspidosperma-type alkaloid tabersonine (**48**) into the Iboga-type compound catharanthine (**49**) and of stemmadenine (**46**) into tabersonine and catharanthine [71,72]; but other workers have, unfortunately, been unable to repeat these experiments.

Recently, the biosynthesis of apparicine (**51**) and uleine (**52**) has been studied. These are structurally unusual in having only a single carbon atom in the link between the indole ring and the nonindolic nitrogen atom. The a-carbon atom of the side chain of the precursor tryptophan is lost and the 3-carbon atom is retained. Tryptophan, however, was only incorporated into apparicine. The fission of the side chain must have occurred at a late biosynthetic stage as stemmadenine is incorporated.

1.2.1.3.4 Irregular Structures

Two classes of compounds can be grouped under this heading: first, degraded monoterpenes that contain fewer than 10 carbon atoms; and, second, compounds that apparently break the isoprene rule in its simpler statements [73], in containing C-5 units that are not linked head to tail.

The first class presents no biogenetic problem. An early example was cryptone (**57**) (Figure 1.13), which is almost certainly formed *in vivo* from 6-phellandrene (**71**) with which it cooccurs [74]; others are the arthropod defensive substances (**58**–**60**), the origin of which can be reasonably deduced, although no tracer studies have been carried out. Santene (**61**) is believed to be formed by Eq. (1.5), and all the presumed intermediates have been identified as cooccurring in sandalwood. The oils of *Pinus jeffreyi* and *Pinus sabiniana* consist predominantly (>95 w/w) of *n*-heptane, but as [2-^{14}C]HMG was not incorporated into this compound, it was concluded to be of polyketide rather than of mevalonoid origin. Such conclusions are questionable in view of the negligible incorporations of MVA and biogenetically related compounds into many products that are of undoubted mevalonoid origin. In this context, it is interesting that leucine was incorporated in over 80% yield into amyl alcohol and its acetate in disks of banana fruit and in yeast, and this amino acid may be a precursor of certain unusual "terpenoids."

(1.5)

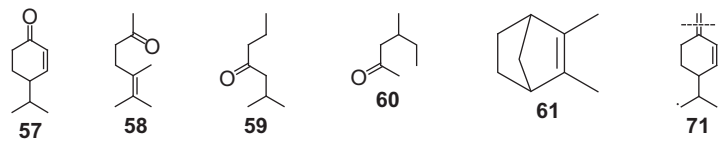


Figure 1.13 Chemical structure of cryptone (**57**), 5, 6-dimethylhept-5-2-one (**58**), 2-methylheptan-4-one (**59**), 4-methylhexan-2-one (**60**), santene (**61**), and 6-phellandrene (**71**).

Some of the irregularly linked C-10 compounds of the second class are very probably formed by well-established rearrangements of precursors biosynthesized with conventional head-to-tail linking of the C-5 units, and thus come within the province of the operation of the biogenetic isoprene rule. Examples are fenchane derivatives such as fenchol (**64**) derived from the ion (**62**) and isocamphane derivatives such as camphene (**65**) (Figure 1.14), derived from **63** by a similar Wagner−Meerwein shift. A more unusual type of rearrangement gives carquejol (**65**) (Figure 1.15), which occurs in the oil of the same name [75] and is the only known naturally occurring α-menthane derivative. Another speculative proposal is the derivation of **66** from thujone.

One of the most discussed compounds of this class is artemisia ketone (**67**) (Figure 1.16). A novel route for its biosynthesis was implied by the discovery that [2-^{14}C]MVA was not detectably incorporated into the compound formed by *Santolina chamaecyparissus* under conditions where the regularly constructed and cooccurring monoterpenes were significantly labeled. These observations have been confirmed, but the same precursor was found to be normally incorporated into the artemisia ketone produced by *Artemisia annua*, such that the position of the label allowed delineation of the route of synthesis. On degradation, about 92% of the incorporated tracer was deduced to be at Ca and CIO and only about 8% was located at C_7 and CS (these pairs of atoms were not distinguished by the degradation scheme); thus asymmetric labeling occurred, although not to such an extreme as in the monoterpenes previously discussed.

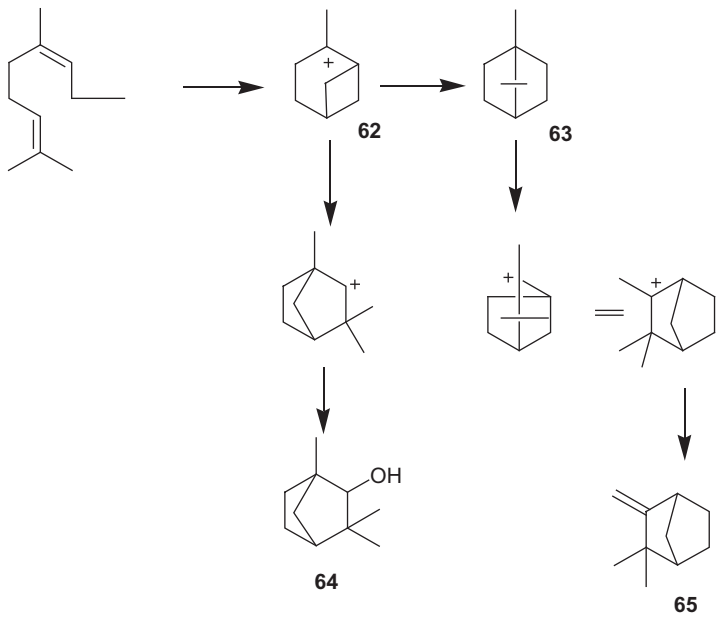
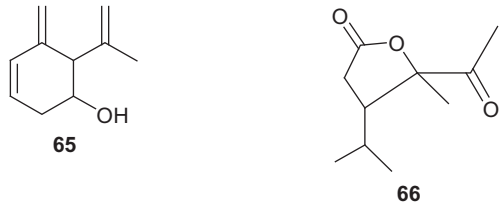


Figure 1.14 Formation of fenchol (**64**) and camphene (**65**).

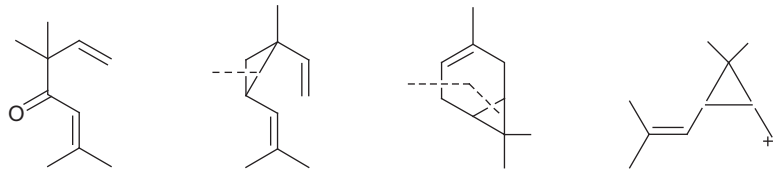
A variety of mechanisms has been proposed, all unbacked by any experimental evidence, for the biogenesis of this compound. These are (a) a ring opening of a cyclopropane intermediate (**68**) derived from linalool fission of a carane skeleton (**69**), (b) Stevens rearrangement of a sulfonium ylide derived from condensation of two molecules of DMAPP, (c) condensation of two units of 1,1-dimethylallyl pyrophosphate, and (d) vague speculations about an origin from a cationic intermediate common to linalool and menthol, the intermediary of the chrysanthemyl ion (**70**) or its biogenetic equivalent [76].

The observed pattern of incorporation of tracer was inconsistent with routes (b), (c), and (d); e.g., a direct condensation of two molecules of DMAPP would, unless specific compartmentation effects were evoked, lead to an equal distribution of tracer between C_7, C_8, C_9, and C_{10} atoms. Also, when [2-^{14}C]geraniol was fed to *A. annua*, considerable scrambling of tracer resulted in artemisia ketone; each carbon now contained at least 6% of the tracer, although C_2 and C_4 were by far the most heavily labeled, accounting for over half of the total. This contrasts with the smooth incorporation of [1-^{14}C]GPP into cineole in an *Eucalyptus* species with negligible scrambling. If routes (a) or (e) were operative, geraniol would reasonably be expected to be a more efficient precursor than MVA and would be incorporated with less randomization, whereas route f would require the additive to be degraded to C-1, C-2, or C-5 fragments that would be incorporated through formation of **70**. The tracer results seem better in accord with the last route, especially as the details of mechanisms (a) and (e) seem biochemically unlikely, but nothing is known about the route to **70**.



65 **66**

Figure 1.15 Chemical structure of carquejol (**65**) and thujone derivative (**66**).



67 **68** **69** **70**

Figure 1.16 Chemical structure of artemisia ketone (**67**), cyclopropane intermediate (**68**), carane skeleton (**69**), and chrysanthemyl ion (**70**).

1.3 Monoterpenes Isolated from African Medicinal Plants and Their Pharmacological Activities

Ajuga remota is the most frequently used medicinal herb for malaria treatment in Kenya. Its two known isolates ajugarin-1 and ergosterol-5,8-endoperoxide and a new isolate 8-*O*-acetylharpagide were evaluated for their *in vitro* antiplasmodial activity. Ajugarin-1 was moderately active with an IC_{50} of 23.0 μM, as compared to chloroquine (IC_{50} of 0.01 μM) against the chloroquine-sensitive (FCA20/GHA) strain of *Plasmodium falciparum*. Ergosterol-5,8-endoperoxide was about threefold as potent (IC_{50} of 8.2 μM) [77].

8-*O*-Acetylharpagide, isolated for the first time from the east African *A. remota*, did not exhibit any antiplasmodial activity even at the highest concentration of about 500 μM used against the chloroquines-sensitive strain of *P. falciparum* (FCA20/GHA). However, the compound exhibited *in vitro* cytotoxicity against the A431 human skin carcinoma cell line. It showed a concentration-dependent inhibition of cell proliferation with an IC_{50} of 310 μM, approximately sevenfold less active than the standard antineoplastic agent (fluorouracil) [77].

Compounds from *Plocamium suhrii* were tested for their *in vitro* antiproliferative effects against WHCO1 esophageal cancer cells using the MTT assay. (1*E*,3*R**,4*S**,5*E*,7*Z*)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, (1*E*,3*R**,4*S**,5*E*,7*Z*)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, (1*E*,3*R**,4*R**,5*E*,7*Z*)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, (3*R**,4*S**,5*E*,7*Z*)-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, (1*E*,3*R**,4*R**,5*E*,7*Z*)-1,8-dibromo-3,4-dichloro-3,7-dimethylocta-1,5,7-triene, and (3*R**,4*S**)-3,4,6,7-tetrachloro-3,7-dimethylocten-1-ene showed greater cytotoxicity (IC_{50} of 6.6−9.9 μM) than the known cancer drug cisplatin (IC_{50} of 13 μM) in the cancer cell line [78].

Furthermore, compounds from *Plocamium cornutum* were evaluated for their antiplasmodial activity against the chloroquine-sensitive *P. falciparum* strain (Figure 1.17). Although the compounds tested here were significantly less active than the standard drug chloroquine (IC_{50} of 0.036 μM), it is interesting to note that (3*R**,4*S**,5*E*,7*Z*)-3,4,-dichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene and (3*R**,4*S**,5*E*,7*Z*)-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene containing the 7-dichloromethyl moiety were the most active (IC_{50} of 16 and 17 μM, respectively) [79] (Table 1.1).

1.4 New Monoterpenes Isolated in African Medicinal Plants

In this section, we report the new monoterpenes isolated from African medicinal plants (Figure 1.18) without any reported pharmacological activity (Table 1.2).

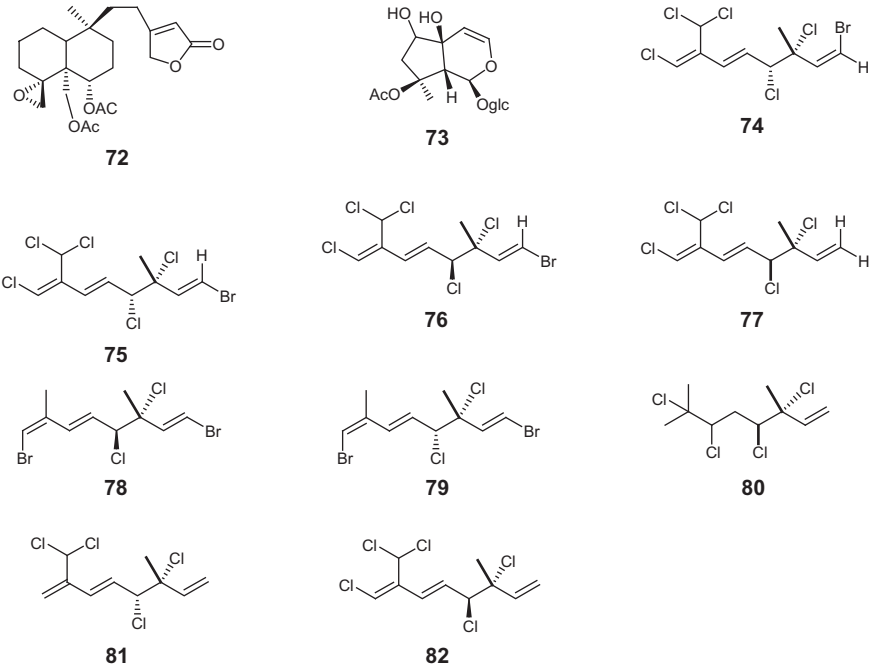


Figure 1.17 Some bioactive monoterpenes identified in African medicinal plants.

Table 1.1 Selected Bioactive Monoterpenes from African Medicinal Plants

Compounds	Plants (Family)	Activities with Reference
Ajugarin-1 (**72**) 8-*O*-Acetylharpagide (**73**)	*A. remota* (Lamiaceae)	Antiplasmodial [77]
(1*Z*,3*R**,4*S**,5*E*,7*Z*)-1-Bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**74**) (1*E*,3*R**,4*S**,5*E*,7*Z*)-1-Bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**75**) (1*E*,3*R**,4*R**,5*E*,7*Z*)-1-Bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**76**) (3*R**,4*S**,5*E*,7*Z*)-3,4,8-Trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**77**) (1*E*,3*R**,4*R**,5*E*,7*Z*)-1,8-Dibromo-3,4-dichloro-3,7-dimethylocta-1,5,7-triene (**78**) (1*E*,3*R**,4*S**,5*E*,7*Z*)-1,8-Dibromo-3,8-dichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**79**) (3*R**,4*S**)-3,4,6,7-Tetrachloro-3,7-dimethylocten-1-ene (**80**)	*P. suhrii* (Plocamiaceae)	Anticancer activity [78]
(3*R**,4*S**,5*E*,7*Z*)-3,4,-Dichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**81**) (3*R**,4*S**,5*E*,7*Z*)-3,4,8-Trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**82**)	*P. cornutum* (Plocamiaceae)	Antiplasmodial [79]

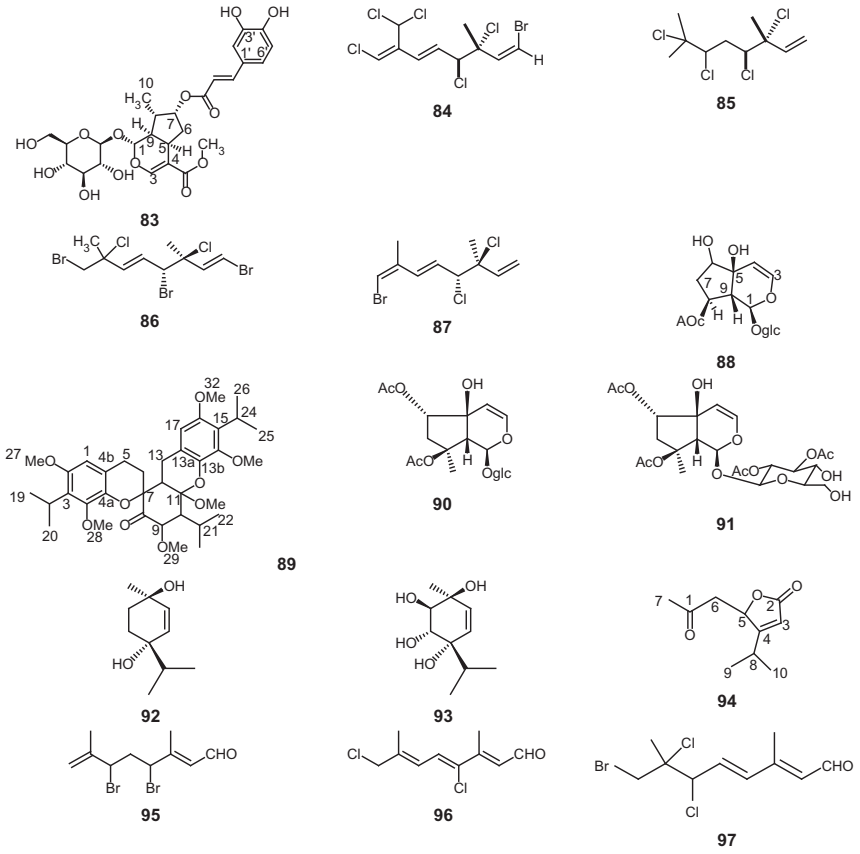


Figure 1.18 Newly isolated compounds identified in African plants: 7-caffeoylloganin (**83**); (1*Z*,3*R**,4*S**,5*E*,7*Z*)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**84**); (3*R**,4*S**)-3,4,6,7-tetrachloro-3,7-dimethylocten-1-ene (**85**); (1*Z*,3*E*,5*S**,6*S**)-1-bromo-5,6-dichloro-2,6-dimethyl-octa-1,3,7-triene (**86**); (1*Z*,3*E*,5*R**,6*S**)-1-bromo-5,6-dichloro-2,6-dimethyl-octa-1,3,7-triene (**87**); 8-*O*-acetylharpagide (**88**); (±)-Schefflone (**89**); 6,8-diacetylharpagide (**90**); 6,8-diactyl-1-*O*-β-(3′,4′-di-*O*-acetylglucoside) (**91**); (−) (1*R*′,4*S*)-1,4-dihydroxy-*p*-menth-2-ene (**92**); (−)(1*R*′,2*S**,3*S**,4*S*)-1,2,3,4-tetrahydroxy-*p*-menthane (**93**); chenopanone (**94**); 4,6-dibromo-3,7-dimethylocta-2,7-dienal (**95**); 4,8-chloro-3,7-dimethylocta-2,4,6-trienal (**96**); 8-bromo-6,7-dichloro-3,7-dimethylocta-2,4-dienal (**97**); 4-bromo-8-chloro-3,7-dimethylocta-2,6-dienal (**98**); 3-formyl-2,2,6-trimethyl-3,5-cyclohexadienyl angelate (**99**); 3-formyl-2,2,4-trimethyl-3,5-cyclohexadienyl angelate (**100**); 7-hydroxymyrthenal (**101**); 7-hydroxymyrtenol (**102**); (+)-quebrachitol (**103**); (1*S**,2*S**,4*R**)-trihydroxy-*p*-menth-5-ene (**104**); (1*S**,2*R**,4*R**)-trihydroxy-*p*-menth-5-ene (**105**); 5′-epi-isoethuliacoumarin B (**106**); 5′-epi-isoethuliacoumarin A (**107**); ethuliaconyzophenone (**108**); ferulagol A (**109**); ferulagol B (**110**); plocoralide A (**111**); plocoralide B (**112**); plocoralide C (**113**); shanzhisin methyl ester gentiobioside (**114**); and djalonenol (**115**).

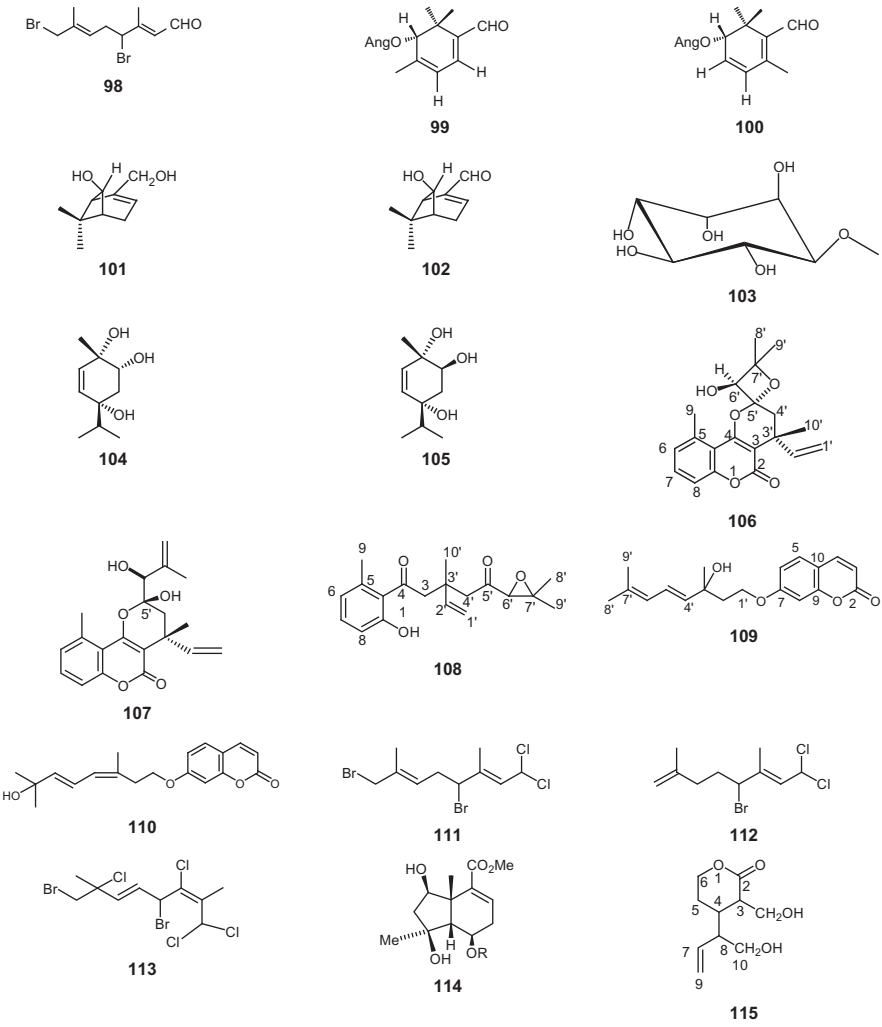


Figure 1.18 (Continued)

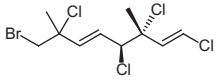
1.5 Other Monoterpenes in African Medicinal Plants

Several other monoterpenes were identified as known compounds in African plants, but no data were documented in regard to their biological activities. Some of them were isolated as monoterpene coumarins. They are summarized in Figure 1.19 and Table 1.3.

Table 1.2 Newly Isolated Monoterpenes from African Medicinal Plants

Name	Plant (Family)	Area of Plant Collection	Physical Properties
7-Caffeoylloganin (**83**)	*Cassinopsis madagascariensis* [80]	Leaves	mp 123−125°C; $[\alpha]_D$ −29.3°
(1*Z*,3*R**,4*S**,5*E*,7*Z*)-1-Bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene (**84**)	*P. suhrii* [78]	Aerial parts	$[\alpha]_D$ +16.9°
(3*R**,4*S**)-3,4,6,7-Tetrachloro-3,7-dimethylocten-1-ene (**85**)			$[\alpha]_D$ −8.8°
(1*Z*,3*E*,5*S**,6*S**)-1-Bromo-5,6-dichloro-2,6-dimethyl-octa-1,3,7-triene (**86**)	*P. cornutum* [81]	Aerial parts	$[\alpha]_D$ +5.0°
(1*Z*,3*E*,5*R**,6*S**)-1-Bromo-5,6-dichloro-2,6-dimethyl-octa-1,3,7-triene (**87**)			$[\alpha]_D$ −38.6°
8-*O*-Acetylharpagide (**88**)	*A. remota* [82]	Aerial parts	−
(±)-Schefflone (**89**)	*Uvaria scheffleri* [83]	Stem bark	mp 210°C, $[\alpha]_D$ ±0.0°
6,8-Diacetylharpagide (**90**)	*A. remota* [77]	Aerial parts	mp 166−168°C, $[\alpha]_D$ +65°
6,8-Diactyl-1-*O*-β-(3′,4′-di-*O*-acetylglucoside) (**91**)		Aerial parts	mp 174−176°C, $[\alpha]_D$ +92°
(−)-(1*R*′,4*S*)-1,4-Dihydroxy-*p*-menth-2-ene (**92**)	*Chenopodium ambrosioides* [84]	Aerial parts	$[\alpha]_D$ −2.6°
(−)-(1*R*′,2*S**,3*S**,4*S*)-1,2,3,4-Tetrahydroxy-*p*-menthane (**93**)			$[\alpha]_D$ −1.6°
Chenopanone (**94**)			$[\alpha]_D$ −7.5°
4,6-Dibromo-3,7-dimethylocta-2,7-dienal (**95**)	*Plocamium corallorhiza* [85]	Aerial parts	$[\alpha]_D$ −27°
4,8-Chloro-3,7-dimethylocta-2,4,6-trienal (**96**)			−
8-Bromo-6,7-dichloro-3,7-dimethylocta-2,4-dienal (**97**)			$[\alpha]_D$ −68°

4-Bromo-8-chloro-3,7-dimethylocta-2,6-dienal (**98**)			$[\alpha]_D$ −24°
3-Formyl-2,2,6-trimethyl-3,5-cyclohexadienyl angelate (**99**)	*Bupleurum gibraltaricum* [86]	Leaves	$[\alpha]_D$ +196.6°
3-Formyl-2,2,4-trimethyl-3,5-cyclohexadienyl angelate (**100**)			$[\alpha]_D$ +194.2°
7-Hydroxymyrthenal (**101**)	*Artemisia suksdorfii* [87]	Aerial parts	$[\alpha]_D$ −5.1°
7-Hydroxymyrtenol (**102**)			$[\alpha]_D$ +15.6°
(+)-Quebrachitol (**103**)			$[\alpha]_D$ +20°
(−)-(1*S**,2*S**,4*R**)-Trihydroxy-*p*-menth-5-ene (**104**)			$[\alpha]_D$ −24°
(+)-(1*S**,2*R**,4*R**)-trihydroxy-*p*-menth-5-ene (**105**)			$[\alpha]_D$ +20°
5′-Epi-isoethuliacoumarin B (**106**)	*Ethulia conyzoides* [88]	Aerial parts	–
5′-Epi-isoethuliacoumarin A (**107**)			–
Ethuliaconyzophenone (**108**)			–
Ferulagol A (**109**)	*Ferula ferulago* [89]	Roots	–
Ferulagol B (**110**)		Roots	–
Plocoralide A (**111**)	*P. corallorhiza* [81]	Aerial parts	–
Plocoralide B (**112**)		Aerial parts	$[\alpha]_D$ − 15°
Plocoralide C (**113**)		Aerial parts	$[\alpha]_D$ −43°
Shanzhisin methyl ester gentiobioside (**114**)	*Canthium subcordatum* [90]	Stem bark	$[\alpha]_D$ −56°
Djalonenol (**115**)	*Anthocleista djalonensis* [91]	Stem, roots, leaves	–



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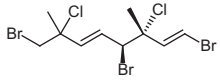

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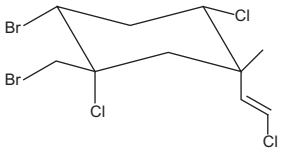

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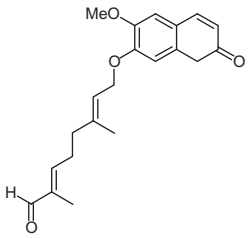

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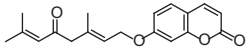

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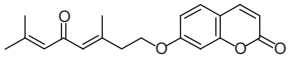

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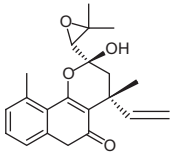

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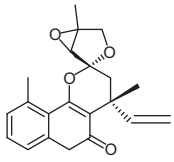

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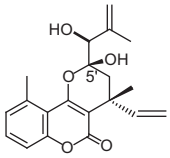

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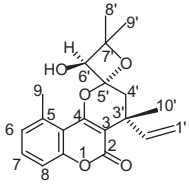

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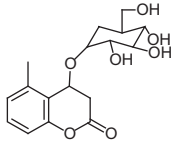

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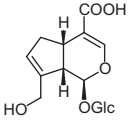

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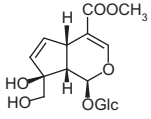

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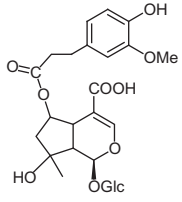

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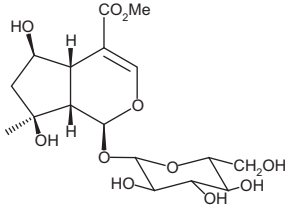

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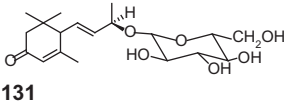

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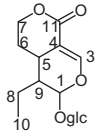

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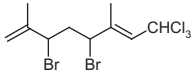

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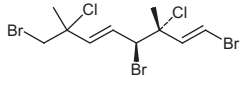

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Table 1.3 Monoterpenes Identified as Known Compounds in African Plants with No Biological Data

Name	Plant (Family)	Reference
8-Bromo-1,3,4,7-tetrachloro-3,7-dimethyl-1*E*,5*E*-octadiene (**116**)	*P. corallorhiza*	[89]
1,4,8-Tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**117**)		
(1*R**,2*S**,4*S**,5*S**)-4-Bromo-5-bromomethyl-1*E*-chlorovinyl-2,5-dichloromethylcyclohexane (**118**)		
6-Methoxy-7-geranyloxy coumarin (**119**)	*F. ferulago*	[88]
Diversinin (**120**)		
Diversin (**121**)		
Ethuliacoumarin (**122**)	*E. conyzoides*	[87]
Cycloethuliacoumarin (**123**)		
Isoethuliacoumarin A (**124**)		
Isoethuliacoumarin B (**125**)		
4-Hydroxy-5-methyl-coumarin-4-*O*-β-D-glucopyranoside (**126**)		
Geniposide acid (**127**)	*Tarenna madagascariensis*	[92]
Gardenoside (**128**)		
Tarenin (**129**)		
Shanzhiside methyl ester (**130**)	*C. subcordatum*	[89]
Roseoside (**131**)		
Djalonenoside (**132**)	*A. djalonensis*	[81]
4,6-Dibromoo-1,1-dichloro-3,7-dimethyl-2*E*,7-octadiene (**133**)	*P. corallorhiza*	[88]
1,4,8-Tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**134**)		

◀ **Figure 1.19** Chemical structures of monoterpenes identified as known compounds in African plants, with no biological data: 8-bromo-1,3,4,7-tetrachloro-3,7-dimethyl-1*E*,5*E*-octadiene (**116**); 1,4,8-tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**117**); (1*R**,2*S**,4*S**,5*S**)-4-bromo-5-bromomethyl-1*E*-chlorovinyl-2,5-dichloromethylcyclohexane (**118**); 6-methoxy-7-geranyloxy coumarin (**119**); diversinin (**120**); diversin (**121**); ethuliacoumarin (**122**); cycloethuliacoumarin (**123**); isoethuliacoumarin A (**124**); isoethuliacoumarin B(**125**); 4-hydroxy-5-methyl-coumarin-4-*O*-β-D-glucopyranoside (**126**); geniposide acid (**127**); gardenoside (**128**); tarenin (**129**); shanzhiside methyl ester (**130**); roseoside (**131**); djalonenoside (**132**); 4,6-dibromoo-1,1-dichloro-3,7-dimethyl-2*E*,7-octadiene (**133**); and 1,4,8-tribromo-3,7-dichloro-3,7-dimethyl-1*E*,5*E*-octadiene (**134**).

1.6 Conclusion

In this chapter, we discussed the biosynthesis of monoterpenes as well as the pharmacological potencies of those identified in African plants. Only a few pharmacological activities have been reported. Antiplasmodial activities were evaluated for compounds isolated from *A. remota* and *P. cornutum*, while anticancer properties were reported for those from *P. suhrii*.

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2 Sesquiterpenes from the Medicinal Plants of Africa

Maurice D. Awouafack[a,b], *Pierre Tane*[b], *Victor Kuete*[c] *and Jacobus N. Eloff*[a]

[a]Department of Paraclinical Sciences, University of Pretoria, Onderstepoort, South Africa, [b]Laboratory of Natural Products Chemistry, Department of Chemistry, University of Dschang, Dschang, Cameroon, [c]Department of Biochemistry, University of Dschang, Dschang, Cameroon

2.1 Introduction

Sesquiterpenes are C15-terpenoids built from three isoprene units. They are found particularly in higher plants and in other many living systems such as marine organisms and fungi. They occur in nature as hydrocarbons or in oxygenated forms including lactones, alcohols, acids, aldehydes, and ketones. Sesquiterpenes also include essential oils, as well as aromatic components from plants and have numerous basic skeletons with different nomenclature. The information provided in this chapter was collected online from Scifinder, Scopus, ScienceDirect, Pubmed, and the Dictionary of Natural Products. Knowing that such a review could never be 100% complete, we will appreciate it if anyone could provide additional data to us if there is something missing.

2.1.1 Detection of Sesquiterpenes in Plant Extracts

The detection of sesquiterpenes in plant extracts has no specific simple chemical techniques like those for other classes of secondary metabolites such as triterpenes, phytosterols, and flavonoids. Nevertheless, some analytical techniques have been used successfully for their identification and/or isolation [1−3]. Merfort [1] reported some analytical techniques for sesquiterpenes, including the use of chromatographic methods such as gas chromatography (GC), high-performance liquid chromatography (HPLC), and supercritical fluid chromatography, as well as multidimensional and chromatography coupling techniques (GC-MS, HPLC-MS) for separation of constituents [1]. Other techniques like Fourier transformation infrared, ultraviolet, or atomic emission spectroscopy are also useful [1].

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2.1.2 Basic Skeletons and Nomenclature of Sesquiterpenes

Sesquiterpenes are divided into several classes based on their linear or cyclic natures. Apart from the simple farnesane and some irregular acyclic sesquiterpenoids, most sesquiterpenes have cyclic skeletons. Basic skeletons of most of this class of secondary metabolite due to their occurrence in plants are provided in Figure 2.1, along with their nomenclature (**1**−**49**).

2.1.3 Known Pharmacological Activities of Sesquiterpenes

Sesquiterpenes have been reported to possess several pharmacological activities such as antimalarial [4−8], cytotoxic [8−12], antifungal [13−18], antibacterial [18,19], antiviral [18], antifeedant [9], anti-inflammatory [20,21], antinociceptive [22], inhibition of nitric oxide production [20], antileishmanial [23], lipid peroxidation effect [24], lymphocyte proliferation, and hydroxyl radical scavenging [12]. Many therapeutic drugs and current pharmaceutical agents are derived from natural products. Several sesquiterpenes have been used as drugs (Figure 2.2). The sesquiterpene lactone artemisinin (**50**), isolated from *Artemisia annua* and its derivatives [dihydroartemisinin (**51**), arteether (**52**), artemether (**53**), sodium artesunate (**54**), and sodium artelinate (**55**)] are promising agents used against chloroquine-resistant strain of *Plasmodium falciparum* [25,26]. The (−)-isomer (**56**) of the dimeric sesquiterpene gossypol (**56**, **57**), a constituent of the seeds of some *Gossipium* species, has contraceptive activity, while the (+)-isomer (**57**) has antitumoral and antiviral activities [25,26].

2.2 Biosynthesis and Structural Diversity

The biosynthesis of sesquiterpenes occurs via the mevalonic acid pathway and the recently described deoxyxylulose phosphate (1-deoxy-D-xylulose 5-phosphate) pathway [26−28]. The biochemically active isoprene units diphosphate (pyrophosphate) esters isopentenyl diphosphate [IPP, Figure 2.3 (**58**)] and dimethylallyl diphosphate [DMAPP (**59**)], from the two pathways, undergo linear head-to-tail combinations to a primary sesquiterpene precursor, farnesyl pyrophosphate [FPP (**60**)]. Farnesyl cations (*E*,*E* and *E*,*Z*) (**61**, **63**) and nerolidyl cation (**62**) are formed after an ionization at C-2 of the FPP and the alteration of the stereochemistry (*E* or *Z* configuration) from of double bond nearest the diphosphate [26]. Further modifications such as reduction, oxidation, and cyclization from (*E*,*E*)-farnesyl (**61**) and (*E*,*Z*)-farnesyl (**63**) cations therefore give rise to diverse linear and cyclic sesquiterpenes (**64**−**75**).

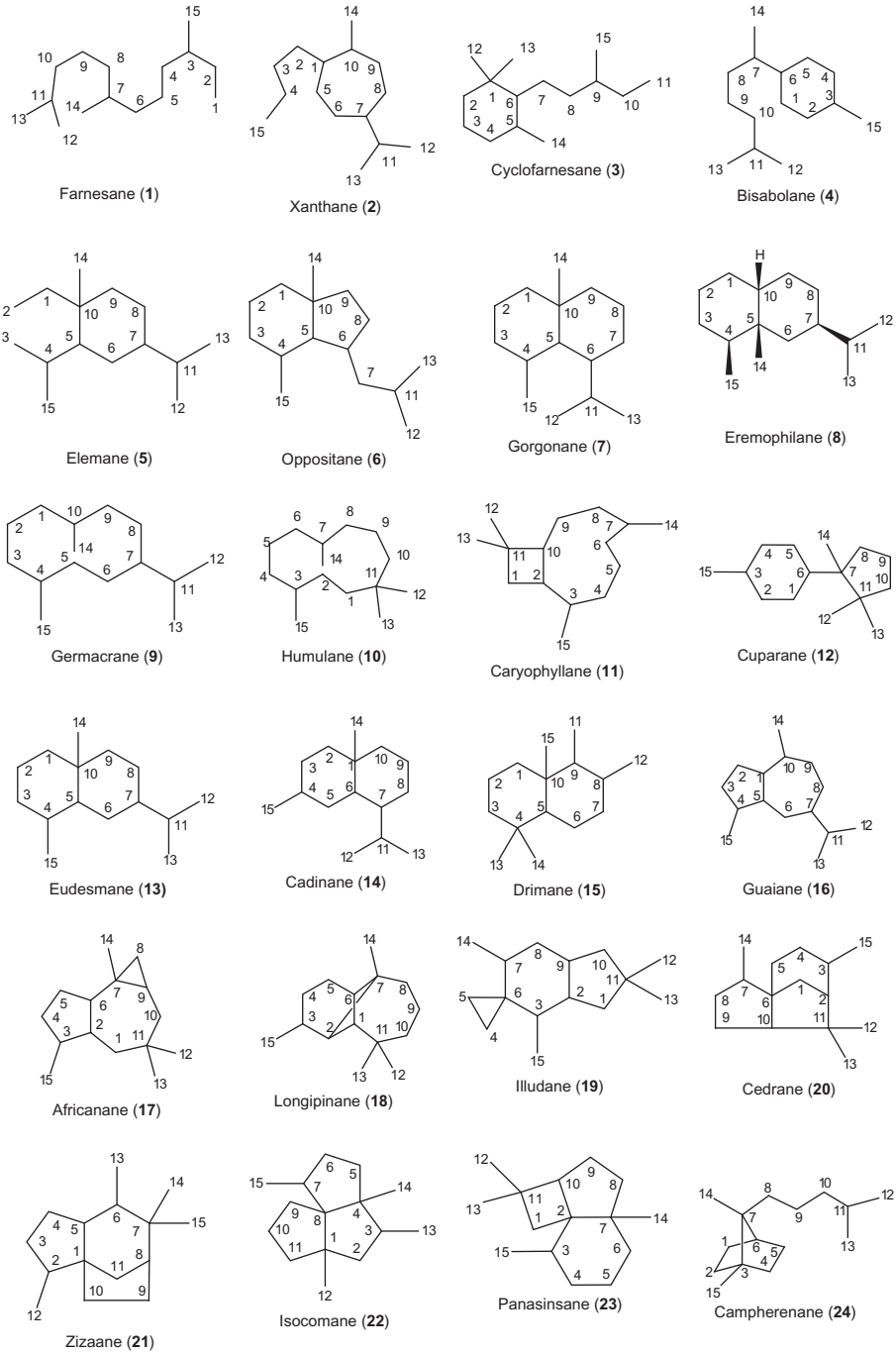


Figure 2.1 Basic skeletons and nomenclature of sesquiterpenes.

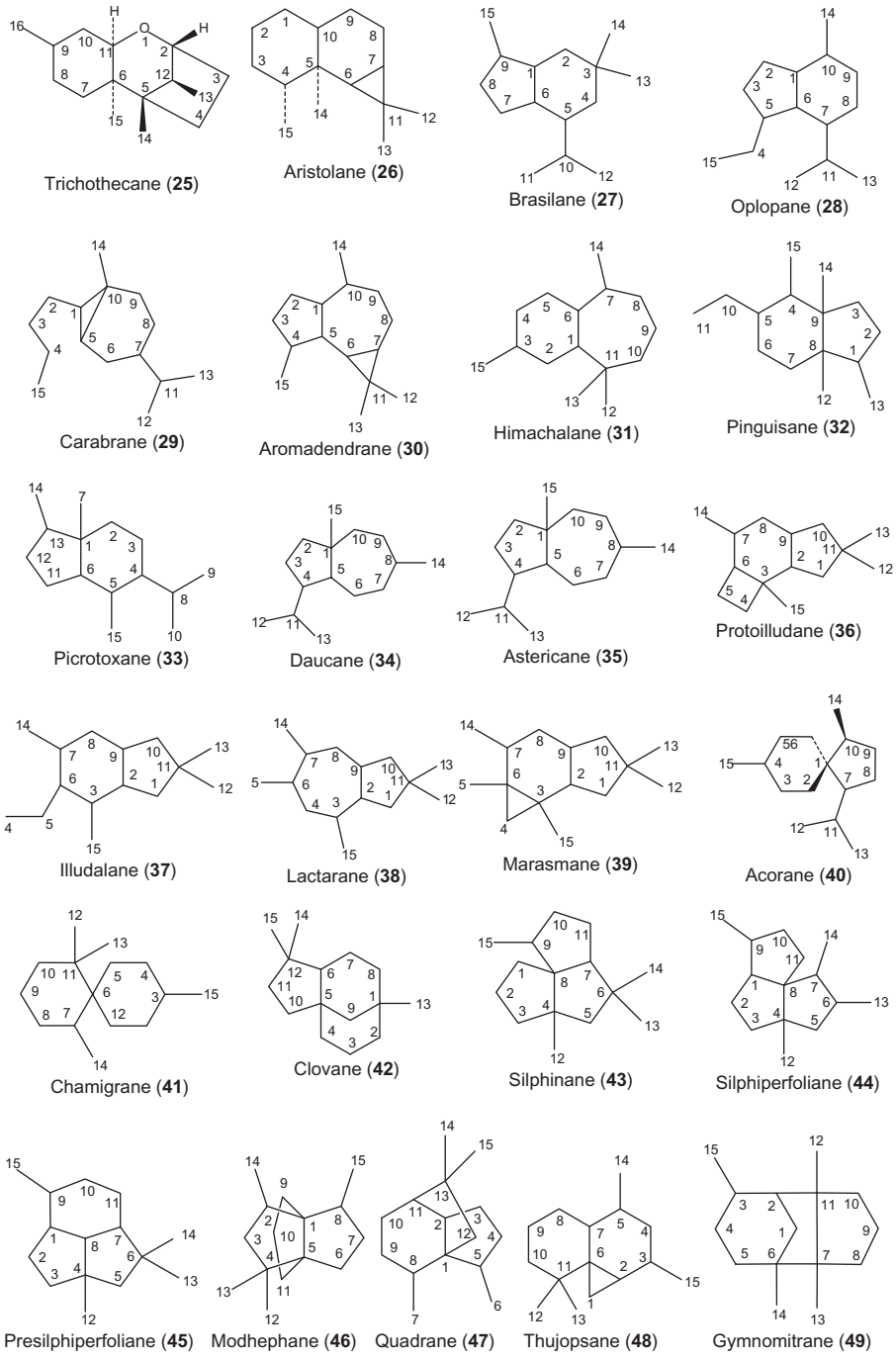


Figure 2.1 (Continued)

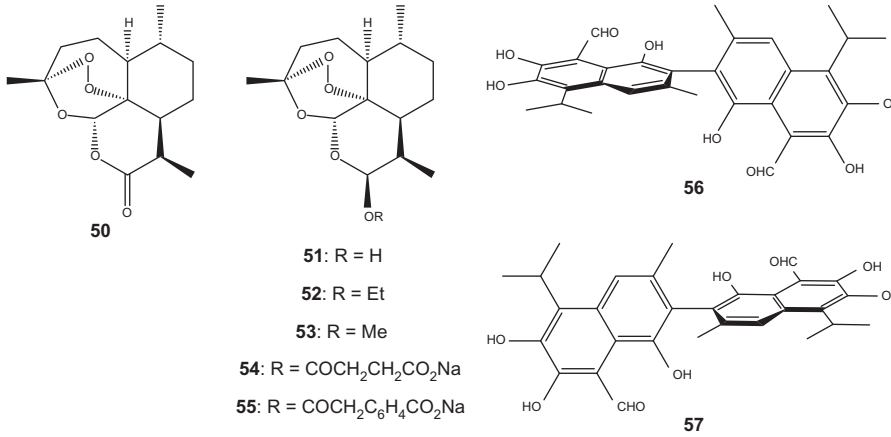


Figure 2.2 Some sesquiterpenes used as pharmaceutical agents.

2.3 Pharmacological Activities of Sesquiterpenes Isolated from African Medicinal Plants

Several bioactive sesquiterpenes have been isolated from African medicinal plants (Figures 2.4 and 2.5; Table 2.1). Many of them have antimicrobial and antiplasmodial activities, while some have anticancer, antifeedant, antimycotoxigenic, antioxidant, vascular myorelaxing, mollucidal, trypanocidal, anti-inflammatory, antiprotozoal, herbicidal, hepatoprotective, neuroproliferative, antidiabetic, analgesic, and cytotoxic activities.

2.3.1 Antimicrobial Activity of Sesquiterpenes Identified in African Medicinal Plants

Two sesquiterpene lactones (**76**, **77**) were isolated from the dichloromethane and methanol extracts of the leaves and stem bark of *Magnolia grandiflora* and had promising antifungal agents against the foliar fungi. Costunolide (**76**), parthenolide (**77**), and their prepared derivative 1,10-epoxyparthenolide were active against *Helminthosporium* spp., with activities (EC_{50} of 48, 2.92, and 2.96 μg/mL) better than that of the reference standard thiophanate-methyl (EC_{50} of 55.96 μg/mL); **77** was most active against *Alternaria alternata* (EC_{50} of 4.07 μg/mL) and *Fusarium culmorium* (EC_{50} of 50.27 μg/mL) [16]. The methanol extracts of the bark of *W. stuhlmannii* and *W. ugandensis* led to the isolation of sesquiterpene dialdehydes with antifungal activity. Polygodial (**78**) had excellent activity against *Saccharomyces cerevisiae* (Minimum Inhibitory Concentration (MIC) of 0.78 μg/mL), *Hansenula anomala*, *Candida utilis*, and *Sclerotinia libertiana* (MIC of

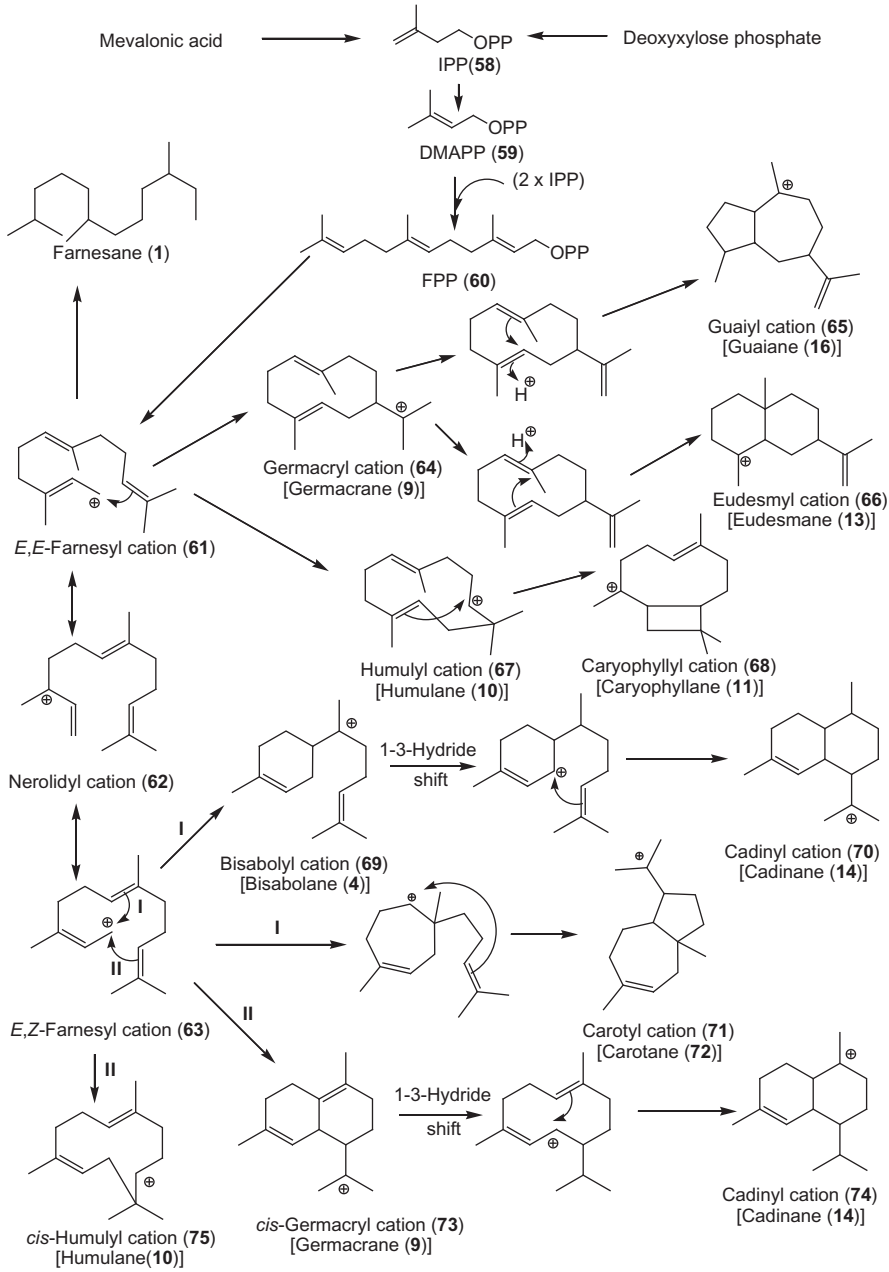


Figure 2.3 General biosynthetic pathway of sesquiterpenes [26–28].

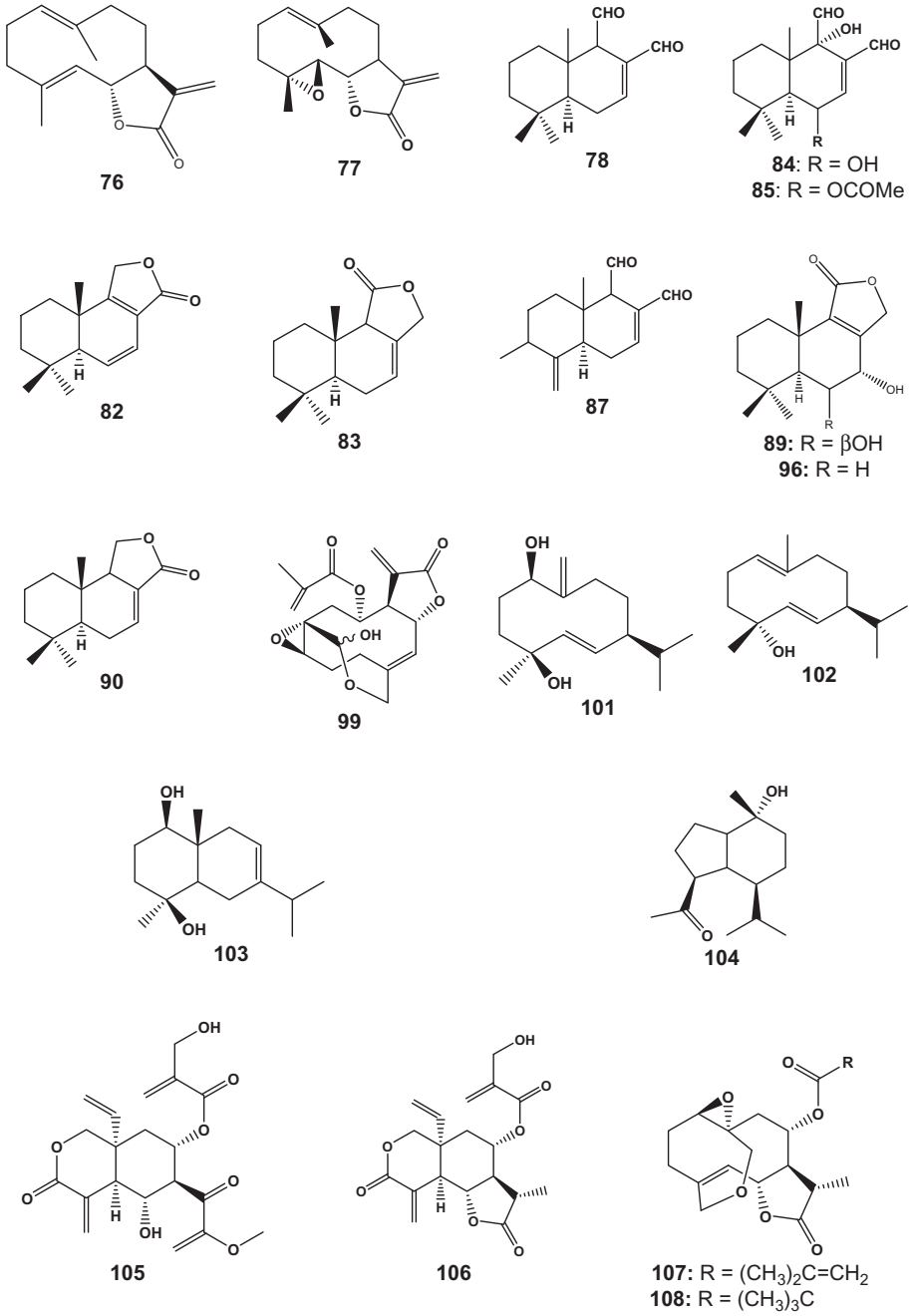
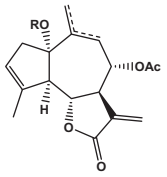
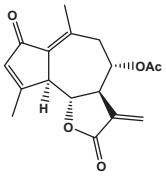


Figure 2.4 Bioactive sesquiterpenes from African medicinal plants (ax, axial orientation; Fuc, fucose).



	R	Δ
109	OH	10
110	OH	9
111	H	10
112	H	10



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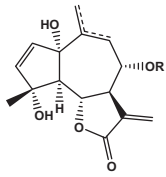
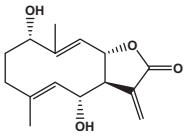


	R	Δ
114	H	10
115	Ac	9



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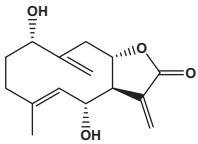

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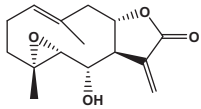

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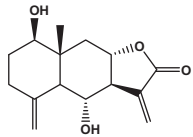

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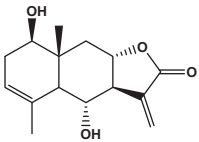

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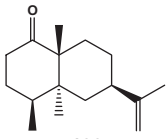

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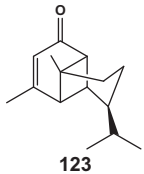

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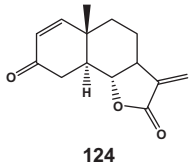

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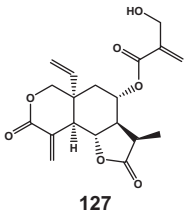

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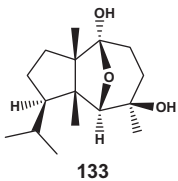

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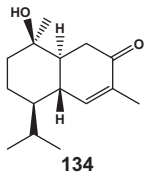

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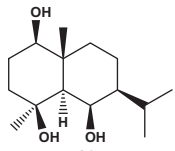

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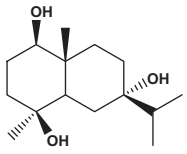

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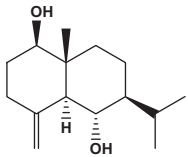

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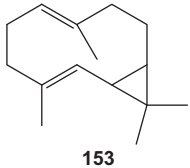

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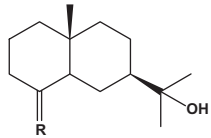
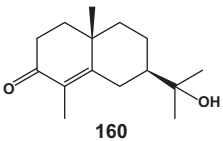


161: R = αOH, βMe
162: R = CH_2



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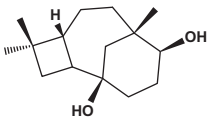

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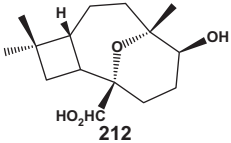

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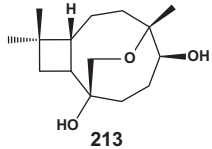

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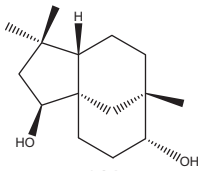
Figure 2.4 (Continued)



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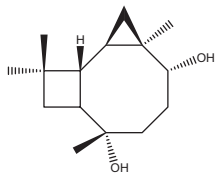

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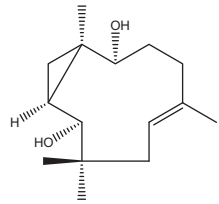

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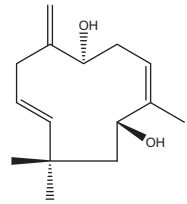

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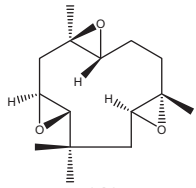

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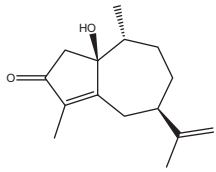

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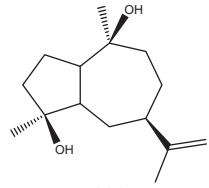

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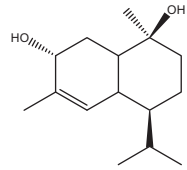

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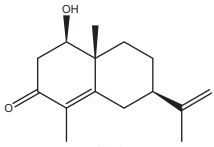

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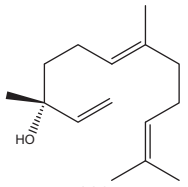

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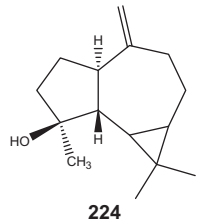

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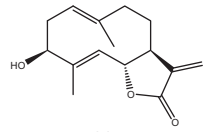

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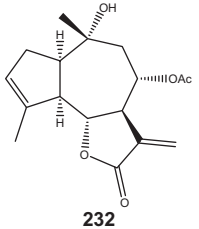

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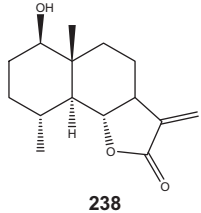

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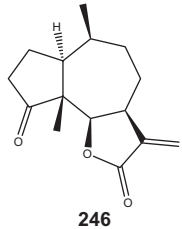

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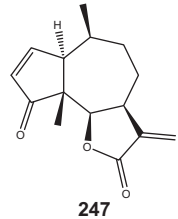

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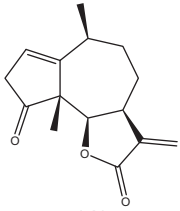

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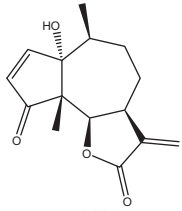

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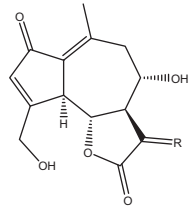

253: R = CH_2
254: R = αMe, H

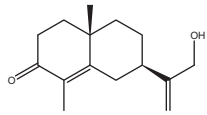

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Figure 2.4 (Continued)

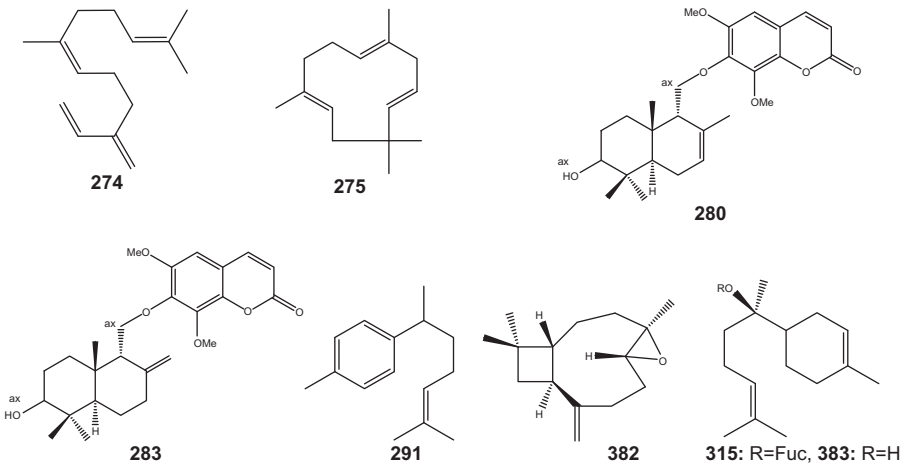
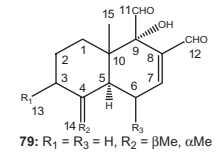
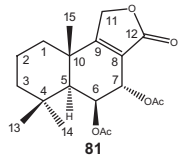


Figure 2.4 (Continued)

1.56 μg/mL). Warburganal (**79**) and muzigadial (**80**) also had significant antifungal activities against *S. cerevisiae* (MIC values of 3.13 and 1.56 μg/mL), *C. utilis*, and *Sc. libertiana* (MIC of 3.13 μg/mL) [35]. Further investigation of the *n*-hexane and ethyl acetate extracts of the stem bark of *W. ugandensis* yielded the first report of 7α-acetylugandensolide (**81**) and 13 known antimicrobial sesquiterpenes, including bemadienolide (**82**), drimenin (**83**), polygodial (**78**), warburganal (**79**), muzigadial (**80**), mukaadial (**84**), ugandensidial (**85**), 6α-hydroxymuzigadial (**86**), 9-deoxymuzigadial (**87**), ugandensolide (**88**), deacetoxyugandensolide (**89**), cinnamolide (**90**), and cinnamolide-3β-acetate (**91**) [36]. These compounds had limited antimicrobial activities, with MIC values ranging between 12.5 and 200 mg/mL, the lowest value of 12.5 mg/mL being obtained with polygodial (**78**) against *Fusarium solani*, warburganal (**79**) against *F. solani* and *Aspergillus niger*, and mukaadial (**84**) against *A. niger* [36]. Before the report on the biological activity of ugandensolide (**88**), it was isolated for the first time, together with ugandensidial (**85**) and warburgin (**145**) from the heartwood of *W. ugandensis* [110]. Three new coloratane sesquiterpenes, 6α,9α-dihydroxy-4(13),7-coloratadien-11,12-dial or 6α-hydroxymuzigadial (**86**), 4(13),7-coloratadien-12,11-olide (**92**), and 7β-hydroxy-4(13),8-coloratadien-11,12-olide (**93**), along with nine other sesquiterpenes, cinnamolide-3β-acetate (**91**), muzigadial (**80**), muzigadiolide (**94**), 11α-hydroxymuzigadiolide (**95**), cinnamolide (**90**), 7α-hydroxy-8-drimen-11,12-olide (**96**), ugandensolide (**88**), mukaadial (**84**), and ugandensidial (**85**), were isolated from the dichloromethane extract of the stem bark of *W. ugandensis* [40]. Regarding their antimycobacterial activity, muzigadial (**80**) was most active against *Mycobacterium fortuitum* (MIC of 16 μg/mL), *Mycobacterium aurum* (MIC of 32 μg/mL), and *Mycobacterium phlei* and *Mycobacterium smegmatis* (MIC of 64 μg/mL), followed by muzigadiolide (**94**) against *M. phlei* (MIC of 64 μg/mL) [40]. Pallescensin E (**97**) was isolated for the first time along with muzigadial (**80**)



79: $R_1 = R_3 = H$, $R_2 = \beta Me$, αMe
80: $R_1 = Me$, $R_2 = CH_2$, $R_3 = H$
86: $R_1 = Me$, $R_2 = CH_2$, $R_3 = OH$



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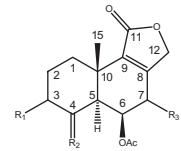
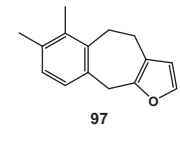


88: $R_1 = H$, $R_2 = \beta Me$, αMe, $R_3 = \alpha OH$
93: $R_1 = \beta Me$, $R_2 = CH_2$, $R_3 = \beta OH$



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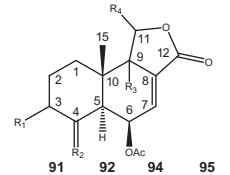
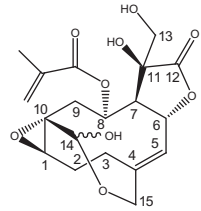


	91	**92**	**94**	**95**
R_1	OAc	βMe	βMe	βMe
R_2	βMe, αMe	CH_2	CH_2	CH_2
R_3	H	H	αOH	αOH
R_4	H	H	H	αOH



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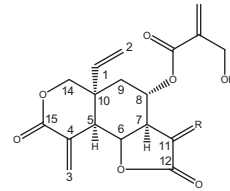
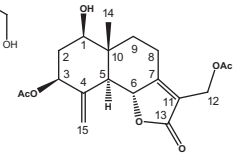


100: R = CH_2
146: R = αMe, H



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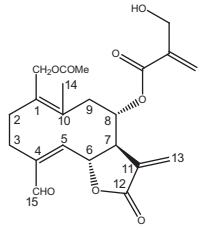

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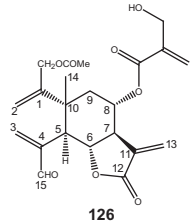

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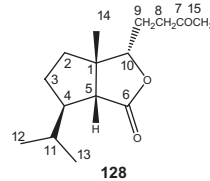

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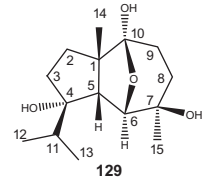

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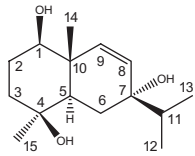

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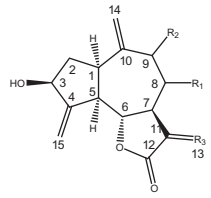
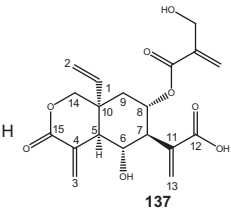


	R_1	R_2	R_3
131	H	βOH	CH_2
132	αOH	H	αMe, H



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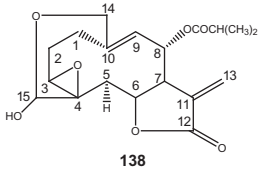

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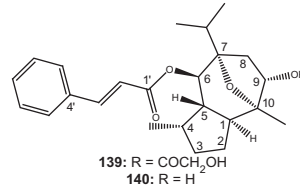
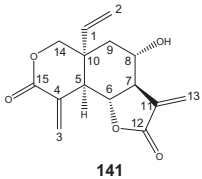


139: R = $COCH_2OH$
140: R = H



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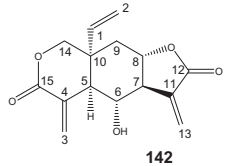

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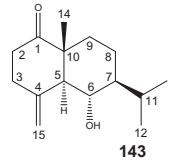

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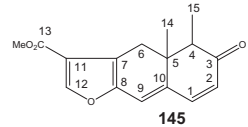
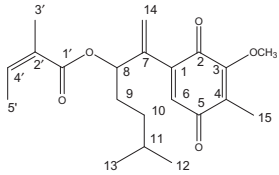


145

Figure 2.5 Chemical structures of sesquiterpenes and related compounds isolated as new compounds in African medicinal plants (ax, axial orientation; eq, equatorial orientation).



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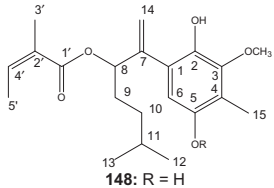
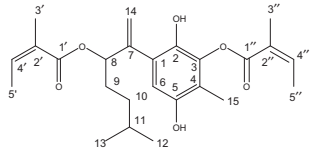


148: R = H
149: R = CH_3



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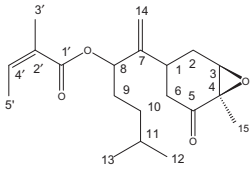

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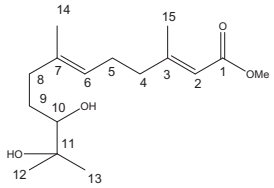

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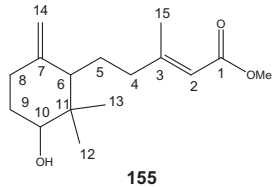
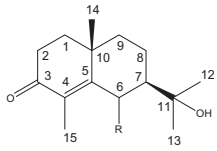
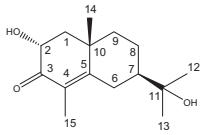


155



156: R = αOH
157: R = βOH



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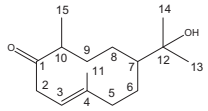

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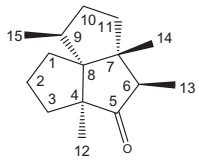

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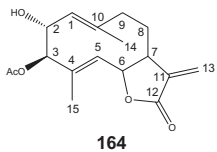

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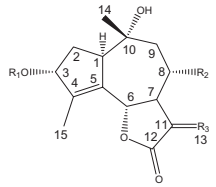
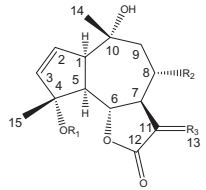
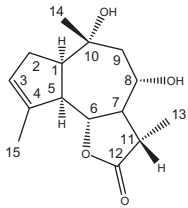


165: R_1 = OH, R_2 = H, R_3 = CH_2
168: R_1 = H, R_2 = OAc, R_3 = αMe, H
169: R_1= OH, R_2 = OAc, R_3 = αMe, H



166: R_1 = OH, R_2 = H, R_3 = CH_2
171: R_1 = OH, R_2 = OAc, R_3 = αMe, H
172: R_1 = H, R_2 = OAc, R_3 = αMe, H



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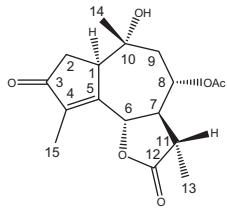

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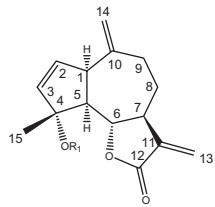

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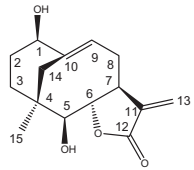

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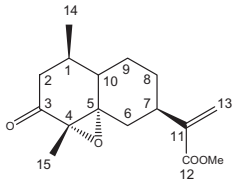

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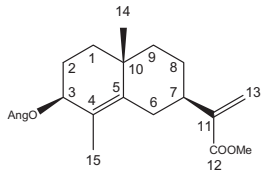
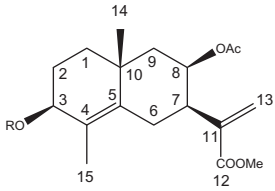
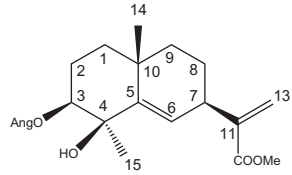


176

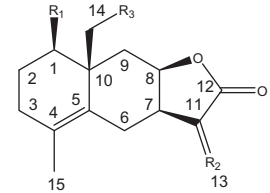
Figure 2.5 (Continued)



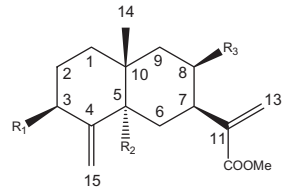
	177	178	179	180
R:	Ang	iBu	Prop	Mesen



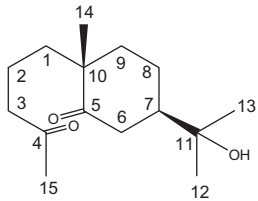
181



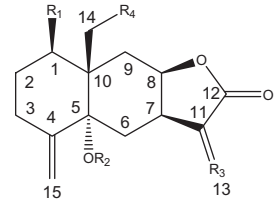
	193	194	195
R_1:	OAc	H	H
R_2:	αMe,H	CH_2	βMe, H
R_3:	H	OH	OAc



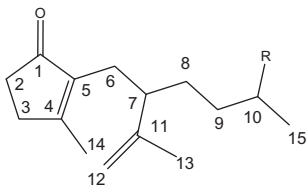
	182	183	184	185	186	187	188	189	190	191	192
R_1:	H	OH	OH	OAng	OAng	OAng	OiBu	OiBu	αOH	αOAng	αOAng
R_2:	OOH	OOH	OH	OOH	OOH	OH	OOH	OH	OH	OOH	OOH
R_3:	H	H	H	H	OAc	OAc	OAc	OAc	H	H	OAc



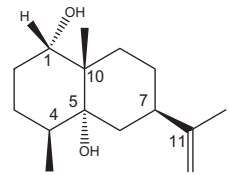
201



	196	197	198	199	200
R_1:	H	H	H	OH	OH
R_2:	OH	OH	OH	OH	H (5βOH)
R_3:	CH_2	CH_2	βMe,H	CH_2	CH_2
R_4:	OH	OAc	OAc	H	H



202: R == O
207: R = (*S*) OH
208: R = (*R*) OH



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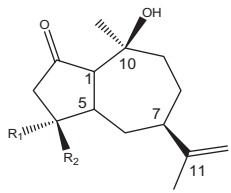
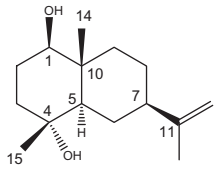
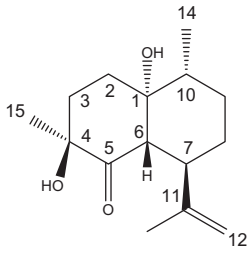


205: R_1 = OH, R_2 = Me
206: R_1 = Me, R_2 = OH

Figure 2.5 (Continued)



209



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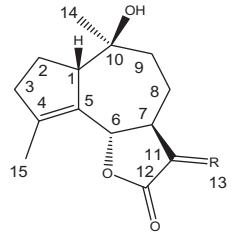
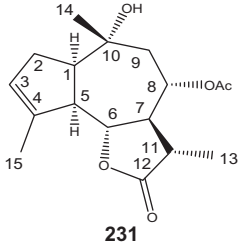
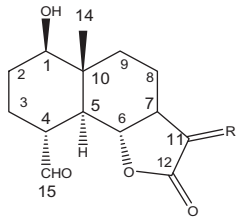


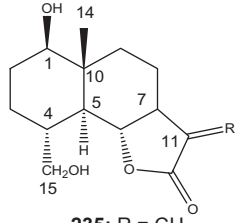
229: R = CH_2
230: R = αMe, H



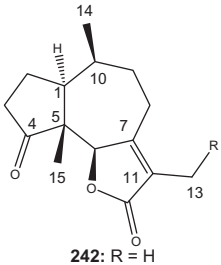
231



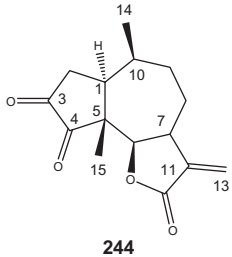
233: R = CH_2
234: R = αMe, H



235: R = CH_2
236: R = Me, H



242: R = H
243: R = OH



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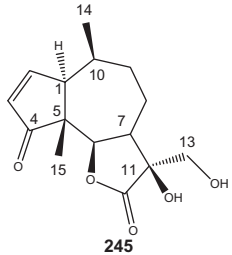

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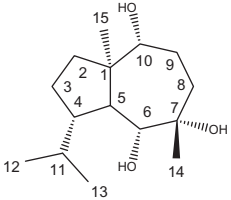

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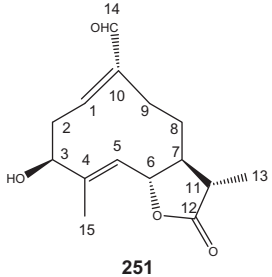

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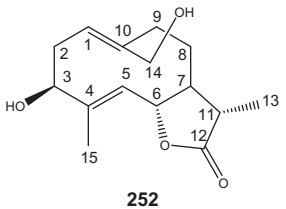

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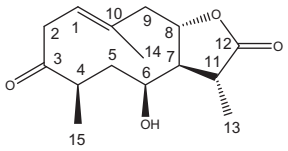

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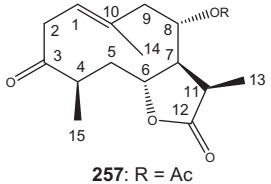
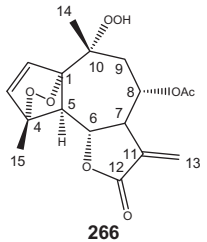
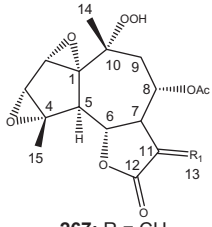


257: R = Ac
259: R = H

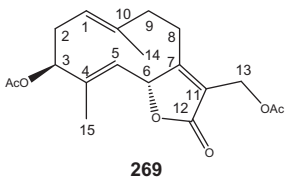


266

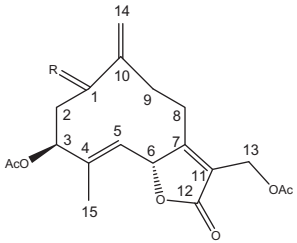
Figure 2.5 (Continued)



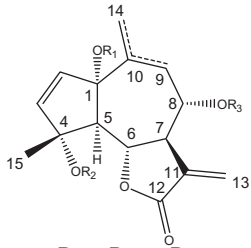
267: R = CH_2
268: R = αMe, H



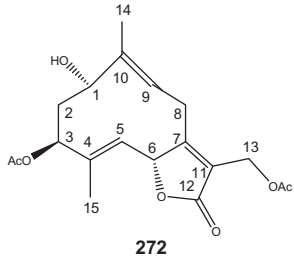
269



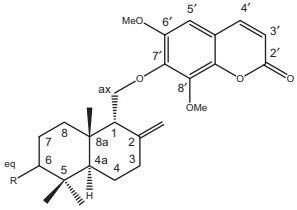
270: R = αOH, H
271: R = βOH, H



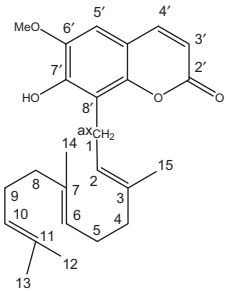
	R_1	R_2	R_3	Δ
260:	OH	OH	Ac	10
261:	H	H	H	10
262:	OH	OH	H	10
263:	OH	H	Ac	9
264:	H	OH	Ac	9
265:	OH	OH	Ac	9



272



	R
276:	OH
277:	OCOMe



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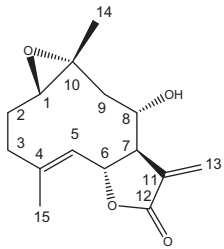

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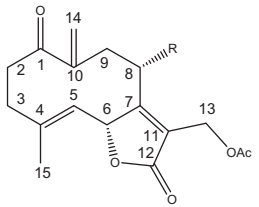
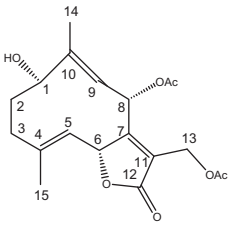


286: R = OH
287: R = OAc



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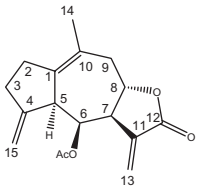

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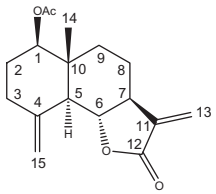

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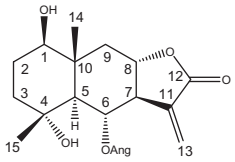
Figure 2.5 (Continued)



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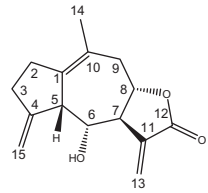

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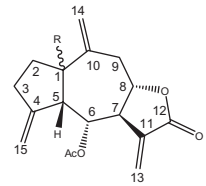
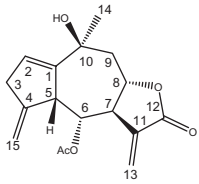


298: R = βOH,
299: R = βOOH
300: R = αOH



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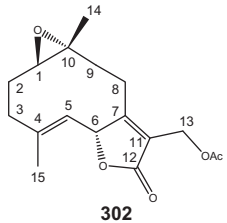

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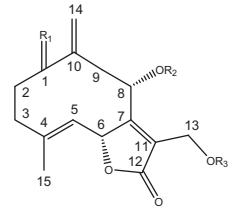
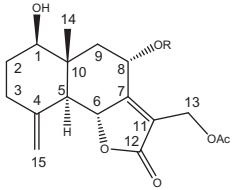
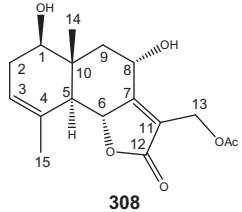


303: R_1 = αOH, H; R_2 = R_3 = Ac
304: R_1 = βOH, H; R_2 = R_3 = Ac
305: R_1 = O; R_2 = R_3 = H



306: R = H, **307:** R = Ac



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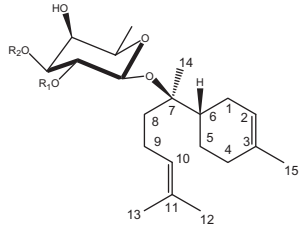
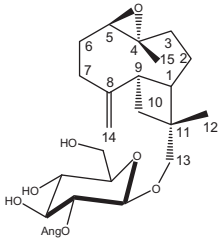


309: R_1 = Ang, R_2 = Ac
310: R_1 = MeBu, R_2 = Ac
311: R_1 = R_2 = Ang
312: R_1 = Ang, R_2 = H



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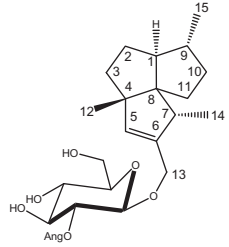

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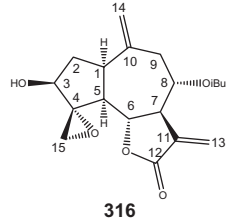

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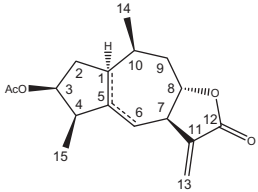
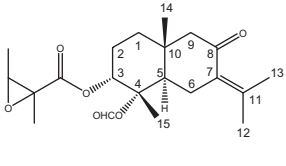


317: $\Delta^{1(5)}$, **318:** Δ^5



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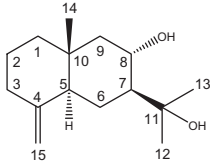
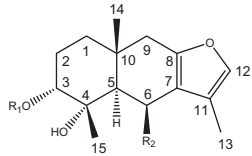
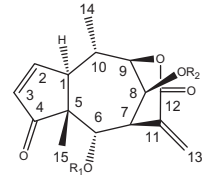


320

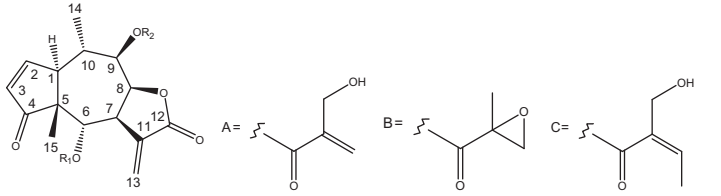
Figure 2.5 (Continued)



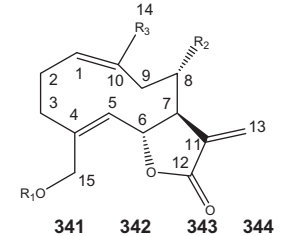
	321	322	323	324	325
R_1	H	Epang	iVal	Ang	Epang
R_2	H	H	H	H	OH



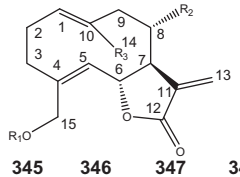
	337	338	339	340
R_1	A	A	C	C
R_2	Ang	iVal	Ang	iVal



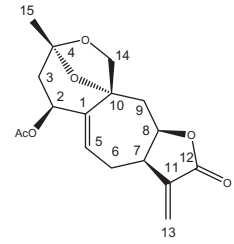
	326	327	328	329	330	331	332	333	334	335	336
R_1	A	Ang	Meacr	Meacr	Meacr	B	B	C	A	A	C
R_2	iBu	Ang	Ang	iBu	Meacr	Ang	iVal	Ang	Ang	iVal	iBu



	341	342	343	344
R_1	Ac	H	Ac	H
R_2	OH	H	H	H
R_3	CHO	CH_2OAc	CHO	CHO



	345	346	347	348
R_1	Ac	Ac	H	Ac
R_2	H	OH	H	H
R_3	CHO	CH_2OAc	CH_2OAc	CH_2OAc



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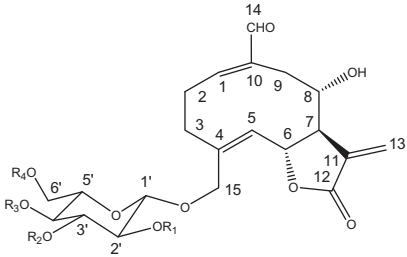
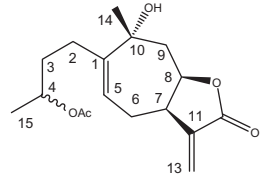


351: $R_1 = R_2 = R_3 = H$, $R_4 = COCH_2C_6H_4OH$ (p); **352:** $R_1 = R_2 = R_3 = R_4 = H$



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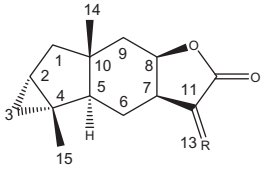
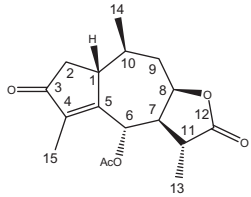


355: R = CH_2
356: R = αMe, H



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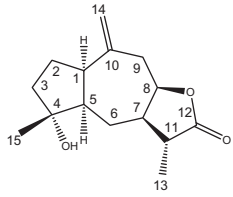

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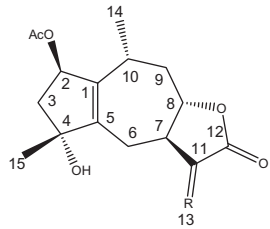
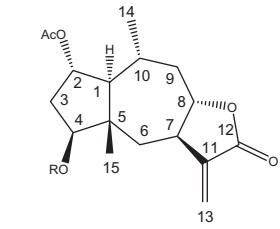
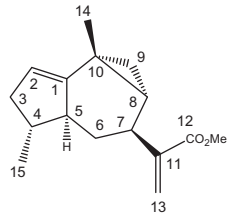
Figure 2.5 (Continued)



359: R = CH_2; **360:** R = αMe, H



361: R = H; **362:** R = Ac, **363:** R = Ac, 8αH



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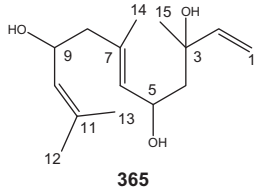

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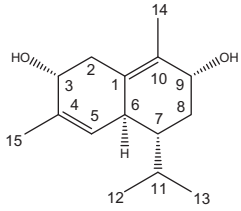

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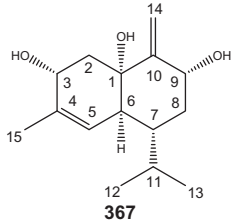

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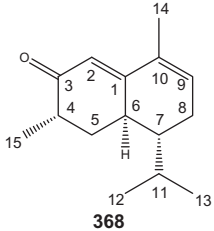

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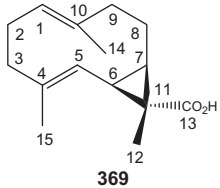

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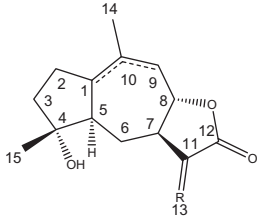
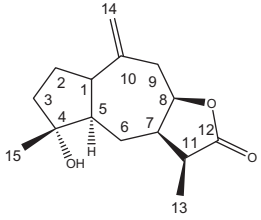


370: R = CH_2, $\Delta^{1,10}$
371: R = βMe, H; Δ^9



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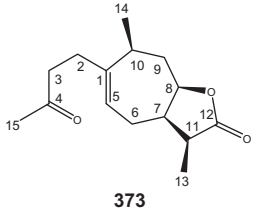

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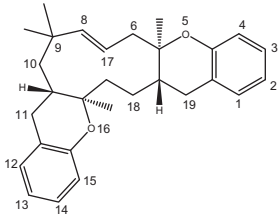

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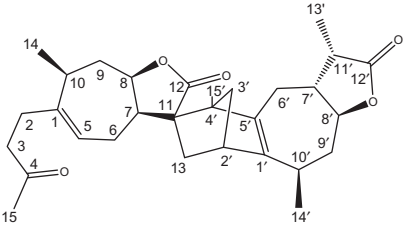

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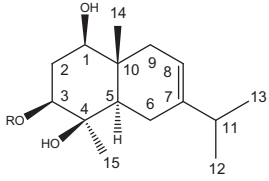
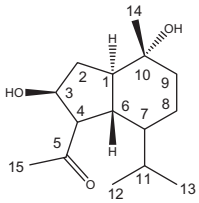


376: R = H
377: R = Ac

Figure 2.5 (Continued)



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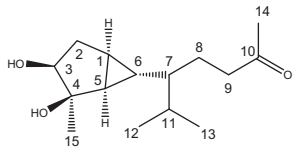

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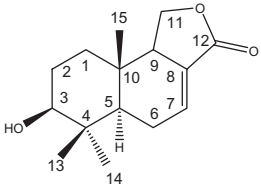

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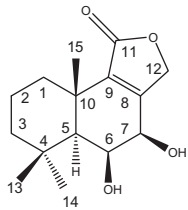

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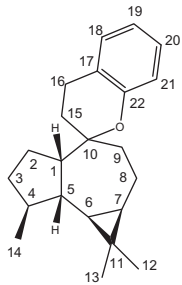

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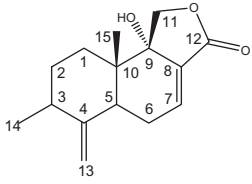

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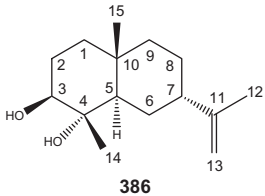

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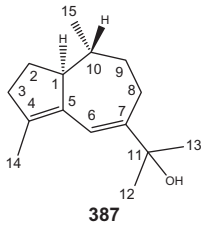

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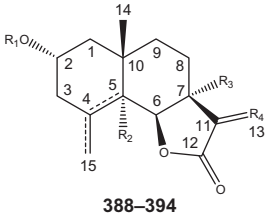
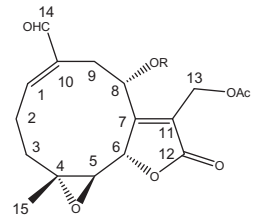
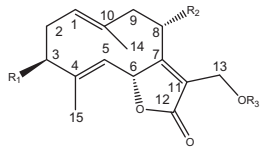


388–394

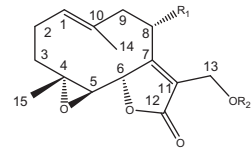
	388	389	390	391	392	393	394
R_1	H	Ac	H	Ac	H	Ac	Ac
R_2	H	H	OH	OH	OH	H	H
R_3	H	H	H	H	H	H	OH
R_4	CH_2	CH_2	CH_2	CH_2	βMe, H	CH_2	CH_2
Δ	4	4	4	4	4	4(15)	4(15)



395: R = iVal; **396:** R = iBu

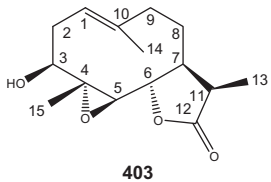


397: R_1 = H, R_2 = OH, R_3 = H
398: R_1 = OAc, R_2 = H, R_3 = H
399: R_1 = OH, R_2 = H, R_3 = Ac



400: R_1 = OH, R_2 = H
401: R_1 = OH, R_2 = Ac
402: R_1 = H, R_2 = H

Figure 2.5 (Continued)



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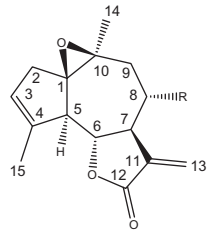
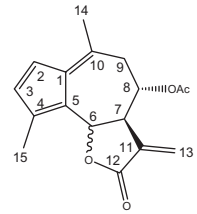
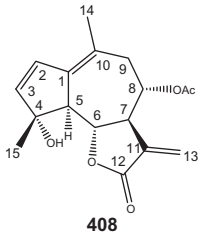


404: R = H, **405:** R = OAc



406: 6βH, **407:** 6αH



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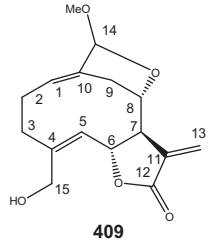

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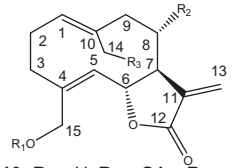
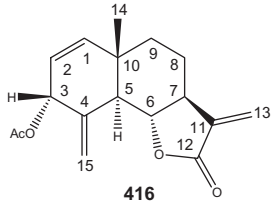


410: R_1 = H, R_2 = OAc, R_3 = OH
411: R_1 = Ac, R_2 = OAc, R_3 = OH
412*: R_1 = H, R_2 = OAc, R_3 = OA
413: R_1 = Ac, R_2 = H, R_3 = H
414: R_1 = Ac, R_2 = H, R_3 = OH
415: R_1 = Ac, R_2 = OH, R_3 = H
*OA = OCOCH(Me)CH(OH)Me



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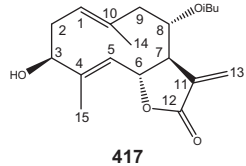

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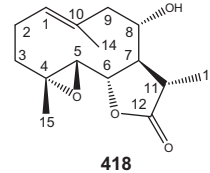

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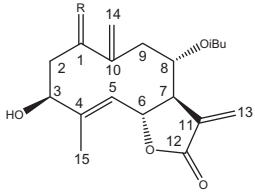
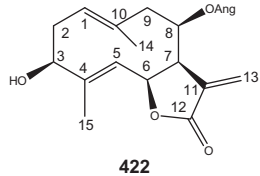


419: R = βOH, H;
420: R = βOOH, H; **421**: R = O



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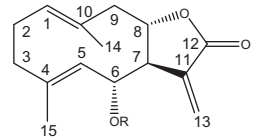
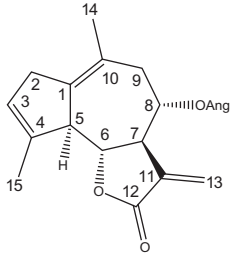


423: R = H; 11α,13H
424: R = Tigl; 4α, 5βepoxide
425: R = H; 4α, 5βepoxide; 11α, 13H



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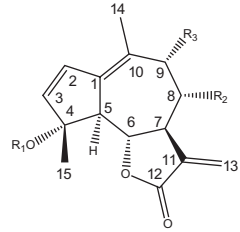

427: R_1= R_3= H, R_2= OAng
428: R_1= R_3= H, R_2= OAng, 4-epi
429: R_1=OH, R_3= H, R_2= OMe, 4-epi

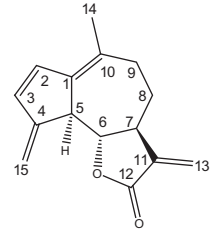

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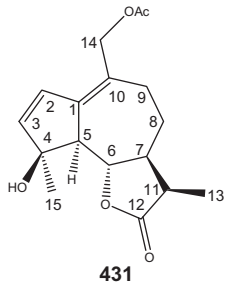
Figure 2.5 (Continued)



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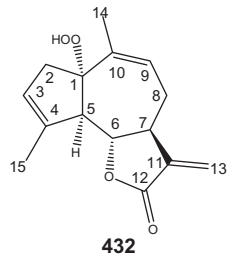

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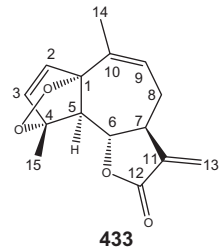
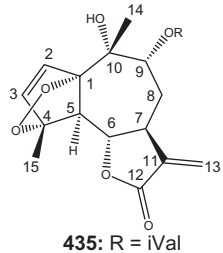
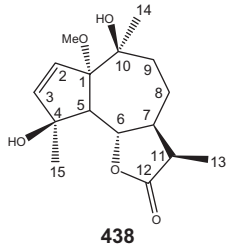


433
434: 11α,13H



435: R = iVal
436: R = Mebu
437: R = iBu



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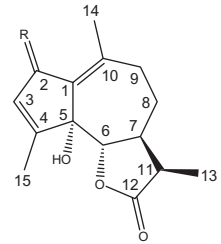
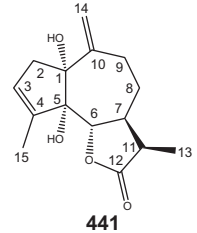


439: R = αOMe, H
440: R = O



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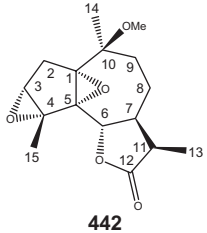

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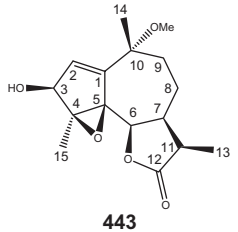

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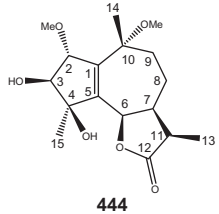

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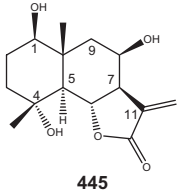

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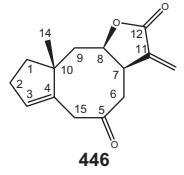

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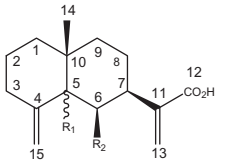
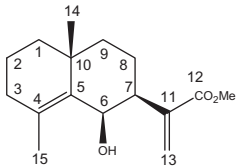


447: R_1 = αOOH, R_2 = OH
448: R_1 = βOOH, R_2 = H



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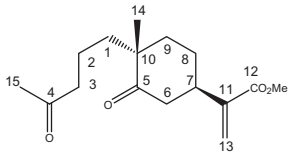
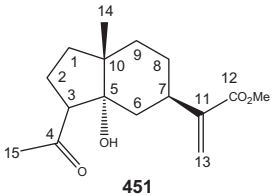


450

Figure 2.5 (Continued)



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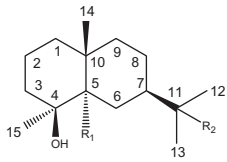
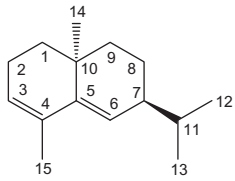
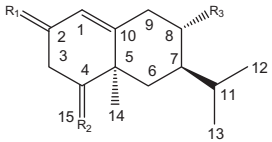


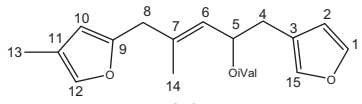
452: R_1 = OH, R_2 = H
453: R_1 = H, R_2 = OH



454



	455	456	457	458
R_1	αOH,H	O	αOH,H	O
R_2	βOH, αMe	βOH, αMe	αMe, H	αMe H
R_3	H	H	αOH	αOH



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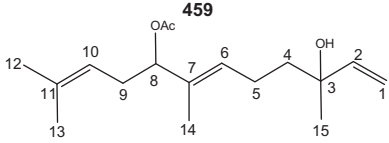

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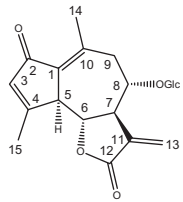

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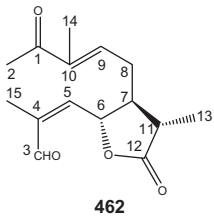

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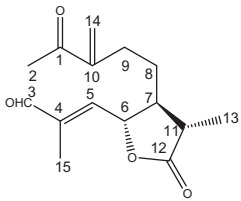

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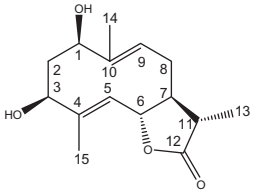

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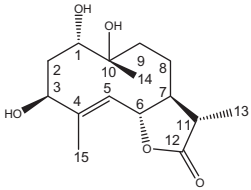

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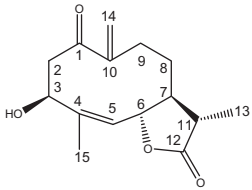

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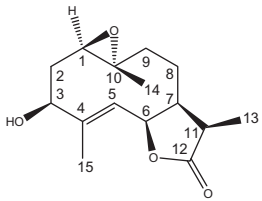

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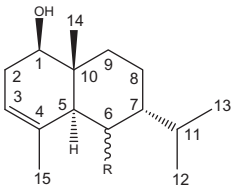
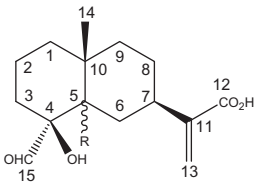
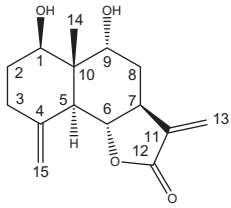


468: R = αOH; **469:** R = βOH



470: R = αOH; **471:** R = βOH

Figure 2.5 (Continued)



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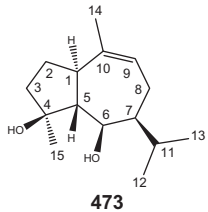

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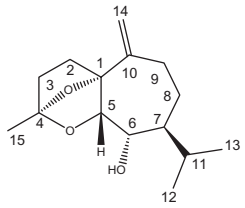

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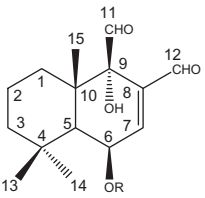
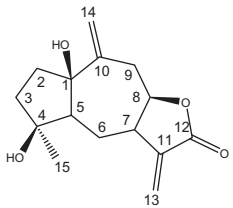


475: R = α-L-Rhamnose
476: R = β-D-Glucose



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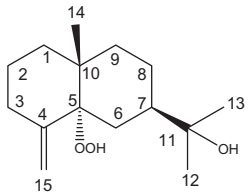

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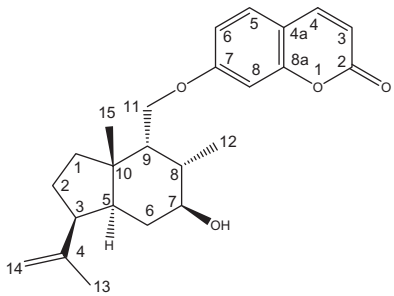

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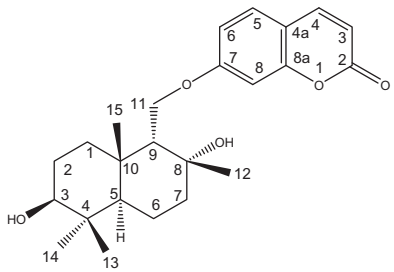

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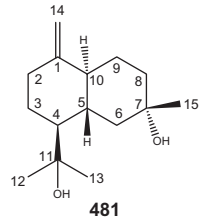

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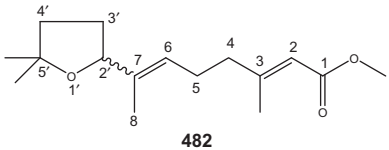

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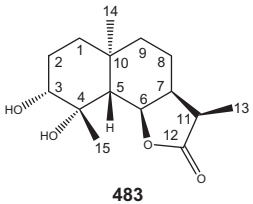

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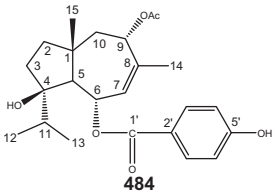

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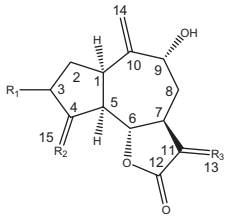

486: R_1 = αOH, R_2 = CH_2, R_3 = αMe, H
487: R_1 = βOH, R_2 = βMe, H, R_3 = CH_2

Figure 2.5 (Continued)

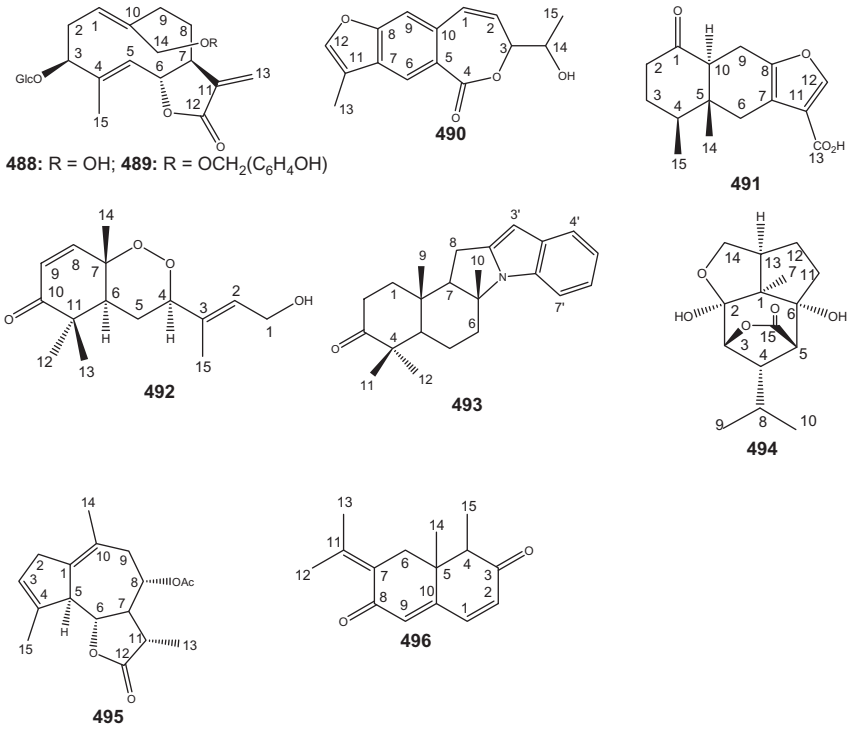

Figure 2.5 (Continued)

and drimenin (**83**) from the stem bark of *W. salutaris*; their antimycotoxigenic activity was also reported against *Fusarium moniliforme* and *Aspergillus flavus* using bioautographic techniques [39]. The antibacterial activity of muzigadial (**80**) against *Staphylococcus aureus* (MIC value of 12.5 μg/mL), *Bacillus subtilis* (MIC value of 12.5 μg/mL), and *Micrococcus luteus* (MIC value of 50.0 μg/mL) was also documented [111]. A new sesquiterpene lactone, 11β,13-dihydrovernolide (**98**), was isolated together with two other sesquiterpenes, vernolide (**99**) and vernodalin (**100**), from the ethyl acetate extract of the leaves of *V. colorata* [41]. The novel compound (**98**) had significant antibacterial activity against *B. subtilis* (MIC of 4.0 μg/mL), while compounds **99** and **100** had excellent activity against *S. aureus* (MIC values of 0.5 and 0.25 μg/mL) and *B. subtilis* (MIC values of 0.1 and 0.1 μg/mL), respectively [41]. Two new sesquiterpenes, 3β,9β-dihydroxyguaian-4(15),10(14),11(13)-trien-6,12-olide (**131**) and 8α-hydroxy-4α(13),11β(15)-tetrahydrozaluzanin C (**132**), isolated from the aerial parts of a Cameroonian medicinal plant *Crepis cameroonica*, had antimicrobial activities against *S. aureus* and *Escherichia coli*, with the inhibition zone (IZ) diameter ranging between 5 and 16 mm at a concentration of 1 mg/mL [112].

Carissone (**160**), cryptomeridiol (**161**), and β-eudesmol (**162**) were isolated from the roots of *C. edulis* [62]. Compound **160** inhibited the growth of *Aspergillus*

Table 2.1 Bioactive Sesquiterpenes from African Medicinal Plants

Compounds	Plants (Family)	Pharmacological Activities
Costunolide (**76**)	*Magnolia grandiflora* L. (Magnoliaceae) [16]	Antifungal [16], antimycobacterial [29], cytotoxicity [30], nitric oxide synthase inhibitory [31−33], antioxidant [34]
Parthenolide (**77**)	*M. grandiflora* L. (Magnoliaceae) [16]	Antifungal [16], antimycobacterial [29], cytotoxicity [30]
Polygodial (**78**)	*Warburgia stuhlmannii*, *W. ugandensis* (Canellaceae) [35,36]	Antimicrobial [35,36]
Bemadienolide (**82**)	*Warburgia ugandensis* (Canellaceae) [36], *W. stuhlmannii* (Canellaceae) [37]	Antimicrobial [36], antiplasmodial [38], antifeedant [37]
Drimenin (**83**)	*W. ugandensis* [36], *W. stuhlmannii* [39] (Canellaceae)	Antimicrobial [36], antimycotoxigenic [39]
Mukaadial (**84**)	*W. ugandensis* (Canellaceae) [36,40]	Antimicrobial [36], antimycobacterial [40], antiprotozoal [38]
Cinnamodial or ugandensidial (**85**)	*W. stuhlmannii* (Canellaceae) [37], *W. ugandensis* (Canellaceae) [36,40]	Antifeedant [37], antimicrobial [36], antimycobacterial [40]
9-Deoxymuzigadial (**87**)	*W. ugandensis* (Canellaceae) [36]	Antimicrobial [36]
Deacetoxyugandensolide (**89**)	*W. ugandensis* (Canellaceae) [36]	Antimicrobial [36]
Cinnamolide (**90**)	*W. ugandensis* (Canellaceae) [36,40]	Antimicrobial [36], antimycobacterial [40], antiprotozoal [38], antiplasmodial [38]
7α-Hydroxy-8-drimen-11,12-olide (**96**)	*W. ugandensis* (Canellaceae) [40]	Antimycobacterial [40], antiprotozoal [38], antiplasmodial [38]
Vernolide (**99**)	*Vernonia colorata* (Asteraceae) [41], *Vernonia amygdalina* (Asteraceae) [42]	Antimicrobial [41,43], antiplasmodial [44], cytotoxicity [44], antioxidant [45], tumor inhibitor [42]

(*Continued*)

Table 2.1 (Continued)

Compounds	Plants (Family)	Pharmacological Activities
5*E*,10(14)-Germacradien-1β,4β-diol (**101**)	*Reneilmia cincinnata* (Zingiberaceae) [7]	Antiplasmodial [7]
1(10)*E*,5*E*-Germacradien-4β-ol (**102**)	*R. cincinnata* (Zingiberaceae) [7]	Antiplasmodial [7]
Oplodiol (**103**)	*R. cincinnata* (Zingiberaceae) [7]	Antiplasmodial [7]
Oplopanone (**104**)	*R. cincinnata* (Zingiberaceae) [7], *Teucrium ramosissimum* (Lamiaceae) [46]	Antiplasmodial [7,46], cytotoxicity [46]
Vernodalol (**105**)	*V. amygdalina* (Asteraceae) [47], *V. colorata* (Asteraceae) [48], *Distephanus angulifolius* (Asteraceae) [49]	Antifeedant [47], antiplasmodial [48,49], antimicrobial [43], antioxidant [45]
11α,13-Dihydrovernodalin (**106**)	*V. colorata* (Compositae) [48]	Antiplasmodial [48]
11α,13-Dihydrovernolide (**107**)	*V. colorata* (Compositae) [48]	Antiplasmodial [48]
11α,13,17,18-Tetrahydrovernolide (**108**)	*V. colorata* (Compositae) [48]	Antiplasmodial [48]
1-Desoxy-1α-peroxy-rupicolin A-8-*O*-acetate (**109**)	*Artemisia afra* (Asteraceae) [48]	Antiplasmodial [48]
1-Desoxy-1α-peroxy-rupicolin B-8-*O*-acetate (**110**)	*A. afra* (Asteraceae) [48]	Antiplasmodial [48]
Rupicolin A-8-*O*-acetate (**111**)	*A. afra* (Asteraceae) [48]	Antiplasmodial [48]
Rupicolin B-8-*O*-acetate (**112**)	*A. afra* (Asteraceae) [48]	Antiplasmodial [48]
11,13-Dehydromatricarin (**113**)	*A. afra* (Asteraceae) [48]	Antiplasmodial [48]
1α,4α-Dihydroxybishopsolicepolide (**114**)	*A. afra* (Asteraceae) [48]	Antiplasmodial [48]
1α,4α,8α-Trihydroxyguaia-2,9,11(13)-triene-12,6α-olide-8-*O*-acetate (**115**)	*A. afra* (Asteraceae) [48]	Antiplasmodial [48]
Tatridin A or tavulin (**117**)	*Oncosiphon piluliferum* (Asteraceae) [50]	Antiplasmodial [50], cytotoxicity [50]
Tanachin (**118**)	*O. piluliferum* (Asteraceae) [50]	Antiplasmodial [50], cytotoxicity [50]
5α-Epoxy-6α-hydroxy-1(10)*E*,11(13)-germacradien-12,8α-olide (**119**)	*O. piluliferum* (Asteraceae) [50]	Antiplasmodial [50], cytotoxicity [50]
Desacetyl-β-cyclopyrethrosin (**120**)	*O. piluliferum* (Asteraceae) [50]	Antiplasmodial [50], cytotoxicity [50]
Sivasinolide (**121**)	*O. piluliferum* (Asteraceae) [50]	Antiplasmodial [50], cytotoxicity [50]

Corymbolone (**122**)	*Cyperus articulatus* L. (Cyperaceae) [51,52]	Antiplasmodial [51]
Mustakone (**123**)	*C. articulatus* L. (Cyperaceae) [51,53]	Antiplasmodial [51]
Dehydrobrachylaenolide (**124**)	*Dicoma anomala* subsp. *gerrardii* (Asteraceae) [54]	Antiplasmodial [54]
11,13β-Dihydrovernodalin (**127**)	*D. angulifolius* (Asteraceae) [49]	Antiplasmodial [49]
Homalomenol C (**133**)	*T. ramosissimum* (Lamiaceae) [46]	Antiplasmodial [46], cytotoxicity [46]
Oxo-T-cadinol (**134**)	*T. ramosissimum* (Lamiaceae) [46]	Antiplasmodial [46], cytotoxicity [46]
1β,4β,6β-Trihydroxyeudesmane (**135**)	*T. ramosissimum* (Lamiaceae) [46]	Antiplasmodial [46], cytotoxicity [46]
1β,4β,7α-Trihydroxyeudesmane (**136**)	*T. ramosissimum* (Lamiaceae) [46], *R. cincinnata* (Zingiberaceae) [7]	Antiplasmodial [46], cytotoxicity [46], stimulative effect on proliferation and differentiation of cultured osteoblasts [55]
1β,6α-Dihydroxy-4(15)-eudesmene (**144**)	*Urginea epigea* (Urgineoideae, Hyacinthaceae) [56]	Anti-inflammatory [57]
Bicyclogermacrene (**153**)	*Senecio oxyodontus* (Compositae) [58], *Epaltes gariepina* (Compositae) [59]	Antifungal [60], trypanocidal, and antileishmanial [61]
Carissone (**160**)	*Carissa edulis* (Apocynaceae) [62]	Antifungal [63], antibacterial [64]
Cryptomeridiol (**161**)	*C. edulis* (Apocynaceae) [62]	Melanogenesis-inhibitory [65], cytotoxicity [65], platelet-activating factor (PAF) antagonistic activity [66]
β-Eudesmol (**162**)	*C. edulis* (Apocynaceae) [62]	Gastric emptying and small intestinal motility [67]
Caryolane 1,9β-diol (**211**)	*Cyperus longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
3,7-Epoxycaryophyllane-5,15-diol (**212**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
7,15-Epoxycaryophyllane-3,5α-diol (**213**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
Clovanediol (**214**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
Tricyclohumuladiol (**215**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]

(*Continued*)

Table 2.1 (Continued)

Compounds	Plants (Family)	Pharmacological Activities
1,5,8,8-Tetramethyl-8-bicyclo[8.1.0] undecene-2,9-diol (**216**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
2,10,10-Trimethyl-6-methylene-2,8-cycloundecadiene-1,5-diol (**217**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
1,6,6,10-Tetramethyl-4,9,14-trioxatetracyclotetradecane (**218**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
1β-Hydroxy-10βH-guaia-4,11-dien-3-one (**219**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
Guaidiol (**220**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
Muurolane-2α,9β-diol-3-ene (**221**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
Ligucyperonol (**222**)	*C. longus* L. (Cyperaceae) [68]	Hepatoprotective [68]
Nerolidol (**223**)	*Eriocephalus* sp.n. (Compositae) [69], *Osteospermum rigidum* (Compositae) [70]	Antibacterial [29,71], antileishmanial [72], antiulcerogenic [73], genotoxicity [74]
Spathulenol (**224**)	*Eriocephalus* sp.n. (Compositae) [69], *Eriocephalus giessii* (Compositae) [69,75], *E. gariepina* (Compositae) [59]	Antimicrobial [76]
Hanphyllin (**225**)	*Eriocephalus* sp.n. (Compositae) [69]	Antiplasmodial [77], cytotoxicity [77]
Cumambrin A (**232**)	*Chrysanthemum coronarium* (Compositae) [78]	Cytotoxicity [79]
Reynosin (**238**)	*Sonchus macrocarpus* (Compositae) [80]	Tumor inhibitory [81,82]
Damsin (**246**)	*Ambrosia maritime* (Compositae) [83]	Antifungal [84], herbicidal [85], antimycobacterial [29]
Ambrosin (**247**)	*A. maritime* (Compositae) [83]	Antifungal [84], herbicidal [85]
Neoambrosin (**248**)	*A. maritime* (Compositae) [83]	Antifungal [84], herbicidal [85]
Parthenin (**249**)	*A. maritime* (Compositae) [83]	Herbicidal [86,87], antimycobacterial [29]

Lactucin (**253**)	*Lactuca sativa* (Compositae) [88]	Cytotoxicity [89], antimalarial [90], analgesic [91]
11β,13-Dihydrolactucin (**254**)	*L. sativa* (Compositae) [88]	Analgesic [91], antidiabetic [92]
12-Hydroxy-α-cyperone (**273**)	*A. afra* (Compositae) [93]	Cytotoxicity [94], anti-inflammatory [94], neuroproliferative [94]
β-Farnesene (**274**)	*A. afra* (Compositae) [93]	Estrus inducing [95]
α-Humulene (**275**)	*A. afra* (Compositae) [93]	Anti-inflammatory [96]
Drimartol A (**280**)	*Brocchia cinerea* (Compositae) [97]	Cytotoxicity [98]
Pectachol (**283**)	*B. cinerea* (Compositae) [97]	Antiplasmodial [99]
α-Curcumene (**291**)	*C. cinerea* (Compositae) [100]	Antimycobacterial [101], anti-inflammatory [102]
α-Bisabolol-6-desoxy-β-altropyranoside (**315**)	*Osteospermum microcarpum* (Compositae) [70]	Cytotoxicity and antimicrobial [103,104]
6,7-Epoxy-3(15)-caryophyllene (**382**)	*Aframomum arundinaceum* (Zingiberaceae) [105], *E. giessii* (Compositae) [69]	Antifeedant [106]
α-Bisabolol (**383**)	*A. arundinaceum* (Zingiberaceae) [105]	Antinociceptive [107], anti-inflammatory [107], gastroprotective [108], antimutagenic [109]

fumigatus with an MIC value of 1.0 mg/mL [63] but had low activity against *E. coli* and *S. aureus* (MIC between 0.1 and 0.5 mg/mL) and *Pseudomonas aeruginosa* (MIC values of 1 and 2 mg/mL), respectively [64]. A guaianolide sesquiterpene, 10β-hydroxycichopumilide (**229**), isolated for the first time from an Egyptian medicinal plant *Cichorium pumilum* [113], was active against *Pyricularia oryzae* and *Pellicularia sasakii*, *B. subtilis*, and *Alternaria kikuchiana*, and *Corynebacterium michiganense* and *S. cerevisiae* when tested at 125 mg/disk [114].

Damsin (**246**), ambrosin (**247**), neoambrosin (**248**), and parthenin (**249**), isolated from the aerial parts of *A. maritime* [83], exhibited antifungal activity [84]. Neoambrosin (**248**) had low activity (EC_{50} values of 316.6 and 204.3 μg/mL), while damsin (**246**) and ambrosin (**247**) had relatively high *in vitro* mycelial radial growth inhibitory activities against plant fungi *Botrytis cinerea* and *Fusarium oxysporum* [84].

Because many factors influence the IZ in agar diffusion assays, including the polarity of the tested compounds, it is difficult if not impossible to compare antimicrobial activities of different compounds. Nevertheless, two sesquiterpene coumarins, ferusinol (**478**) and samarcandin diastereomer (**479**), were isolated for the first time from the roots of *Ferula sinaica* [115]. Ferusinol (**478**) had *in vitro* antibacterial activity against gram-positive strains *B. cereus* and *S. aureus* and gram-negative strains *Serratia* sp., *Pseudomonas* sp., and *E. coli*, with the IZ varying between 5 and 18 mm at concentrations of 200 and 400 μg/mL, whereas samarcandin diastereomer (**479**) was only active against gram-negative bacteria (IZ of 13−19 mm) at the same concentrations as **478** [115]. α-Curcumene (**291**), isolated from the aerial parts of *C. cinerea* [100], had some antimycobacterial activities against the drug-resistant strains [Multi-Drug Resistant (MDR)-R (MIC of 31.25 μg/mL) and MDR-40 (MIC of 62.5 μg/mL)] of *M. smegmatis* [101].

Four sesquiterpene derivatives [9α-hydroxy-11β,13-dihydro-3-epi-zaluzanin C (**486**), 9α-hydroxy-4α,15-dihydro-zaluzanin C (**487**), 3β,14-dihydroxycostunolide-3-*O*-β-glycopyranoside (**488**), and 3β,14-dihydroxycostunolide-3-*O*-β-glucopyranosyl-14-*O*-*p*-hydroxyphenylacetate (**489**)] were reported for the first time from the Algerian plant *Launaea arborescens* [116]. These compounds (**486**−**489**) were tested for antimicrobial activity at a concentration of 5 μg/mL, and no growth inhibition was observed against *C. albicans*, *E. coli*, or *S. aureus* [116].

2.3.2 Antiplasmodial Activity and Cytotoxicity of Sesquiterpenes Identified in African Medicinal Plants

Among the biological properties of sesquiterpenes from African medicinal plants, the antiplasmodial activities of several compounds were determined. This could be ascribed to the success obtained with the current pharmaceutical use of the sesquiterpene lactone artemisinin and derivatives as antiplasmodial agents.

The antiplasmodial activity of compounds **80**, **84**−**86**, **88**, **90**, **91**, **94**, **95**, and **96**, earlier reported for their antimicrobial properties, was further evaluated, and muzigadiolide (**94**) (IC_{50} of 7.3 μM), mukaadial (**84**) (IC_{50} of 7.9 μM), 6α-hydroxymuzigadial (**86**) (IC_{50} of 11.0 μM), and ugandensidial (**85**) (IC_{50} of 10.6 μM) were significantly active against the chloroquine-resistant strain (K1) of *P. falciparum in vitro* [38].

The strong antiplasmodial activity of vernolide (**99**) (IC_{50} of 1.87 μg/mL) [41] and vernodalin (**100**) (IC_{50} of 0.52 μg/mL) [41] against *P. falciparum*, as well as their cytotoxicity, were further reported by Chukwujekwu et al. [44]. The antiplasmodial activity was also reported for four sesquiterpenes isolated from the fruits of a Cameroonian medicinal plant, *R. cincinnata* [7]. 5*E*,10(14)-Germacradien-1β,4β-diol (**101**) (IC_{50} values of 1.63 and 31.90 μg/mL) and 1(10)*E*,5*E*-germacradien-4β-ol (**102**) (IC_{50} values of 1.54 and 1.90 μg/mL) were highly active, whereas oplodiol (**103**) (IC_{50} values of 4.17 and 25.50 μg/mL) as well as oplopanone (**104**) (IC_{50} value >50.50 μg/mL) had lower activities against (D4) and (W2) *P. falciparum* clones, respectively [7]. Two elemanes, vernodalol (**105**) and 11α,13-dihydrovernodalin (**106**), and two germacranolides, 11α,13-dihydrovernolide (**107**) and 11α,13,17,18-tetrahydrovernolide (**108**), were isolated from the lipophilic extract of the leaves of *V. colorata* [48]. From their *in vitro* antiplasmodial activity, compounds **105** and **106** had excellent activity, with IC_{50} values between 1.1 and 4.8 μg/mL against *P. falciparum* [48]. From the lipophilic extract of the epigeal parts of *A. afra*, eight sesquiterpenes [1-desoxy-1α-peroxy-rupicolin A-8-*O*-acetate (**109**), 1-desoxy-1α-peroxy-rupicolin B-8-*O*-acetate (**110**), rupicolin A-8-*O*-acetate (**111**), rupicolin B-8-*O*-acetate (**112**), 11,13-dehydromatricarin (**113**), 1α,4α-dihydroxybishopsolicepolide (**114**), 1α,4α,8α-trihydroxyguaia-2,9,11(13)-triene-12,6α-olide-8-*O*-acetate (**115**), and eudesmaafraglaucolide (**116**)] were isolated, and compounds **109**, **111**, and **114** had good to moderate *in vitro* antiplasmodial activity (IC_{50} values of 8.6−17.5 μg/mL) against *P. falciparum* [48]. The antiplasmodial activity of five sesquiterpenes isolated from the aerial parts of *O. piluliferum* were determined against D10 *P. falciparum* strains, and tatridin A, also named tavulin (**117**) (IC_{50} of 0.4 μg/mL), and tanachin (**118**) (IC_{50} of 0.5 μg/mL) were active as was the acetate derivative (IC_{50} of 0.5 μg/mL) of 5α-epoxy-6α-hydroxy-1(10)*E*,11(13)-germacradien-12,8α-olide (**119**) [50]. Desacetyl-β-cyclopyrethrosin (**120**) (IC_{50} of 4.4 μg/mL) and sivasinolide (**121**) (IC_{50} of 2.6 μg/mL) had moderate activity [50]. Compounds **117**−**121** were, however, toxic to mammalian (Chinese hamster ovarian) cells (IC_{50} values between 2.2 and 6.4 μg/mL) [50]. Two sesquiterpenes, corymbolone (**122**) and mustakone (**123**), isolated from the rhizomes of *C. articulatus*, had significant antiplasmodial activity (IC_{50} values of 1.07 and 1.92 μg/mL and 0.14 and 0.25 μg/mL) against *P. falciparum*, chloroquine-sensitive (NF54), and chloroquine-resistant (ENT30) strains, respectively [51]. The dichloromethane-soluble fraction of the rootstocks of *D. anomala* subsp. *gerrardii* yielded an eudesmanolide-type sesquiterpene, dehydrobrachylaenolide (**124**), that had *in vitro* antiplasmodial activity against a chloroquine-sensitive strain (D10) of *P. falciparum*, with IC_{50} of 1.865 μM [54]. Vernangulides A (**125**) and B (**126**) were obtained for the first time, along with the known sesquiterpenes vernodalol (**105**), vernodalin (**100**), and 11,13β-dihydrovernodalin (**127**), from the aerial parts of a South African medicinal plant, *D. angulifolius*, and had good activity against chloroquine-sensitive (D10) and chloroquine-resistant (W2) *P. falciparum*, with IC_{50} values of 1.6−3.8 and 2.1−4.9 μM, respectively [49]. Teucmosin (**128**), 4α-hydroxy-homalomenol C (**129**), and 1β,4β,7α-trihydroxy-8,9-eudesmene (**130**) were isolated for the first time, together with homalomenol C (**133**), oxo-T-cadinol (**134**), 1β,4β,6β-trihydroxyeudesmane

(**135**), oplopanone (**104**), and 1β,4β,7α-trihydroxyeudesmane (**136**) from the aerial parts of a Tunisian medicinal plant, *T. ramosissimum* [46]. Among these, compounds **133**−**135** had significant *in vitro* antiplasmodial activities against *P. falciparum* (IC_{50} values of 1.2−5.0 μg/mL), while none of the isolated compounds had cytotoxicity effects on the human diploid lung cell line MRC-5 at the highest level tested [46].

Two new cytotoxic sesquiterpene lactones, vernomygdin (**138**) (ED_{50} of 1.5 μg/mL) and vernodalin (**100**) (ED_{50} of 1.8 μg/mL), were isolated, along with vernolide (**99**) (ED_{50} of 2.0 μg/mL), from the chloroform extract of *V. amygdalina* Del. and had significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) [42]. Englerins A (**139**) and B (**140**), isolated for the first time from the stem bark of the Tanzanian medicinal plant *Phyllanthus engleri* had good anticancer activity, with englerin A (**139**) having 1000-fold selective activity against six renal cancer cell lines (GI_{50} values of 1−87 nM) [117]. Vernolepin (**141**) and vernomenin (**142**), were also reported for the first time from the leaves of the Ethiopian medicinal plant *Vernonia hymenolepis*; vernolepin (**141**) had significant *in vitro* cytotoxicity (KB cells) and *in vivo* tumor inhibitory activity against Walker intramuscular carcinosarcoma in rats [118]. Warburganal (**79**) had high toxicity activity in brine shrimp [119]. The cytotoxicity of cryptomeridiol (**161**), isolated from the roots of *C. edulis*[62], was further reported on the B16 mouse melanoma cell line, with 101.9, 107.2 and 86.9% cell viability at 10, 50 and 100 μM, respectively [65].

Hanphyllin (**225**), isolated from the aerial parts of a new species of *Eriocephalus* [69], had good antiplasmodial activity against *P. falciparum* FcB1 (IC_{50} of 2.3 μg/mL) and was less toxic against the Vero cell line (IC_{50} of 26.4 μg/mL) [77]. Dihydrocumambrin A (**231**) was isolated for the first time from the flower heads of *C. coronarium* together with cumambrin A (**232**) [78]. Their cytotoxicity *in vitro* was determined, and cumambrin A (**232**) was strongly toxic (GI_{50} of 5.3, 3.8, and 3.2 μg/mL), while dihydrocumambrin A (**231**) had poor activity (GI_{50} >30 μg/mL) against human cancer cell lines A549 (lung cancer cells), PC-3 (prostate adenocarcinoma cells), and HCT-15 (colorectal adenocarcinoma cells), respectively [79]. Two sesquiterpenes, lactucin (**253**) and 11β,13-dihydrolactucin (**254**), were isolated from the aerial parts of the Egyptian medicinal plant *Lactuca sativa*[88], and compound **253** had strong activity against the A2780 cell line, with IC_{50} value of 1.81 μM [89]. Its antimalarial activity against *P. falciparum* (complete inhibitory activity at 10 μg/mL) was also reported [90]. Drimartol A (**280**) and pectachol (**283**) were isolated from the roots of *B. cinerea* [97], and **280** had potential cytotoxic activities against the human tumor cell lines of HO8910 (ovary), 95-D (lung), QGY (liver), and HeLa (cervix), with IC_{50} values ranging between 17.94 and 22.3 μM [98], while **283** exhibited weak antiplasmodial activity (IC_{50} of 50 μg/mL) against *P. falciparum* [99].

The sesquiterpene α-bisabolol-6-desoxy-β-altropyranoside or α-bisabolol-β-D-fucopyranoside (**315**), isolated from the aerial parts of *O. microcarpum* subsp. *septentrionale*, had significant cytotoxicity against *Artemia salina*, with the median lethal dose (LD_{50}) of 27.97 μg/mL [103,104]. Urospermal A-15-*O*-acetate (**341**) was isolated for the first time from *Dicoma tomentosa* [120] and had a very strong antiplasmodial activity, with IC_{50} <1 μg/mL against both chloroquine-sensitive and -resistant *P. falciparum* strains (3D7 and W2) [121].

Hemolytic activity of **341** was not detected, though it was found to be cytotoxic against WI38 human fibroblasts, with a IC_{50} value of 3.0 μg/mL and a selectivity index of 3.3 [121]. A bis(benzopyranyl) sesquiterpene, lucidene (**375**), reported for the first time from the petroleum ether extract of the root bark of *Uvaria lucida* ssp. *lucida*, did not have an *in vitro* activity against the multidrug-resistant K strain of *P. falciparum* at the highest level tested [122]. Further investigation of the petroleum ether extract of the root bark of *Uvaria tanzaniae* yielded a new spiro benzopyranyl sesquiterpene, tanzanene (**384**). It had no antimalarial activity against *P. falciparum in vitro* ($IC_{50} \geq 250$ μg/mL) [123]. A new and skeletally unique bicyclofarnesyl sesquiterpene endoperoxide, okundoperoxide (**492**), isolated from the Cameroonian medicinal plant *Scleria striatinux* (syn. *S. striatonux*), had moderate antimalarial activity with the IC_{50} values ranging between 0.47 and 1.50 μg/mL against chloroquine-resistant and -sensitive strains of *P. falciparum* [124].

2.3.3 Other Activities of Sesquiterpenes Isolated from African Medicinal Plants

Vernodalinol (**137**) was isolated from *D. angulifolius* [49] and from the leaves of *V. amygdalina*; it had cytotoxic activity (LC_{50} values of 70−75 μg/mL) against breast cancer MCF-7 cells [125], while 1β,4β,7α-trihydroxyeudesmane (**136**), from *R. cincinnata* [7], stimulated the proliferation and differentiation of cultured osteoblasts *in vitro* [55]. *In vitro* trypanocidal activity (against IL3338 and IL1180) of warburganal (**79**) was also reported [119].

The antiprotozoal activity of compounds **80**, **84**−**86**, **88**, and **90**−**96** were further reported, and muzigadial (**80**), 6α-hydroxymuzigadial (**86**), mukaadial (**84**), and ugandensidial (**85**) had good antitrypanosomal activity against *Trypanosoma brucei rhodesiense*, with IC_{50} values of 0.56−6.4 μM [38].

Good antioxidant activity was also reported for vernolide (**99**) and vernodalol (**105**), with IC_{50} values of 0.03 and 0.04 μg/mL, respectively [45]. An eudesmane-type sesquiterpene, 6α-hydroxy-4(15)-eudesmen-1-one (**143**), was isolated for the first time with the known 1β,6α-dihydroxy-4(15)-eudesmene (**144**) from the bulbs of the South African medicinal plant *U. epigea* [56]. The new compound had a moderate concentration-dependent relaxation (vascular myorelaxing) activity [126], while compound **144** had anti-inflammatory activity against ear edema in mice produced by 12-*O*-tetradecanoylphorbol-13-acetate [57]. Warburganal (**79**) and muzigadial (**80**) were isolated for the first time, together with ugandensidial (**85**), from *W. ugandensis* [37,127], while polygodial (**78**), cinnamolide (**90**), and bemadienolide (**82**) were obtained from *W. stuhlmannii* [37]. Compounds **78**−**80** and **85** had strong antifeedant activity against the African army worms *Spodoptera littoralis* and *Spodoptera exempta* [37,127]. Antifeedant activity (against *S. exempta*) was also reported for a new cytotoxic sesquiterpene lactone, 11,13-dihydrovernodalin (**146**), isolated from the leaves of the Kenyan medicinal plant *V. amygdalina* together with vernodalin (**100**) and vernodalol (**105**) [47]. Bicyclogermacrene (**153**) was isolated from the aerial parts of *S. oxyodontus* [58], and its fungitoxic activity was further reported [60], as along with its contribution to trypanocidal and antileishmanial activities of the *Annona coriacea* oil, in which it was found in high concentration [61].

Further biological activity was investigated for cryptomeridiol (**161**) and β-eudesmol (**162**), reported earlier from the roots of *C. edulis* [62]. Cryptomeridiol (**161**) inhibited melanogenesis activity, with a 72.6−43.1% reduction of melanin content at 50 and 100 μM [65]; it had a significant effect on PAF receptor binding, with an IC_{50} value of 17.5 μM [66]. β-Eudesmol (**162**) stimulated small intestine motility in normal mice, and inhibited the reduction in gastric emptying and gastrointestinal motility induced by dopamine [67]. It also inhibited the atropine-induced decrease in small intestine motility and gastric emptying caused by 5-HT or the 5-HT3 receptor agonist 1-(3-chlorophenyl) biguanide [67].

Mandassidione (**202**) was isolated for the first time from the rhizomes of the Cameroonian medicinal plant *C. articulatus* with corymbolone (**122**) and mustakone (**123**) [52,53]. Six novel sesquiterpenes, cyperusols A1 (**205**), A2 (**206**), B1 (**207**), B2 (**208**), C (**209**), and D (**210**), were isolated from the Egyptian plant *C. longus* [68], together with 13 known compounds including caryolane 1,9β-diol (**211**), 3,7-epoxycaryophyllane-5,15-diol (**212**), 7,15-epoxycaryophyllane-3,5α-diol (**213**), clovanediol (**214**), tricyclohumuladiol (**215**), 1,5,8,8-tetramethyl-8-bicyclo [8.1.0]undecene-2,9-diol (**216**), 2,10,10-trimethyl-6-methylene-2,8-cycloundecadiene-1,5-diol (**217**), 1,6,6,10-tetramethyl-4,9,14-trioxatetracyclotetradecane (**218**), 1β-hydroxy-10βH-guaia-4,11-dien-3-one (**219**), guaidiol (**220**), muurolane-2α,9β-diol-3-ene (**221**), mandassidione (**202**), and ligucyperonol (**222**) [68]. Their inhibitory activity on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes was reported, and caryolane 1,9β-diol (**211**) (IC_{50} of 100 μM), 1,5,8,8-tetramethyl-8-bicyclo[8.1.0]undecene-2,9-diol (**216**) (IC_{50} of 70 μM), 2,10,10-trimethyl-6-methylene-2,8-cycloundecadiene-1,5-diol (**217**) (IC_{50} of 27 μM), 1,6,6,10-tetramethyl-4,9,14-trioxatetracyclotetradecane (**218**) (IC_{50} of 95 μM), and 1β-hydroxy-10βH-guaia-4,11-dien-3-one (**219**) (IC_{50} of 83 μM) had inhibitory activity [68]. Compound **217** was more potent than the reference standard, silybin (IC_{50} of 41 μM), under similar experimental conditions [68].

The aerial parts of a new species of *Eriocephalus* were investigated and yielded nerolidol (**223**), spathulenol (**224**), and costunolide (**76**) [69]. Compound **223** inhibited the growth of *Leishmania amazonensis*, *Leishmania braziliensis*, and *Leishmania chagasi* promastigotes and *L. amazonensis* amastigotes *in vitro*, with IC_{50} values of 85, 74, 75, and 67 μM, respectively [72]. The antiulcerogenic activity of **223** related to a significant reduction of the ulcerative lesion index in rats [73], and it also induced clastogenicity; weak genotoxicity in the mouse cells [74] was also reported. Costunolide (**76**) had strong nitric oxide synthase inhibitory activity in the endotoxin-activated murine macrophage [31], inhibited the inducible nitric oxide synthase (iNOS) gene in the human monocyte cell line THP-1 [32], and also exhibited nitric oxide production in lipopolysaccharide (LPS) activated murine macrophages [33]. The antioxidant activity of costunolide (**76**) was also reported as a protective effect on oxidative stress, measured by tissue thiobarbituric acid reactive substances, reduced glutathione content, and enzymatic activities of superoxide dismutase, catalase, and glutathione peroxidase in brain, liver, heart, kidney, and pancreas [34]. Reinvestigation of the roots of *S.*

macrocarpus yielded reynosin (**238**) and two compounds **233** and **234** reported earlier from the same species [80]. Reynosin (**238**) inhibited the production of tumor necrosis factor-α (IC_{50} of 87.4 μM) [81]; it also showed a dose-dependent inhibition on cytokine-induced neutrophil chemoattractant-1 induction in LPS-stimulated Normal rat kidney epithelial-52E cells (IC_{50} of ca. 1 μM) [82]. Compounds **246**−**248**, previously reported from *A. maritime* [83], had a very strong herbicidal effect on germination and root and shoot growth, with EC_{50} values of 0.24, 0.22, and 0.48 mM; these activities being greater than that of the reference herbicide, imazamethabenz (EC_{50} of 0.74 mM) [85]. The phytotoxicity of parthenin (**249**) was determined, and it severely reduced seedling growth (root and shoot) and dry weight of four weedy species, *Amaranthus viridis*, *Cassia occidentalis*, *Echinochloa crus-galli*, and *Phalaris minor*, with the EC_{50} values varying between 0.5 and 2 mM [86]. The analgesic and sedative activities in mice of lactucin (**253**) and 11β,13-dihydrolactucin (**254**), from *L. sativa* [88], were determined, and they had significant analgesic effects at doses of 15 and 30 mg/kg in the hot plate test, similar to that of the standard drug ibuprofen (30 mg/kg) [91]. 12-Hydroxy-α-cyperone (**273**), β-farnesene (**274**), and α-humulene (**275**) were isolated from the roots of *A. afra* [93], and the anti-inflammatory and neuroproliferative activities of **273** was determined [94], whereas the anti-inflammatory activity of **275** was also reported [96]. β-Farnesene (**274**) and α-curcumene (**291**) were also isolated from the aerial parts of *C. cinerea* [100], and it was found that β-farnesene (**274**), combined with its isomer α-farnesene (**274**), induced the estrous cycles in grouped female mice [95], while α-curcumene (**291**) had anti-inflammatory activity [102]. 6,7-Epoxy-3(15)-caryophyllene (**382**) and α-bisabolol (**383**) were isolated from the Cameroonian medicinal plant *A. arundinaceum* [105], and **382** had moderate antifeedant activity against three aphid species, *Diuraphis noxia*, *Rhopalosiphum padi*, and *Metopolophium dirhodum*, with EC_{50} values of 38.4, 43.3, and 70.5 nmol/cm^2, respectively [106]. α-Bisabolol (**383**) had antinociceptive and anti-inflammatory activity [107] as well as gastroprotective [108] and antimutagenic properties [109]. A new sesquiterpene lactone, drypemolundein A (**490**), isolated from the Cameroonian medicinal plant *Drypetes molunduana* [128], significantly reduced carrageenan-induced acute edema, with 57.57% and 66.66% inhibition at doses of 10 and 20 mg/kg [129]. Compound **490** also had anti-inflammatory and analgesic activity [129]. A new furanoeudesm-1-on-13-oic acid (**491**), isolated from another Cameroonian species of *Drypetes* (*D. chevalieri beille*), had significant antileishmanial activity, with an IC_{50} value of 40.0 μg/mL, when compared to that of the reference pentamidine (IC_{50} of 38.0 μg/mL) [130]. A new indolosesquiterpene alkaloid, polysin (**493**), isolated from the stem bark of the Cameroonian plant *Polyalthia suaveolens*, was a good competitive reversible inhibitor (Ki of 10 μM) of phosphofructo kinase of *T. brucei* [131].

Several sesquiterpenes were reported as constituents of essential oils from African medicinal plants [132−142]. Details on the constituents of essential oils are discussed in Chapter 5.

2.4 New Sesquiterpenes Isolated from Medicinal Plants of Africa

Several sesquiterpenes were isolated from African plants as new compounds; for most, no pharmacological activity has been reported. Their structures (Figure 2.5) and nomenclatures, along with some physical properties such as melting point (mp) and rotatory power ($[\alpha]_D$) or circular dichroism (CD), are summarized (Table 2.2). The area where the plant material was collected and the plant part investigated are also summarized in Table 2.2.

2.5 Other Sesquiterpenes in Medicinal Plants of Africa

Some sesquiterpenes were isolated from African medicinal plants as known compounds, and their pharmacological activities were not reported (Figure 2.6; Table 2.3). Germacra-1(10),4(15),5-triene (**152**) was obtained from the aerial parts of *S. oxyodontus* [58], while isopatchoul-4(5)-en-3-one (**204**) was isolated from *C. articulatus* [53]. The aerial parts of a new species of *Eriocephalus* led to the isolation of 8-desoxycumambrin B (**226**), parishin (**227**), and estaliatin (**228**) [69]. From the roots of *S. macrocarpus* methyl-1β,6α,15-trihydroxy-4β,15-dihydrocostate (**237**), 11β,13-dihydroreynosin (**239**), 10β-hydroxycichopumilode (**240**), and 10β-hydroxy-11β,13-dihydrocichopumilode (**241**) were isolated [80], while lactucopicrin (**255**) was obtained from the aerial parts of *L. sativa* [88]. Phytochemical investigation of the aerial parts of *A. argentea* afforded arborescin (**258**) [151], whereas sesquiterpene-coumarin ethers, farnochrol (**279**), acetyldrimartol A (**281**), acetyldrimartol B (**282**), and scopofarnol (**284**) were isolated from the roots of *B. cinerea* [97]. 8α-Acetoxydihydrokauniolide (**290**) was obtained from the aerial parts of the South African medicinal plant *A. afra* [93], while the isolation of γ-curcumene (**292**), desacyl laurenobiolide angelate (**293**), and 6α-angeloyloxy-1α-hydroxygermacra-4*E*,9*Z*,11-trien-8α,12-olide (**294**) was reported from the aerial parts of the Egyptian medicinal plant *C. cinerea* [100].

Urospermal A (**349**) and 11β,13-dihydrourospermal A (**350**) were isolated from *D. tomentosa* [120]. A sesquiterpene amine derivative, farnesylamine (**485**), which was reported from an extract of the ant *Monomorium fieldi* Forel [179], was isolated for the first time from a plant source (*V. auriculifera*); its biological activity was not determined due to its decomposition [178].

2.6 Conclusion

From the data presented here, it is clear that much work has been done on sesquiterpenes from African plant species. The information provided was collected online from Scifinder, Scopus, ScienceDirect, Pubmed, and the Dictionary of Natural

Table 2.2 New Sesquiterpenes Isolated from African Plants

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
Warburganal (**79**)	*W. ugandensis* (Canellaceae) [37]	Kenya	Bark	–
Muzigadial (**80**)	*W. ugandensis* (Canellaceae) [127], *W. stuhlmannii* (Canellaceae) [35,36,40]	Kenya	Bark	mp 122–124°C [127]
7α-Acetylugandensolide (**81**)	*W. ugandensis* (Canellaceae) [36]	Kenya	Stem bark	mp 228–230°C [36]; $[\alpha]_D$ +24° (*c* 0.001, MeOH) [36]
6α-Hydroxymuzigadial (**86**)	*W. ugandensis* (Canellaceae) [40]	Ethiopia	Stem bark	mp 137–139°C [40]; $[\alpha]_D$ −40° (*c* 1.6, CH_2Cl_2) [40]
Ugandensolide (**88**)	*W. ugandensis* (Canellaceae) [36,40,110]	Kenya	Heartwood	mp 218°C; $[\alpha]_D$ +23° ($CHCl_3$) [110]
Cinnamolide-3β-acetate (**91**)	*W. ugandensis* and *W. stuhlmannii* (Canellaceae) [36,40,143]	Kenya	Stem bark	mp 147–149°C [40]; $[\alpha]_D$ +37° (*c* 0.5, MeOH) [143]; $[\alpha]^{25}_D$ −2.4° (*c* 1.3, CH_2Cl_2) [40]
4(13),7-Coloratadien-12,11-olide (**92**)	*W. ugandensis* (Canellaceae) [40]	Ethiopia	Stem bark	mp 85–87°C; $[\alpha]_D$ +84.7° (*c* 1.5, CH_2Cl_2) [40]
7β-Hydroxy-4(13),8-coloratadien-11,12-olide (**93**)	*W. ugandensis* (Canellaceae) [40]	Ethiopia	Stem bark	mp 139–142°C; $[\alpha]_D$ +242.1° (*c* 1.9, CH_2Cl_2) [40]
Muzigadiolide (**94**)	*W. ugandensis* and *W. stuhlmannii* (Canellaceae) [40,143]	Kenya	Stem bark	mp 140–145°C; $[\alpha]_D$ +380° (*c* 0.6, MeOH) [143]
11α-Hydroxymuzigadiolide (**95**)	*W. ugandensis* (Canellaceae) [40,144]	Kenya	Stem bark	mp 182–183°C [144]
Pallescensin E (**97**)	*Warburgia salutaris* (Canellaceae) [39]	South Africa	Stem bark	–
11β, 13-Dihydrovernolide (**98**)	*V. colorata* (Compositae) [41]	South Africa	Leaves	–
Vernodalin (**100**)	*V. amygdalina* (Asteraceae) [42,47], *V. colorata* (Asteraceae) [41]	Ethiopia, Ivory Coast	Leaves	$[\alpha]^{24}_D$ +125° (*c* 1.35 $CHCl_3$) [42]
Eudesmaafraglaucolide (**116**)	*A. afra* (Compositae) [93], *A. afra* (Asteraceae) [48]	South Africa	Aerial parts	CD: ε_{280} −11 (MeCN) [93]

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
Vernangulide A (**125**)	*D. angulifolius* (DC) H. Rob. & B. Kahn [syn. *V. angulifolia* DC] (Asteraceae) [49]	South Africa	Aerial parts	$[\alpha]^{20}_{D}$ −9.2° (*c* 0.68, $CHCl_3$) [49]
Vernangulide B (**126**)	*D. angulifolius* (DC) H. Rob. & B. Kahn [syn. *V. angulifolia* DC] (Asteraceae) [49]	South Africa	Aerial parts	$[\alpha]^{20}_{D}$ +26.3° (*c* 17, $CHCl_3$) [49]
Teucmosin (**128**)	*T. ramosissimum* (Lamiaceae) [46]	Tunisia	Aerial parts	$[\alpha]^{20}_{D}$ +6.5° (*c* 0.30, $CHCl_3$) [46]
4α-Hydroxy-homalomenol C (**129**)	*T. ramosissimum* (Lamiaceae) [46]	Tunisia	Aerial parts	$[\alpha]^{20}_{D}$ +2° (*c* 0.25, $CHCl_3$) [46]
1β,4β,7α-Trihydroxy-8,9-eudesmene (**130**)	*T. ramosissimum* (Lamiaceae) [46]	Tunisia	Aerial parts	$[\alpha]^{20}_{D}$ −6.2° (*c* 0.22, $CHCl_3$) [46]
3β,9β-Dihydroxyguaian-4(15),10(14),11(13)-trien-6,12-olide (**131**)	*C. cameroonica* (Asteraceae) [112]	Cameroon	Aerial parts	mp 220−222°C; $[\alpha]_{D}$ +15.90° (*c* 0.2, MeOH) [112]
8α-Hydroxy-4α(13),11β(15)-tetrahydrozaluzanin C (**132**)	*C. cameroonica* (Asteraceae) [112]	Cameroon	Aerial parts	mp 214−217°C; $[\alpha]^{31.2}_{D}$ −40° (*c* 0.2, MeOH) [112]
Vernodalinol (**137**)	*V. amygdalina* (Asteraceae) [125] *D. angulifolius* (Asteraceae) [49]	Nigeria South Africa	Leaves Aerial parts	mp 217−218°C [125]
Vernomygdin (**138**)	*V. amygdalina* (Asteraceae) [42]	Ethiopia	Leaves	mp 208−210°C; $[\alpha]^{28}_{D}$ +65° (*c* 1.00, acetone) [42]
Englerin A (**139**)	*P. engleri* (Euphorbiaceae) [117]	Tanzania	Stem bark	–
Englerin B (**140**)	*P. engleri* (Euphorbiaceae) [117]	Tanzania	Stem bark	–
Vernolepin (**141**)	*V. hymenolepis* (Asteraceae) [118]	Ethiopia	Leaves	mp 179−180°C; $[\alpha]^{28}_{D}$ +72° (*c* 1.04, acetone) [118]
Vernomenin (**142**)	*V. hymenolepis* (Asteraceae) [118]	Ethiopia	Leaves	$[\alpha]^{27}_{D}$ −62° (*c* 1.44, acetone) [118]
6α-Hydroxy-4(15)-eudesmen-1-one (**143**)	*U. epigea* (Urgineoideae, Hyacinthaceae) [56]	South Africa	Bulbs	mp 68−70°C; $[\alpha]^{25}_{D}$ +5° (*c* 0.06) [56]
Warburgin (**145**)*	*W. ugandensis* (Canellaceae) [110,145]	Kenya, Uganda	Heartwood	mp 159−161°C; $[\alpha]_{D}$ +120° [145]
11,13-Dihydrovernodalin (**146**)	*V. amygdalina* (Asteraceae) [47]	Kenya	Leaves	–
3-*O*-Methyl-2.5-dehydrosenecioodontol (**147**)*	*S. oxyodontus* (Compositae) [58]	South Africa	Aerial parts	$[\alpha]_{24}^{589}$ + 12.4° (*c* 0.6) [58]
3-*O*-Methylsenecioodontol (**148**)*	*S. oxyodontus* (Compositae) [58]	South Africa	Roots, aerial parts	–

2,5-Di-*O*-methylsenecioodontol (**149**)*	*S. oxyodontus* (Compositae) [58]	South Africa	Roots, aerial parts	–
3-*O*-Angeloylsenecioodontol (**150**)*	*S. oxyodontus* (Compositae) [58]	South Africa	Roots	–
8-Angeloyloxy-3,4-dihydro-3,4-epoxy-β-bisabolen-5-one (**151**)*	*S. oxyodontus* (Compositae) [58]	South Africa	Roots	–
Methyl-(−)-(*trans*)-(*trans*)-10,11-dihydroxyfarnesoate (**154**)*	*Cleistopholis patens* (Annonaceae) [146], *Cleistopholis staudtii* (Annonaceae) [147], *Lettowianthus stellatus* (Annonaceae) [148]	Ghana Cameroon Tanzania	Root bark Stem bark Root bark	$[\alpha]^{25}_{D}$ −9.6° (*c* 0.1, $CHCl_3$) [146]
Methyl-(+)-(*trans*)-l0-hydroxy-6,l1-cyclofarnes-7(14)-oate (**155**)*	*C. patens* (Annonaceae) [146]	Ghana	Root bark	$[\alpha]^{25}_{D}$ +15° (*c* 0.1, $CHCl_3$) [146]
Carissanol (**156**)*	*C. edulis* (Apocynaceae) [62]	Ghana	Roots	$[\alpha]^{20}_{D}$ +66.4° (*c* 0.25, $CHCl_3$) [62]
6β-Carissanol (**157**)*	*C. edulis* (Apocynaceae) [62]	Ghana	Roots	mp 115−118°C; $[\alpha]^{20}_{D}$ +10° (*c* 0.3, $CHCl_3$) [62]
α-Carissanol (**158**)*	*C. edulis* (Apocynaceae) [62]	Ghana	Roots	$[\alpha]^{20}_{D}$ +124° (*c* 0.07, $CHCl_3$) [62]
Germacrenone (**159**)*	*C. edulis* (Apocynaceae) [62]	Ghana	Roots	$[\alpha]^{20}_{D}$ +173.2° (*c* 1.1, $CHCl_3$) [62]
5-Oxo-5,6α-H-isocomene (**163**)*	*Helichrysum nudifolium* (L.) Less. var. *nudifolium* (Compositae) [149]	South Africa	Roots	$[\alpha]^{24}_{D}$ −49° (*c* 0.91, $CHCl_3$) [149]
2-Hydroxyhanphyllin-3-*O*-acetate (**164**)*	*Eriocephalus* sp.n. (Compositae) [69]	Namibia	Aerial parts	mp 188°C; $[\alpha]^{24}_{D}$ +131° (*c* 0.37, $CHCl_3$) [69]
3α-Hydroperoxi-3-desoxoparishin A (**165**)*	*Eriocephalus* sp.n. (Compositae) [69]	Namibia	Aerial parts	CD: $\Delta\varepsilon_{262}$ −1.3 (MeCN) [69]
4α-Hydroperoxi-l0α-hydroxy-lα,5αH-guaia-2,11(13)-dien-12,6α-olide (**166**)*	*Eriocephalus* sp.n. (Compositae) [69]	Namibia	Aerial parts	CD: $\Delta\varepsilon_{260}$ −1.1 (MeCN) [69]
1lβ,13-Dihydro-epi-ligustrin (**167**)*	*E. giessii* (Compositae) [69]	Namibia	Aerial parts	mp 67°C; $[\alpha]^{24}_{D}$ +61° (*c* 0.30, $CHCl_3$) [69]
3α-Hydroxy-8α-acetoxy-3-desoxo-11β,l3-dihydroparishin A (**168**)*	*E. giessii* (Compositae) [69]	Namibia	Aerial parts	–
3α-Hydroperoxi-8α-aetoxy-3-desoxo-11β,13-dihydroparishin A (**169**)*	*E. giessii* (Compositae) [69]	Namibia	Aerial parts	–

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
8α-Acetoxy-11β,13-dihydroparishin A (**170**)*	*E. giessii* (Compositae) [69]	Namibia	Aerial parts	CD: $\Delta\varepsilon_{323}$ −2.5 (MeCN) [69]
4α-Hydroperoxi-l0α-hydroxy-8α-acetoxy-lα,5α,11βH-guaia-2-en-12,6α-olide (**171**)*	*E. giessii* (Compositae) [69]	Namibia	Aerial parts	–
4α,l0α-Dihydroxy-8-acetoxy-lα,5α,l1βH-guaia-2-en-12,6α-olide (**172**)*	*E. giessii* (Compositae) [69]	Namibia	Aerial parts	–
4α-Hydroxy-1α,5αH-guaia-2,10(14),11(13)-trien-12,6α-olide (**173**)*	*Eriocephalus kingesii* (Compositae) [69]	Namibia	Aerial parts	CD: $\Delta\varepsilon_{265}$ −1.1 (MeCN) [69]
1β,5β-Dihydroxyeriocephaloide (**174**)*	*E. kingesii* (Compositae) [69]	Namibia	Aerial parts	CD: $\Delta\varepsilon_{288}$ −1.9 (MeCN) [69]
4α,5α-Epoxy-3-oxo-4(15)-dihydrocostic acid methyl ester (**175**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	–
3β-Angeloyloxyisocostic acid methyl ester (**176**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ −26° (*c* 0.86, $CHCl_3$) [69]
8β-Acetoxy-3β-angeloyloxyisocostic acid methyl ester (**177**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 68°C; $[\alpha]^{24}_{D}$ −51° (*c* 0.1, $CHCl_3$) [69]
8β-Acetoxy-3β-isobutyryloxyisocostic acid methyl ester (**178**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 103°C; $[\alpha]^{24}_{D}$ −32° (*c* 0.25, $CHCl_3$) [69]
8β-Acetoxy-3β-propionyloxyisocostic acid methyl ester (**179**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 111°C; $[\alpha]^{24}_{D}$ −30° (*c* 0.34, $CHCl_3$) [69]
8β-Acetoxy-3β-[4-methylsenecioyloxy] isocostic acid methyl ester (**180**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	–
3β-Angeloyloxy-4β-hydroxy-Δ^5-costic acid methyl ester (**181**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 101°C; $[\alpha]^{24}_{D}$ +56° (*c* 0.05, $CHCl_3$) [69]

5α-Hydroperoxycostic acid methyl ester (**182**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	–
3β-Hydroxy-5α-hydroperoxycostic acid methyl ester (**183**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 123°C; $[\alpha]_D$ +73° (*c* 0.04, $CHCl_3$) [69]
3β,5α-Dihydroxycostic acid methyl ester (**184**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 131°C; $[\alpha]^{24}_D$ +99° (*c* 0.19, $CHCl_3$) [69]
3β-Angeloyloxy-5α-hydroperoxycostic acid methyl ester (**185**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 133°C [69]
8β-Acetoxy-3β-angeloyloxy-5α-hydroperoxycostic acid methyl ester (**186**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 160°C; $[\alpha]^{24}_D$ +37° (*c* 0.22, $CHCl_3$) [69]
8β-Acetoxy-3β-angeloyloxy-5α-hydroxycostic acid methyl ester (**187**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 172–173°C; $[\alpha]^{24}_D$ +17 (*c* 0.23, $CHCl_3$) [69]
8β-Acetoxy-3β-isobutyryloxy-5α-hydroperoxycostic acid methyl ester (**188**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 145°C [69]
8β-Acetoxy-3β-isobutyryloxy-5α-hydroxycostic acid methyl ester (**189**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 151°C; $[\alpha]^{24}_D$ +16° (*c* 0.1, $CHCl_3$) [69]
3α,5α-Dihydroxycostic acid methyl ester (**190**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	$[\alpha]^{24}_D$ +7° (*c* 0.57, $CHCl_3$) [69]
3α-Angeloyloxy-5α-hydroperoxycostic acid methyl ester (**191**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 80°C; $[\alpha]^{24}_D$ −16° (*c* 0.68, $CHCl_3$) [69]
8β-Acetoxy-3α-angeloyloxy-5α-hydroxycostic acid methyl ester (**192**)*	*E. pauperrimus* (Compositae) [69]	Namibia	Aerial parts	mp 97°C; $[\alpha]^{24}_D$ −11° (*c* 0.27, $CHCl_3$) [69]
11β,13-Dihydroxyivangustin acetate (**193**)*	*Eriocephalus scariosus* (Compositae) [69]	Namibia	Aerial parts	$[\alpha]^{24}_D$ +38° (*c* 0.31, $CHCl_3$) [69]
14-Hydroxydexoxyivangustin (**194**)*	*Eriocephalus africanus* (Compositae) [69]	South Africa	Aerial parts	mp 137°C; $[\alpha]^{24}_D$ +54° (*c* 0.24, $CHCl_3$) [69]

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
14-Acetoxy-11α,13-dihydrodesoxyivangustin (**195**)*	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +105° (*c* 0.02, $CHCl_3$) [69]
14-Hydroxy-5α-hydroperoxyisoalantolactone (**196**)	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	mp 70°C; $[\alpha]^{24}_{D}$ +223° (*c* 0.25, $CHCl_3$) [69]
14-Acetoxy-5α-hydroperoxyisoalantolactone (**197**)*	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	mp 173°C; $[\alpha]^{24}_{D}$ +290° (*c* 0.15, $CHCl_3$) [69]
14-Acetoxy-5α-hydroperoxy-11α,13-dihydroisoalantolactone (**198**)*	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	mp 170°C; [α]24$_D$ +94° (*c* 0.2, $CHCl_3$) [69]
5α-Hydroperoxyasperilin (**199**)*	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +144° (*c* 0.34, $CHCl_3$) [69]
5β-Hydroxyasperilin (**200**)*	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +53° (*c* 0.28, $CHCl_3$) [69]
11-Hydroxy-4,5-seco-eudesmane-4,5-dione (**201**)*	*E. africanus* (Compositae) [69]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +46° (*c* 0.39, $CHCl_3$) [69]
Mandassidione (**202**)	*C. articulatus* (Cyperaceae) [53], *C. longus* L. (Cyperaceae) [68]	Cameroon, Egypt	Rhizomes	$[\alpha]^{25}_{D}$ −9.1° (*c* 0.74, $CHCl_3$) [53]
α-Corymbolol (**203**)*	*C. articulatus* (Cyperaceae) [52]	Cameroon	Rhizomes	$[\alpha]^{25}_{D}$ +43° (*c* 2.9, $CHCl_3$) [53]
Cyperusol A1 (**205**)	*C. longus* L. (Cyperaceae) [68]	Egypt	Whole plant	$[\alpha]^{23}_{D}$ +12.5° (*c* 0.50, MeOH) [68]
Cyperusol A2 (**206**)	*C. longus* L. (Cyperaceae) [68]	Egypt	Whole plant	$[\alpha]^{23}_{D}$ +32.1° (*c* 0.30, MeOH) [68]
Cyperusol B1 (**207**)	*C. longus* L. (Cyperaceae) [68]	Egypt	Whole plant	$[\alpha]^{25}_{D}$ +32.2° (*c* 0.20, $CHCl_3$) [53]
Cyperusol B2 (**208**)	*C. longus* L. (Cyperaceae) [68]	Egypt	Whole plant	$[\alpha]^{25}_{D}$ +45.8° (*c* 0.30, $CHCl_3$) [68]
Cyperusol C (**209**)	*C. longus* L. (Cyperaceae) [68]	Egypt	Whole plant	$[\alpha]^{24}_{D}$ −42.3° (*c* 1.10, MeOH) [68]
Cyperusol D (**210**)	*C. longus* L. (Cyperaceae) [68]	Egypt	Whole plant	$[\alpha]^{22}_{D}$ +5.8° (*c* 0.45, MeOH) [68]
10β-Hydroxycichopumilide (**229**)	*C. pumilum* (Compositae) [113]	Egypt	Roots	mp 137° [113]
10β-Hydroxy-11β,13-dihydrocichopumilide (**230**)*	*C. pumilum* (Compositae) [113]	Egypt	Roots	mp 176°C; $[\alpha]^{489}_{D}$ +38° (*c* 0.1, $CHCl_3$) [113]
Dihydrocumambrin A (**231**)	*C. coronarium* (Compositae) [78]	Egypt	Flower head	mp 174°C; $[\alpha]^{24}_{D}$ +44° (*c* 0.08, $CHCl_3$) [78]

Sonchucarpolide (**233**)*	*S. macrocarpus* (Compositae) [80,150]	Egypt	Aerial parts and roots	$[\alpha]^{24}_{D}$ −3° (*c* 0.3, $CHCl_3$) [150]
11β,13-Dihydrosonchucarpolide (**234**)*	*S. macrocarpus* (Compositae) [80,150]	Egypt	Aerial parts and roots	$[\alpha]^{24}_{D}$ −3° (*c* 0.3, $CHCl_3$) [150]
15-Hydroxy-4β,15-dihydroreynosin (**235**)*	*S. macrocarpus* (Compositae) [80]	Egypt	Roots	–
15-Hydroxy-4β,15,11β,13-tetrahydroreynosin (**236**)*	*S. macrocarpus* (Compositae) [80]	Egypt	Roots	mp 185−187°C [80]
Tetrahydroanhydroparthenin (**242**)*	*A. maritime* (Compositae) [83]	Egypt	Aerial parts	–
13-Hydroxytetrahydroanhydroparthenin (**243**)*	*A. maritime* (Compositae) [83]	Egypt	Aerial parts	$[\alpha]^{24}_{D}$ +12° (*c* 1.3, $CHCl_3$) [83]
3-Oxo-damsin (**244**)*	*A. maritime* (Compositae) [83]	Egypt	Aerial parts	–
11β,13-Dihydroxyambrosin (**245**)*	*A. maritime* (Compositae) [83]	Egypt	Aerial parts	–
Reneilmol (**250**)*	*R. cincinnata* (Zingiberaceae) [7]	Cameroon	Fruits	mp 143−145° C; $[\alpha]^{22}_{D}$ −56° (*c* 0.55, MeOH) [7]
3β-Hydroxy-11β,13-dihydroacanthospermolide (**251**)*	*L. sativa* (Compositae) [88]	Egypt	Aerial parts	mp 197°C; $[\alpha]^{24}_{D}$ −87° (*c* 0.6, $CHCl_3$) [88]
3β,14-Dihydroxy-11β,13-dihydrocostunolide (**252**)*	*L. sativa* (Compositae) [88]	Egypt	Aerial parts	mp 110°C; $[\alpha]^{24}_{D}$ +110° (*c* 0.1, MeOH) [88]
Argentiolid A (**256**)*	*Artemisia argentea* (Compositae) [151,152]	Egypt	Aerial parts	mp 197−199°C; CD: ε_{294} +4.8 and ε_{193} +9.2 (MeCN) [151]
Argentiolid B (**257**)*	*A. argentea* (Compositae) [151,152]	Egypt	Aerial parts	mp 177°C [151]
Deacetylargentiolide B (**259**)*	*A. argentea* (Compositae) [152]	Egypt	Aerial parts	mp 183°C; $[\alpha]^{22}_{D}$ +142.6° (*c* 0.82, $CHCl_3$) [152]
8α-Acteoxy-1α,4α-dihydroperoxy-guaia-2,10(14),11(13)-trien-12,6α-olide (**260**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
1α,4α,8α-Trihydroxyguaia-2,10(14),11(13)-trien-12,6α-olide (**261**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
1α,4α-Dihydroperoxy-8α-hydroxyguaia-2,10(14),11(13)-trien-12,6α-olide (**262**)*	*A. afra* (Compositae) [108]	South Africa	Aerial parts	–
8α-Acteoxy-1α-hydroperoxy-4α-hydroxyguaia-2,9(14),11(13)-trien-12,6α-olide (**263**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
8α-Acteoxy-4α-hydroperoxy-1α-hydroxyguaia-2,9(14),11(13)-trien-12,6α-olide (**264**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
8α-Acteoxy-1α,4α-dihydroperoxyguaia-2,9(14),11(13)-trien-12,6α-olide (**265**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
8α-Acetoxy-1α(4α)-endoperoxy-10α-hydroperoxyguaia-2,11(13)-dien -12,6α-olide (**266**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
8α-Acetoxy-1α(2α), 3α(4α)-diepoxy-10α-hydroperoxyguaia-7(13)-en-12,6α-olide (**267**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
8α-Acetoxy-1α(2α),3α(4α)-diepoxy-10α-hydroperoxy-11α-methylguaian-12,6α-olide (**268**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
Artemisia glaucolide (**269**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
1α-Hydrohyafraglaucolide (**270**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
1β-Hydrohyafraglaucolide (**271**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	–
1α-Hydroxyisoafraglaucolide (**272**)*	*A. afra* (Compositae) [93]	South Africa	Aerial parts	CD: ε_{239} −11 (MeCN) [93]
Pectachol B (**276**)*	*B. cinerea* (Compositae) [97]	Egypt	Roots	CD (EtOH) nm: 294 (− 0.65), 228 (+ 1.8) [97]

Acetylpectachol B (**277**)*	*B. cinerea* (Compositae) [97]	Egypt	Roots	CD (EtOH) nm: 340 (− 0.2), 294 (− 0.9), 205 (+ 10.5) [97]
8-Farnesylscopoletin (**278**)*	*B. cinerea* (Compositae) [97]	Egypt	Roots	mp 120−121°C [97]
Deacetyl tulipinolide-1β,10α-epoxide (**285**)*	*C. cinerea* (Compositae) [100]	Egypt	Aerial parts	CD: $\Delta\varepsilon_{243}$ −0.1 (MeCN) [100]
13-Acetoxy-8α-hydroxy-7,11-dehydro-11,13-dihydroanhydroverlotorin (**286**)*	*C. cinerea* (Compositae) [100]	Egypt	Aerial parts	$\Delta\varepsilon_{257}$ + 1.3 (MeCN) [100]
8α,13-Diacetoxy-7,11-dehydro-11,13-dihydroanhydroverlotorin (**287**)*	*C. cinerea* (Compositae) [100]	Egypt	Aerial parts	
8α,13-Diacetoxy-1α-hydroxygermacra-4*E*,7(11),9*Z*-trien-6α,12-olide (**288**)*	*C. cinerea* (Compositae) [100]	Egypt	Aerial parts	CD: $\Delta\varepsilon_{260}$ −0.26 (MeCN) [100]
6-Epi-1,10-dehydro-10,14-dihydrochrysostamolide acetate (**289**)*	*C. cinerea* (Compositae) [100]	Egypt	Aerial parts	CD: $\Delta\varepsilon_{297}$ −0.25 (MeCN) [100]
Reynosin acetate (**295**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
6α-Angeloyloxy-1β,4α-dihydroxy-eudesm-l1(13)-en-8α,l2-olide (**296**)	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
6α-Hydroxyguaia-1(10),4(15),11(13)-trien-8α,12-olide (**297**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
6α-Acetoxy-1β-hydroxyguaia-4(15),10(14),11(13)-trien-8α,12-olide (**298**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
6α-Acetoxy-1β-hydroxyperoxy-guaia-4(15),10(14),11(13)-trien-8α,12-olide (**299**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
6α-Acetoxy-1α-hydroxyguaia-4(15),10(14),11(13)-trien-8α,12-olide (**300**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial Parts	–
6α-Acetoxy-10β-hydroxyguaia-1,4(15),11 (13)-trien-8α,12-olide (**301**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
13-Acetoxy-9β-hydroxy-1β,10α-epoxygermacra-4,7(11)-dien-6α,12-olide (**302**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
8α,13-Diacetoxy-1α-hydroxygermacra-4,7(11),10(14)-trien-6α,12-olide (**303**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
8α,13-Diacetoxy-1β-hydroxygermacra-4,7(11),10(14)-trien-6α,12-olide (**304**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
8α,13-Dihydroxy-1-oxo-germacra-4,7(11),10(14)-trien-6α,12-olide (**305**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
13-Acetoxy-1β,8α-dihydroxyeudesma-4(15),7(13)-dien-6α,12-olide (**306**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
8α,13-Diacetoxy-1β-hydroxyeudesma-4(15),7(13)-dien-6α,12-olide (**307**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
13-Acetoxy-1β,8α-dihydroxyeudesma-3,7(13)-dien-6α,12-olide (**308**)*	*B. cinerea* (Compositae) [153]	Egypt	Aerial parts	–
3′-*O*-Acetyl-2′-*O*-angeloyl-α-bisabolol-β-D-fucopyranoside (**309**)*	*O. microcarpum* (Compositae) [70]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ +4° (*c* 1.0, $CHCl_3$) [70]
2′-*O*-[-2-methylbutyryl]-3′-*O*-Acetyl-α-bisabolol-β-D-fucopyranoside (**310**)*	*O. microcarpum* (Compositae) [70]	Namibia	Aerial parts	–
2′-*O*,3′-*O*-Diangeloyl-α-bisabolol-β-D-fucopyranoside (**311**)*	*O. microcarpum* (Compositae) [70]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ +12° (*c* 0.18, $CHCl_3$) [70]
2′-*O*-Angeloyl-α-bisabolol-β-D-fucopyranoside (**312**)*	*Gibbaria ilicifolia* (Compositae) [70]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +15° (*c* 0.2, $CHCl_3$) [70]
13-Hydroxy-4α,5β-epoxycaryophyllen-[4-*O*-angeloyl-β-D-glucopyranoside] (**313**)*	*O. rigidum* (Compositae) [70]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +100° (*c* 0.05, $CHCl_3$) [70]

13-Hydroxy-7βH-silphiperfol-5-ene-[4-*O*-angeloyl-β-D-glucopyranoside] (**314**)*	*O. rigidum* (Compositae) [70]	South Africa	Aerial parts	–
3β-Hydroxy-8α-isobutyryloxy-4,15-epoxyguaian-10(14)-en-6α,12-olide (**316**)*	*Pleiotaxis rugosa* (Compositae) [154]	South Africa	Aerial parts	–
3β-Acetoxy-4α,10αH-guaia-1(5),11(13)-dien-12,8α-olide (**317**)*	*Pechuel-Loeschea leibnitziae* (Compositae) [59]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ +7° (*c* 1.04, $CHCl_3$) [59]
3β-Acetoxy-1α,10αH-guaia-5,11(13)-dien-12,8α-olide (**318**)*	*P. leibnitziae* (Compositae) [59]	Namibia	Aerial parts	–
3-*O*-[2′,3′-epoxy-2′-methylbutyroyl]-Cuauthemon-*O*-formiate (**319**)*	*Laggera alata* (Compositae) [59]	Namibia	Aerial parts	–
5-Desoxylongilobol (**320**)*	*L. alata* (Compositae) [59]	Namibia	Aerial parts	mp 160°C; $[\alpha]^{24}_{D}$ +73° (*c* 0.20, $CHCl_3$) [59]
3α-Hydroxyfuroepaltol (**321**)*	*E. gariepina* (Compositae) [59]	Namibia	Aerial parts	–
3α-[2′,3′-epoxy-2′-methylbutyryloxy]-Furoepaltol (**322**)*	*E. gariepina* (Compositae) [59]	Namibia	Aerial parts	–
3α-Isovaleryloxyfuroepaltol (**323**)*	*E. gariepina* (Compositae) [59]	Namibia	Aerial parts	–
3α-Angeloyloxyfuroepaltol (**324**)*	*E. gariepina* (Compositae) [59]	Namibia	Aerial parts	$[\alpha]^{22}_{D}$ +23° (*c* 0.44, $CHCl_3$) [59]
6β-Hydroxy-3α-[2′,3′-epoxy-2′-methylbutyryloxy]-furoepaltol (**325**)*	*E. gariepina* (Compositae) [59]	Namibia	Aerial parts	–
9β-Isobutyryloxyhelenalin-[4-hydroxymethacrylate] (**326**)*	*Anisopappus pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ −21° (*c* 6.38, $CHCl_3$) [155]
9β-Angeloyloxyhelenalin angelate (**327**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Angeloyloxyhelenalin methacrylate (**328**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Isobutyryloxyhelenalin methacrylate (**329**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Methacryloyloxyhelenalin methacrylate (**330**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ −15 (*c* 3.26, $CHCl_3$) [155]

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
9β-Angeloyloxyhelenalin-[2,3-epoxyisobutyrate] (**331**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Isovaleryloxyhelenalin-[2,3-epoxyisobutyrate] (**332**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Angeloyloxyhelenalin-[5-hydroxyangelate] (**333**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Angeloyloxyhelenalin-[4-hydroxymethacrylate] (**334**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Isovaleryloxyhelenalin-[4-hydroxymethacrylate] (**335**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
9β-Isobutyryloxyhelenalin-[5-hydroxyangelate] (**336**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
6α-[Hydroxymethacryloyloxy]-6-cesacyloxy-linearifolin B angelate (**337**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
6α-[Hydroxymethacryloyloxy]-6-desacyloxy-linearifolin B isovalerate (**338**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
6α-[4-Hydroxymethacryloyloxy]-6-cesacyloxy-linearifolin B angelate (**339**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
6α-[4-Hydroxymethacryloyloxy]-6-cesacyloxy-linearifolin B isovalerate (**340**)*	*A. pinnatifidus* (Compositae) [155]	Namibia	Aerial parts	–
Urospermal A-15-*O*-acetate (**341**)	*D. tomentosa* (Compositae) [120], *A. pinnatifidus* (Compositae) [155]	South Africa Namibia	Aerial parts	$[\alpha]^{24}_{D}$ +91° (*c* 1.0, $CHCl_3$) [120]

1,10-*cis*-Albicolide-14-*O*-acetate (**342**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	$[\alpha]_D$ +8.5° (*c* 0.14, $CHCl_3$) [120]
1,10-*cis*-8-Desoxyurospermal A-15-*O*-acetate (**343**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	–
8-Desoxyurospermal A (**344**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	$[\alpha]^{24}_D$ −20° (*c* 0.26, $CHCl_3$) [120]
8-Desoxyurospermal A-15-*O*-acetate (**345**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	–
8α-Hydroxyalbicolide-14-*O*-acetate (**346**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	$[\alpha]^{24}_D$ +41° (*c* 0.32, $CHCl_3$) [120]
Albicolide-14-*O*-acetate (**347**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	–
Albicolide diacetate (**348**)*	*D. tomentosa* (Compositae) [120]	South Africa	Aerial parts	–
Urospermal A-15-*O*-[4′-(p-hydroxyphenylacetyl)]-β-D-glucopyranoside (**351**)*	*Urospermum picroides* (Compositae) [156,157]	Egypt	Aerial parts	mp 112–115°C [156]
Urospermal A-15-*O*-β-D-glucopyranoside (**352**)*	*U. picroides* (Compositae) [157]	Egypt	Aerial parts	mp 124–126°C [157]
2β-Acetoxydihydrogriesenin (**353**)*	*Geigeria burkei* Harv. subsp. *burkei* var. *intermedia* (S. Moore) Merxm. (Compositae) [158]	South Africa	Aerial parts	–
10β-Hydroxy-10-epi-tomentosin-4-*O*-acetate (**354**)*	*G. burkei* Harv. subsp. *burkei* var. *intermedia* (S. Moore) Merxm. [158]	South Africa	Aerial parts	–
Geigeranolide (**355**)*	*G. burkei* subsp. *diffusa*, *G. burkei* subsp. *burkei* var. *burkei*, *G. aspera* var. *aspera*, *G. brevifolia* (Compositae) [158]	South Africa	Aerial parts and roots	mp 92°C; $[\alpha]^{24}_D$ +59° (*c* 3.0, $CHCl_3$) [158]
11β,13-Dihydrogeigeranolide (**356**)*	*G. burkei* subsp. *diffusa*, *G. burkei* subsp. *burkei* var. *burkei* (Compositae) [158]	South Africa	Aerial parts and roots	$[\alpha]^{24}_D$ +10° (*c* 0.09, $CHCl_3$) [158]
Geigerin acetate (**357**)*	*G. aspera* var. *aspera* (Compositae) [158]	South Africa	Roots	-
11β,13-Dihydroinuviscolide (**358**)*	*G. aspera* var. *aspera* (Compositae) [158]	South Africa	Roots	$[\alpha]^{24}_D$ +28° (*c* 0.13, $CHCl_3$) [158]
2β-Acetoxy-4α-hydroxyburkeolide (**359**)*	*G. burkei* subsp. *burkei* var. *zeyheri* (Compositae) [158]	South Africa	Roots	–

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
2β-Acetoxy-4α-hydroxy-11β,13-dihydroburkeolide (**360**)*	*G. burkei* subsp. *burkei* var. *zeyheri* (Compositae) [158]	South Africa	Roots	–
4-Epipulchellin-2-*O*-acetate (**361**)	*G. burkei* Harv. subsp. *burkei* var. *intermedia* (S. Moore) Merxm. (Compositae) [158]	South Africa	Aerial parts	–
4-Epipulchellin-2,4-*O*-diacetate (**362**)*	*G. burkei* Harv. subsp. *burkei* var. *intermedia* (S. Moore) Merxm. (Compositae) [158]	South Africa	Aerial parts	mp 137°C; $[\alpha]^{24}_{D}$ +36.6° (*c* 0.71, $CHCl_3$) [158]
4-Epineopulchellin-2,4-*O*-diacetate (**363**)*	*G. burkei* Harv. subsp. *burkei* var. *intermedia* (S. Moore) Merxm. (Compositae) [158]	South Africa	Aerial parts	CD: $\Delta\varepsilon_{260}$ −0.1 (MeCN) [158]
Methyl asperageigerate (**364**)*	*G. aspera* var. *aspera* (Compositae) [158]	South Africa	Roots	$[\alpha]^{24}_{D}$ −43° (*c* 0.3, $CHCl_3$) [158]
5,9-Dihydroxynerolidol (**365**)*	*G. aspera* var. *aspera* (Compositae) [158]	South Africa	Roots	$[\alpha]_{D}$ +11° (*c* 0.11, $CHCl_3$) [158]
3α,9α-Dihydroxy-δ-cadinene (**366**)	*Helichrysum dasyanthum* (Willd) Sweet (Compositae) [159]	South Africa	Aerial parts	–
1α,3α,9α-Trihydroxymuurolene (**367**)	*H. dasyanthum* (Willd) Sweet (Compositae) [159]	South Africa	Aerial parts	–
3-Oxo-cadina-1,9-diene (**368**)	*Helichrysum petiolare* Hilhard et Burtt (Compositae) [159]	South Africa	Aerial parts	–
Bicyclogermacran-13-oic acid (**369**)	*H. dasyanthum* (Willd) Sweet (Compositae) [159]	South Africa	Aerial parts	–
4α-Hydroxyguaia-1(10),11(13)-dien-12,8α-olide (**370**)	*H. dasyanthum* (Willd) Sweet (Compositae) [159]	South Africa	Aerial parts	–
4α-Hydroxy-11αH-guai-9-en-12,8α-olide (**371**)	*Helichrysum splendidum* (Thunb) Less. (Compositae) [159]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ −99° (*c* 0.19, $CHCl_3$) [159]

4α-Hydroxy-11αH-guai-10(14)-en-12,8β-olide (**372**)	*H. splendidum* (Thunb) Less. (Compositae) [159]	South Africa	Aerial parts	–
11α,13-Dihydroxytomentosin (**373**)	*H. splendidum* (Thunb) Less. (Compositae) [159]	South Africa	Aerial parts	$[\alpha]^{24}_{D}$ +33° (*c* 0.58, $CHCl_3$) [159]
Helisplendidilactone (**374**)	*H. splendidum* (Thunb) Less. (Compositae) [159]	South Africa	Aerial parts	mp 172°C; $[\alpha]^{24}_{D}$ −64 (*c* 0.21, $CHCl_3$) [159]
Lucidene (**375**)	*U. lucida* ssp. *lucida* (Annonaceae) [122]	Tanzania	Root bark	mp 208−210°C [122]
3β-Hydroxyoplodiol (**376**)*	*Pallenis spinosa* (Compositae) [160]	Egypt	Aerial parts	–
3β-Acetoxyoplodiol (**377**)*	*P. spinosa* (Compositae) [160]	Egypt	Aerial parts	–
3β-Hydroxyoplopanone (**378**)*	*P. spinosa* (Compositae) [160]	Egypt	Aerial parts	–
3β,4β-Dihydroxypallenone (**379**)*	*P. spinosa* (Compositae) [160]	Egypt	Aerial parts	–
Cinnamolide-3β-ol (**380**)*	*W. ugandensis* and *W. stuhlmannii* (Canellaceae) [143]	Kenya	Stem bark	mp 153−155°C; $[\alpha]_D$ +7° (*c* 3.0, $CHCl_3$) [143]
Deacetylugandensolide (**381**)*	*W. ugandensis* and *W. stuhlmannii* (Canellaceae) [143]	Kenya	Stem bark	mp 260−265°C; $[\alpha]_D$ +70° (*c* 0.1, MeOH) [143]
Tanzanene (**384**)	*U. tanzaniae* (Annonaceae) [123]	Tanzania	Root bark	mp 84−85°C; $[\alpha]_D$ −4.5° (*c* 0.47, $CHCl_3$) [123]
Salutarisolide (**385**)	*W. salutaris* (Canellaceae) [161]	South Africa	Stem bark	mp 139−140°C; $[\alpha]_D$ −5.7° (*c* 1.09, $CHCl_3$) [161]
3β,4α-Dihydroxy-7-epi-eudesm-11 (13)-ene (**386**)	*Laggera crispate* (Asteraceae) [162]	Ethiopia	Aerial parts	–
11-Hydroxyguaia-4,6-diene (**387**)	*L. stellatus* (Annonaceae) [148]	Tanzania	Root bark	$[\alpha]_D$ −55° (*c* 0.25, $CHCl_3$) [148]
2α-Hydroxysphaerantholide (**388**)*	*Sphaeranthus suaveolens* (Compositae) [163]	Kenya	Aerial parts	mp 80°C; $[\alpha]^{24}_{D}$ −60° (*c* 0.36, $CHCl_3$) [163]
2α-Acetoxysphaerantholide (**389**)*	*S. suaveolens* and *S. buttalus* (Compositae) [163]	Kenya	Aerial parts	mp 131°C; $[\alpha]^{24}_{D}$ −99° (*c* 0.57, $CHCl_3$) [163]
2α,7α-Dihydroxysphaerantholide (**390**)*	*S. suaveolens* (Compositae) [163]	Kenya	Aerial parts	mp 176°C; $[\alpha]^{24}_{D}$ −32° (*c* 0.36, MeOH) [163]

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
2α-Acetoxy-7α-hydroxysphaerantholide (**391**)*	*S. suaveolens* (Compositae) [163]	Kenya	Aerial parts	mp 167°C; $[\alpha]^{24}_{D}$ −91° (*c* 2.88, $CHCl_3$) [163]
2α,7α-Dihydroxy-11α,13-dihydrosphaerantholide (**392**)*	*S. suaveolens* (Compositae) [163]	Kenya	Aerial parts	mp 229°C; $[\alpha]^{24}_{D}$ −18° (*c* 0.67, MeOH) [163]
2α-Acetoxy-5α-hydroxyisosphaerantholide (**393**)*	*S. suaveolens* (Compositae) [163]	Kenya	Aerial parts	–
2α-Acetoxy-5α-hydroperoxyisosphaerantholide (**394**)*	*S. suaveolens* (Compositae) [163]	Kenya	Aerial parts	–
Glaucogalamensolide isovalerate (**395**)*	*Vernonia galamensis* ssp. *nairobensis* (Compositae) [164]	Kenya	Aerial parts	mp 138°C; $[\alpha]_D$ −114° (*c* 0.6, $CHCl_3$) [164]
Glaucogalamensolide isobutyrate (**396**)*	*V. galamensis* ssp. *nairobensis* (Compositae) [164]	Kenya	Aerial parts	mp 183°C [164]
8α,13-Dihydroxygermacra-1(10)*E*,4*E*,7(11)-trien-12,6α-olide (**397**)*	*Pentzia pinnatisecta* Hutch (Compositae) [165]	Namibia	Aerial parts	–
13-Hydroxy-3β-acetoxygermacra-1(10)*E*,4*E*,7(11)-trien-12,6α-olide (**398**)*	*Pentzia eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	$[\alpha]^{24}_{D}$ +123° (*c* 0.91, $CHCl_3$) [165]
13-Hydroxy-13-acetoxygermacra-1(10)*E*,4*E*,7(11)-trien-12,6α-olide (**399**)*	*P. eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	–
8α,13-Dihydroxy-4α,5β-epoxygermacra-1(10)*E*,7(11)-dien-12,6α-olide (**400**)*	*P. pinnatisecta* Hutch (Compositae) [165]	Namibia	Aerial parts	mp 182°C; $[\alpha]^{24}_{D}$ +32° (*c* 0.17, MeOH) [165]
8α-Hydroxy-13-acetoxy-4α,5β-epoxygermacra-1(10)*E*,7(11)-dien-12,6α-olide (**401**)*	*P. pinnatisecta* Hutch (Compositae) [165]	Namibia	Aerial parts	–
13-Hydroxy-4α,5β-epoxygermacra-1(10)*E*,7(11)-dien-12,6α-olide (**402**)*	*P. pinnatisecta* Hutch (Compositae) [165]	Namibia	Aerial parts	–

3β-Hydroxy-11α,13-dihydroparthenolide (**403**)	*Pentzia calva* S Moore (Compositae) [165]	Namibia	Aerial parts	mp 186°C; $[\alpha]^{24}_{D}$ +38° (*c* 2.44, $CHCl_3$) [165]
1β,10β-Epoxyguaia-3,11(13)-dien-12,6α-olide (**404**)*	*P. eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	mp 98°C; $[\alpha]^{24}_{D}$ +103° (*c* 0.3, $CHCl_3$) [165]
8α-Acetoxy-1β,10β-epoxy-3,11(13)-dien-12,6α-olide (**405**)*	*P. eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	mp 190°C [165]
Pentziafulvenolide (**406**)*	*P. eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	CD: $\Delta\varepsilon_{296}$ −0.13 and $\Delta\varepsilon_{263}$ +1.25 (Et_2O) [165]
6-epi-Pentziafulvenolide (**407**)*	*P. eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	–
8α-Acetoxy-4α-hydroxyguaia-1(10),2,11(13)-trien-12,6α-olide (**408**)*	*P. eenii* S. Moore (Compositae) [165]	Namibia	Aerial parts	mp 98°C; $[\alpha]^{24}_{D}$ −33° (*c* 0.09, $CHCl_3$) [165]
Urospermal A-14-*O*-methyl acetal (**409**)*	*D. anomala* ssp. *anomala* (Compositae) [166]	Namibia	Aerial parts	–
8α-Acetyoxy-14,15-dihydroxycostunolide (**410**)*	*D. anomala* ssp. *anomala* (Compositae) [166]	Namibia	Aerial parts	–
8α,15-Diacetoxy-14-hydroxycostunolide (**411**)*	*D. anomala* ssp. *anomala* (Compositae) [166]	Namibia	Aerial parts	–
8α-Acetoxy-15-hydroxy-14-[2-methyl-3-hydroxybutyryloxy]-costunolide (**412**)*	*D. anomala* ssp. *anomala* (Compositae) [166]	Namibia	Aerial parts	–
15-Acetoxycostunolide (**413**)*	*Dicoma capensis* Less. *Dicoma schinzii* O. Hoffm (Compositae) [166]	Namibia	Aerial parts	–
15-Acetoxy-14-hydroxycostunolide (**414**)*	*D. capensis* Less. *Dicoma schinzii* O. Hoffm (Compositae) [166]	Namibia	Aerial parts	$[\alpha]_D$ +77° (*c* 1.09, $CHCl_3$) [166]
15-Acetoxy-8α-hydroxycostunolide (**415**)*	*Dicoma schinzii* O. Hoffm (Compositae) [166]	Namibia	Aerial parts	–
3α-Acetoxy-eudesma-1,4(15),11(13)-trien-12,6α-olide (**416**)*	*D. capensis* Less. (Compositae) [166]	Namibia	Aerial parts	mp 139°C [166]
3β-Hydroxy-8α-isobutyryloxy-costunolide (**417**)*	*Ursinia tenuifolia* (Compositae) [167]	South Africa		–

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
8α-Hydroxy-4α,5β-epoxy-11βH-germacr-1(10)*E*-en-12,6α-olide (**418**)*	*Ursinia sericea* (Compositae) [167]	South Africa	Aerial parts	–
1β,3β-Dihydroxy-8α-isobutyryloxy-germacra-4*E*,10(14),11(13)-trien-12,6α-olide (**419**)*	*U. tenuifolia* (Compositae) [167]	South Africa	Aerial parts	–
1β-Hydroperoxy-3β-hydroxy-8α-isobutyryloxy-germacra-4*E*,10(14),11(13)-trien-12,6α-olide (**420**)*	*U. tenuifolia* (Compositae) [167]	South Africa	Aerial parts	–
3β-Hydroxy-8α-isobutyryloxy-1-oxo-germacra-4*E*,10(14)-11(13)-trien-12,6α-olide (**421**)*	*U. tenuifolia* (Compositae) [167]	South Africa	Aerial parts	–
3β-Hydroxy-8β-angeloyloxy-germacra-1(10)*E*,4*E*,11(13)-trien-12,6β-olide (**422**)*	*Ursinia cakilefolia* (Compositae)	South Africa	Aerial parts	–
6α-Hydroxy-11αH-germacra-1(10)*E*,4*E*-dien-12,8α-olide (**423**)*	*U. sericea* (Compositae) [167]	South Africa	Aerial parts	–
6α-Tigloyloxy-4α,5β-epoxygermacra-1(10)*E*,11(13)-dien-12,8α-olide (**424**)*	*Ursinia rigidula* (Compositae) [167]	South Africa	Aerial parts	–
6α-Hydroxy-4α,5β-epoxy-11αH-germacr-1(10)*E*-en-12,8α-olide (**425**)*	*U. sericea* (Compositae) [167]	South Africa	Aerial parts	–
8α-Angeloyloxy-5αH-guaia-1(10),3,11(13)-trien-12,6α-olide (**426**)*	*U. cakilefolia* (Compositae) [167]	South Africa	Aerial parts	–
8α-Angeloyloxy-4α-hydroxy-5αH-guaia-1(10),3,11(13)-trien-12,6α-olide (**427**)*	*U. cakilefolia* (Compositae) [167]	South Africa	Aerial parts	–
8α-Angeloyloxy-4β-hydroxy-5αH-guaia-1(10),3,11(13)-trien-12,6α-olide (**428**)*	*U. cakilefolia* (Compositae) [167]	South Africa	Aerial parts	–

4β-Hydroperoxy-9α-methoxy-5αH-guaia-1(10),3,11(13)-trien-12,6α-olide (**429**)*	*Ursinia nudicaulis* (Compositae) [167]	South Africa	Aerial parts	–
14-Acetoxy-4β-hydroxy-5αH-guaia-1(10),2-dien-12,6α-olide (**431**)*	*U. nudicaulis* (Compositae) [167]	South Africa	Aerial parts	–
1α-Hydroperoxy-5αH-guaia-3,9,11(13)-trien-12,6α-olide (**432**)*	*U. nudicaulis* (Compositae) [167]	South Africa	Aerial parts	–
5αH-Guaia-1(10),2,4(15)-trien-12,6α-olide (**430**)*	*U. nudicaulis* (Compositae) [167]	South Africa	Aerial parts	–
1α,4α-Endoperoxy-5αH-guaia-2,9,11(13)-trien-12,6α-olide (**433**)*	*U. nudicaulis* (Compositae) [167]	South Africa	Aerial parts	–
1α,4α-Endoperoxy-5α,11αH-guaia-2,9-dien-12,6α-olide (**434**)*	*U. nudicaulis* (Compositae) [167]	South Africa	Aerial parts	–
10α-Hydroxy-9α-[isovaleryloxy]-1α,4α-endoperoxyguaia-2,11(13)-dien-12,6α-olide (**435**)*	*Ursinia dentata* (Compositae) [167]	South Africa	Aerial parts	–
10α-Hydroxy-9α-[2-methylbutyryloxy]-1α,4α-endoperoxyguaia-2,11(13)-dien-12,6α-olide (**436**)*	*U. dentata* (Compositae) [167]	South Africa	Aerial parts	–
10α-Hydroxy-9α-isobutyryloxy-1α,4α-endoperoxyguaia-2,11(13)-dien-12,6α-olide (**437**)*	*U. dentata* (Compositae) [167]	South Africa	Aerial parts	–
4β,10β-Dihydroxy-1α-methoxy-5α,11αH-guaia-2-en-12,6α-olide (**438**)*	*U. sericea, U. nudicaulis* (Compositae)	South Africa	Aerial parts	–
5α-Hydroxy-2α-methoxy-11αH-guaia-1(10),3-dien-12,6α-olide (**439**)*	*Ursinia nana* (Compositae) [167]	Namibia	Aerial parts	–
5α-Hydroxy-2-oxo-11αH-guaia-1(10),3-dien-12,6α-olide (**440**)*	*U. nana* (Compositae) [167]	Namibia	Aerial parts	–
1α,5α-Dihydroxy-11αH-guaia-3,10(14)-dien-12,6α-olide (**441**)*	*U. nana* (Compositae) [167]	Namibia	Aerial parts	–

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
1α,5α,3α,4α-Bisepoxy-10β-methoxy-11αH-guaian-12,6α-olide (**442**)*	*U. nana* (Compositae) [167]	Namibia	Aerial parts	–
4β,5β-Epoxy-3β-hydroxy-10α-methoxy-11αH-guaia-1-en-12,6β-olide (**443**)*	*U. nana* (Compositae) [167]	Namibia	Aerial parts	–
3β,4β-Dihydroxy-2α,10α-dimethoxy-11αH-guaia-1(5)-en-12,6β-olide (**444**)*	*U. nana* (Compositae) [167]	Namibia	Aerial parts	–
1β,4α,8β-Trihydroxy-eudesm-11(13)-en-12,6α-olide (**445**)*	*Ursinia abrotanifolia* (Compositae) [167]	South Africa	Roots	–
5-Oxo-jasoniolide (**446**)*	*Ursinia eckloniana* (Compositae) [167]	South Africa	Aerial parts	–
Methyl-5α-hydroperoxy-6β-hydroxycostoate (**447**)*	*U. tenuifolia* (Compositae) [167]	South Africa	Aerial parts	–
Methyl-5β-hydroperoxycostoate (**448**)*	*U. eckloniana* (Compositae) [167]	South Africa	Aerial parts	–
Methyl-6β-hydroxyisocostoate (**449**)*	*U. tenuifolia* (Compositae) [167]	South Africa	Aerial parts	–
Methyl-4,5-dioxo-seco-isocostoate (**450**)*	*U. eckloniana* (Compositae) [167]	South Africa	Aerial parts	–
Methyl-5β-hydroxy-4-oxo-11(13)-dehydroiphionoate (**451**)*	*U. eckloniana* (Compositae) [167]	South Africa	Aerial parts	–
4β,5β-Dihydroxy-10-epi-eudesmane (**452**)*	*Ursinia trifida* Less. (Compositae) [167]	South Africa	Aerial parts	–
4β,11-Dihydroxy-10-epi-eudesmane (**453**)*	*U. trifida* Less. (Compositae) [167]	South Africa	Aerial parts	–
10-epi-Eudesma-3,5-diene (**454**)*	*U. trifida* Less. (Compositae) [167]	South Africa	Aerial parts	–
2α,4β-Dihydroxy-5-epi-eremophil-1(10)-ene (**455**)*	*U. trifida* Less. (Compositae) [167]	South Africa	Aerial parts	–
4β-Hydroxy-5-epi-eremophil-1(10)-en-2-one (**456**)*	*U. trifida* Less. (Compositae) [167]	South Africa	Aerial parts	CD: $\Delta\varepsilon_{345}$ −0.33 (MeCN) [167]

2α,8α,11-Trihydroxy-5-epi-eremophil-1(10)-ene (**457**)*	*U. trifida* Less. (Compositae) [167]	South Africa	Aerial parts	–
8α,11-Dihydroxy-5-epi-eremophil-1(10)-en-2-one (**458**)*	*U. trifida* Less. (Compositae) [167]	South Africa	Aerial parts	CD: $\Delta\varepsilon_{347}$ −0.35 (MeCN) [167]
5-Isovaleryloxydehydrolasiospermane (**459**)*	*U. sericea* (Compositae) [166]	South Africa	Aerial parts	–
8-Acetoxynerolidol (**460**)*	*U. dentata* (Compositae) [167]	South Africa	Roots	–
15-Desoxylactucin-α-D-glucopyranoside (**461**)*	*Reichardia tingitana* (Compositae) [168]	Egypt	Aerial parts	$[\alpha]^{24}_{D}$ +10° (*c* 0.32, $CHCl_3$) [168]
1,3-Dioxo-7α,11βH-2,3-secogermacra-4*Z*,9*Z*-dien-12,6α-olide (**462**)*	*Pyrethrum santolionoides* (Compositae) [169]	Egypt	Aerial parts	$[\alpha]^{26}_{D}$ −61.2° (*c* 4.886, $CHCl_3$) [169]
1,3-Dioxo-7α,11βH-2,3-secogermacra-4*E*,10(14)-dien-12,6α-olide (**463**)*	*P. santolionoides* (Compositae) [169]	Egypt	Aerial parts	$[\alpha]^{26}_{D}$ +26.4° (*c* 1.194, $CHCl_3$) [169]
1β,3β-Dihydroxy-7α,11βH-germacra-4*Z*,9*Z*-dien-12,6α-olide (**464**)*	*P. santolionoides* (Compositae) [169]	Egypt	Aerial parts	mp 191°C [169], $[\alpha]^{26}_{D}$ +53.8° (*c* 1.0, $CHCl_3$) [169]
1α,3β,10α-Trihydroxy-7α,11βH-germacra-4*Z*-en-12,6α-olide (**465**)*	*P. santolionoides* (Compositae) [169]	Egypt	Aerial parts	mp 145°C; $[\alpha]^{25}_{D}$ −115.4° (*c* 1.0, $CHCl_3$) [169]
3β-Hydroxy-oxo-7α,11β-germacra-4*Z*,10(14)-dien-12,6α-olide (**466**)*	*P. santolionoides* (Compositae) [169]	Egypt	Aerial parts	mp 156°C; $[\alpha]^{25}_{D}$ −46° (*c* 1.0, $CHCl_3$) [169]
1β,10α-Epoxy-3β-hydroxy-7α,11αH-germacra-4*Z*-en-12,6β-olide (**467**)*	*P. santolionoides* (Compositae) [169]	Egypt	Aerial parts	mp 164°C; $[\alpha]^{24}_{D}$ −17° (*c* 1.0, $CHCl_3$) [169]
1β,6α-Dihydroxy-7-epi-eudesm-3-ene (**468**)*	*Pluchea dioscoridis* (Asteraceae) [170]	Egypt	Leaves	$[\alpha]^{25}_{D}$ +44 (*c* 0.52, $CHCl_3$) [170]
1β,6β-Dihydroxy-7-epi-eudesm-3-ene (**469**)*	*P. dioscoridis* (Asteraceae) [170]	Egypt	Leaves	–
4β,5α-Dihydroxy-15-oxo-eudesm-11(13)-en-12-oic acid (**470**)*	*P. dioscoridis* (Asteraceae) [170]	Egypt	Leaves	$[\alpha]^{26}_{D}$ +22.5° (*c* 1.136, $CHCl_3$) [170]
4β,5β-Dihydroxy-15-oxo-eudesm-11(13)-en-12-oic acid (**471**)*	*P. dioscoridis* (Asteraceae) [170]	Egypt	Leaves	$[\alpha]^{26}_{D}$ −2.5° (*c* 0.54, $CHCl_3$) [170]

(*Continued*)

Table 2.2 (Continued)

Compounds	Plants	Area of Plant Collection	Plant Part	Physical Properties
1β,9α-Dihydroxyeudesm-4(15),11(13)-dien-5α,7αH-12,6α-olide (**472**)*	*P. dioscoridis* (Asteraceae) [170]	Egypt	Leaves	$[\alpha]^{25}_{D}$ +17.5° (*c* 0.39, $CHCl_3$) [170]
4β,6β-Dihydroxy-1α,5β(H)-guaia-9-ene (**473**)*	*P. dioscoridis* (Asteraceae) [170]	Egypt	Leaves	$[\alpha]^{25}_{D}$ +10.5° (*c* 0.60, $CHCl_3$) [170]
6α-Hydroxy-1,4,1α,5α-diepoxyxanth-10(14)-ene (**474**)*	*P. dioscoridis* (Asteraceae) [170]	Egypt	Leaves	$[\alpha]^{25}_{D}$ +22.6° (*c* 0.52, $CHCl_3$) [170]
Mukaadial 6-*O*-α-L-rhamnopyranoside (**475**)*	*W. stuhlmannii* (Canellaceae) [171]	Kenya	Leaves	mp >250°C [171]
Mukaadial 6-*O*-β-D-glucopyranoside (**476**)*	*W. stuhlmannii* (Canellaceae) [171]	Kenya	Leaves	mp 180−183°C [171]
1β,4β-Dihydroxy-5α(H)-guaia-10(14),11(13)-dien-8α,12-olide (**477**)*	*Pulicaria crispa* (Asteraceae) [172]	Algeria	Aerial parts	$[\alpha]^{22}_{D}$ +40.82° (*c* 1.23, $CHCl_3$) [172]
Ferusinol (**478**)	*F. sinaica* (Apiaceae) [115]	Egypt	Roots	–
Samarcandin diastereomer (**479**)	*F. sinaica* (Apiaceae) [115]	Egypt	Roots	–
5α-Hydroxyperoxy-β-eudesmol (**480**)*	*Cymbopogon proximus* (Gramineae) [173]	Egypt	Herb	–
7α,11-Dihydroxy-cadin-10(14)-ene (**481**)*	*C. proximus* (Gramineae) [173]	Egypt	Herb	–
Cazolobine (**482**)*	*Isolona hexaloba* (Annonaceae) [174]	Gabon	Roots	$[\alpha]^{20}_{D}$ 0° (*c* 0.2, CH_2Cl_2 or EtOH) [174]
3α,4β-Dihydroxy-5βH,11αH-eudesman-6,12-olide (**483**)*	*F. sinaica* (Apiaceae) [175]	Egypt	Leaves	–
Lancerotriol 9-acetate-6-*p*-hydroxybezoate (**484**)*	*F. sinaica* (Apiaceae) [175]	Egypt	Leaves	–
9α-Hydroxy-11β,13-dihydro-3-epi-zaluzanin C (**486**)	*Launaea arborescens* (Asteraceae) [116]	Algeria	Roots	$[\alpha]^{25}_{D}$ −3° (*c* 0.06, $CHCl_3$) [116]
9α-Hydroxy-4α,15-dihydro-zaluzanin C (**487**)	*L. arborescens* (Asteraceae) [116]	Algeria	Roots	$[\alpha]^{25}_{D}$ −11° (*c* 0.10, $CHCl_3$) [116]

3β,14-Dihydroxycostunolide-3-*O*-β-glycopyranoside (**488**)	*L. arborescens* (Asteraceae) [116]	Algeria	Roots	$[\alpha]^{25}_{D}$ +4° (*c* 0.10, MeOH) [116]
3β,14-Dihydroxycostunolide-3-*O*-β-glucopyranosyl-14-*O*-*p*-hydroxyphenylacetate (**489**)	*L. arborescens* (Asteraceae) [116]	Algeria	Roots	$[\alpha]^{25}_{D}$ −0.4° (*c* 0.55, MeOH) [116]
Drypemolundein A (**490**)	*D. molunduana* (Euphorbiaceae) [128]	Cameroon	Whole stems	mp 148−150°C; $[\alpha]^{25}_{D}$ −137.0° (*c* 1.01, $CHCl_3$) [128]
Furanoeudesm-1-on-13-oic acid (**491**)	*D. chevalieri beille* (Euphorbiaceae) [130]	Cameroon	Whole stems	mp 206−208°C; $[\alpha]^{25}_{D}$ −114° (*c* 0.07, MeOH) [130]
Okundoperoxide (**492**)	*S. striatinux* (Cyperaceae) [124]	Cameroon	Roots	$[\alpha]^{21}_{D}$ +72.9° (*c* 1.6, $CHCl_3$) [124]
Polysin (**493**)	*P. suaveolens* (Annonaceae) [131]	Cameroon	Stem bark	mp 170−171°C [131]
Picrotoximaesin (**494**)*	*Maesobotrya floribunda* (Phyllanthaceae) [176]	Cameroon	Berries	mp 208−209°C; $[\alpha]_{D}$ −8° (*c* 0.2, MeOH) [176]
Zuurbergenin (**495**)*	*Matricaria zuurbergenis* (Compositae) [177]	South Africa	Aerial parts	mp 176°C; $[\alpha]^{589}_{D}$ +92° (*c* 0.17, $CHCl_3$) [177]
Warburgiadione (**496**)*	*W. ugandensis* (Canellaceae) [145]	Uganda	Heartwood	mp 127−128°C; $[\alpha]_{D}$ +25° [145]

mp, melting point; −, not reported.
*No reported pharmacological activity.

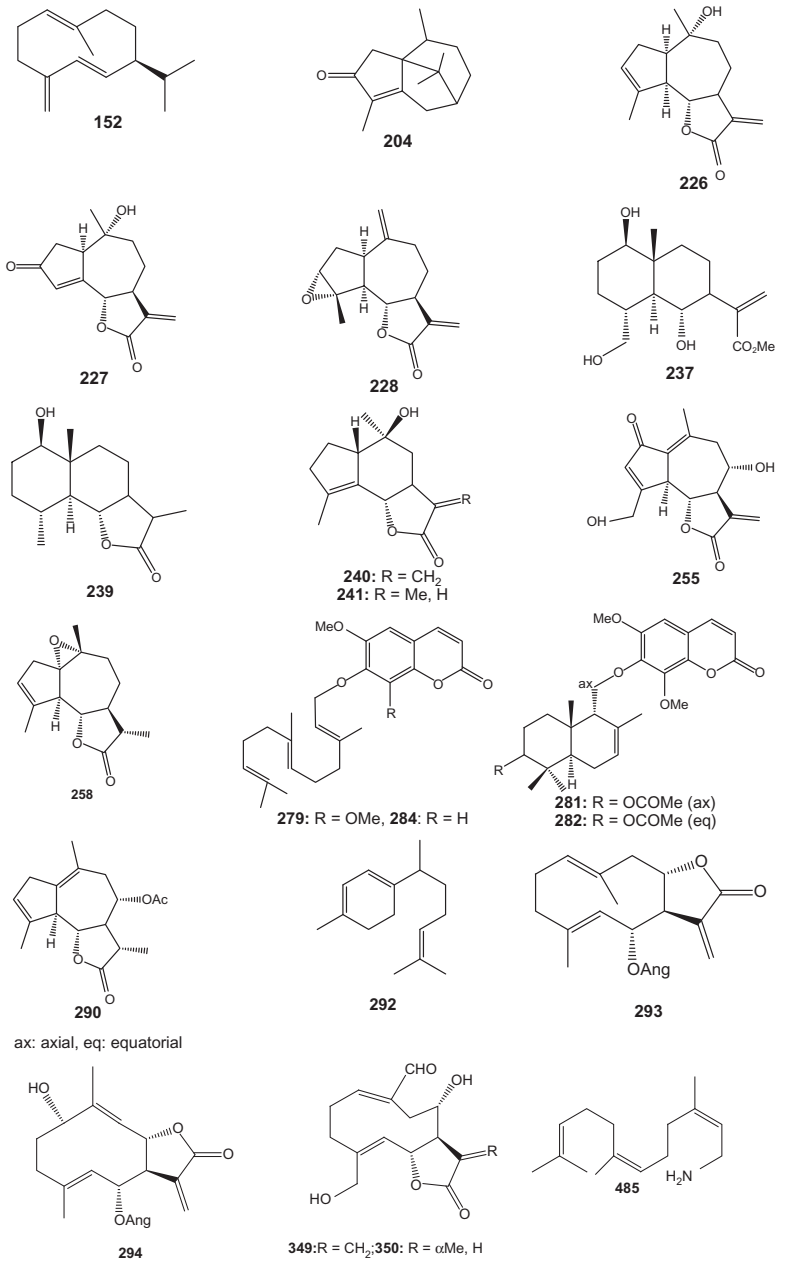

Figure 2.6 Chemical structures of sesquiterpenes and related compounds isolated in African medicinal plants without any activity or known to be pharmacologically inactive (ax, axial orientation; eq, equatorial orientation).

Table 2.3 Known Sesquiterpenes with No Reported Pharmacological Activity Isolated from African Plants

Compounds	Plants (Family)	Area of Plant Collection	Plant Part	Reference
Germacra-1(10),4(15),5-triene (**152**)	*S. oxyodontus* (Compositae)	South Africa	Aerial parts	[58]
Isopatchoul-4(5)-en-3-one (**204**)	*C. articulatus* (Cyperaceae)	Cameroon	Rhizomes	[53]
8-Desoxycumambrin B (**226**)	*Eriocephalus* sp.n. (Compositae)	Namibia	Aerial parts	[69]
Parishin (**227**)	*Eriocephalus* sp.n. (Compositae)	Namibia	Aerial parts	[69]
Estaliatin (**228**)	*Eriocephalus* sp.n. (Compositae)	Namibia	Aerial parts	[69]
Methyl-1β,6α,15-trihydroxy-4β,15-dihydrocostate (**237**)	*S. macrocarpus* (Compositae)	Egypt	Roots	[80]
11β,13-Dihydroreynosin (**239**)	*S. macrocarpus* (Compositae)	Egypt	Roots	[80]
10β-Hydroxycichopumilode (**240**)	*S. macrocarpus* (Compositae)	Egypt	Roots	[80]
10β-Hydroxy-11β,13-dihydrocichopumilode (**241**)	*S. macrocarpus* (Compositae)	Egypt	Roots	[80]
Lactucopicrin (**255**)	*L. sativa* (Compositae)	Egypt	Aerial parts	[88]
Arborescin (**258**)	*A. argentea* (Compositae)	Egypt	Aerial parts	[151,152]
Farnochrol (**279**)	*B. cinerea* (Compositae)	Egypt	Roots	[97]
Acetyldrimartol A (**281**)	*B. cinerea* (Compositae)	Egypt	Roots	[97]
Acetyldrimartol B (**282**)	*B. cinerea* (Compositae)	Egypt	Roots	[97]
Scopofarnol (**284**)	*B. cinerea* (Compositae)	Egypt	Roots	[97]
8α-Acetoxydihydrokauniolide (**290**)	*A. afra* (Compositae)	South Africa	Aerial parts	[93]
γ-Curcumene (**292**)	*C. cinerea* (Compositae)	Egypt	Aerial parts	[100]
Desacyl laurenobiolide angelate (**293**)	*C. cinerea* (Compositae)	Egypt	Aerial parts	[100]
6α-Angeloyloxy-1α-hydroxygermacra-4*E*,9*Z*,11-trien-8α,12-olide (**294**)	*C. cinerea* (Compositae)	Egypt	Aerial parts	[100]
Urospermal A (**349**)	*D. tomentosa* (Compositae), *A. pinnatifidus* (Compositae), *U. picroides* (Compositae)	South Africa, Namibia, Egypt	Aerial parts	[120,147,155]
11β,13-Dihydrourospermal A (**350**)	*D. tomentosa* (Compositae)	South Africa	Aerial parts	[120]
Farnesylamine (**485**)	*Vernonia auriculifera* (Asteraceae)	Kenya	Leaves	[178]

Products. There may be some sesquiterpenes and/or pharmacological activities we missed during the collection of data. The pharmacological activities of many of these compounds in a very wide variety of applications are very interesting. Many of the compounds isolated were not investigated for different activities. It is obvious that closer collaboration between phytochemists, pharmacologists, microbiologists, parasitologists, and other disciplines could lead to the application of many sesquiterpenoids as products in human and animal health and different applications in agriculture.

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3 Diterpenoids from the Medicinal Plants of Africa

Louis Pergaud Sandjo[a] *and Victor Kuete*[b]

[a]Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon, [b]Department of Biochemistry, University of Dschang, Dschang, Cameroon

3.1 Introduction

Diterpenoids are secondary metabolites containing 20 atoms of carbon derived from the condensation of four isoprenyl units. As other terpenoids, they are widespread in the plant kingdom, and most of them biosynthetically derive from geranylgeranyl diphosphate, which forms acyclic (phytanes), bicyclic (labdanes, halimanes, clerodanes), tricyclic (pimaranes, abietanes, cassanes, rosanes, vouacapanes, podocarpanes), tetracyclic (trachylobanes, kauranes, aphidicolanes, stemodanes, stemaranes, atisanes, gibberellanes), and macrocyclic diterpenes (taxanes, cembranes, daphnanes, tiglianes, ingenanes) according to the cyclization that occurs [1]. Diterpenoids are divided into more than 45 classes; they are also found in marine organisms, which provide interesting skeletons (Figure 3.1) such as elisapterane (**39**). Figure 3.1 presents the structural diversity and some of the skeletons of this class of compounds.

Plants produce secondary metabolites in response to some external factors from their biotope. To fight against these, the host plant produces diterpenes, which could represent a problem in the living ecosystem of that species because of the allelopathic activity of some of these terpenoids against surrounding flora [24]. In addition, diterpenoid quinones from the roots of *Salvia officinalis* were earlier reported to display DNA-damaging effect on colonic and hepatic human cells cultured *in vitro*, although cytotoxic activity was observed [25]. Nevertheless, these structures are synthesized in the plant cells following a well-established mechanism.

3.2 Biosynthesis and Structural Diversity

Biosynthesis of terpenoids, including monoterpenes, sesquiterpenes, diterpenes, and triterpenes, starts with isoprene of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). These sequences of reactions occur in the plant along two synthetic pathways: the mevalonic acid synthesis pathway (MEV) and the

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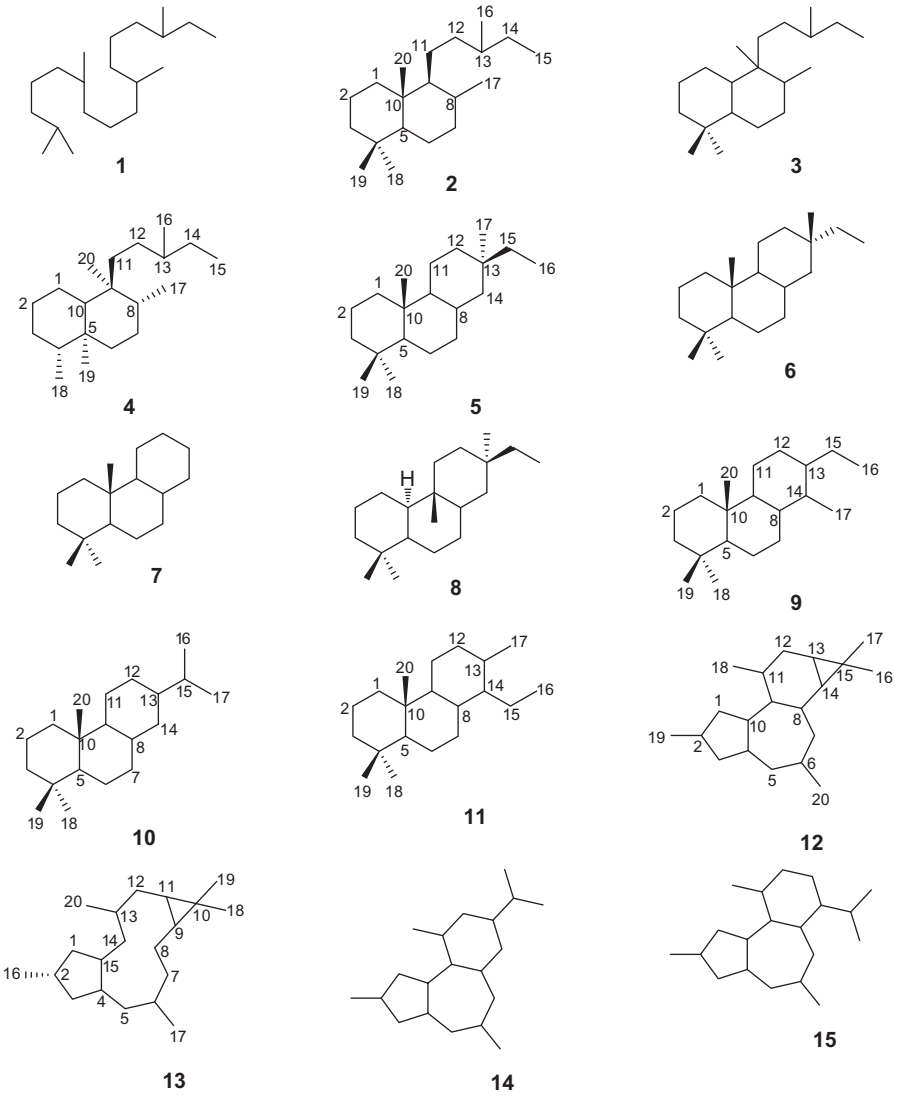
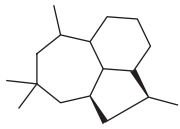


Figure 3.1 Diterpenoid skeletons from terrestrial and marine sources: Phytane (**1**) [1], Labdane (**2**), Halimane (**3**), Clerodane (**4**), Pimarane (**5**), Isopimarane (**6**), Podocarpane (**7**), Rosane (**8**), Cassane (**9**), Abietane (**10**), Cleistanthane (**11**), Tigliane (**12**), Lathyrane (**13**), Daphnane (**14**), Rhamnofolane (**15**) [1], Endromedane (**16**) [2], Cembrane (**17**) [2], Cyathane (**18**) [2], *Ent*-atisane (**19**) [2], Atisane (**20**) [3], Vouacapane or furanocassane (**21**) [4], Trachylobane (**22**) [5], Phyllocladane or *syn*-kaurane, *Ent*-Phyllocladane (**24**) [6], Kaurane (**25**) [6], *Ent*-kaurane (**26**) [6], Aphidicolane (**27**) [7], Stemodane (**28**) [7], Stemarane (**29**) [8], Ingenane (**30**) [9], Totarane (**31**) [10], Jatrophane (**32**) [11], Amphilectane (**33**) [12], Elisabethane (**34**) [12], Ileabethane (**35**) [12], Dolabellane (**36**) [13], Asbestinane (**37**) [13], Serrulatane (**38**) [14], Elisapterane (**39**) [14], *Ent*-Gibberellane (**40**) [15], Dolastane (**41**) [16], Verticillane (**42**) [17], Spongiane (**43**) [18], Cubitane (**44**) [19], Beyerane (**45**) [20], Taxane (**46**) [21], Casbane (**47**) [22], Capnosane (**48**) [23], Basmane (**49**) [23], Triervitane (**50**) [23], Rippertane (**51**) [23], Kempane (**52**) [23], Longipane (**53**) [23], Gersolanoid (**54**) [23].



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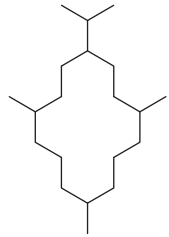

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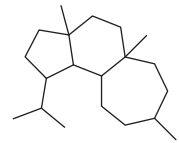

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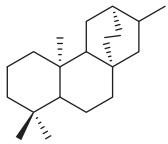

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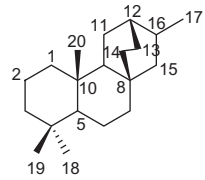

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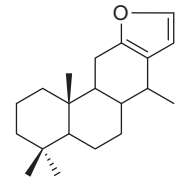

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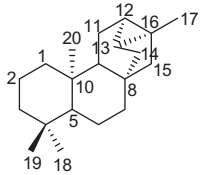

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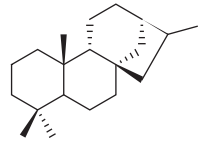

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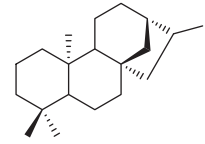

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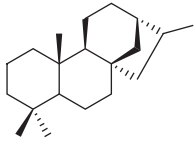

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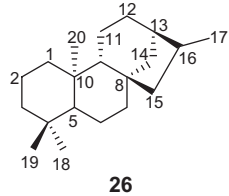

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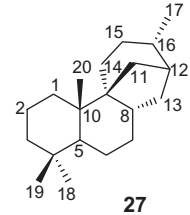

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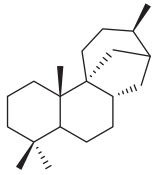

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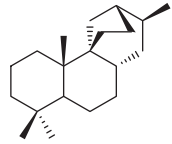

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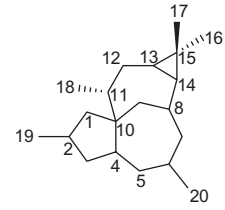

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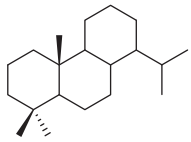

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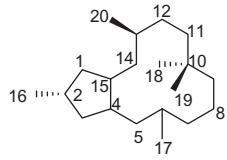

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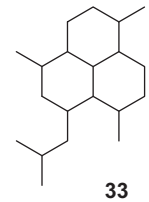

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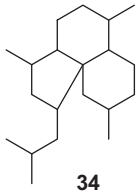

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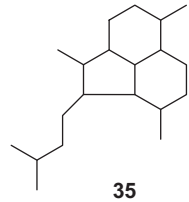

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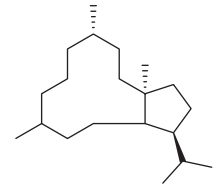

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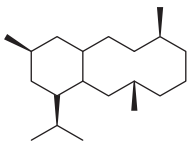

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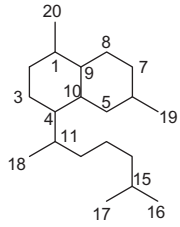

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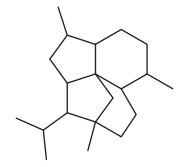

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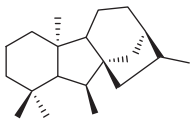

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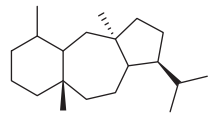

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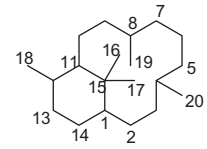

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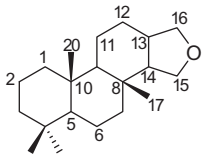

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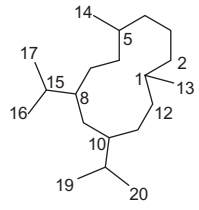

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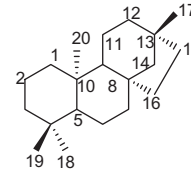

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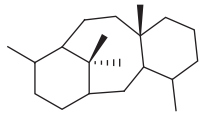
Figure 3.1 (Continued)



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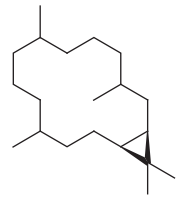

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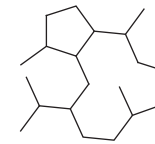

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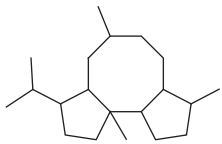

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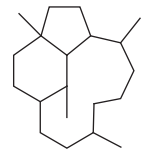

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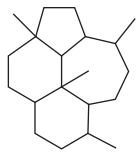

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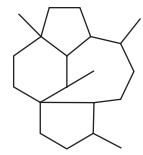

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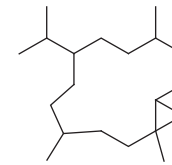

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Figure 3.1 (Continued)

1-deoxyxylulose-5-phosphate pathway, also known as the non-mevalonate pathway (MEP). However, IPP and DMAPP are contributors in both synthesis pathways [26]. The formation of diterpenoids starts with the condensation of DMAPP and IPP in a head-to-tail process by prenyltransferases to form geranyl diphosphate (GPP) [27]. Furthermore, GPP condenses with two more IPP isomerases yielding, through a farnesyl diphosphate intermediate, geranylgeranyl diphosphate (GGPP), which is the common precursor for diterpenes [28].

Each diterpenoid is synthesized according to a precise mechanism and specifically catalyzed by a given enzyme. Thus, taxadiene synthase catalyzes the formation of taxa-4,11-diene as well as abietadiene synthase, pimaradiene synthase, or *ent*-kaurene synthase for the classes abietane, pimarane, and *ent*-kaurane, respectively [31−33]. Some of these terpenoids are formed directly; others require two distinct steps or more to be biosynthesized. For instance, *ent*-cassa-12,15-diene is formed from the cyclization of GGPP catalyzed by *ent*-CPP synthase and *ent*-cassadiene synthase in two different steps (Figure 3.2). Simple rotation around the δ-bond attached to the olefinic carbons can give the GGPP an adequate conformation to form other types of diterpenes such as casbene and cembrene (Figure 3.3). The latter is produced in plants under the effect of an unknown enzyme [36,37].

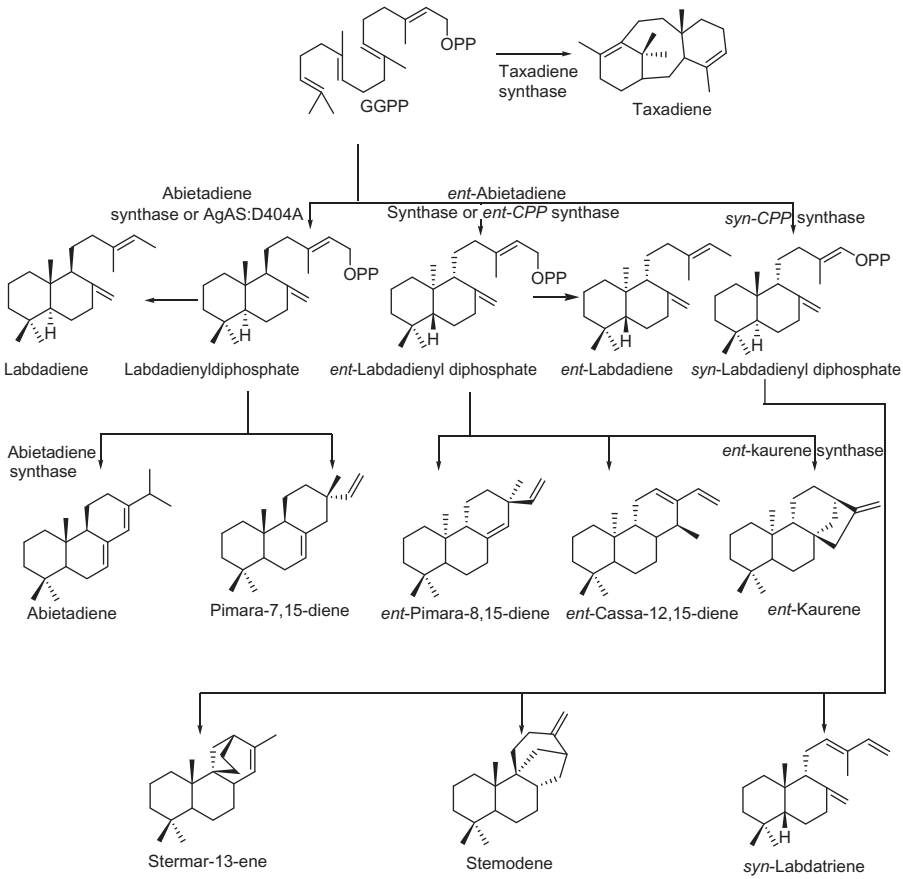


Figure 3.2 Biosynthesis of diterpenoids, Part 1 [28−35].

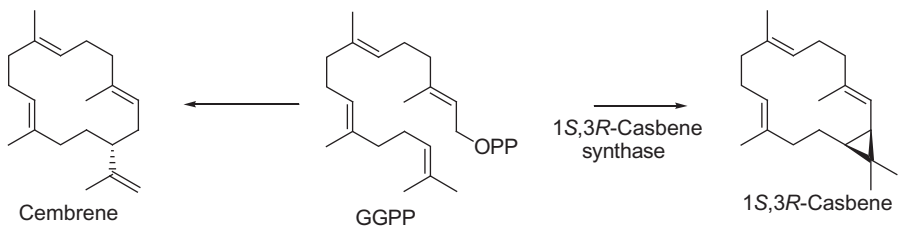


Figure 3.3 Biosynthesis of diterpenoids, Part 2 [36,37].

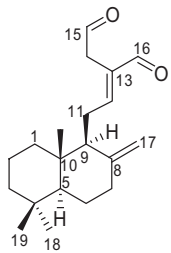
3.3 Nomenclature and Identification of Diterpenoids

3.3.1 Nomenclature of Diterpenoids

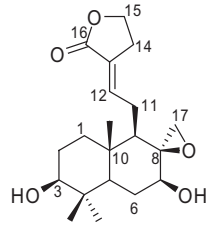
Similar to other terpenoids, diterpenoids are named using the main name of their skeletons (Figure 3.4). For example, the main name of structure **55** will be labdane. If the backbone contains many functions such as olefinic carbons, carboxylic, lactone, or aldehyde groups, their position will be given with respect to the numbering of the skeleton, and the main name will be flanked by the suffix -en, -oic, -olide, or -al, respectively. Therefore, the name of compound **55** will be labda-8(17),12-diene-15,16-dial. The presence of hydroxyl and epoxide groups is mentioned before the main name. Greek letters α or β are used when a hydroxyl, acetoxyl, epoxide, or coumaroyl group in the molecule is, respectively, behind or upon the plan of the skeleton (**56**). The position of hydroxyl groups, epoxide, and other substituents in the diterpene cores are given between the terms *ent*, *syn*, or *neo* and the name of the skeleton.

The stereochemistry at C-9 and C-10 in the decalin part of some diterpenoids can be *cis* or *trans*, according to their orientation, and the nomenclatures *syn* and *ent* are used. Thus, if C-20 and C-11 are behind the molecule plan, the prefix *ent* will precede the main name (**57**), whereas *syn* is employed if C-11 is up and C-20 is behind the molecule plan. Structure **23**, called phyllocladane, can also be named *syn*-kaurane.

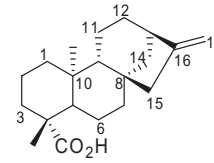
As with triterpenoids, the terms *seco* and *nor* are used as prefixes to the main name to express when one of the cycles is cleaved (*seco*) or a carbon is missing (*nor*). In addition, the position of the missing carbon and where the cleavage occurs will be given before the prefix. Biosynthetically, clerodanes are derived from a labdane skeleton by the migration of methyls 19 and 20 from positions 4 and 10 to positions 5 and 9, respectively. Meanwhile, the reduction of the $C_8{=}C_{17}$ double bond in conjunction with the rearrangement gives a number of diastereomers. According to the stereochemistry through carbon bonds $C_5{-}C_{10}$ and $C_8{-}C_9$ in the decalin moiety, and specifically the spatial orientation of H-10, C-19, C-20, and C-17, clerodanes are classified as *trans*−*cis*, *trans*−*trans, cis*−*cis*, and *cis*−*trans*



Labda-8(17),12-diene-15,16-dial (**55**) [38]



8β,17-Epoxide-3β,7β-dihydroxylabd-12-en-15,16-olide (**56**) [39]



ent-Kaur-16-en-19-oic acid (**57**) [40]

Figure 3.4 Structures used to illustrate diterpene name.

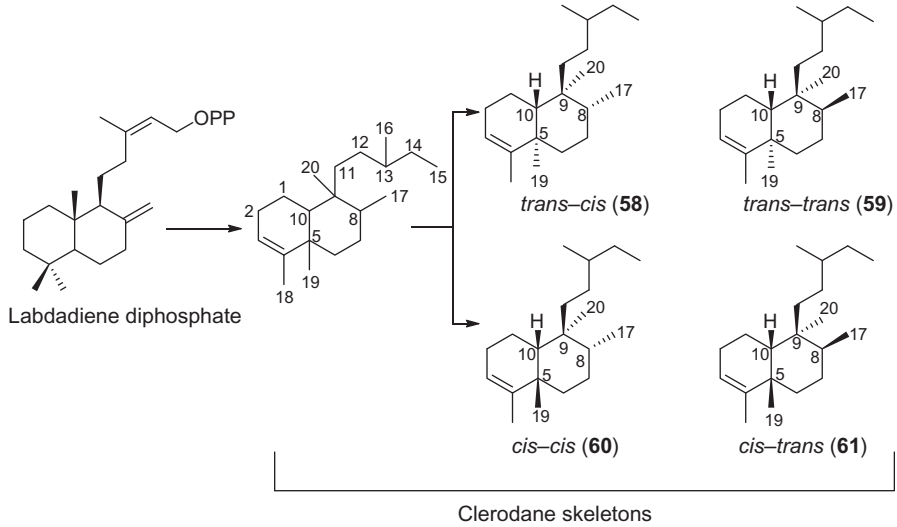


Figure 3.5 Some clerodane backbones [41].

backbones (Figure 3.5). Usually, the backbones below with a precise stereochemistry at the C-5, C-8, C-9, and C-10 are named *neo*-clerodane and their enantiomer, *ent-neo*-clerodane [41].

3.3.2 Identification of Diterpenoids

There is no real chemical test to reveal the presence of diterpenes in a crude organic extract of a plant; nevertheless, NMR analysis is crucial for structure determination. Thus, the number of carbons (20 signals of carbons) depicted on the ^{13}C-NMR spectrum could be indicative of diterpenoids. Besides, the kaurane, abietane, and labdane backbones without any function on the decalin moiety show signals of carbons C-1 (CH_2), C-2 (CH_2), C-3 (CH_2), C-5 (CH), and C-6 (CH_2) around δ 40.1, 18.2, 42.0, 56.0, and 20.0, respectively [42]. The methyl groups C-18, 19, and 20 appear around δ 33.1, 21.5, and 18.0, respectively. C-18 and 19 together have Heteronuclear Multiple-Bond Correlation spectroscopy (HMBC) contacts and both correlate with C-3 (δ 42.0), C-4 (δ 33.1), and C-5 (δ 56.0). The latter also has HMBC cross peaks with Me-20 [42]. Clerodane skeletons have a trisubstituted double bond, which is rather characteristic when the core is a *trans*−*cis* or a *cis*−*cis* (Figure 3.5). In addition to the overall number of carbon atoms indicative of diterpenes, the ^{13}C-NMR spectrum of the *trans*−*cis* decalin displays carbons C-3 and C-4 at δ 120.0 and 144.4, while the shifts of the same carbons are around δ 123.1 and 139.9, respectively. In any structural case, C-1 is around δ 18.0, but there is a considerable difference in the shifts of methyl groups at C-18 and C-19, which are revealed at δ 18.0 and 19.5, respectively, for the *trans*−*cis* skeletons, while those in the *cis*−*cis* cores are disclosed at δ 33.0 (C-18) and 20.0 (C-19) [42].

Nevertheless, the structures of other classes of diterpenoids, either with complex backbones or complex structures, can only be elucidated by collection and careful diagnosis of their NMR data.

3.4 Pharmacological Activities of Diterpenoids Isolated from African Medicinal Plants

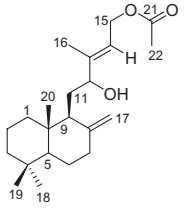
3.4.1 Structural Diversities of Diterpenoids Isolated from African Medicinal Plants

Diverse, structurally interesting compounds were isolated from African medicinal plants. These include bafoudiosbulbins A and B (**71**, **72**), which are clerodane type, containing two and three lactone rings, respectively. Both are obtained from *Dioscorea bulbifera*, harvested in Cameroon (Figure 3.6). The cyclic ester systems were also found in the structure of antadiosbulbins A and B (**83**, **84**), 8-epidiosbulbin E (**85**), and caseanigrescens A–D (**87**–**90**). This structural behavior seems to be frequently found in clerodane backbones. Compounds (**83**–**85**) and (**87**–**90**) were all isolated from the species found in Madagascar. Likewise, glabrescin from *Neoboutonia glabrescens*, another Cameroonian plant species, has a remarkable orthoester-containing structure. In addition, guyonianin F (**128**), a polyhydroxylated jatrophane diterpene from *Euphorbia guyoniana*, an Egyptian medicinal plant, has three extra carbons, which form with the jatrophane skeleton a nine-member macrolactone ring. Table 3.1 reports some physical properties of new diterpenes isolated from plant species collected in Africa.

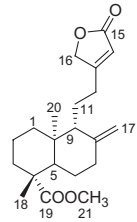
3.4.2 Antimicrobial Activities of Diterpenes Identified in African Medicinal Plants

Several antimicrobial diterpenoids reported in African plants showed different extents of antimicrobial activities, varying from significant (minimal inhibitory concentration (MIC) below 10 μg/mL), to moderate ($10 < \text{MIC} < 100$ μg/mL), to low (MIC > 100 μg/mL) activities (Table 3.2) [71].

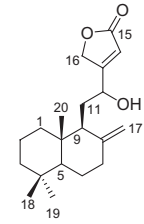
The labdane diterpenoids aframolins A and B (**91**, **92**), labda-8(17),12(*E*)-diene-15,16-dial (**55**), and aframodial (**161**), isolated from the seeds of *Aframomum longifolius*, were tested for their antimicrobial activities, but only aframodial was active against *Cryptococcus neoformans*, *Staphylococcus aureus*, and methycillin-resistant *S. aureus*, with similar MIC value of 20 μg/mL (Figure 3.7) [38]. 16-Acetoxy-12,15-epoxy-15β-hydroxy-labda-8(17),13(16)-diene (**66**), from the stem bark of *Turraeanthus mannii*, displayed qualitative antimicrobial activities against *Bacillus subtilis*, *S. aureus*, *Escherichia coli*, *Mucor miehei*, and *Chlorella vulgaris* [44]. Aulacocarpinolide (**67**) and aulacocarpins A and B (**68**, **69**), isolated from the seeds of *Aframomum aulacocarpos* harvested in Cameroon, exhibited moderate antibacterial activities against *B. subtilis* (MIC of 25 μg/mL for the three compounds)



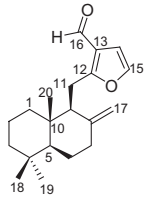
15-Acetoxy-12-hydroxy-16-methyl-labda-8(17),13*E*-diene (**62**) [43]



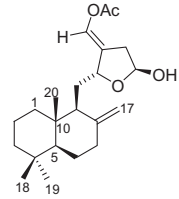
ent-Labda-8(17),13-dien-15,16-olid-19-oic acid methyl ester (**63**) [43]



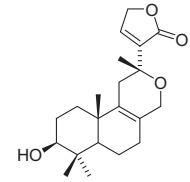
12-Hydroxy-labda-8(17),13-dien-15,16-olide (**64**) [43]



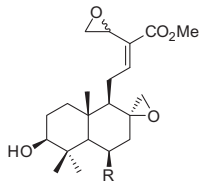
12,15-Epoxylabda-8(17),12,14-trien-16-al(**65**)[44]



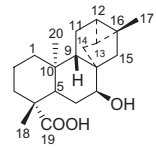
16-Acetoxy-12(*R*),15-epoxy-15β-hydroxylabda-8(17),13(16)-diene (**66**) [44]



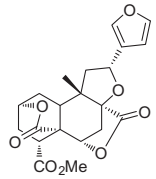
Aulacocarpinolide (**67**) [45]



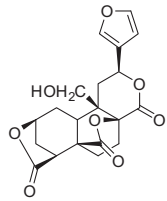
R = H: Aulacocarpin A (**68**) [45]
R = OH: Aulacocarpin B (**69**) [45]



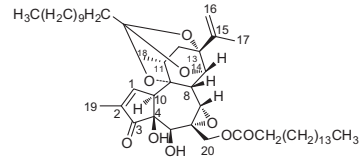
7α-Hydroxytrachyloban-19β-oic acid (**70**) [46]



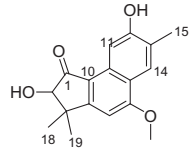
Bafoudiosbulbin A (**71**) [47]



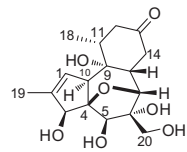
Bafoudiosbulbin B (**72**) [47]



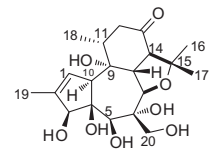
Glabrescin (**73**) [48]



Neoboutonin (**74**) [48]

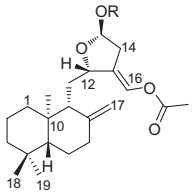


Neoglabrescin A (**75**) [48]

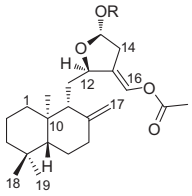


Neoglabrescin B (**76**) [48]

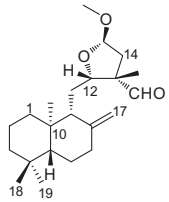
Figure 3.6 Diterpenes isolated as new compound in African medicinal plants.



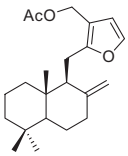
R = $CH(CH_3)_2$:
Turraeanin A (**77**) [49]
R = CH_3:
Turraeanin C (**78**) [49]



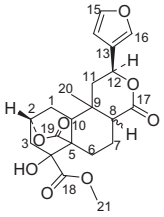
R = $CH(CH_3)_2$: Turraeanin B (**79**) [49]
R = CH_3: Turraeanin D (**80**) [49]



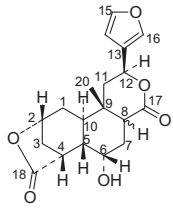
Turraeanin E (**81**) [49]



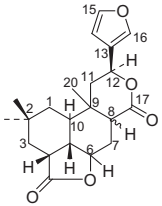
(+)-16-acetoxy-12,
15-epoxylabda-8(17),
12,14-triene (**82**) [49]



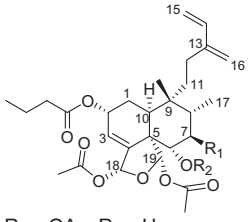
8α-H: Antadiosbulbin A (**83**) [50]
8β-H: Antadiosbulbin B (**84**) [50]



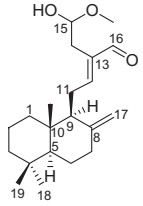
8β-H: 8-epidiosbulbin E (**85**) [50]



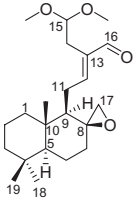
8-Epidiosbulbin G (**86**) [50]



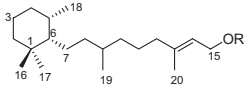
R_1 = OAc; R_2 = H:
caseanigrescen A (**87**) [51]
R_1 = OH; R_2 = H:
caseanigrescen B (**88**) [51]
R_1 = OH; R_2 = Ac:
caseanigrescen C (**89**) [51]
R_1 = α-Ac; R_2 = H:
caseanigrescen D (**90**) [51]



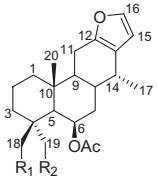
Aframolin A (**91**) [38]



AframolinB (**92**) [38]

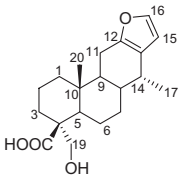


R = H: cassipourol (**93**) [52]
R = Ac: cassipouryl acetate (**94**) [52]

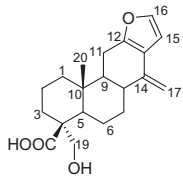


R_1 = OAc; R_2 = OH:
cordylane A (**95**) [53]
R_1 = OH; R_2 = OAc:
cordylane B (**96**) [53]

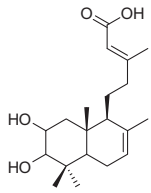
Figure 3.6 (Continued)



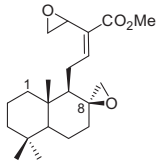
Cordylane C (**97**) [53]



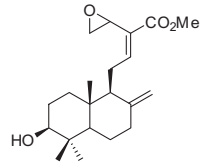
Cordylane D (**98**) [53]



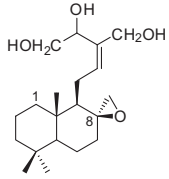
2,18-Dihydroxylabda-7,13(*E*)-dien-15-oic acid (**99**) [54]



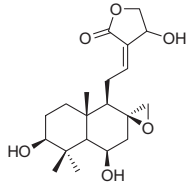
3-Deoxyaulacocarpin A (**100**) [55]



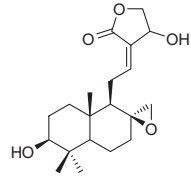
Methyl-14ξ,15-epoxy-3β-hydroxy-8(17),12*E*-labdadien-16-oate (**101**) [55]



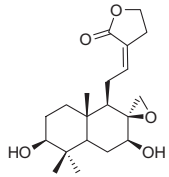
8β,17-Epoxy-12*E*-labdene-14ξ,15,16-triol (**102**) [55]



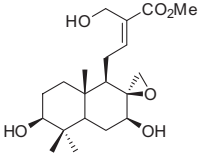
Zambesiacolactone B (**103**) [55]



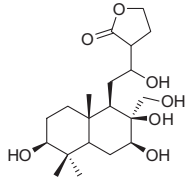
Zambesiacolactone A (**104**) [55]



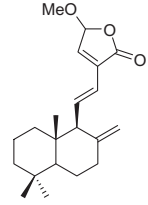
8β,17-Epoxy -3β,7β-dihydroxy-12(*E*)-labden-16,15-olide (**105**) [56]



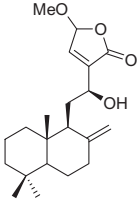
Methyl 8β,17-epoxy-3β,7β,15-trihydroxy-12(*E*)-labden-16-oate (**106**) [56]



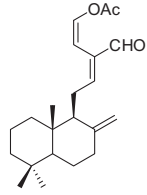
3β,7β,8β,12ξ,17-Pentahydroxylabdan-16,15-olide (**107**) [56]



Sceptrumlabdalactone A (**108**) [57]

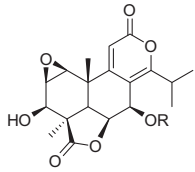


Sceptrumlabdalactone B (**109**) [57]

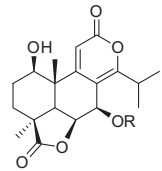


15-Acetoxy-labda-8(17),12*E*,14*Z*-trien-16-al (**110**) [58]

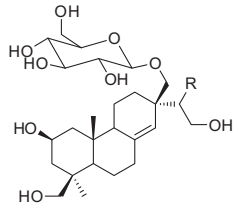
Figure 3.6 (Continued)



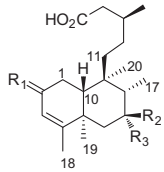
R = α-D-Arabinopyranosyl (1→4)β-D-xylopyranoside
nagilactone C 7-*O*-α-larabinopyranosyl-(1→4)-β-D-xylopyranoside (**111**) [59]
R = β-D-glucopyranosyl (1→4)β-D-xylopyranoside
nagilactone C 7-*O*-β-D-glucopyranosyl-(1→4)-β-D-xylopyranoside (**112**) [59]
R = β-D-xylopyranoside
nagilactone C 7-*O*-β-D-xylopyranoside (**113**) [59]



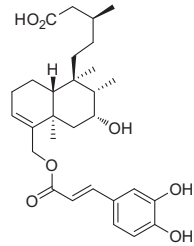
R = α-D-Arabinopyranosyl (1→4) β-D-xylopyranoside
nagilactone A 7-*O*-α-larabinopyranosyl-(1→4)-β-D-xylopyranoside (**114**) [59]



R = α-OH
2β,15*S*,16,17,19-Pentahydroxy-isopimar-8(14)-ene 17-*O*-β-D-glucopyranoside (**115**) [59]
R = β-OH
2β,15*R*,16,17,19-Pentahydroxy-isopimar-8(14)-ene 17-*O*-β-D-glucopyranoside (**116**) [59]

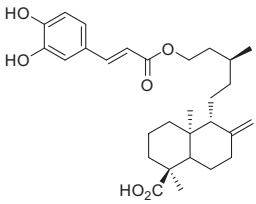


R_1 = H; R_2 = OH; R_3 = H
(13*S*)-*ent*-7β-Hydroxy-3-cleroden-15-oic acid (**117**) [60]
R_1 = O; R_2 = OH; R_3 = H
ent-7β-Hydroxy-2-oxo-3-cleroden-15-oic acid (**118**) [60]
R_1 = O; R_2= R_3 = O
ent-2,7-Dioxo-3-clero-den-15-oic acid (**119**) [60]

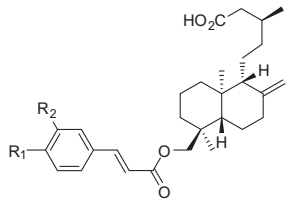


ent-18-(*E*)-Caffeoyloxy-7β-hydroxy-3-cleroden-15-oic acid (**120**) [60]

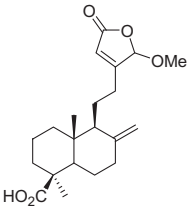
Figure 3.6 (Continued)



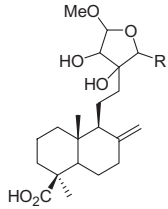
ent-15-(*E*)-Caffeoyloxy-8(17)-labden-18-oic acid (**121**) [60]



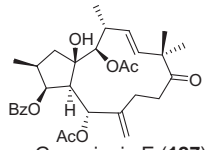
R_1= OH; R_2= H
(13*S*)-*ent*-18-(*E*)-Coumaroyloxy-8(17)-labden-15-oic acid (**122**) [60]
R_1= OH; R_2= OH
ent-18-(*E*)-caffeoyloxy-8(17)-labden-15-oic acid (**123**) [60]



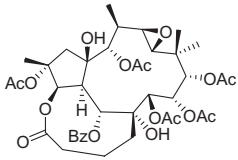
16-Methoxy-labda-8(17),13-diene-15,19-dioic acid butenolide (**124**) [61]



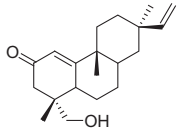
R = α-OH
Conyzanol A (**125**) [61]
R = β-OH



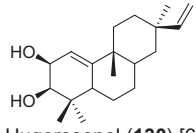
Guyonianin E (**127**) [62]



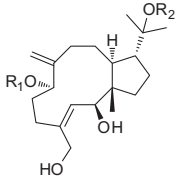
GuyonianinF (**128**) [62]



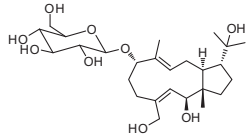
18-Hydroxy-3-deoxyhugorosenone (**129**) [63]



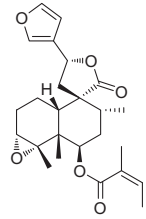
Hugorosenol (**130**) [63]



R_1= β-D-glucopyranosyl; R_2= H;
Chrozophoroside A 1 (**131**) [64]
R_1= H; R_2= β-D-glucopyranosyl
Chrozophoroside A 2 (**132**) [64]

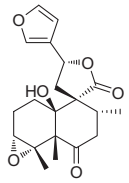


Chrozophoroside B (**133**) [64]

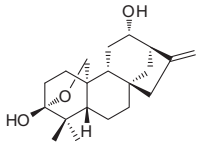


6β-(2-Methylbut-2(*Z*)-enoyl)-3α,4α,15,16-bis-epoxy-8β,10βH-*ent*-cleroda-13(16),14-dien-20,12-olide (**134**) [65]

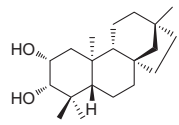
Figure 3.6 (Continued)



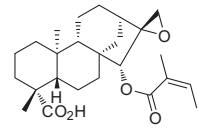
10β-Hydroxy-6-oxo-3α,4α,15,16-bis-epoxy-8βH-cleroda-13 (16),14-dien-20,12-olide (**135**) [65]



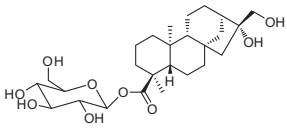
Thecacorine A (**136**) [66]



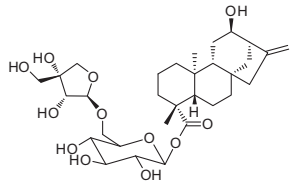
Thecacorin B (**137**) [66]



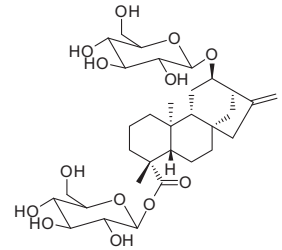
15-Angeloyloxy-16,17-epoxy-19-kauronic acid (**138**) [67]



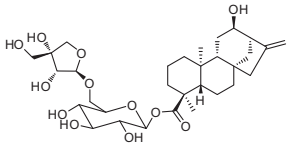
Cussoracoside A (**139**) [68]



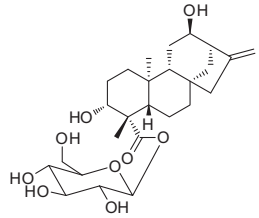
Cussoracoside B (**140**) [68]



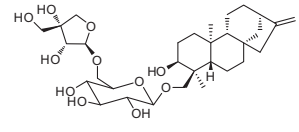
Cussoracoside C (**141**) [68]



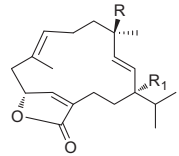
Cussoracoside D (**142**) [68]



Cussoracoside E (**143**) [68]

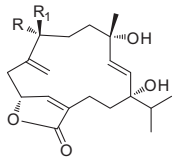


Cussoracoside F (**144**) [68]



R = OMe, R_1 = H
(−)-(1*R**,4*R**,10*R**)-4-Methoxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide (**145**) [69]
R = OMe, R_1 = OH
(−)-(1*S**,4*R**,10*R**)-1-Hydroxy-4-methoxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide (**146**) [69]
R = OH, R_1 = OH
(−)-(1*S**,4*S**,10*R**)-1,4-Dihydroxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide (**147**) [69]

Figure 3.6 (Continued)

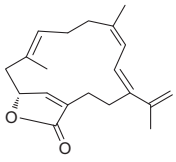


R = OH, R_1 = H

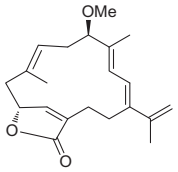
(+)-(1*S**,4*S**,7R*,10*R**)-1,4,7-Trihydroxycembra-2*E*,8(19),11*Z*-trien-20,10-olide (**148**) [69]

R = H, R_1= OH

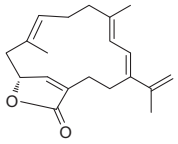
(−)-(1*S**,4*S**,7*S**,10*R**)-1,4,7-Trihydroxycembra-2*E*,8(19),11*Z*-trien-20,10-olide (**149**) [69]



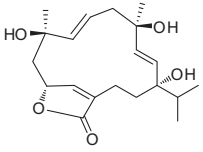
(+)-(10*R**)-Cembra-1*Z*,3*Z*,7*E*,11*Z*,15-pentaen-20,10-olide (**150**) [69]



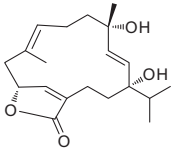
(+)-(5*R**,10*R**)-5-Methoxycembra-1*E*,3*E*,7*E*,11*Z*,15-pentaen-20,10-olide (**151**) [69]



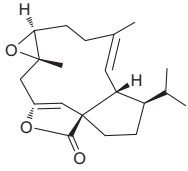
(+)-(10*R**)-Cembra-1*E*,3*E*,7*E*,11*Z*,16-pentaen-20,10-olide (**152**) [69]



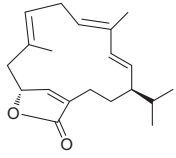
(+)-(1*S**,4*R**,8*S**,10*R**)-1,4,8-Trihydroxycembra-2*E*,6*E*,11*Z*-trien-20,10-olide (**153**) [69]



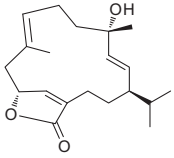
(−)-(1*S**,4*S**,10*R**)-1,4-Dihydroxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide (**154**) [69]



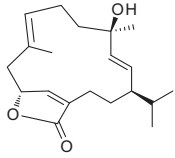
(+)-[1*R**,2*S**,7*S**,8*S**,12*R**]-7,8-Epoxy-2,12-cyclocembra-3*E*,10*Z*-dien-20,10-olide (**155**) [70]



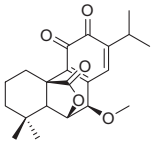
(+)-[1*R**,10*R**]-Cembra-2*E*,4*E*,7*E*,11*Z*-tetraen-20,10-olide (**156**) [70]



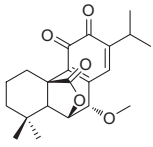
(+)-[1*R**,4*S**,10*R**]-4-Hydroxy cembra-2*E*,7*E*,11*Z*-trien-20,10-olide (**157**) [70]



(-)-[1*R**,4*S**,10*R**]-4-Hydroxy cembra-2*E*,7*E*,11*Z*-trien-20,10-olide (**158**) [70]



Rosmaquinone A (**159**) [71]



Rosmaquinone B (**160**) [71]

Figure 3.6 (Continued)

Table 3.1 New Diterpenes from African Medicinal Plants and Their Physical Properties

Compounds	Type	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Antadiosbulbin A (**83**)	Clerodane	*Dioscorea antaly* Jum. and H. Perrier (Dioscoreaceae) [50]	Madagascar	Tubers	Colorless amorphous solid; [α] −45° (*c* 0.7, $CHCl_3$) [50]
Antadiosbulbin B (**84**)	Clerodane	*D. antaly* Jum. and H. Perrier (Dioscoreaceae) [50]	Madagascar	Tubers	Colorless amorphous solid; [α] −28° (*c* 0.4, $CHCl_3$) [50]
8-Epidiosbulbin E (**85**)	Norclerodane	*D. antaly* Jum. and H. Perrier (Dioscoreaceae) [50]	Madagascar	Tubers	Colorless amorphous solid; [α] −20° (*c* 0.3, $CHCl_3$) [50]
8-Epidiosbulbin G (**86**)	Norclerodane	*D. antaly* Jum. and H. Perrier (Dioscoreaceae) [50]	Madagascar	Tubers	Colorless amorphous solid [50]
Caseanigrescen A (**87**)	Clerodane	*Casearia nigrescens* Tul. (Flacourtiaceae) [51]	Madagascar	Leaves and flowers	Colorless amorphous solid; [α] +59.6° (*c* 0.77, MeOH) [51]
Caseanigrescen B (**88**)	Clerodane	*C. nigrescens* Tul. (Flacourtiaceae) [51]	Madagascar	Leaves and flowers	Colorless amorphous solid; [α] +59.6° (*c* 0.21, MeOH) [51]
Caseanigrescen C (**89**)	Clerodane	*C. nigrescens* Tul. (Flacourtiaceae) [51]	Madagascar	Leaves and flowers	Colorless amorphous solid; [α] +45.3° (*c* 0.57, MeOH) [51]
Caseanigrescen D (**90**)	Clerodane	*C. nigrescens* Tul. (Flacourtiaceae) [51]	Madagascar	Leaves and flowers	Colorless amorphous solid; [α] +33.2° (*c* 0.31, MeOH) [51]
Aframolin A (**91**)	Labdane	*A. longifolius* (Zingiberaceae) [38]	Cameroon	Seeds	Colorless oil; $[\alpha]^{27}_D$ +8.33° (*c* 0.24, $CHCl_3$) [38]
Aframolin B (**91**)	Labdane	*A. longifolius* (Zingiberaceae) [38]	Cameroon	Seeds	Colorless oil; $[\alpha]^{26}_D$ +22.23° (*c* 0.24, $CHCl_3$) [38]
7α-Hydroxytrachyloban-19β-oic acid (**70**)	Trachylobane	*Xylopia aethiopica* A. Rich (Annonaceae) [46]	Cameroon	Bark	Colorless needles; mp 128−129°C; $[\alpha]^{27}_D$ +48° (*c* 1.7, pyridine) [46]

(*Continued*)

Table 3.1 (Continued)

Compounds	Type	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Aulacocarpinolide (**67**)	Labdane	*A. aulacocarpos* (Hook. f.) K. Schum. (Zingiberaceae) [45]	Cameroon	Seeds	Colorless needles; mp 150−151°C; $[\alpha]^{20}_{D}$ + 61.5° (*c* 0.02, MeOH) [45]
Aulacocarpin A (**68**)	Labdane	*A. aulacocarpos* (Hook. f.) K. Schum. (Zingiberaceae) [45]	Cameroon	Seeds	Colorless prisms; mp 102−103°C; $[\alpha]^{20}_{D}$ + 11° (*c* 0.43, MeOH) [45]
Aulacocarpin B (**69**)	Labdane	*A. aulacocarpos* (Hook. f.) K. Schum. (Zingiberaceae) [45]	Cameroon	Seeds	Colorless crystals; mp 140−141°C; $[\alpha]^{20}_{D}$ + 61.5° (*c* 0.7, MeOH) [45]
12,15-Epoxylabda-8(17),12, 14-trien-16-al (**65**)	Labdane	*T. africanus* (Welv. ex CDC) Pellegr. (Meliaceae) [44]	Cameroon	Seeds	Yellowish oil; $[\alpha]^{20}_{D}$ + 35.0° (*c* 1.4, $CHCl_3$) [44]
16-Acetoxy-12(*R*),15-epoxy-15β-hydroxylabda-8(17),13(16)-diene (**66**)	Labdane	*T. africanus* (Welv. ex CDC) Pellegr. (Meliaceae) [44]	Cameroon	Seeds	White crystals; mp 122−124°C; $[\alpha]^{20}_{D}$ − 190° (*c* 1.3, $CHCl_3$) [44]
15-Acetoxy-12-hydroxy-16-methyl-labda-8(17),13*E*-diene (**62**)	Labdane	*T. mannii* Bail. (Meliaceae) [43]	Cameroon	Stem bark	Yellow oil; $[\alpha]^{20}_{D}$ + 5° (*c* 1.0, MeOH) [43]
ent-Labda-8(17),13-dien-15,16-olid-19-oic acid methyl ester (**63**)	Labdane	*T. mannii* Bail. (Meliaceae) [43]	Cameroon	Stem bark	Yellow oil; $[\alpha]^{20}_{D}$ − 28° (*c* 1.0, MeOH) [43]
12-Hydroxy-labda-8(17),13-dien-15,16-olide (**64**)	Labdane	*T. mannii* Bail. (Meliaceae) [43]	Cameroon	Stem bark	Yellow oil; $[\alpha]^{20}_{D}$ + 10° (*c* 1.0, MeOH) [43]
Bafoudiosbulbin A (**71**)	Clerodane	*D. bulbifera* L. var *sativa* (Dioscoreaceae) [47]	Cameroon	Tubers	White needles; mp 252.8°C; $[\alpha]^{21}_{D}$ −64.6° (*c* 0.025, dimethylsulfoxide (DMSO)) [47]
Bafoudiosbulbin B (**72**)	Clerodane	*D. bulbifera* L. var *sativa* (Dioscoreaceae) [47]	Cameroon	Tubers	White crystals; mp 312.9°C; $[\alpha]^{21}_{D}$ + 52° (*c* 0.010, pyridine) [47]
Glabrescin (**73**)	Daphnane		Cameroon	Stem bark	

		N. glabrescens Prain (Euphorbiaceae) [48]			Orange oil; $[\alpha]^{24}_{D}$ + 82° (*c* 0.35, $CHCl_3$) [48]
Neoboutonin (**74**)	Degraded skeleton	*N. glabrescens* Prain (Euphorbiaceae) [48]	Cameroon	Stem bark	Pale yellow crystals; mp 277−278°C; $[\alpha]^{20}_{D}$ − 41° (*c* 0.2, MeOH) [48]
Neoglabrescin A (**75**)	Rhamnofolane	*N. glabrescens* Prain (Euphorbiaceae) [48]	Cameroon	Stem bark	–
Neoglabrescin B (**76**)	Rhamnofolane	*N. glabrescens* Prain (Euphorbiaceae) [48]	Cameroon	Stem bark	–
Turraeanin A (**77**)	Labdane	*T. africanus* (Welv. ex CDC) Pellgr. (Meliaceae) [49]	Cameroon	Stem bark	Yellow oil; $[\alpha]^{27}_{D}$ − 3.6° (*c* 0.55, $CHCl_3$) [49]
Turraeanin B (**79**)	Labdane	*T. africanus* (Welv. ex CDC) Pellgr. (Meliaceae) [49]	Cameroon	Stem bark	–
Turraeanin C (**78**)	Labdane	*T. africanus* (Welv. ex CDC) Pellgr. (Meliaceae) [49]	Cameroon	Stem bark	–
Turraeanin D (**80**)	Labdane	*T. africanus* (Welv. ex CDC) Pellgr. (Meliaceae) [49]	Cameroon	Stem bark	Yellow oil; $[\alpha]^{26}_{D}$ + 103.2° (*c* 0.93, $CHCl_3$) [49]
Turraeanin E (**80**)	Labdane	*T. africanus* (Welv. ex CDC) Pellgr. (Meliaceae) [49]	Cameroon	Stem bark	–
Cassipourol (**93**)	Monocyclic	*C. madagascariensis* DC. (Rhizophoraceae) [52]	Madagascar	Leaves and roots	Colorless liquid; $[\alpha]_{D}$ + 10.9° (*c* 0.042, $CHCl_3$) [52]
Cassipouryl acetate (**94**)	Monocyclic	*C. madagascariensis* DC. (Rhizophoraceae) [52]	Madagascar	Leaves and roots	Colorless liquid; $[\alpha]_{D}$ + 10.6° (*c* 0.034, MeOH) [52]
Cordylane A (**95**)	Cassane	*Cor. madagascariensis* [53]	Madagascar	Fruits	White powder; $[\alpha]^{23}_{D}$ + 17.7° (*c* 0.2, MeOH) [53]
Cordylane B (**96**)	Cassane	*Cor. madagascariensis* [53]	Madagascar	Fruits	White powder; $[\alpha]^{23}_{D}$ + 15.0° (*c* 0.2, MeOH) [53]

(*Continued*)

Table 3.1 (Continued)

Compounds	Type	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Cordylane C (**97**)	Cassane	*Cor. madagascariensis* [53]	Madagascar	Fruits	White powder; $[\alpha]^{23}_{D}$ + 68.0° (*c* 0.1, MeOH) [53]
Cordylane D (**98**)	Cassane	*Cor. madagascariensis* [53]	Madagascar	Fruits	White powder; $[\alpha]^{23}_{D}$ + 40.0° (*c* 0.1, MeOH [53]
3-Deoxyaulacocarpin A (**100**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Cameroon	Seeds	White powder; mp 88−89; $[\alpha]^{20}_{D}$ + 40.3° (*c* 1.14, $CHCl_3$) [55]
Methyl-14ξ,15-epoxy-3b-hydroxy-8 (17),12*E*-labdadien-16-oate (**101**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Cameroon	Seeds	Colorless oil; $[\alpha]^{20}_{D}$ + 28.2° (*c* 1.3, $CHCl_3$) [55]
8β,17-Epoxy-12*E*-labdene-14ξ,15,16-triol (**102**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Cameroon	Seeds	White powder; mp 154−155°C; $[\alpha]^{20}_{D}$ + 13.2° (*c* 1.19, $CHCl_3$) [55]
8β,17-Epoxy-3b,7β-dihydroxy-12(*E*)-labden-16,15-olide (**105**)	Labdane	*A. sceptrum* K. Schum (Zingiberaceae) [56]	Cameroon	Seeds	White needles; mp 139−140°C; $[\alpha]^{22}_{D}$ + 27.9° (*c* 1.24, CH_2Cl_2) [56]
Methyl 8β,17-epoxy-3β,7β,15-trihydroxy-12(*E*)-labden-16-oate (**106**)	Labdane	*A. sceptrum* K. Schum (Zingiberaceae) [56]	Cameroon	Seeds	White crystals; mp 85−86°C; $[\alpha]^{22}_{D}$ + 13.7° (*c* 0.35, CH_2Cl_2) [56]
3β,7β,8β,12ξ,17-Pentahydroxylabdan-16,15-olide (**107**)	Labdane	*A. sceptrum* K. Schum (Zingiberaceae) [56]	Cameroon	Seeds	White powder; mp 189−190°C; $[\alpha]^{22}_{D}$ − 7.14° (*c* 0.49, MeOH) [56]
Sceptrumlabdalactone A (**108**)	Labdane	*A. sceptrum* K. Schum (Zingiberaceae) [57]	Ivory Coast	Rhizomes	Yellow dark oil; $[\alpha]^{28}_{D}$ + 24.9° (*c* 0.41, $CHCl_3$) [57]
Sceptrumlabdalactone B (**109**)	Labdane	*A. sceptrum* K. Schum (Zingiberaceae) [57]	Ivory Coast	Rhizomes	Colorless oil; $[\alpha]^{28}_{D}$ + 17.4° (*c* 0.40, $CHCl_3$) [57]
(13*S*)-*ent*-7β-Hydroxy-3-cleroden-15-oic acid (**117**)	Clerodane	*N.sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 32.2° (*c* 0.4, $CHCl_3$) [60]

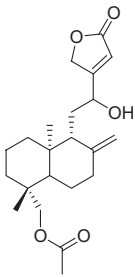
ent-7β-Hydroxy-2-oxo-3-cleroden-15-oic acid (**118**)	Clerodane	*N. sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 30° (*c* 0.195, $CHCl_3$) [60]
ent-2,7-Dioxo-3-clero-den-15-oic acid (**119**)	Clerodane	*N. sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 10° (*c* 0.215, $CHCl_3$) [60]
ent-18-(*E*)-Caffeoyloxy-7β-hydroxy-3-cleroden-15-oic acid (**120**)	Clerodane	*N. sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 29° (*c* 0.165, MeOH) [60]
(13*S*)-*ent*-18-(*E*)-Coumaroyloxy-8(17)-labden-15-oic acid (**122**)	Labdane	*N. sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 2.4° (*c* 0.365, MeOH) [60]
ent-18-(*E*)-Caffeoyloxy-8(17)-labden-15-oic acid (**123**)	Labdane	*N. sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 8.9° (*c* 0.373, MeOH) [60]
ent-15-(*E*)-Caffeoyloxy-8(17)-labden-18-oic acid (**121**)	Labdane	*N. sphaerocephala* Baker (Loganiaceae) [60]	Madagascar	Leaves	Colorless oil; $[\alpha]^{20}_{D}$ − 21° (*c* 0.21, $CHCl_3$) [60]
Guyonianin E (**127**)	Jatrophane	*E. guyoniana* Boiss. and Reut. (Euphorbiaceae) [61]	Algeria	Aerial parts	Oily material; $[\alpha]_{D}$ − 28° (*c* 0.11, $CHCl_3$) [61]
Guyonianin F (**128**)	Jatrophane	*E. guyoniana* Boiss. and Reut. (Euphorbiaceae) [61]	Algeria	Aerial parts	Oily material; $[\alpha]_{D}$ − 30° (*c* 0.86, $CHCl_3$ [61]

Table 3.2 Biologically Active Diterpene from African Medicinal Plants

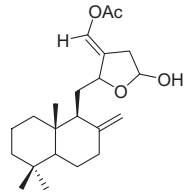
Compounds	Type	Plants (Family)	Pharmacological Activities
Labda-8(17),12(*E*)-diene-15,16-dial (**55**)	Labdane	*A. longifolius* (Zingiberaceae) [38]	Antimicrobial, no effect [38]
Aframodial (**163**)	Labdane	*A. aulacocarpos* (Hook. f.) K. Schum (Zingiberaceae) [45] *A. longifolius* (Zingiberaceae) [38]	Antimicrobial [38]
ent-Kaur-16-en-19-oic acid (**168**)	Kaurene	*S. umbellifera* (Araliaceae) [40]	Antimalarial [40]
19-Acetoxy-*ent*-labda-8 (17),13-dien-15,16-olide (**161**)	Labdane	*T. mannii* Bail. (Meliaceae) [43]	–
16-Acetoxy-12,15-epoxy-15β-hydroxy-labda-8 (17),13(16)-diene (**162**)	Labdane	*T. mannii* Bail. (Meliaceae) [43]	–
Montanin (**169**)	Daphnane	*N. glabrescens* Prain (Euphorbiaceae) [48]	–
Baliospermin (**170**)	Tigliane	*N. glabrescens* Prain (Euphorbiaceae) [48]	–
Aulacocarpin A (**68**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Antiplasmodial [55]
Aulacocarpin B (**69**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Antiplasmodial [55]
Galanolactone (**171**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Antiplasmodial [55]
Zambesiacolactone A (**103**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Antiplasmodial [55]
Zambesiacolactone B (**104**)	Labdane	*A. zambesiacum* (Baker) K. Schum [55]	Antiplasmodial [55]
5,7,14-Triacetoxy-3-benzoyloxy-15-hydroxy-9-oxojatropha-6(17),11*E*-diene (**172**)	Jatrophane	*E. guyoniana* Boiss. and Reut. (Euphorbiaceae) [61]	Cytotoxic [61]

and *M. miehei* (MIC of 50 μg/mL for the three compounds) [45]. Turraeanin E (**81**), isolated from the Cameroonian plant *Turraeanthus africanus*, showed antibacterial activities against *S. aureus* and methycillin-resistant *S. aureus*, with a MIC value of 5 μg/mL [49].

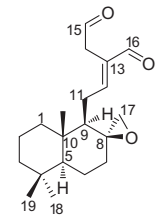
The clerodane diterpenoids bafoudiosbulbins A and B (**71**, **72**), isolated from the tubers of *D. bulbifera* harvested in Cameroon, displayed moderate to low antimicrobial activities against *Pseudomonas aeruginosa* (MIC of 50 μg/mL and 25 μg/mL, respectively), *Salmonella typhi* (MIC of 50 μg/mL for the two compounds), *Salmonella paratyphi A* (MIC of 50 μg/mL and 25 μg/mL, respectively), and *Salmonella paratyphi B* (MIC of 50 μg/mL for the two compounds) [47].



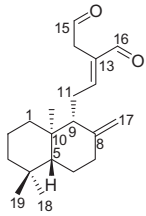
19-Acetoxy-*ent*-labda-8(17),13-dien-15,16-olide (**161**) [43]



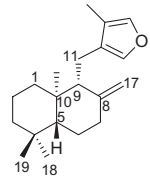
16-Acetoxy-12,15-epoxy-15β-hydroxy-labda-8(17),13(16)-diene (**162**) [43]



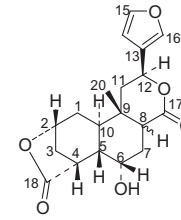
Aframodial (**163**) [45]



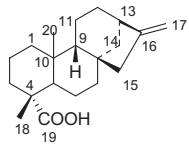
ent-Labda-8(17),12(*E*)-diene-15,16-dial (**164**) [49]



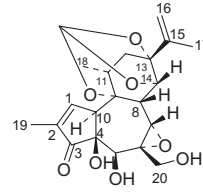
Pumiloxide (**165**) [49]



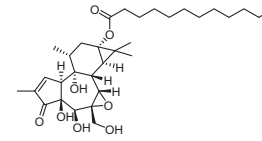
8α-H:
Diosbulbin E (**166**) [50]
8β-H
8-Epidiosbulbin G (167) [50]



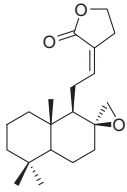
ent-Kaur-16-en-19-oic acid (**168**) [40]



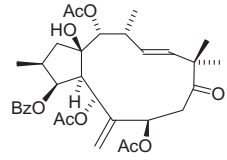
Montanin (**169**) [48]



Baliospermin (**170**) [48]



Galanolactone (**171**) [55]



5,7,14-Triacetoxy-3-benzoyloxy-15-hydroxy-9-oxojatropha-6(17),11*E*-diene (**172**) [62]

Figure 3.7 Other known diterpenes identified in African plants.

ent-Kaur-16-en-19-oic acid (**57**), isolated from the South African medicinal plant *Schefflera umbellifera*, showed antimalarial activity against a chloroquine-susceptible strain (D10) of *Plasmodium falciparum* (IC_{50} of 32.2 μM) [40]. The labdane diterpenoids isolated from the seeds of the Cameroonian medicinal plant

Aframomum zambesiacum, namely, aulacocarpins A (IC_{50} of 13.68 μM) and B (IC_{50} of 21.10 μM) (**68**, **69**) [45], 3-deoxyaulacocarpin A (IC_{50} of 4.97 μM), methyl-14ξ,15-epoxy-3b-hydroxy-8(17),12*E*-labdadien-16-oate (IC_{50} of 39.94 μM), galanolactone (IC_{50} of 92.79 μM) (**171**), and zambesiacolactones A (IC_{50} of 17.20 μM) and B (IC_{50} of 15.51 μM) (**103**, **104**), displayed antiplasmodial activity against the FCB1 line of *P. falciparum* [55]. The clerodane diterpenoids (13*S*)-*ent*-7β-hydroxy-3-cleroden-15-oic acid (**117**) (IC_{50} of 14.6 μM), *ent*-7β-hydroxy-2-oxo-3-cleroden-15-oic acid (**118**) (IC_{50} of 4.3 μM), *ent*-2,7-dioxo-3-clero-den-15-oic acid (**119**) (IC_{50} of 8 μM), and *ent*-18-(*E*)-caffeoyloxy-7β-hydroxy-3-cleroden-15-oic acid (**120**) (IC_{50} of 7.3 μM), as well as the labdane diterpenes (13*S*)-*ent*-18-(*E*)-coumaroyloxy-8(17)-labden-15-oic acid (IC_{50} of 11.4 μM), *ent*-18-(*E*)-caffeoyloxy-8(17)-labden-15-oic acid (**123**) (IC_{50} of 21 μM), and *ent*-15-(*E*)-caffeoyloxy-8(17)-labden-18-oic acid (**121**) (IC_{50} of 16 μM), isolated from leaves of *Nuxia sphaerocephala* harvested in Madagascar, showed antiplasmodial activity against *P. falciparum* [60].

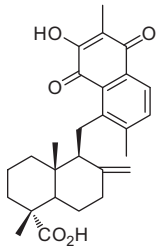
Sceptrumlabdalactone A (**108**) and sceptrumlabdalactone B (**109**), isolated from the Ivorian plant *Aframomum sceptrum*, were active against *Trypanosoma brucei brucei*, with the respective IC_{50} values of 204 and 35.7 μM, and against the promastigotes of *Leishmania donovani* (IC_{50} of 25 and 5.7 μM, respectively) [57].

3.4.3 Cytotoxicity of Diterpenes Identified in African Medicinal Plants

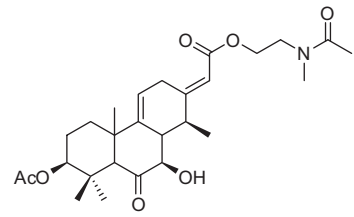
The anticancer potential of diterpenoids has been documented, with well-known and hit compounds involved in cancer therapy. Thus, caseanigrescens (**87**−**90**) A (IC_{50} of 1.4 μM), B (IC_{50} of 0.83 μM), C (IC_{50} of 1.0 μM), and D (IC_{50} of 1.0 μM) displayed cytotoxicity against the A2780 human cell line [51]. Aulacocarpinolide (**67**) (IC_{50} of 12.5 μg/mL) and aulacocarpin B (**69**) (IC_{50} of 25 μg/mL) were found to be cytotoxic toward murine leukemia L1210 cells [45]. The monocyclic diterpenes cassipourol (**93**) and cassipouryl acetate (**94**), isolated from *Cassipourea madagascariensis* harvested in Madagascar, displayed good cytotoxic activity against A2780 cells, with IC_{50} values of 2.4 and 2.8 μg/mL, respectively [52]. The cassane diterpenoids cordylane A (**95**) and B (**96**), isolated from another species from Madagascar, *Cordyla madagascariensis*, showed antiproliferative activities, with IC_{50} values of 10 and 36 μM, respectively [53]. The jatrophane diterpenes, isolated from the Algerian plant *E. guyoniana*, 5,7,14-triacetoxy-3-benzoyloxy-15-hydroxy-9-oxojatropha-6(17),11*E*-diene (**172**) (IC_{50} of 35 μM) and guyonianin E (**127**) and F (**128**) (IC_{50} of 70 and 100 μM, respectively), were found to be cytotoxic against human embryonic kidney 293 (HEK293) cells [61].

3.4.4 Other Diterpenoids from African Medicinal Plants

The phytochemical works performed on medicinal plants from Africa have led to new molecules of diverse known diterpenes. They belong to different skeletons, including labdane, *ent*-labdane, *ent*-clerodane, *ent*-kaurane, daphnane, and jatrophane (Figure 3.7).



Pycnanthuquinone C (**173**) [73]



Erythrosuavine (**174**) [74]

Figure 3.8 Particluar diterpenes identified in African plants.

Particular diterpenoids were also identified in African plants (Figure 3.8). Pycnanthuquinone C is a naphtoquinone terpenoid with a decalin moiety similar to labd-8(17)-ene. This compound was isolated from *Pycnanthus angolensis* harvested from Cameroon. Likewise, a diterpenic alkaloid was obtained from *Erythrophleum suaveolens*, which is a plant from the same country. This compound has a cassane skeleton with three additional fragments.

3.5 Conclusions

Diterpenoids, as with many other classes of natural products, are widespread in plants, although few of them show significant expected biological activity. These compounds are grouped within jatrophane, labdane, clerodane, cembrane, daphnane, cassane, and trachylobane skeletons. Up to now, limited numbers of these secondary metabolites have been introduced in the market as pharmaceutical drugs or are undergoing clinical trial phases. However, these are not directly from African medicinal plants but from species growing elsewhere. Some of these plants have family members growing in Africa, representing a great source of bioactive compounds. The genus *Taxus* is widespread around the world and produces one of the chemotherapy drugs, namely, taxol, used to treat cancer. From this molecule, several derivatives have been developed, such as milataxel and tesetaxel, for the treatment of colorectal neoplasms and breast cancer, respectively [74]. Another diterpene, ingenol, is under the clinical development against basal cell carcinomas, while its semisynthetic derivative ingenol meburate is in a phase-three trial for treatment of actinis keratosis [74]. In addition to the aforementioned, there are other diterpenic metabolites from plant and marine sources in the way of drug delivery. Recent concerned compounds include PG490-88, prostatin, 4-acetoxydictylolactone, dictyolide A, dictyolide B, nordictyolide, and crenuladial [75].

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4 Triterpenes and Steroids from the Medicinal Plants of Africa

Louis Pergaud Sandjo[a] *and Victor Kuete*[b]

[a]Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon, [b]Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon

4.1 Introduction

Triterpenoids constitute a wide, biologically interesting group of terpenoids and include a large structural diversity of secondary metabolites with more than 100 carbon skeletons (Figure 4.1) identified from terrestrial and marine living organisms [11]. This class of natural products, including triterpenes, steroids, limonoids, quassinoids, and triterpenoidal and steroidal saponins, consists of over 30,000 compounds isolated and identified [12]. Most of triterpenic skeletons are tetracycles, containing three six-membered and one five-membered rings, and pentacycles, either with four six-membered and one five-membered rings or five six-membered rings. However, acyclic, mono-, di-, tri-, and hexacyclic scaffolds (Figure 4.1) have also been isolated and identified from natural sources. The term triterpene refers to three monoterpenes and consequently to 30 carbons grouped in six isoprenyl units (**1**). Depending on the plant species, secondary metabolites belonging to this family are mostly stocked in the mitochondria, microsomes, or chloroplasts of cells [13]. These components and their glycosylated homologs play crucial roles in protecting the plant against insects, fungi, and bacteria [14]. Moreover, many tetranortriterpenes derived from apotirucallane skeletons (**29**), by losing an isobutyl moiety, have proved their antifeeding and antiherbivore activities [15,16].

Steroids possess a fully or partially reduced cyclopenta[a]phenanthrene scaffold, sometimes bearing methyl groups at C-10 and C-13 (Figure 4.2). However, the backbone of the side chain at C-17, its length, and the stereochemistry of some of its chiral centers lead to different steroid skeletons (Figure 4.3).

Since the discovery of limonin in 1960 [17], many skeletons of natural limonoids have been characterized. These secondary metabolites derive biosynthetically from the lost of isobutyl moiety in the side chain of apotirucallane, followed by oxidations, intramolecular rearrangements, and ring degradations. The occurrence of both the last structural modifications affords diverse limonoid backbones with 26 carbons, justifying why this class of compounds is called tetranortriterpenoids [18] (Figure 4.4).

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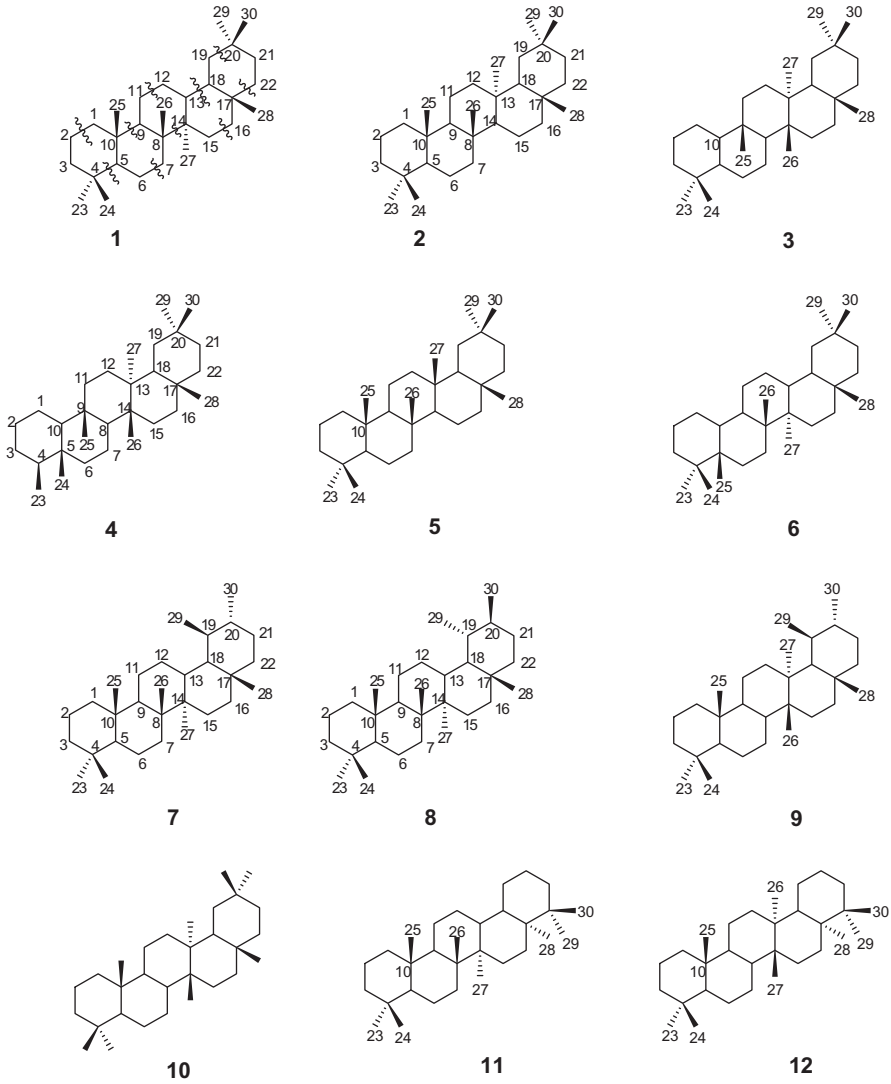
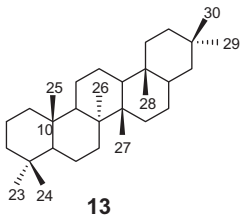


Figure 4.1 Glutinane (**3**) [1], imusopane (**6**) [2], bauerane (**9**) [3], dubosane (**17**) [4], canarene (**26**) [5], cycloartane (**34**) [6], tetranortriterpene (**35**) [7], polypodane (**36**) [8], malabaricane (**37**) [9], podiodane (**38**) [10], and some skeletons of triterpenes: oleanane (**1**), taraxerane (**2**), friedelane (**4**), glutane (**5**), ursane (**7**), taraxastane (**8**), multiflorane (**10**), kairatane (**11**), swertane (**12**), stictane (**13**), gammacerane (**14**), onocerane (**15**), serratane (**16**), lupane (**18**), lactucane (**19**), hopane (**20**), fernane (**21**), pteronane (**22**), filicane (**23**), adianane (**24**), arborane (**25**), dammarane (**27**), lanostane (**28**), apotirucallane (**29**), cucurbitane (**30**), euphane (**31**), tirucallane (**32**), and protostane (**33**) [11].



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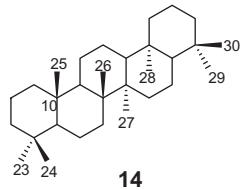

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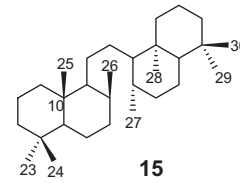

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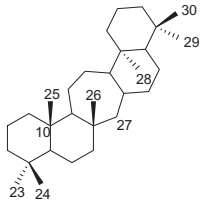

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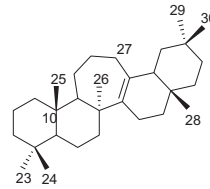

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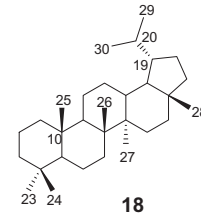

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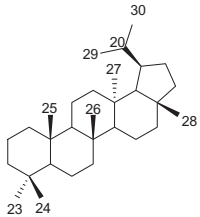

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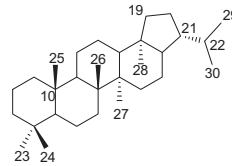

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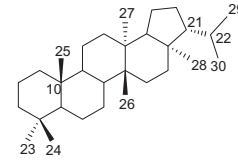

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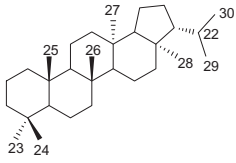

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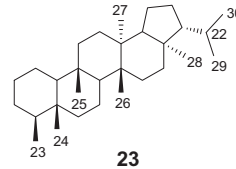

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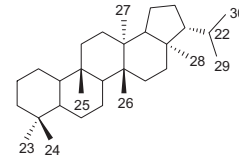

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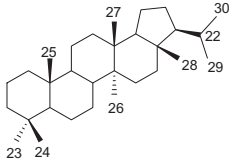

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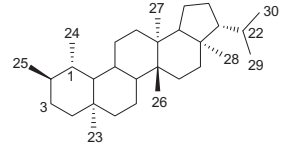

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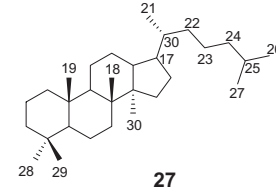

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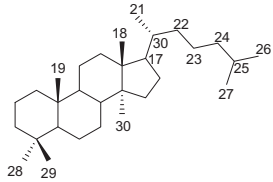

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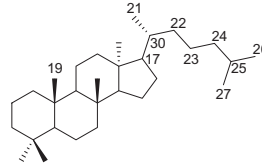

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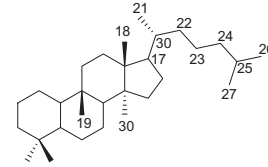

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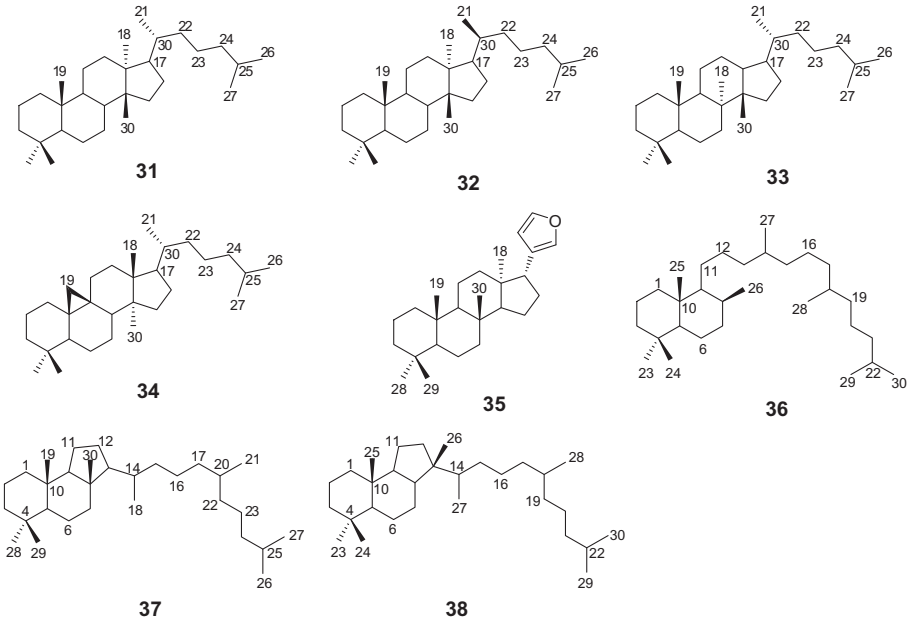

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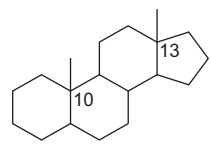


Figure 4.2 General backbone of steroids.

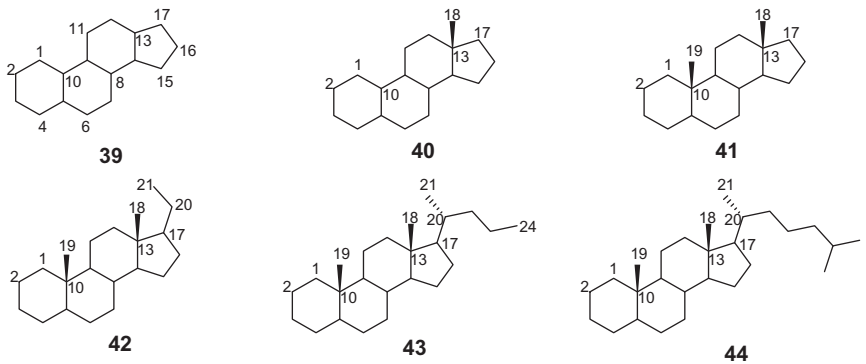


Figure 4.3 Some steroid skeletons: gonane (**39**), estrane (**40**), androstane (**41**), pregnane (**42**), cholane (**43**), cholestane (**44**), ergostane (**45**), campestane (**46**), poriferastane (**47**), stigmastane (**48**), gorgostane (**49**), cardanolide (**50**), bufanolide (**51**), spirostane (**52**), and furostane (**53**) [17].

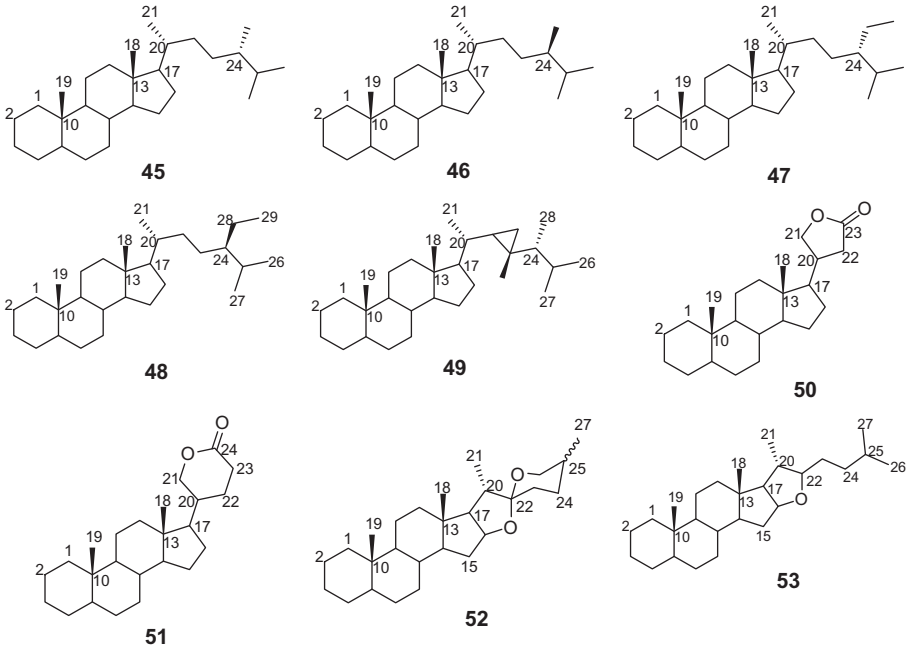


Figure 4.3 (Continued)

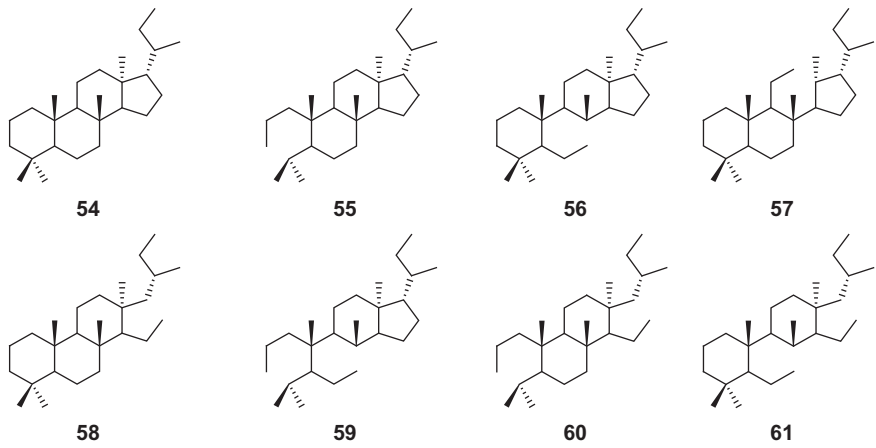


Figure 4.4 Some limonoid skeletons (**54**–**71**) from the plant kingdom.

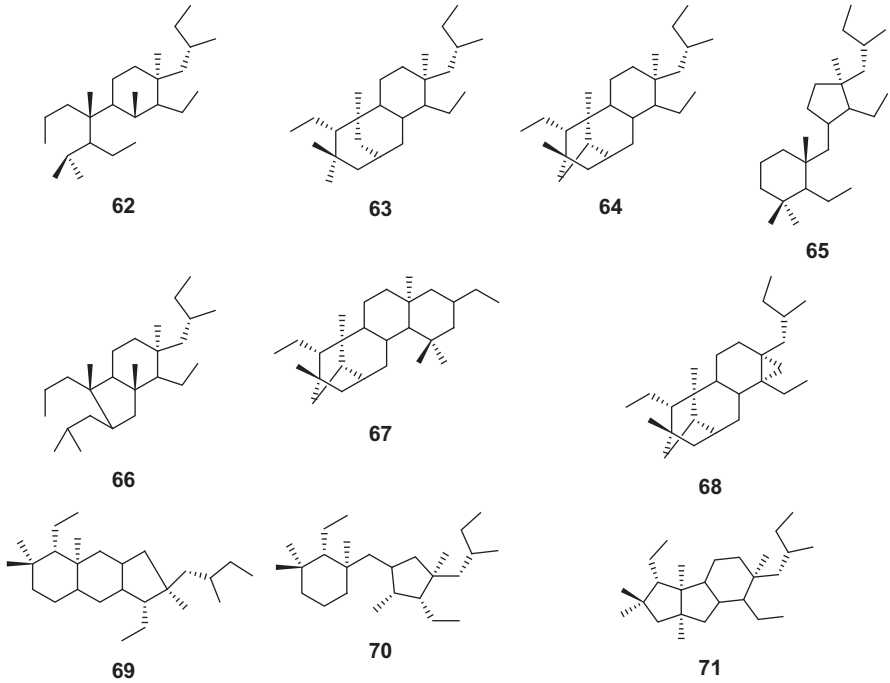


Figure 4.4 (Continued)

4.2 Biosynthesis and Structural Diversity

The biosynthesis pathway of triterpenes and sterols involves isoprenoids, isopentenyl diphosphate (IPP), and dimethylallyl diphosphate forming the precursor (squalene) [19]. However, several theories have proposed three precursors, namely mevalonate [19], deoxyxylulose [20], and amino acids [21] for IPP formation. Previous results obtained from experience with labeled compounds revealed mevalonate to be the preferential precursor for the biosynthesis of sterol and pentacyclic triterpenes [22,23]. Furthermore, many studies dealing with triterpenoid biosynthesis in plants suggested the requirement of different enzymes (lanostane synthase, cycloartane synthase, lupeol synthase, etc.) to catalyze the synthesis of different types of these secondary metabolites [24,25].

Despite the large number of triterpene skeletons, there are still new scaffolds, such as dubosane [4] and canarene [5], which were isolated from plants; their biosyntheses are not yet well established, although postulates have been proposed in order to highlight them [4,5]. Steroids are biosynthetically derived from triterpenes and are characterized by the lack of methyls **28** and **29** in the lanostane or cycloartane backbones [25,26]. These tetracyclic triterpenes are both intermediates leading to cholesterol after the effect of demethylases and the opening of the cyclopropane

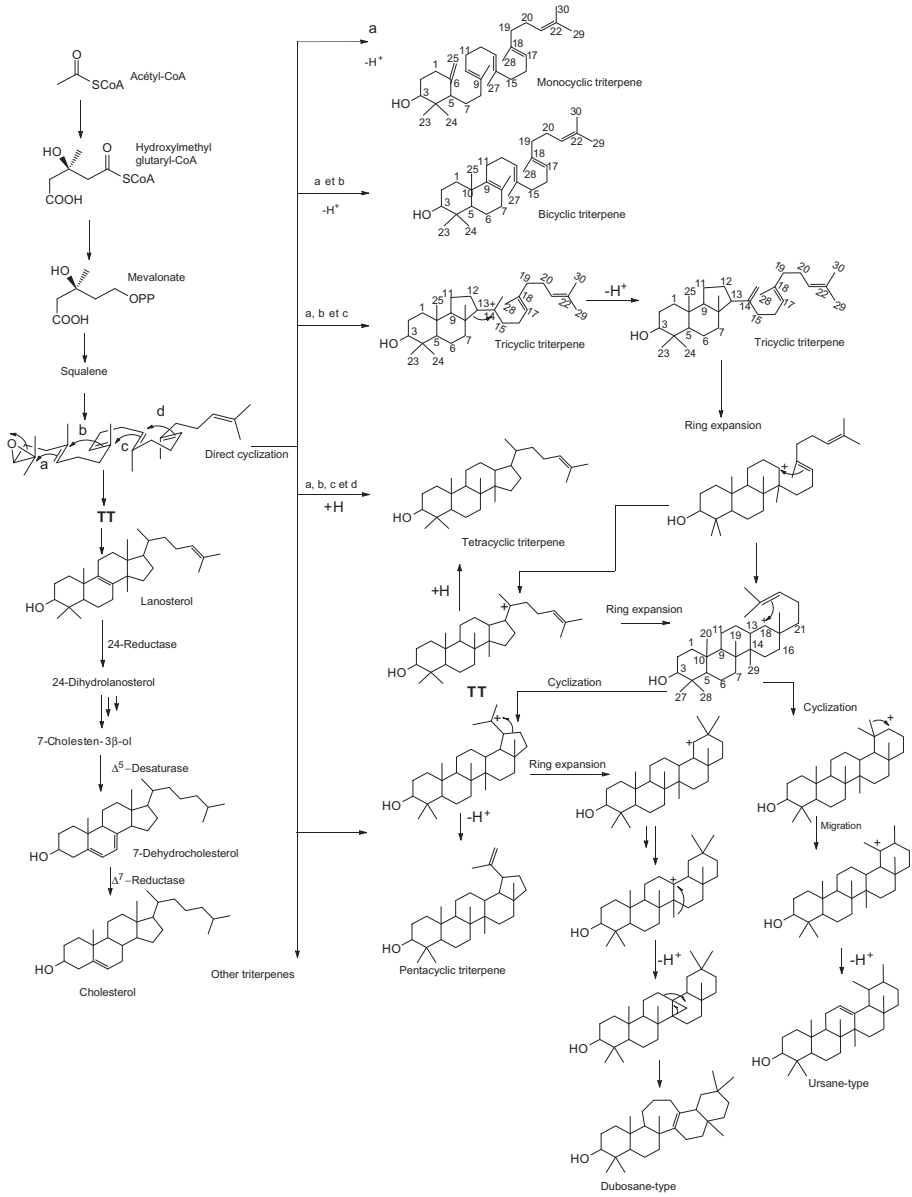


Figure 4.5 Biosynthesis pathway of some triterpenes and steroids.

ring in the cycloartane skeleton [26]. Plants can polyhydroxylate and oxidize terpenoid cores with hydroxylase and oxidase, respectively. Mono- or polyglycosylation can further occur under the effect of one or more specific glycosyltransferases to afford a saponin [27] (Figure 4.5).

4.3 Phytochemical Detection of Triterpenoids and NMR Identification

4.3.1 Phytochemical Identification

This identification is based on the use of chemical reactions. Thus, steroids are easily detected in a crude extract by a colored test obtained by the Liebermann−Burchard reaction, developed by two research groups, Liebermann in 1885 and Burchard in 1889 [28]. This colorimetric method was used to show the presence of cholesterol in the blood, and both research groups used similar treatments for the cholesterol test; the difference in their test process consists in the manner of the sterol extraction from the blood. The test is performed by dissolving in 10 mL of chloroform, 1 mg of the extract, 2 mL of acetic anhydride, and (slowly) 0.2 mL of concentrated sulfuric acid [28]. Steroids are revealed by a positive color which changes from violet to blue and grass green [29], whereas triterpenes give a red color after the same test [30]. Moreover, steroidal and triterpenic saponins need, in addition to the latter reaction, the test of Molisch to be detected [31]. This test involves the Molisch reagent (α-naphtol: ethanol in a ratio of 5:95) to be mixed with a small amount of extract or compound in a sloping test tube; a solution of concentrated sulfuric acid is added slowly without mixing to form a layer. A positive response to the test is indicated by the appearance of a violet ring between the tested phase and the solution of acid [31].

4.3.2 NMR Identification

^{1}H and ^{13}C NMR spectra of sterols and triterpenes are crucial for the determination of their skeleton. In general, the chemical shifts of olefinic carbons revealed on ^{13}C NMR are used. This information is completed by the number of methyl groups observed on the ^{1}H NMR spectrum. Therefore, for the olean-12-ene type, the chemical shifts of the double bond C_{12} and C_{13} are around δ 122.0 and 144.0, respectively, while those of its isomer urs-12-ene are around δ 125.0 and 139.0, respectively, for the same carbons [32]. These olefinic carbon shifts differ from one class of triterpenoid to another depending on their position in the skeleton (Table 4.1). The proton multiplicity of the oxymethine at C_3 is also indicative to distinguish a triterpene and a steroid which is a doublet of a doublet around 3.50 ppm and multiplet in the last one.

Table 4.1 ^{13}C Shifts of Double Bond Carbons in Some Triterpenoid Scaffolds

Scaffold	δ (ppm)		Reference
Lup-20(29)-ene	C_{29}: 109.0	C_{20}: 150.0	[32]
Taraxer-14-ene	C_{14}: 158.1	C_{15}: 117.0	
Taraxast-20(30)-ene	C_{20}: 154.6	C_{30}: 107.2	
Serrat-14-ene	C_{14}: 138.2	C_{15}: 122.8	
Kairat-12-ene	C_{12}: 117.5	C_{13}: 146.7	
Pseudocaraxasterol	C_{20}: 139.8	C_{21}: 118.9	
Cholest-5-ene	C_5: 141.4	C_6: 122.2	[33]

4.4 Nomenclature of Triterpenoids

The concept of triterpenoid nomenclature was introduced by Allard and Ourisson [34]. The nomenclature of triterpenoids is based on about seven rules. The first rule is to determine its name according to its skeleton. Thus, the main name comes from the class of compounds (Figures 4.1 and 4.3). The number of the carbons in the backbone forms the second rule. These numberings are used to define the position of substituents or functionalities, which are added as prefixes or suffixes to the main name. Their stereochemistry inside the core is highlighted by employing Greek letters α and β (Figure 4.6).

The third rule specifies the prefix to add to the main name when one or more methyl groups are missing as well as when there are one or more additional methyl groups in the triterpenoid core. If one, two, three, or four methyl groups are missing, the prefix nor, bisnor, trisnor, and tetrakisnor, respectively, will directly precede the main name along with the position of the missing methyl (**76**). If there are one, two, three, or four more methyl groups in the triterpenoid structure, the prefix homo, bishomo, trishomo, or tetrakishomo, respectively, and their position will precede the main name (**77**). The prefix "nor" is also used if one of the rings is shrunk by abstraction of a carbon. Moreover, the letter given to the ring and the position of the missing carbon are précised (Figure 4.7). However, there are certain points to be respected:

- Generally, the number of the carbon bearing the lower numbering is given for the name if a methylene group is subtracted (**78**) (Figure 4.8).
- If methyl groups were attached to a subtracted carbon, then the lowest number should be given to missing carbon (**79**).

The constriction of the ring and the migration of some hydrocarbon groups can occur in these polycyclic metabolites; therefore, the letter assigned to the modified ring and the prefix "neo" are used for the name of the structure (**80**).

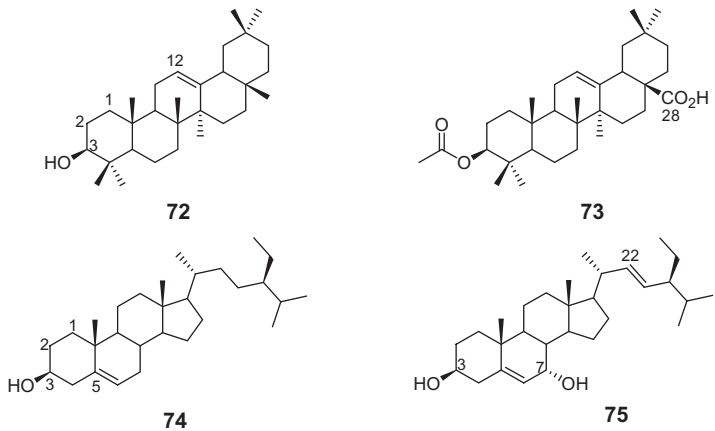


Figure 4.6 How to name triterpenoids: olean-12-en-3β-ol (**72**); 3β-acetoxy-olean-12-en-28-oic acid (**73**); stigmat-5-en-3β-ol (**74**); and (22*E*,24*S*)-stigmasta-5,22-dien-3β,7α-diol (**75**).

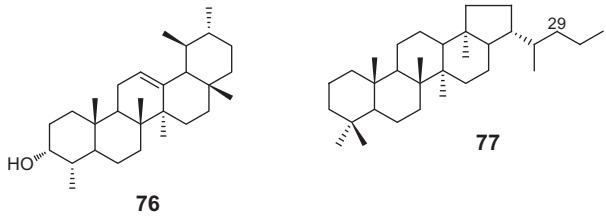


Figure 4.7 Illustration of how to name triterpenoids: 24-nor-urs-12-en-3α-ol (**76**) and 29-bishomo-hopane (**77**).

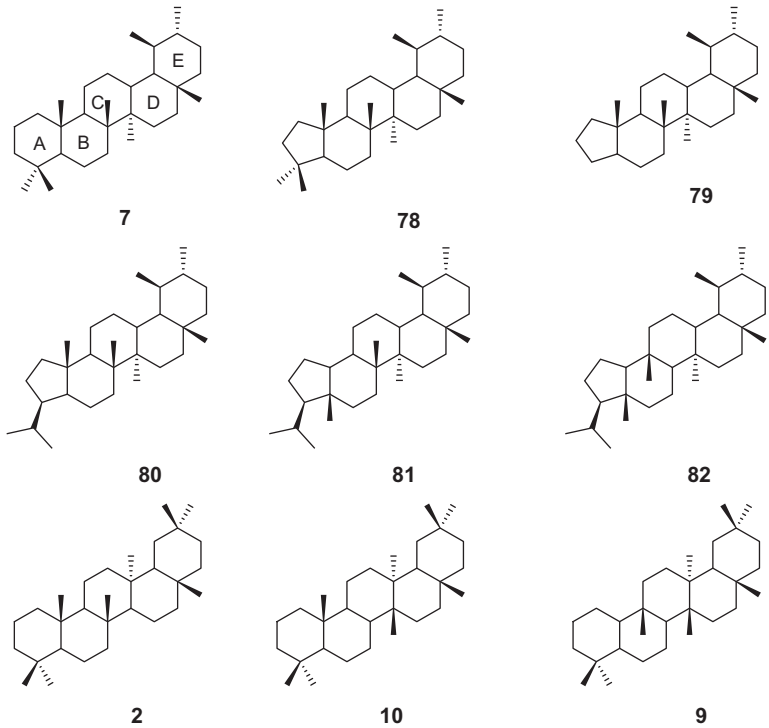
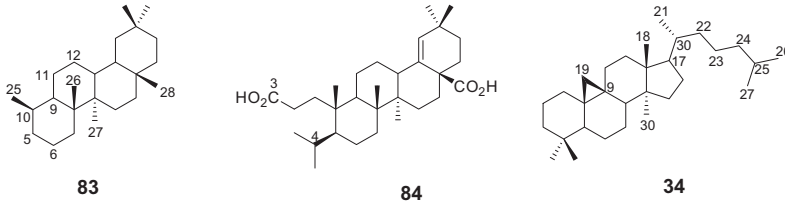


Figure 4.8 Skeletons (**2**, **9**, **10**, **80**−**82**) used for the nomenclature: ursane (**7**), A(1)-nor-ursane (**78**), 23,24-dinor-A(4)-ursane (**79**), A-neo-ursane (**80**), A:B-neo-ursane (**81**), A:C-neo-ursane (**82**), D-friedo-oleane or taraxerane (**2**), D:C-friedo-oleane or multifloran (**10**), and D:B-friedo-oleane or bauerane (**9**).

If the modification of a ring occurs with a migration of a methyl group shared by two rings, the letters assigned to the rings will precede the prefix neo in the name of the molecule (**81** and **82**). The prefix friedo is employed when one of the angular methyl groups migrates from one position to another and the whole



83 84 34

Figure 4.9 Further skeletons useful for the nomenclature: des-A-oleanane (**83**); 3,4-seco-olean-18-ene-3,28-dioic acid (**84**); and 9β,19-cyclolanostane or cycloartane (**34**).

polycyclic scaffold is conserved. This prefix is preceded by the letter assigned to the ring in which the migration took place. However, this prefix is not used for the nomenclature of tetracyclic triterpenes.

The prefix des followed by the letter given to the rings is used when rings A or D are missing. The numbering of carbons is conserved (**83**) (Figure 4.9). The term seco is indicative of when a sigma bond between two carbons contained in a ring is cleaved. This prefix is preceded by the numbers assigned to the carbons involved in the cleavage (**84**) [35].

The skeleton can be modified by further cyclization; therefore, the term cyclo will be employed for the nomenclature of the triterpenoids, and the term assigned is preceded by the numbering of the carbon involved in the new bond (**34**).

4.5 New Triterpenoids Isolated from African Medicinal Plants

4.5.1 Triterpenes Isolated from African Medicinal Plants

Various triterpenoid cores are presented below, including acyclic, tetracyclic, pentacyclic, and hexacyclic triterpenoids. Figure 4.10 summarizes the main new triterpenoid structures identified in African medicinal plants. Some of these compounds are structurally interesting, such as acyclic squalene derivatives (sapelenins G−J, **185**−**188**), isolated from *Entandrophragma cylindricum*, a Cameroonian medicinal plant [70]. Duboscic acid (**89**) and canarene (**98**) are two unprecedented scaffolds obtained from two Cameroonian medicinal plants, *Duboscia macrocarpa* [4] and *Canarium schweinfurthii*, respectively [5]. Further, particular secondary metabolites, namely caloncobalactones A and B (**94** and **95**) [39], glaucartanoic acid B (**104**) [43], donellanic acids A−C (**128**−**130**) [52], and 16,22-diacetyl-2,26-dihydroxy-29-nor-24-methyl-19(9→1)-abeocycloart-9(11),24(24a)-dien-3,23-dione (**167**) [58], have been obtained from Cameroonian medicinal plants *Caloncoba glauca*, *Donella ubanguiensis*, and *Neoboutonia melleri*. As commonly found in the literature, the remaining compounds were isolated as fatty acyls or phenolic esters of triterpenoids as well as polyhydroxylated and oxidized triterpenoids.

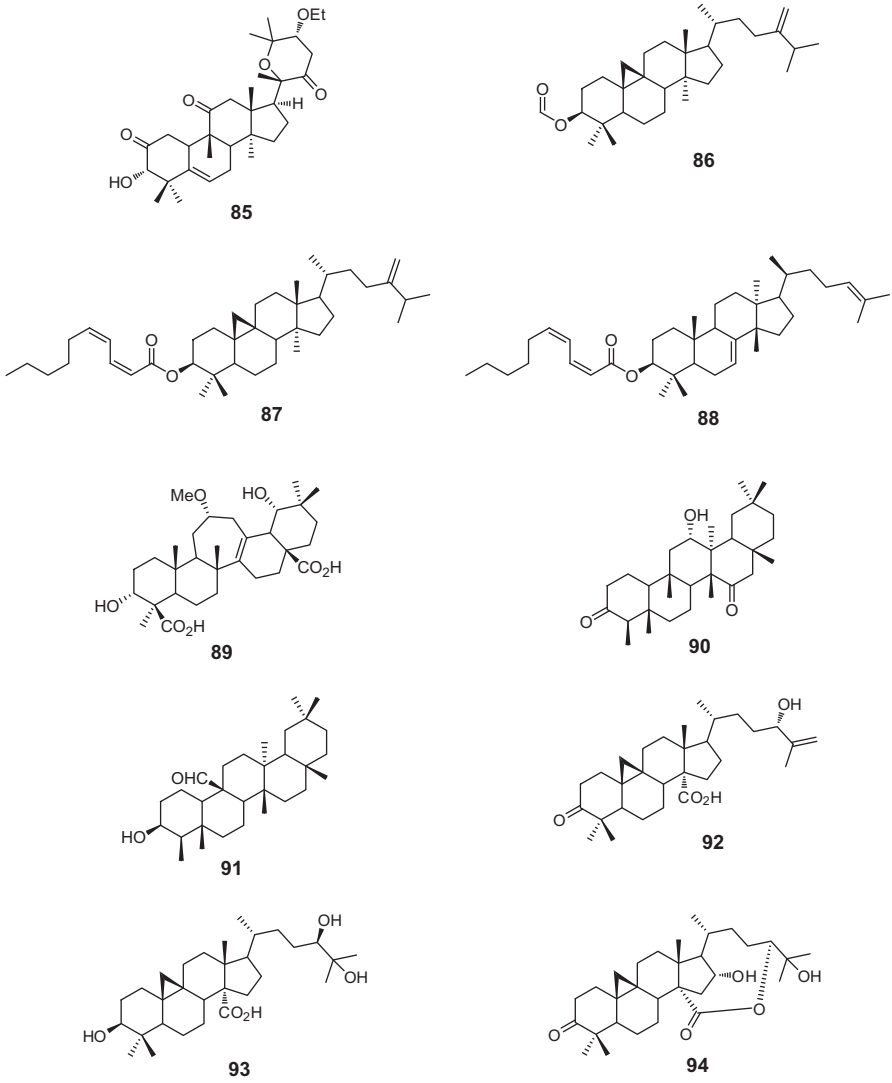
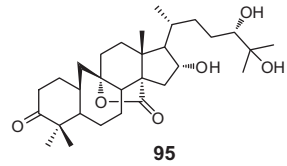


Figure 4.10 New triterpenoids from African medicinal plants. Dendrocyin (**85**) [36], 24-methylenecycloartanylformate (**86**) [37], 24-methylenecycloartanyl-2′*E*,4′*E*-decadienoate (**87**) [37], Tirucalla-7,24-dien-3β-yl-2′*E*,4′*E*-decadienoate (**88**) [37], duboscic acid (**89**) [4], 12α-hydroxyfriedelane-3,15-dione (**90**) [38], 3β-hydroxyfriedelan-25-al (**91**) [38], caloncobic acid A (**92**) [39], caloncobic acid B (**93**) [39], caloncobalactone A (**94**) [39], caloncobalactone B (**95**) [39], glaucalactone (**96**) [39], lupeol-3-isovanniloyl ester (**97**) [40], canarene (**98**) [5], 3,23-dioxotirucalla-7,24-dien-21-al (**99**) [41], 3,4-secotirucalla-23-oxo-4 (28),7,24-trien-21-al-3-oic acid (**100**) [41], 3,4-secotirucalla-23-oxo-4(28),7,24-trien-21-al-3,21-dioic acid (21-methyl ester) (**101**) [41], cecropiacic acid (**102**) [42], glaucartanoic acid A (**103**) [43], glaucartanoic acid B (**104**) [43], 3α-acetoxy-27-hydroxylup-20(29)-



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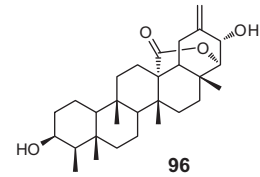

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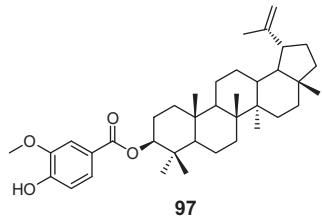

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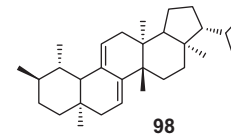

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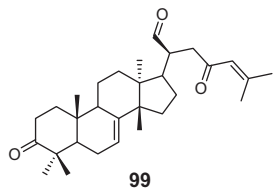

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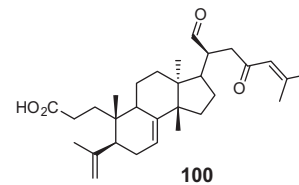

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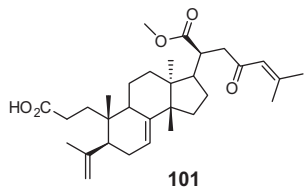

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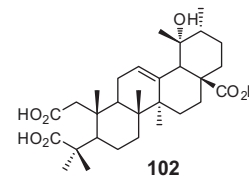

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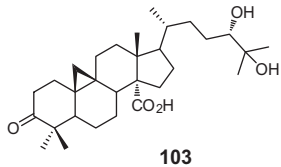
Figure 4.10 (Continued)

◀ en-24-oic acid (**105**) [44], ivorengenin A (**106**) [45], ivorengenin B (**107**) [45], acridocarpusic acid A (**108**) [46], acridocarpusic acid B (**109**) [46], acridocarpusic acid C (**110**) [46], acridocarpusic acid D (**111**) [46], acridocarpusic acid E (**112**) [46], 3β-acetoxy-16β-hydroxybetulinic acid (**113**) [47], 3β,16β-diacetoxybetulinic acid (**114**) [47], 3β-octacosanoyloxy-olean-12-en-28-ol (**115**) [48], 3β-triacontanoyloxy-olean-12-en-28-ol (**116**) [48], 3β-dotriacontanoyloxy-olean-12-en-28-ol (**117**) [48], 3β-tetratriacontanoyloxy-olean-12-en-28-ol (**118**) [48], 3β-hexatriacontanoyloxy-olean-12-en-28-ol (**119**) [48], 2α-19α-dihydroxy-3-oxo-23-nor-urs-12-en-28-oic acid (**120**) [49], 3-*O*-(3′-hydroxyeicosanoyl)lupeol (**121**) [50],



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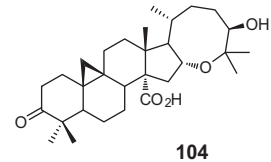

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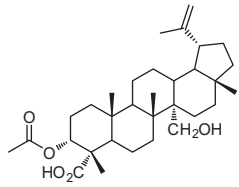

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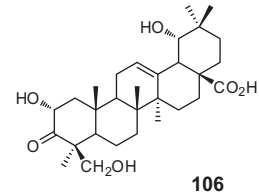

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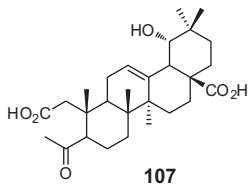

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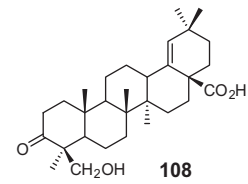

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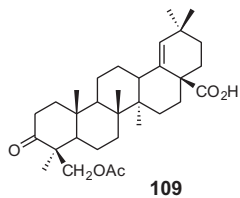

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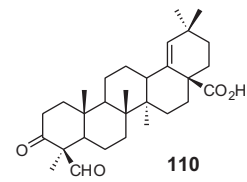

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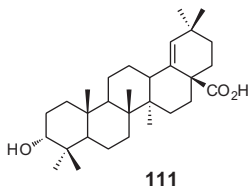

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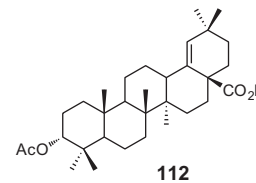


112

Figure 4.10 (Continued)

◀ 3-*O*-[(2′-(tetracosyloxy)acetyl]lupeol (**122**) [50], 3-*O*-[(1″-hydroxyoctadecyloxy)2′-hydroxypropanoyl] lupeol (**123**) [50], calotroprocerol A (**124**) [51], calotroproceryl acetate A (**125**) [51], calotroprocerone A (**126**) [51], calotroproceryl acetate B (**127**) [51], donellanic acid A (**128**) [52], donellanic acid B (**129**) [52], donellanic acid C (**130**) [52], β-amyrin-*n*-nonyl ether (**131**) [53], lup-20(29)-en-3β,6α-diol (**132**) [54], 3β-acetoxylup-20(29)-en-6α-ol (**133**) [54], 3β-caffeoyloxylup-20(29)-en-6α-ol (**134**) [54], 3α-hydroxyfriedelan-25-al (**135**) [54], 1α,3β-dihydroxybauer-7-en-28-oic acid (**136**) [55], 3β-hydroxybauer-7-en-28-oic acid (**137**) [55],

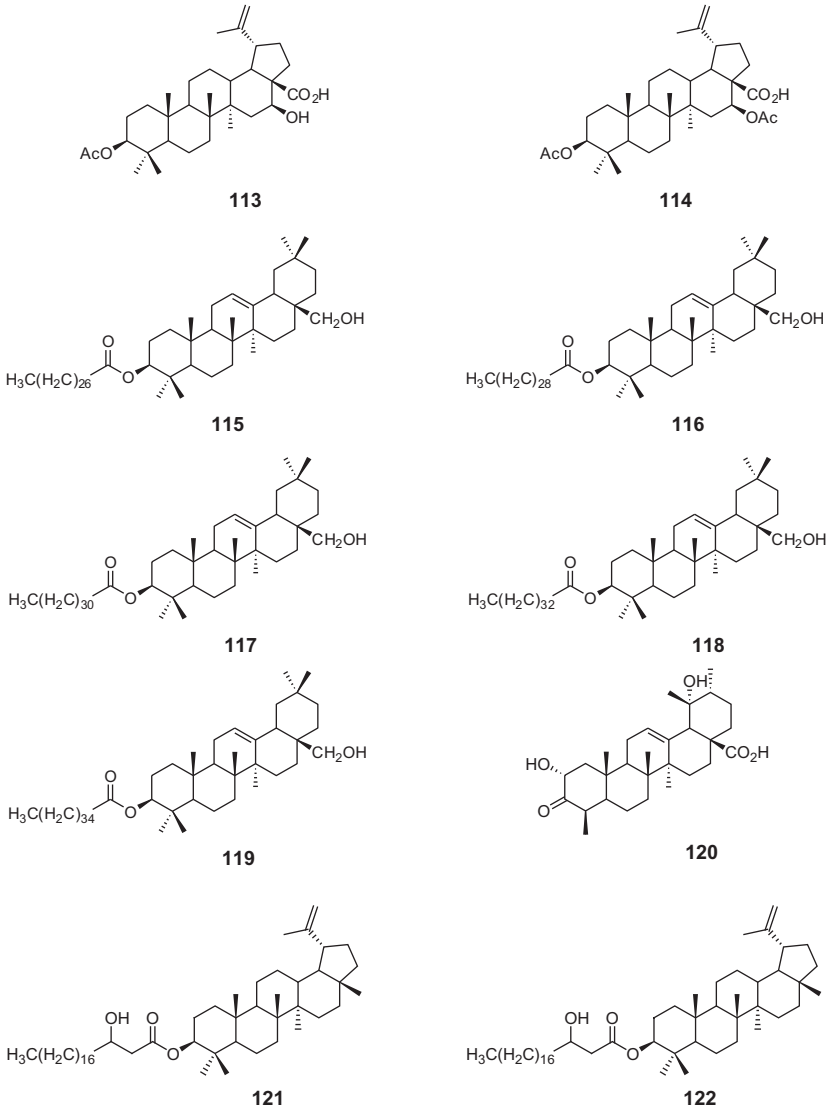
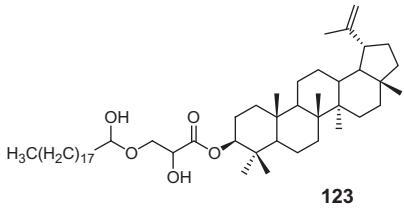


Figure 4.10 (Continued)

◀ gamboukokoensein A (**138**) [56], dinklagenonoate (**139**) [57], neoboutomellerone (**140**) [58], 22-de-*O*-acetylneoboutomellerone (**141**) [58], 26-acetyl-*neo*-boutomellerone (**142**) [58], 1,2-dihydroneoboutomellerone (**143**) [58], 1,2-dihydro-22-de-*O*-acetylneoboutomellerone (**144**) [58], 6β-hydroxyneoboutomellerone (**145**) [58], 6β-hydroxy-22-de-*O*-acetylneoboutomellerone (**146**) [58], 18-hydroxyneoboutomellerone (**147**) [58], 6β,7β-oxidoneoboutomellerone (**148**) [58], 1,2-dihydro-1α-hydroxy-22-de-*O*-acetylneoboutomellerone (**149**) [58], 25-epi-neoboutomellerone (**150**) [58], 9,10-di-epi-25ξ-neoboutomellerone (**151**) [58], 9,10-di-epi-22-de-*O*-acetyl-25ξ-



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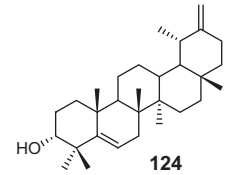

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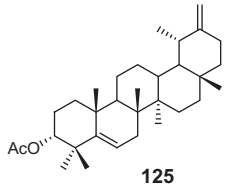

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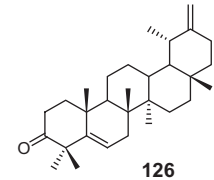

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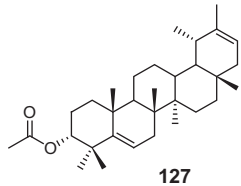

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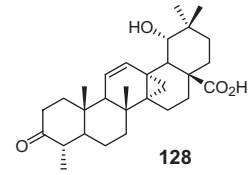

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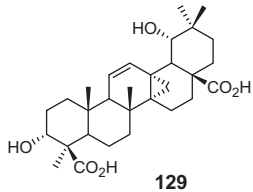

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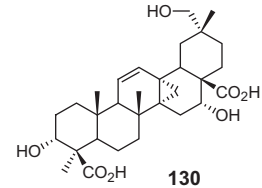

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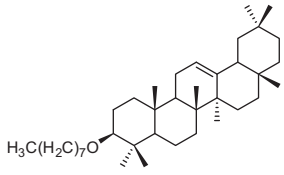

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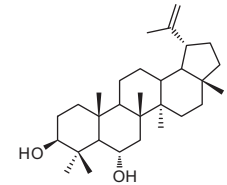


132

Figure 4.10 (Continued)

◀ neoboutomellerone (**152**) [58], 26-deoxyneoboutomellerone (**153**) [58], 22-de-*O*-acetyl-26-deoxyneoboutomellerone (**154**) [58], 6β-hydroxy-26-deoxyneoboutomellerone (**155**) [58], 1,2-dihydro-22-de-*O*-acetyl-26-deoxyneobouto mellerone (**156**) [58], 9,10-di-epi-26-deoxyneoboutomellerone (**157**) [58], 24α-nor-24,25-didehydro-26-deoxyneobouto mellerone (**158**) [58], 22-de-*O*-acetyl-24a-nor-24,25-didehydro-26-deoxyneoboutomellerone (**159**) [58], 9,10-di-epi-24a-nor-24,25-didehydro-26-deoxyneo boutomellerone (**160**) [58], 23,24,24a,25,26,27-hexa-nor-neoboutomelleron-22-al (**161**) [58], 23,24,24a,25,26,27-hexa-

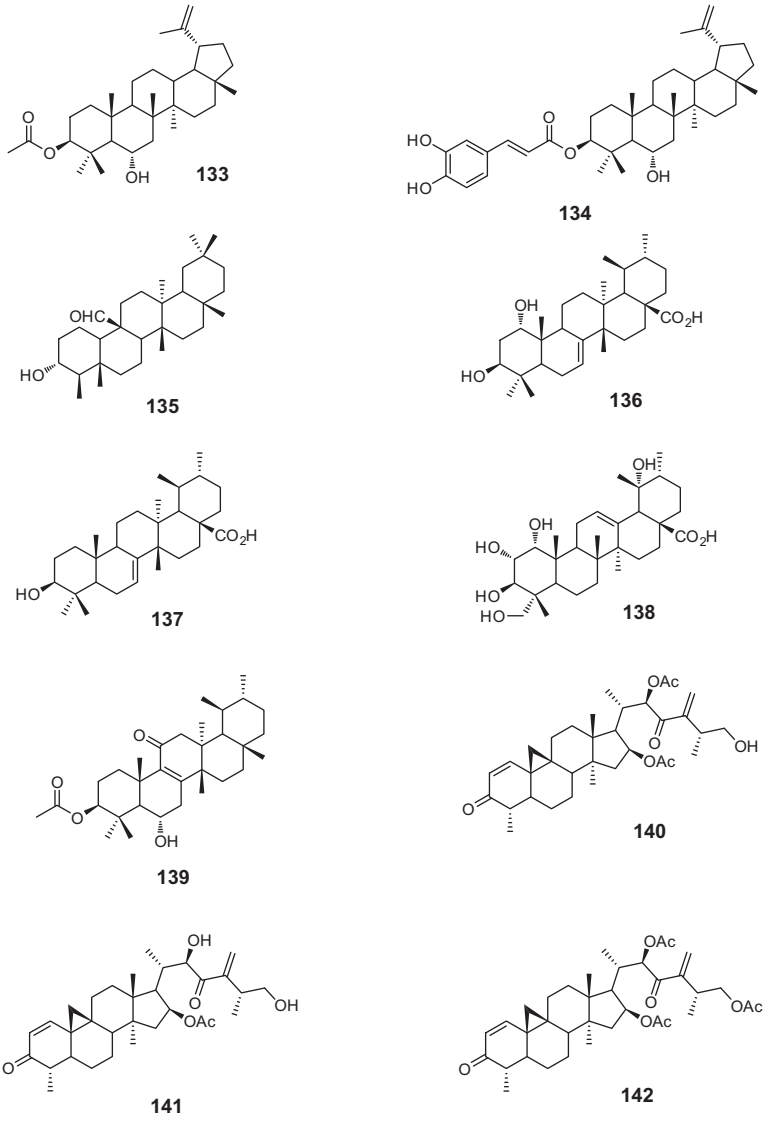
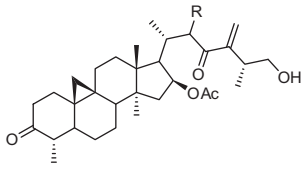


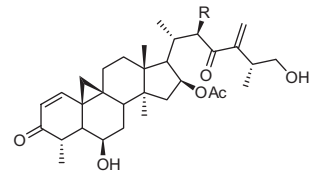
Figure 4.10 (Continued)

◀ nor-neoboutomelleron-22-oic acid (**162**) [58], 16-acetyl-3β,26-dihydroxy-24-methyl-25ξ-cycloart-24(24a)-en-23-on-29-oic acid (**163**) [58], 16-acetyl-3β,22β-dihydroxy-24-methylcycloart-24(24a)-en-23-on-29-oic acid (**164**) [58], 3β-hydroxy-24-methylcycloart-24(24a)-en-23-on-29-oic acid (**165**) [58], 3β,16β,22β-trihydroxy-24-methyl-(16,23:23,26)-diepoxycycloart-24(24a)-en-29-oic acid (**166**) [58], 16,22-diacetyl-2,26-dihydroxy-29-nor-24-methyl-19(9→1)-abeocycloart-9(11),24(24a)-dien-3,23-dione (**167**) [58], 3β-*O*-(*E*)-3,5-dihydroxycinnamoyl-11-oxo-olean-12-ene (**168**) [59], 3β,6α-dihydroxylup-20(29)-ene (**169**) [59], scaphopetalumate (**170**) [60],



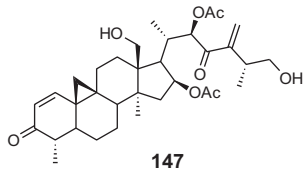
R = OAc **143**

R = OH **144**



R = OAc **145**

R = OH **146**



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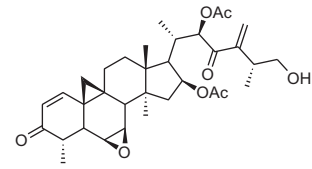

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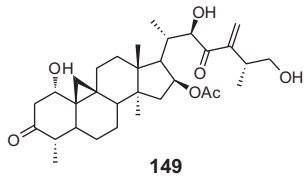

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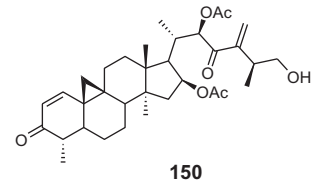

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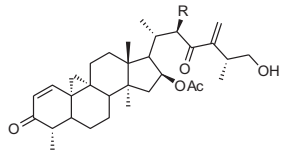
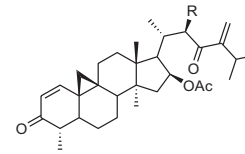


R = OAc **151**

R = OH **152**

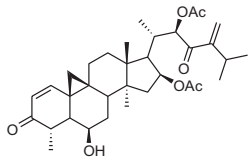


R = OAc **153**

R = OH **154**

Figure 4.10 (Continued)

◀ argentatin E (**171**) [61], argentatin F (**172**) [61], argentatin G diacetate (**173**) [61], argentatin H diacetate (**174**) [61], kairatenyl palmitate (**175**) [62], hopenyl-3β-*O*-palmitate (**176**) [62], 28*R*-acetyloxy-6*R*,7*R*:21α,-28-diepoxytaraxer-3*R*-ol (**177**) [63], 20(29)-lupene-3β-isoferulate (**178**) [64], swinniol (**179**) [65], terminalin A (**180**) [66], 24-methylenecycloartane-3,28-diol (**181**) [67], lanost-24-en-20-ol-3-tetradecanoate (**182**) [68], euphorbol-7-one (**183**) [68], cecropic acid methyl ester (**184**) [69], sapelenin G (**185**) [70], sapelenin H (**186**) [70], sapelenin I (**187**) [70], sapelenin J



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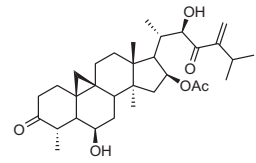

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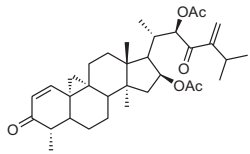

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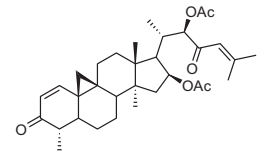

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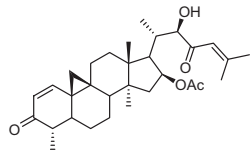

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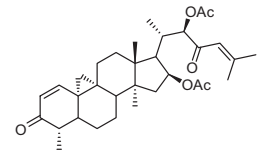

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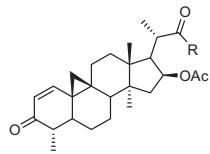
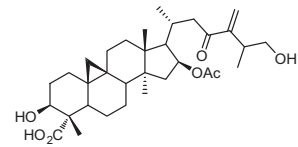


R = H **161**

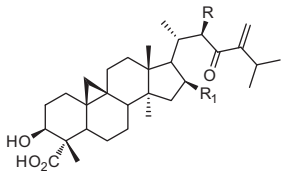
R = OH **162**



163

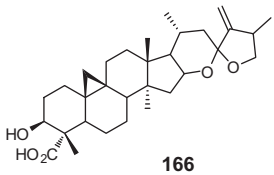
Figure 4.10 (Continued)

◀ (**188**) [70], 1β,3β,11α,26-tetrahydroxy-7,24*E*-euphadiene (**189**) [71], 3β,26-dihydroxy-8,24*E*-euphadien-11-one (**190**) [71], (24*S*)-1β,3β,24,25-tetrahydroxy-7,9(11)-euphadiene (**191**) [71], (22*R*,23*S*)-17α,23-epoxy-22,29-dihydroxy-27-nor-lanost-8-en-3,24-dione (**192**) [72], (22*R*,23*S*)-17α,23-epoxy-3β,22,24ξ-trihydroxy-27,28-bisnor-lanost-8-ene (**193**) [72], (23*S*)-17α,23-epoxy-3β,24ξ-dihydroxy-27,28,29-trisnor-lanost-8-ene (**194**) [72], 7,15-dihydroxy-lup-20(29)-en-3β-*O*-stearate (**195**) [73], 7,15-dihydroxy-lup-20(29)-en-3β-*O*-eicosanoate (**196**) [73], (3*S*,10*S*,17*S*,14*R*,8*S*)-18-(2,2-dimethylbutyl)-8,10,14,17,23,24-hexamethyl-1,2,3,4,5,6,7,8,9,10,11,14,15,16, 17,18-hexadecahydrochrysen-3-ol (**197**) [74].



R = OH, R_1 = OAc **164**

R = R_1 = H **165**



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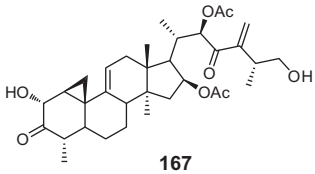

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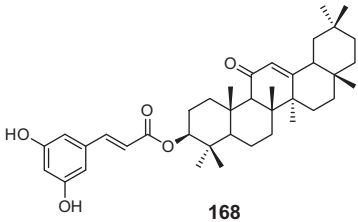

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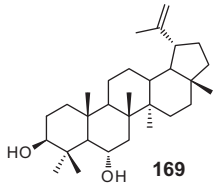

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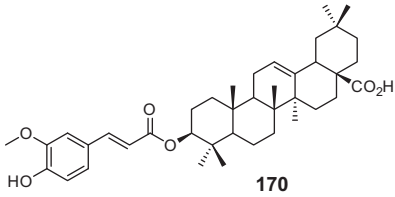

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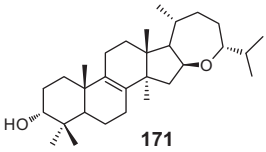

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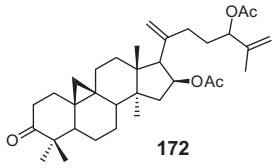

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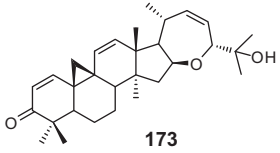

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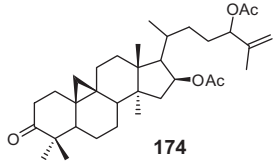

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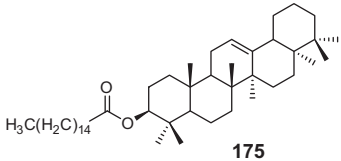

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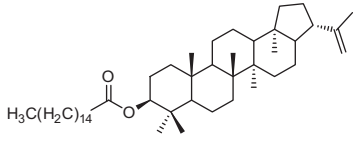

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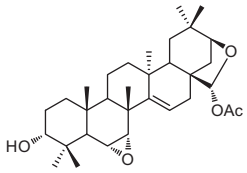

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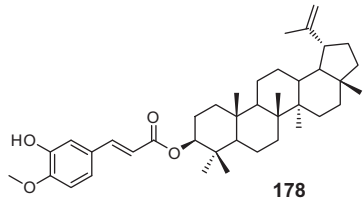

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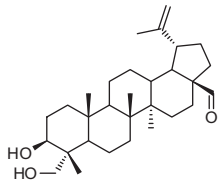

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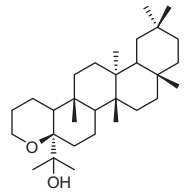

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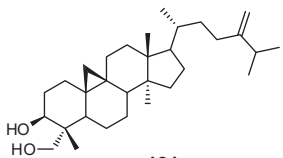

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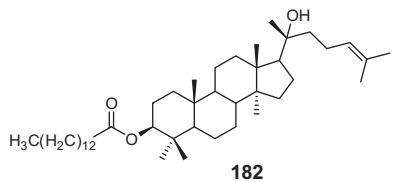

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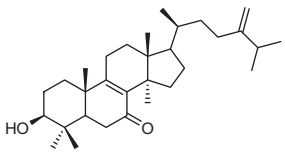

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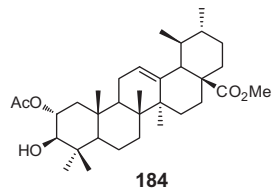

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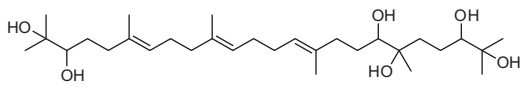

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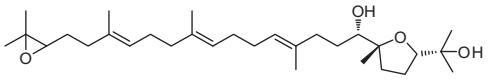

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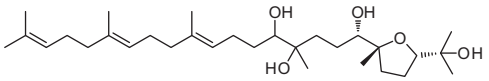

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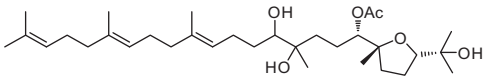

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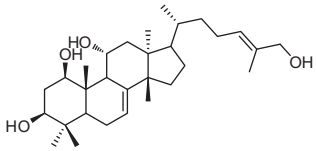

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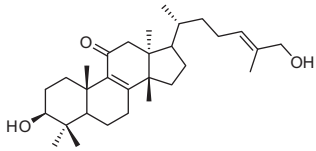

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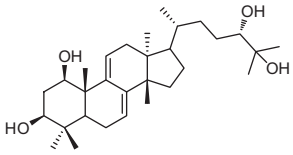

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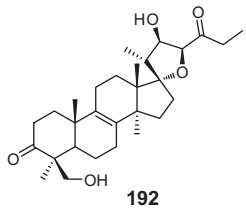

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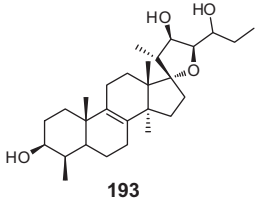

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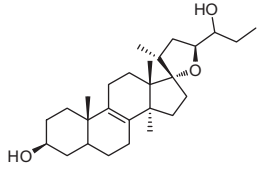

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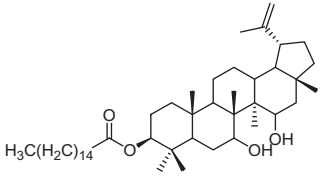

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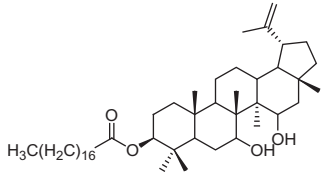

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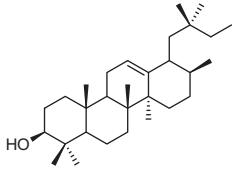


197

Figure 4.10 (Continued)

4.5.2 New Limonoids and Quassinoids Obtained from African Medicinal Plants

The name limonoid comes from limonin, the first tetranortriterpenoid obtained from citrus. Some of these secondary metabolites are responsible for the bitterness of some plants; they are highly oxygenated modified triterpenoids, justifying their use as antifeedants [15]. Many of these tetranortriterpenoids have been reported with interesting structures, such as 1-*O*-acetylkhayanolide A (**205**) (Figure 4.11), obtained from *Khaya senegalensis*, an Egyptian medicinal plant [76], kotschyins A−C (**206**−**208**), isolated from *Pseudocedrela kotschyi*, a Malian medicinal plant [77], khayanolides D and E (**210** and **211**), from *K. senegalensis*, an Egyptian medicinal plant [79], swietephragmins B and C (**214** and **215**) [80], kotschyins D−G (**242**−**245**) [88], and swietenialides A−C (**258**−**260**), from *Swietenia mahogani*, an Egyptian medicinal plant [91]. Among these structures, ortho-ester-containing limonoids represent one of the larger constituents of this secondary metabolite group. However, some of these natural products can have several open rings, giving a structure without any terpenoid feature, such as cedkathryns A and B (**240** and **241**), obtained from *Cedrelopsis gracilis*, a Madagascarian medicinal plant [87].

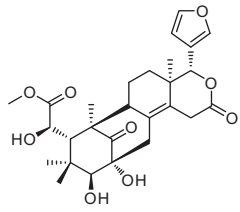
A deep literature review shows that there are not many reports concerning quassinoids from African medicinal plants up to now.

4.5.3 New Steroids Isolated from African Medicinal Plants

Even though steroids are one of the major secondary metabolites from the plant kingdom, there are not many new ones identified from African medicinal plants reported in the literature. However, they can be classified as stigmastane, poriferastane, cardanolide, pregnane, cholestane, and furostane groups. Some of these plant metabolites are structurally interesting, such as vernoguinoside A (**273**) (Figure 4.12), with the side chain cyclized in order to afford a furobicyclic steroid [97]. The same feature exists in the structures of vernoguinosterone (**280**) [101], vernoguinoside (**281**) [101], vernoguinosterol (**284**) [102], and peracetate vernoguinoside (**285**) [102]. These steroids have been obtained from *Vernonia guineensis*, a Cameroonian medicinal plant. Furthermore, a lactol ring formed by C-1, C-2, C-10, and C-19 of the steroid core yields 2β,19-epoxy-3β,14β-dihydroxy-19-methoxy-5α-card-20(22)-enolide (**275**), a structural particularity. Structure **275** was obtained from *Calotropis procera*, an Egyptian medicinal plant [99].

4.5.4 New Saponins Isolated from African Medicinal Plants

Except for 3-sulfate rhamnopyranosyl, the figure below shows carbohydrates frequently found in saponins from African medicinal plants. This class of compounds has been and continues to be well investigated. Most of the attractive structures are those containing, besides sugar and aglycone, an additional



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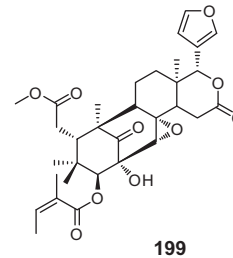

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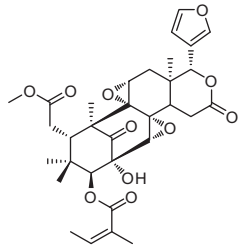

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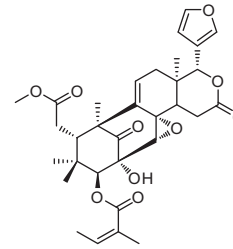

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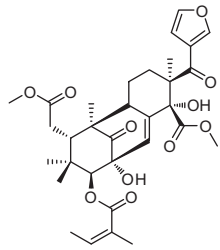

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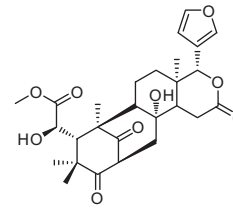

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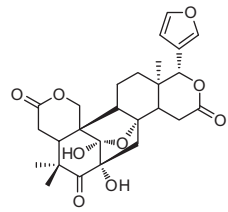

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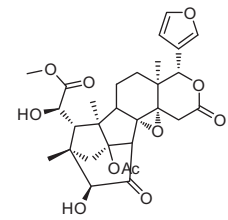

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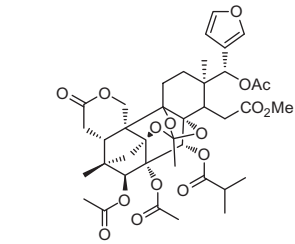
Figure 4.11 Limonoids isolated from African medicinal plants: 2α-hydroxyswietenolide (**198**) [75], 3-angeloyl-3-detigloylruageanin B (**199**) [75], quivisianolide A (**200**) [75], quivisianolide B (**201**) [75], quivisianone (**202**) [75], khayanone (**203**) [76], 2-hydroxyseneganolide (**204**) [76], 1-*O*-acetylkhayanolide A (**205**) [76], kotschyin A (**206**) [77], kotschyin B (**207**) [77], kotschyin C (**208**) [77], deoxyobacunone (**209**) [78], khayanolide D (**210**) [79], khayanolide E (**211**) [79], khayanoside (**212**) [79],



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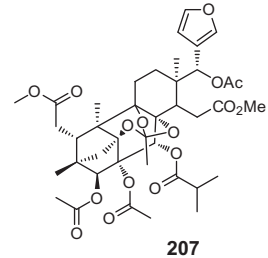

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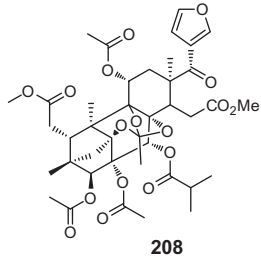

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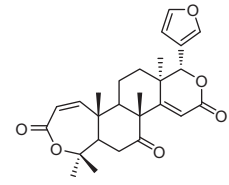

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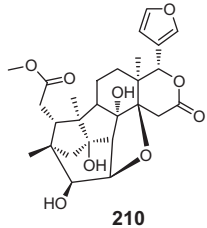

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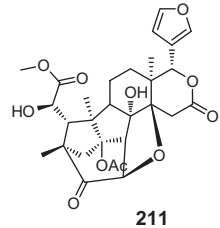

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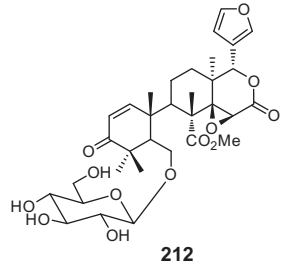

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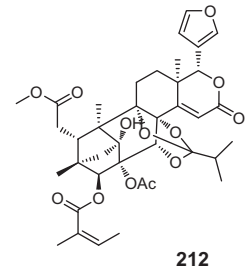
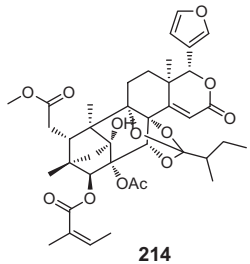


212

Figure 4.11 (Continued)

◀ swietephragmin A (**212**) [80], swietephragmin B (**214**) [80], swietephragmin C (**215**) [80], swietephragmin D (**216**) [80], swietephragmin E (**217**) [80], swietephragmin F (**218**) [80], swietephragmin G (**219**) [80], 2-hydroxy-3-*O*-tigloylswietenolide (**220**) [80], deacetylsecomahoganin (**221**) [80], musidunin (**222**) [81], musiduol (**223**) [81], zumketol (**224**) [82], zumsenin (**225**) [82], zumsenol (**226**) [82], malleastrone A (**227**) [83], malleastrone B (**228**) [83], malleastrone C (**229**) [83], 6α-hydroxyazadiradione (**230**) [84],



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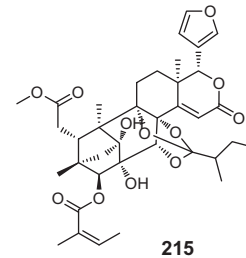

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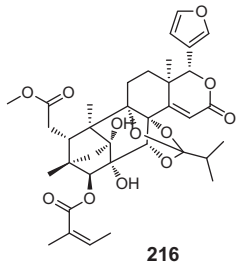

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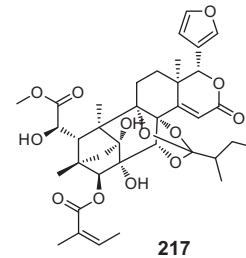

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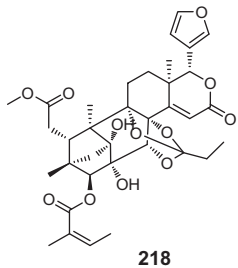

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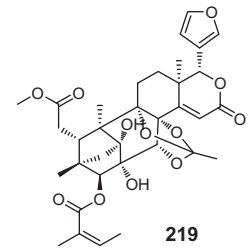

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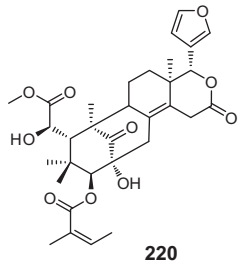

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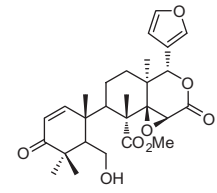

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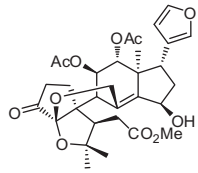
Figure 4.11 (Continued)

◀ 7-deacetyl-7-angeloyl-6α-hydroxyazadiradione (**231**) [84], quivisianthone (**232**) [84], turraflorin D (**233**) [85], turraflorin E (**234**) [85], turraflorin F (**235**) [85], turraflorin G (**236**) [85], turraflorin H (**237**) [85], turraflorin I (**238**) [85], methyl uguenesonate (**239**) [86], cedkathryn A (**240**) [87], cedkathryn B (**241**) [87], kotschyin D (**242**) [88], kotschyin E (**243**) [88], kotschyin F (**244**) [88], kotschyin G (**245**) [88], kotschyin H (**246**) [88], turraparvin A (**247**) [89], 12α-acetoxyazadironolide (**248**) [89], turraparvin B (**249**) [89],



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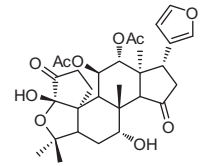

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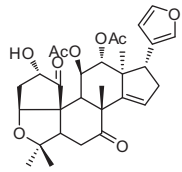

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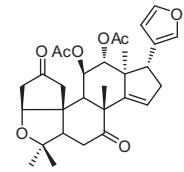

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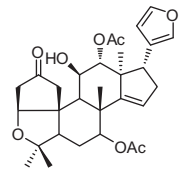

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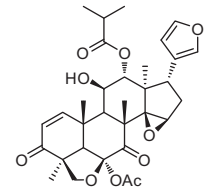

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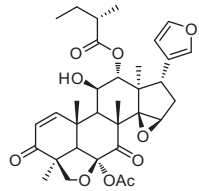

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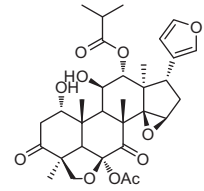

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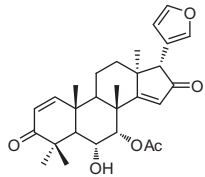

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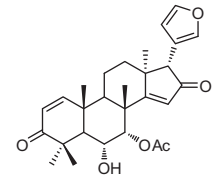

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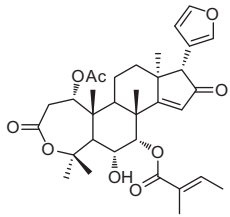
Figure 4.11 (Continued)

◀ turraparvin C (**250**) [89], 11-epi-21-hydroxytoonacilide (**251**) [89], 11-epi-23-hydroxytoonacilide (**252**) [89], turraparvin D (**253**) [89], anthothecanolide (**254**) [90], 3-*O*-acetylanthothecanolide (**255**) [90], 2,3-di-*O*-acetylanthothecanolide (**256**) [90], 6*R*,8α-dihydroxycarapin (**257**) [90], swietenialide A (**258**) [91], swietenialide B (**259**) [91], swietenialide C (**260**) [91], and quassinoids nothospondin (**261**) [92], eurycomaoside (**262**) [93], cedashnine (**263**) [94], and cedphiline (**264**) [94].



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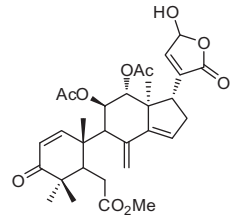

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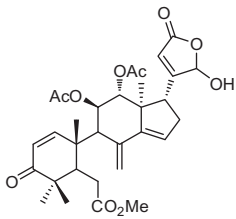

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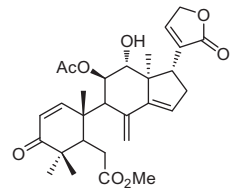

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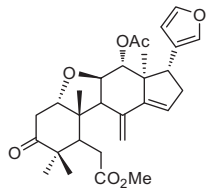

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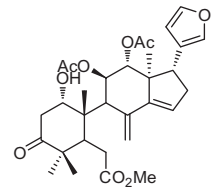

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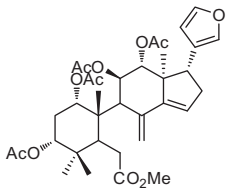

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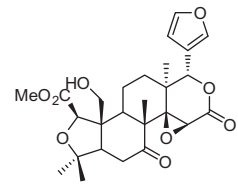

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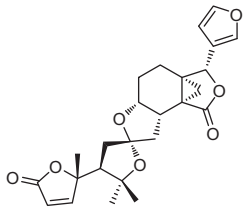

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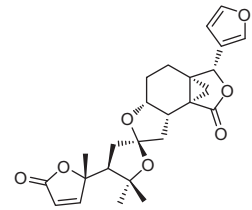

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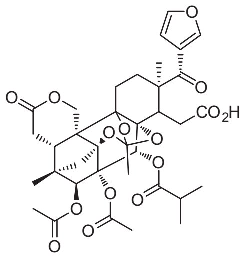

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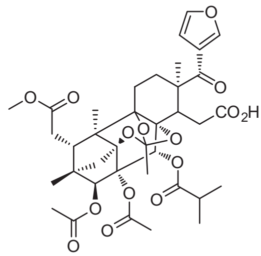

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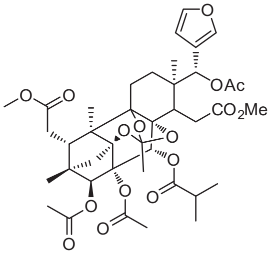

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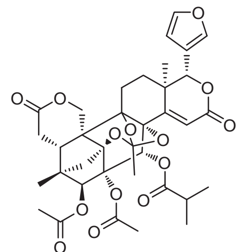

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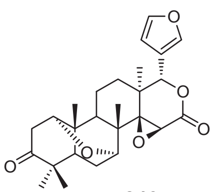

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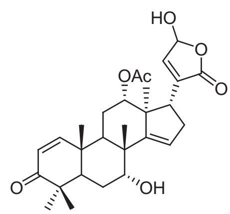

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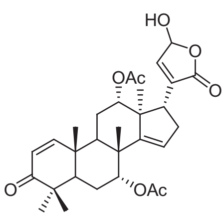

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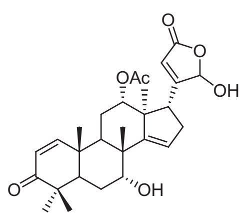

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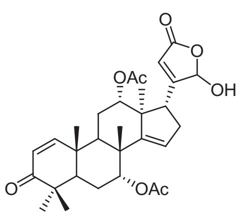

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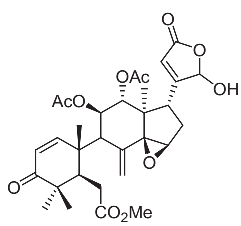

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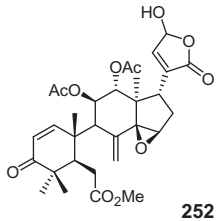

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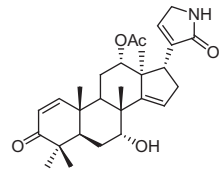

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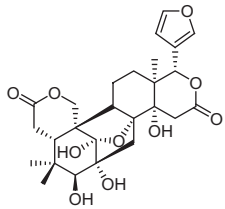

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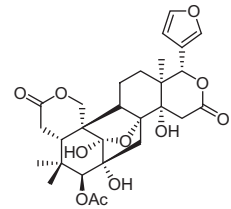

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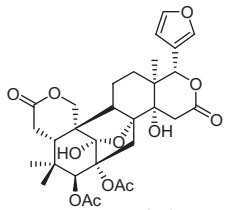

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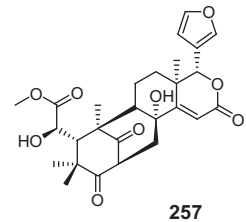

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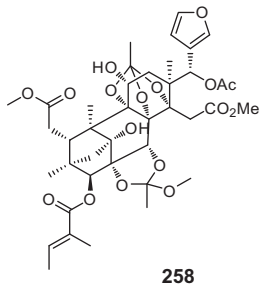

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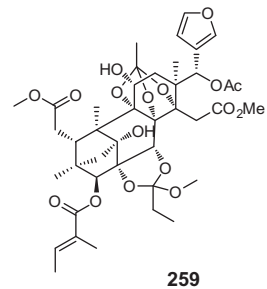

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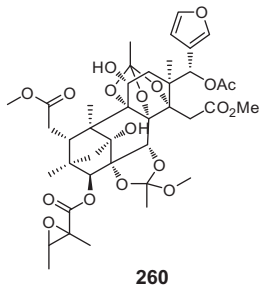

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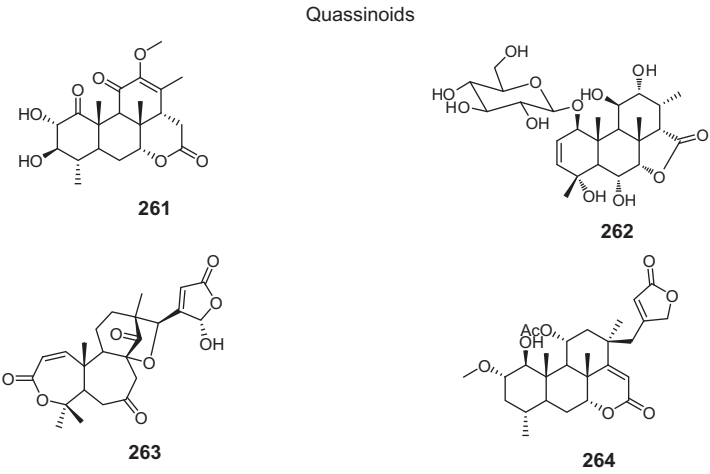

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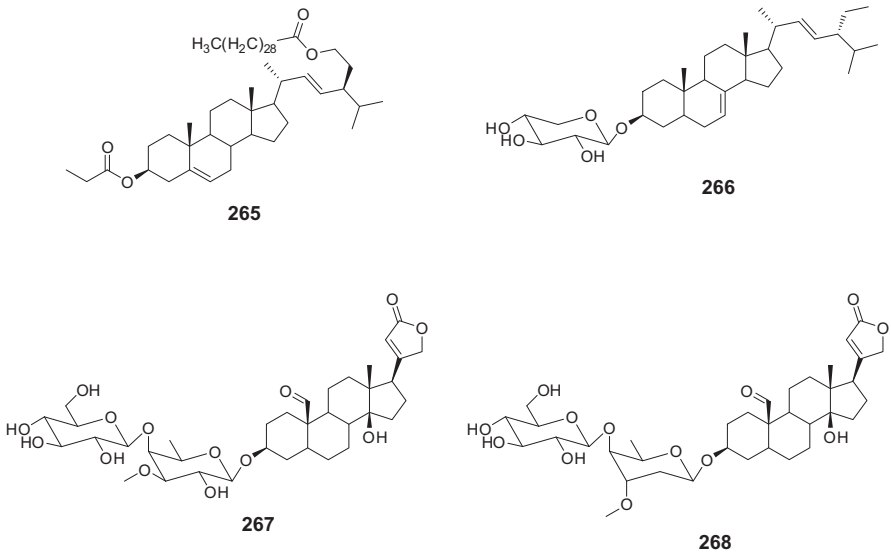
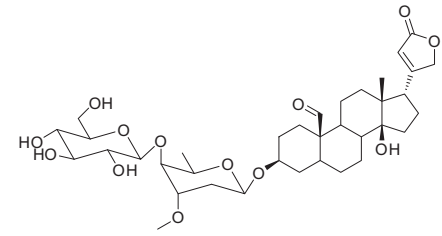


Figure 4.12 Steroids isolated from African medicinal plants: triumfettosterol Id (**265**) [95], 3β-*O*-β-xylopyranosidechondrillasterol (**266**) [48], boivinide A (**267**) [96], boivinide B (**268**) [96], boivinide C (**269**) [96], boivinide D (**270**) [96], boivinide E (**271**) [96], boivinide F (**272**) [96], vernoguinoside A (**273**) [97], 20-hydroxy,24-hydroxymethyl ecdysone (**274**) [98], 2β,19-epoxy-3β,14β-dihydroxy-19-methoxy-5α-card-20(22)-enolide (**275**) [99],



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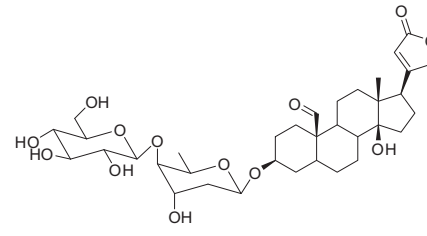

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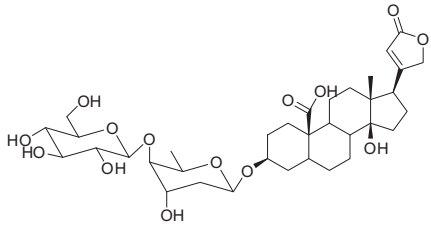

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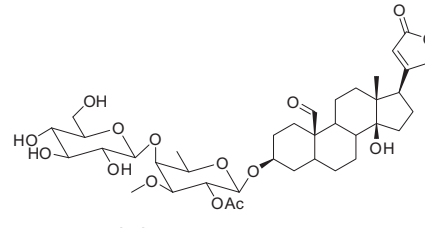

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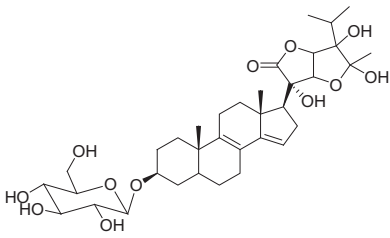

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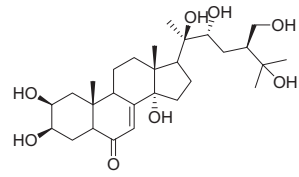

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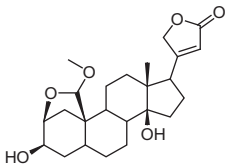

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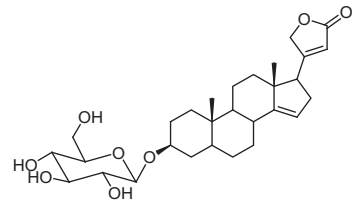

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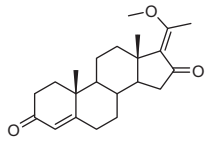
Figure 4.12 (Continued)

◀ β-anhydroepidigitoxigenin-3β-*O*-glucopyranoside (**276**) [99], guggulsterone M (**277**) [100], dehydroguggulsterone M (**278**) [100], guggulsterol Y (**279**) [100], vernoguinosterone (**280**) [101], vernoguinoside (**281**) [101], stigmast-7,20 (21)-diene-3β-hydroxy-6-one (**282**) [73], 3β-hydroxystigmast-23-ene (**283**) [73], vernoguinosterol (**284**) [102], and peracetate vernoguinoside (**285**) [102].



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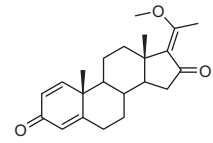

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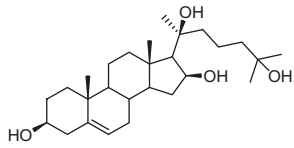

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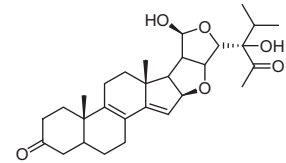

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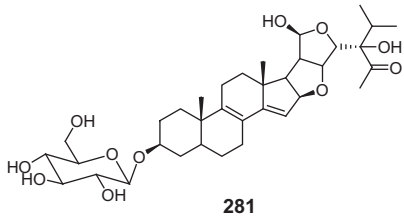

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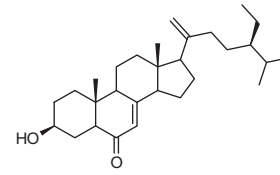

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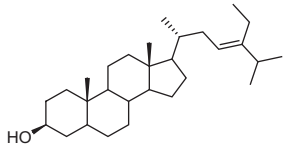

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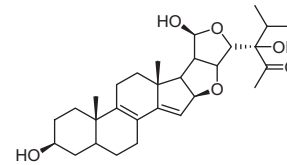

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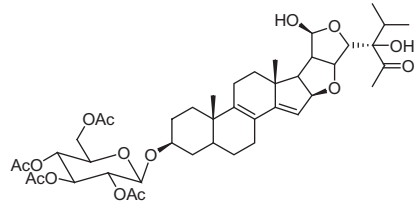

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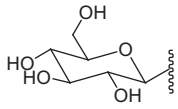
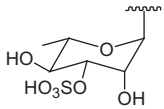
Figure 4.12 (Continued)

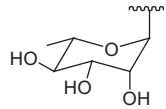
groupment such as benzoyl, nicotinoyl, *O*-aminobenzoyl, 2-methylbutyryl, isovaleryl, but-2-enoyl, monoterpenyl, cinnamoyl, and feruloyl. However, dimeric triterpenic saponins represent a target molecule for actual research, although there is no real phytochemical analytic method to detect them except the Molisch and Liebermann−Burchard tests, which are also used for triterpenic saponins. A further interest of saponin structures concerns those containing one or more glycuronic acid, an amino or a sulfate carbohydrate in the sugar sequence part.



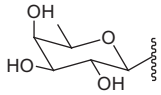
β-Glucopyranosyl (Glu)



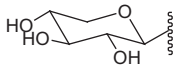
3-SulfateRhamnopyranosyl (SRha)



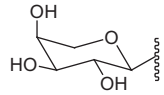
α-Rhamnopyranosyl (Rha)



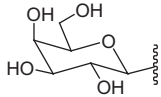
β-Fucopyranosyl (Fuc)



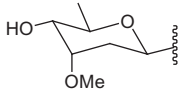
β-Xylopyranosyl (Xyl)



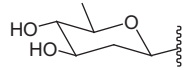
β-Arabinopyranosyl (Ara)



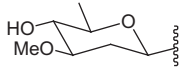
β-Galactopyranosyl (Gal)



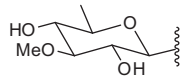
β-Cymaropyranosyl (Cym)



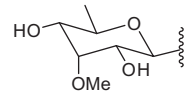
β-Canaropyranosyl (Can)



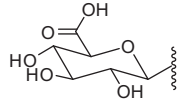
β-Oleandropyranosyl (Ole)



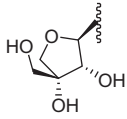
β-Thevetopyranosyl (The)



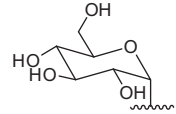
6-Deoxy-3-*O*-methyl-β-allopyranosyl (DMAl)



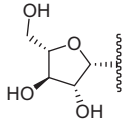
β-Glucuronopyranosyl acid (GlA)



β-D-apiofuranosyl (Api)



α-Glucopyranosyl (aGlu)



α-L-arabinofuranosyl (Araf)

4.6 Triterpene and Steroids Isolated from African Medicinal Plants and Their Pharmacological Activities

The most frequent biological investigation carried out on triterpenoids from African medicinal plants involves cytotoxicity. However, only a few compounds from this class have been tested against tropical endemic diseases, such as malaria and trypanosomiasis (Table 4.2). Among these squalene-derived compounds, some have presented significant cytotoxic activity against various cancer cell lines.

Thus, malleastrones A and B (**228** and **229**), two limonoids isolated from *Malleastrum* sp. collected from the Madagascar rainforest, have shown significant cytotoxic activities against a panel of cancer cell lines, including A2780, MDA-MB-435, HT-29, H522-T1, and U937, with IC_{50} varying between 0.19 and 0.63 μM for the first compound and 0.20 and 0.49 μM for the second compound [83]. Five cardenolide glycosides, namely boivinides A, B, D, and F, from *Roupellina (Strophanthus) boivinii* in the Madagascar rainforest showed cytotoxic effects against the human ovarian cancer cell line A2780 with IC_{50} between 0.17 and 0.54 μM [96]. Moreover, a part of pregnane glycosides isolated from *Caralluma dalzielii*, a Malian medicinal plant, displayed a strong cytotoxic effect against three cancer cell lines, J774.A1 (murine monocyte/macrophage cell lines), HEK-293 (human epithelial kidney cell lines), and WEHI-164 (murine fibrosarcoma cell lines). The IC_{50} of these natural products varied between 0.050 and 20.2 μM, while those of 6-mercaptopurine, used as the standard drug, were 0.003, 0.007, and 0.015 μM, respectively, for the above-mentioned cell lines [107]. Some secondary metabolites among saponins obtained from *Entada africana*, a Malian medicinal plant, showed interesting antiproliferative activity against J774.A1, HEK-293, and WEHI-164, with IC_{50} ranging between 0.031 and 3.9 μM [111]. A dimeric triterpenoid isolated from *Terminalia ivorensis*, a Cameroonian medicinal plant, had a significant cytotoxic effect against MDA-MB-231 and HCT116, with IC_{50} of 3.96 and 3.43 μM, respectively. Its was more active than the standard drug, *cis*platin, which gave an IC_{50} of 7.38 and 5.59 μM, respectively [115]. The remaining compounds in the table showed moderate or weak cytotoxic activities. Further biological investigations were carried out and reported on secondary metabolites from African medicinal plants. Thus, moderate antimalarial activity was observed from three acyl of lupeol (**121**−**123**) from *Holarrhena floribunda*, a Cameroonian medicinal plant [50]. These compounds had, respectively, 106, 282, and 135 μM as IC_{50} against the chloroquine-sensitive strain 3D7 and 97, 269, and 84 μM against the chloroquine-resistance strain FCR-3 [50]. Other bioassays included enzyme inhibition, radical scavenging, antimicrobial, antinociceptive, antiinflammatory, molluscicidal, and antifeedant (Table 4.2). In addition to the above-mentioned new compounds, several known bioactive triterpenoids were also isolated and reported from African medicinal plants (Figure 4.13).

Table 4.2 Bioactivity of Triterpenoids Isolated from African Medicinal Plants

Compound	Plant Source (Family)	Biological Activity
Duboscic acid (**89**)	*D. macrocarpa* (Malvaceae)	α-Glucosidase inhibitor [4]
12α-Hydroxyfriedelane-3,15-dione (**90**)	*Drypetes paxii* (Euphorbiaceae)	Antimicrobial activity [38]
3β-Hydroxyfriedelan-25-al (**91**)	*D. paxii* (Euphorbiaceae)	Antimicrobial activity [38]
Lupeol-3-isovanniloyl ester (**97**)	*P. pinnata* (Sapindaceae)	Antibacterial [40]
Glaucartanoic acids A (**103**) and B (**104**)	*C. glauca* (Flacourtiacea)	Cytotoxic [43]
Ivorengenins A (**106**) and B (**107**)	*T. ivorensis* (Combretaceae)	Radical scavenger [45]
Acridocarpusic acids A (**108**), B (**109**), C (**110**), D (**111**), and E (**112**)	*A. vivy* (Malpiphiaceae)	Cytotoxic [46]
3β-Acetoxy-16β-hydroxybetulinic acid (**113**); 3β,16I-diacetoxybetulinic acid (**114**)	*Fagara tessmannii* (Rutaceae)	α-Glucosidase inhibitor [47]
3-*O*-(3′-Hydroxyeicosanoyl)lupeol (**115**); 3-*O*-[(2′-(tetracosyloxy) acetyl]lupeol bio (**122**); 3-*O*-[(1″-hydroxyoctadecyloxy)2′-hydroxypropanoyl]lupeol (**123**)	*H. floribunda* (Apocynaceae)	Antimalarial [50]
Calotroprocerol A (**124**); calotroprocerone A (**126**)	*C. procera* (Asclepiadaceae)	Cytotoxic [51]
Donellanic acids A (**128**) and B (**129**)	*D. ubanguiensis* (Sapotaceae)	Cytotoxic, antimicrobial [52]
Donellanic acid C (**130**)	*D. ubanguiensis* (Sapotaceae)	Antimicrobial [52]
3β-Acetoxylup-20(29)-en-6α-ol (**133**); 3β-caffeoyloxylup-20(29)-en-6α-ol (**134**); 3α-hydroxyfriedelan-25-al (**135**)	*Drypetes inaequalis* (Euphorbiaceae)	Antimicrobial [54]
22-De-*O*-acetylneoboutomellerone (**141**); 26-acetylneoboutomellerone (**142**); 1,2-dihydroneoboutomellerone (**143**); 1,2-dihydro-22-de-*O*-acetylneoboutomellerone (**144**); 6β-hydroxyneoboutomellerone (**145**); 6β-hydroxy-22-de-*O*-acetylneoboutomelle-rone (**146**); 18-hydroxyneoboutomellerone (**147**); 6β,7β-oxidoneoboutomellerone (**148**); 1,2-dihydro-1α-hydroxy-22-de-*O*-acetylneo boutomellerone (**149**); 25-epi-neoboutomellerone (**150**); 9,10-di-epi-25ξ-neoboutomellerone (**151**); 9,10-di-epi-22-de-*O*-acetyl-25ξ-neobouto mellerone (**152**); 26-	*N. melleri* (Euphorbiaceae)	Proteasome inhibitor [58]

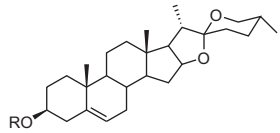
deoxyneoboutomellerone (**153**); 22-de-*O*-acetyl-26-deoxyneoboutomellerone (**154**); 6β-hydroxy-26-deoxyneoboutomellerone (**155**); 1,2-dihydro-22-de-*O*-acetyl-26-deoxyneo boutomellerone (**156**); 9,10-di-epi-26-deoxyneoboutomellerone (**157**); 24α-nor-24,25-didehydro-26-deoxyneobouto mellerone (**158**); 22-de-*O*-acetyl-24a-nor-24,25-didehydro-26-deoxyneoboutomellerone (**159**); 9,10-di-epi-24a-nor-24,25-didehydro-26-deoxyneo boutomellerone (**160**); 23,24,24a,25,26,27-hexa-nor-neobouto melleron-22-al (**161**); 23,24,24a,25,26,27-hexa-nor-neobouto melleron-22-oic acid (**162**); 16-acetyl-3β,26-dihydroxy-24-methyl-25ξ-cycloart-24(24a)-en-23-on-29-oic acid (**163**); 16-acetyl-3β,22β-dihydroxy-24-methylcy cloart-24(24a)-en-23-on-29-oic acid (**164**); 3β-hydroxy-24-methylcycloart-24(24a)-en-23-on-29-oic acid (**165**); 3β,16β,22β-trihydroxy-24-methyl-(16,23:23,26)-diepoxycycloart-24(24a)-en-29-oic acid (**166**); 16,22-diacetyl-2,26-dihydroxy-29-nor-24-methyl-19(9→1)-abeocycloart-9(11),24(24a)-dien-3,23-dione (**167**)		
Kairatenyl palmitate (**175**); hopenyl-3β-*O*-palmitate (**176**)	*Brachylaena ramiflora* (Asteraceae)	Cytotoxic [62]
28*R*-Acetyloxy-6*R*,7*R*:21α,-28-diepoxytaraxer-3*R*-ol (**177**)	*Vepris punctata* (Rutaceae)	Cytotoxic [63]
20(29)-Lupene-3β-isoferulate (**178**)	*Euclea natalensis* (Ebenaceae)	Antibacterial [64]
Sapelenin G (**185**)	*E. cylindricum* (Meliaceae)	Antiinflammatory, cytotoxic [70]
Sapelenin H (**186**)	*E. cylindricum* (Meliaceae)	Antiinflammatory [70]
Sapelenins I (**187**) and G (**188**)	*E. cylindricum* (Meliaceae)	Antiinflammatory, cytotoxic [70]
1β,3β,11α,26-Tetrahydroxy-7,24*E*-euphadiene (**189**); 3β,26-dihydroxy-8,24*E*-euphadien-11-one (**190**)	*Cassipourea lanceolata* (Rhizophoraceae)	Antiproliferative [71]
7,15-Dihydroxy-lup-20(29)-en-3β-*O*-stearate (**195**); 7,15-dihydroxy-lup-20(29)-en-3β-*O*-eicosanoate (**196**)	*Loranthus micrantus* (Loranthaceae)	Immunomodulator [73]

(*Continued*)

Table 4.2 (Continued)

Compound	Plant Source (Family)	Biological Activity
Khayanone (**203**); 2-hydroxyseneganolide (**204**); 1-*O*-acetylkhayanolide A (**205**)	*K. senegalensis* (Meliaceae)	Insect antifeedant [76]
Kotschyin A (**206**)	*P. kotschyi* (Meliaceae)	Antiprotozoal [77]
Musidunin (**222**) and musiduol (**223**)	*Croton jatrophoides* (Euphorbiaceae)	Pest antifeedant [81]
Zumketol (**224**)	*Croton jatrophoides* (Euphorbiaceae)	Pest antifeedant [83]
Malleastrone A (**227**), B (**228**), and C (**229**)	*Malleastrum* sp. (Meliaceae)	Antiproliferative [83]
Methyl uguenesonate (**239**)	*Vepris uguenensis* (Rutaceae)	Antiplasmodial [86]
Kotschyins D (**242**), E (**243**), F (**244**), G (**245**), and H (**246**)	*P. kotschyi* (Meliaceae)	Hsp90 inhibitor [88]
Nothospondin (**261**)	*Nothospondias staudtii* (Simaroubaceae)	AP-1 inhibitor [92]
Boivinides A (**267**), B (**268**), C (**269**), D (**270**), E (**271**), and F (**272**)	*Roupellina (Strophanthus) boivinii* (Apocynaceae)	Antiproliferative [96]
Vernoguinoside A (**273**)	*V. guineensis* (Asteraceae)	Antimicrobial [97]
Guggulsterone M (**274**); dehydroguggulsterone M (**278**)	*Commiphora wightii* (Burseraceae)	Inhibitor of NO production [100]
Stigmast-7,20(21)-diene-3β-hydroxy-6-one (**282**); 3β-hydroxystigmast-23-ene (**283**)	*Loranthus micranthus* (Loranthaceae)	Immunomodulator [73]
Vernoguinosterol (**284**); peracetate vernoguinoside (**285**)	*V. guineensis* (Asteraceae)	Antitrypanocidal [102]
Arboreasaponin A (**286**); deistelianoside B (**288**)	*Dracaena arborea* (Dracaenaceae)	Cytotoxic [103]
Desmettianosides A (**290**) and B (**291**)	*Yucca desmettiana* (Agavaceae)	Molluscicidal [104]

Pennogenin-3-*O*-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranoside (**300**)	*Dracaena mannii* (Dracaenaceae)	Antiinflammatory [105]
Saponins 2 (**301**) and 3 (**302**)	*Dracaena ombet* (Dracaenaceae)	Antinociceptive, antiinflammatory [106]
Saponins 1 (**325**), 2 (**326**), 3 (**327**), 4 (**328**), 5 (**329**), 6 (**330**), 7 (**331**), 8 (**332**), 9 (**333**), 10 (**334**), 11 (**335**), 12 (**336**), 13 (**337**), 14 (**338**), 15 (**339**), 16 (**340**), 17 (**341**), 18 (**342**), 19 (**343**), 20 (**344**), 21 (**345**), 22 (**346**), 23 (**347**), 24 (**348**), 25 (**349**), 26 (**350**)	*C. dalzielii* (Asclepiacaceae)	Cytotoxic [107]
3-*O*-(α-L-arabinopyranosyl)-23-Hydroxyursolic acid (**353**); 3-*O*-(β-D-glucopyranosyl)-23-hydroxyursolic acid (**354**)	*Cussonia bancoensis* (Araliaceae)	Inhibitor of NO production [108]
Bonarienosides A (**360**) and B (**361**)	*Hydrocotyle bonariensis* (Apiaceae)	Cytotoxic [109]
Parkiosides A (**381**), B (**382**), and C (**383**)	*Butyrospermum parkii* (Sapotaceae)	Cytotoxic [110]
Saponins 1 (**395**), 2 (**396**), 3 (**397**), 4 (**398**), 5 (**399**), 6 (**400**), 7 (**401**), 8 (**402**), 9 (**403**)	*E. africana* (Leguminoceae)	Cytotoxic [111]
Coriarioside A (**404**)	*Albizia coriaria* (Mimosaceae)	Cytotoxic [112]
Rheediinosides A (**406**) and B (**407**)	*Entada rheedii* (Leguminoceae)	Cytotoxic, radical scavenger [113]
Gummiferaosides A (**413**), B (**414**), and C (**415**)	*Albizia gummifera* (Mimosaceae)	Cytotoxic [114]
Ivorenosides A (**425**), B (**426**), and C (**427**)	*T. ivorensis*	Cytotoxic, radical scavenger [115]
28β-D-Glucopyranosyl-30-methyl-3β-hydroxyolean-12-en-28, 30-dioate (**433**)	*D. inaequalis* (Euphorbiaceae)	Antimicrobial [54]
1α,23-Dihydroxy-12-oleanen-29-oic acid-3β-*O*-2,4-di-acetyl-L-rhamnopyranoside (**437**)	*Combretum imberbe* (Combretaceae)	Cytotoxic [116]

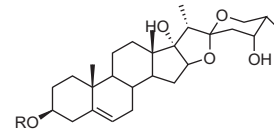


R = SRha(1→4)Glu

286

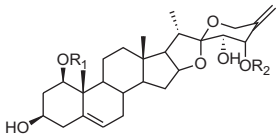
R = 6-Acetoxy-Rha(1→2)[Rha(1→3)]Glu

287



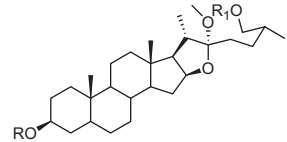
R = Rha(1→2)-Rha(1→3)Glu

288



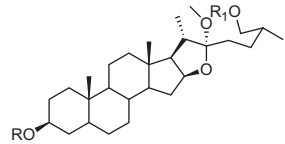
R_1 = Xyl(1→2)-Rha(1→3)Fuc, R_2 = Ara

289



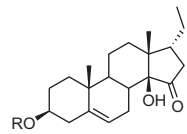
R_1 = Xyl(1→3)-Glu(1→2)Glu[Glu(1→3)]Glu(1→4)]Gal, R_1 = Glu

290



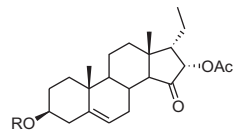
R = Glu(1→2)[Glu(1→3)]Glu(1→4)Gal, R_1 = Glu

291



R = Glu(1→4)-Ole(1→4)-Can(1→4)-Cym(1→4)]Cym

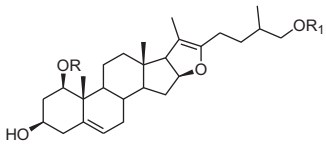
292



R = Glu(1→4)-Ole(1→4)-Can(1→4)-Cym(1→4)]Cym

293

Figure 4.13 Saponins isolated from African medicinal plants: deistelianoside A (**286**) [103], arboreasaponin A (**287**) [103], arboreasaponin B (**288**) [103], deistelianoside B (**289**) [103], desmettianoside A (**290**) [104], desmettianoside B (**291**) [104], stemmoside C (**292**) [104], stemmoside D (**293**) [117], saponin 1 (**294**) [118], saponin 2 (**295**) [118], saponin 3 (**296**) [118], saponin 4 (**297**) [118], saponin 5 (**298**) [118], saponin 9 (**299**) [118], pennogenin-

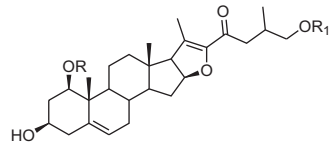


R = Rha(1→2)-Fuc, R_1 = Glu

294

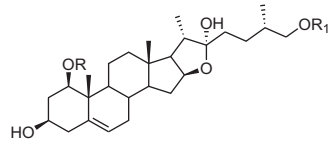
R = Rha(1→2)-4-acetoxyFuc, R_1 = Glu

295



R = Rha(1→2)-Fuc, R_1 = Glu

296

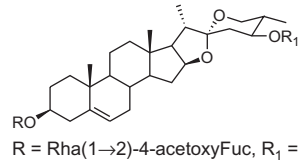


R = Rha(1→4)-6-acetoxyGlu, R_1 = Glu

297

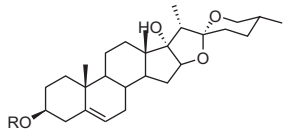
R = Rha(1→2)-Fuc, R_1 = Glu

298



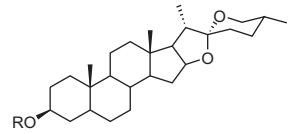
R = Rha(1→2)-4-acetoxyFuc, R_1 = Glu

299



R = Rha(1→3)-Glu

300

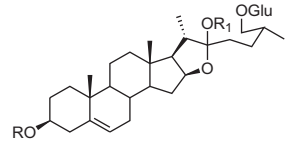


R = Gal(1→4)-Gal(1→3)-Glu

301

R = Gal(1→4)-Glu(1→3)-Glu

302



R = {[Rha(1→2)-Rha(1→4)]-[Xyl(1→2)]-Xyl(1→2)}Xyl; R_1 = H

303

R = [Rha(1→2)]-[Xyl(1→3)]-[Rha(1→4)]-Glu; R_1 = H

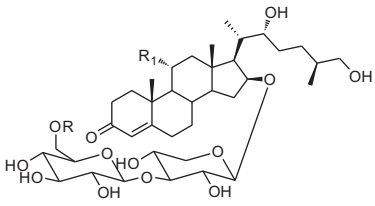
304

R = [Rha(1→2)]-[Xyl(1→3)]-[Rha(1→4)]-Glu; R_1 = Me

305

Figure 4.13 (Continued)

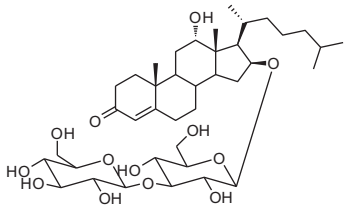
◀ 3-*O*-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranoside (**300**) [105], saponin 2 (**301**) [106], saponin 3 (**302**) [106], balanitesin (**303**) [119], saponin 3 (**304**) [120], saponin 4 (**305**) [120], pentandroside A (**306**) [121], pentandroside B (**307**) [121], pentandroside C (**308**) [121], pentandroside D (**309**) [121], pentandroside E (**310**) [121], pentandroside F (**311**) [121], pentandroside G (**312**) [121], saponin 1 (**313**) [122], saponin 2 (**314**) [122], saponin 3 (**315**) [122], saponin 4 (**316**) [122], saponin 5 (**317**) [122], saponin 6 (**318**) [122], vernionioside D_1



R = H, R_1 = H **306**

R = Ac, R_1 = H **307**

R = H, R_1 = OH **308**



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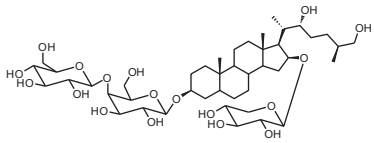

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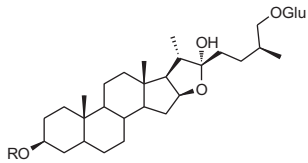
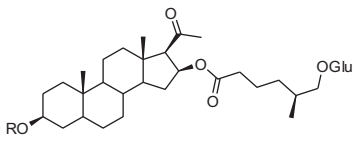


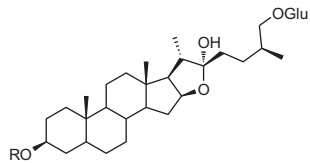
R = {[Glu(1→2)-Glu(1→3)]-Glu(1→4)}-Gal

311



R = {[Xyl(1→2)-Xyl(1→3)]-Glu(1→4)-Rha(1→2)}-Gal

312

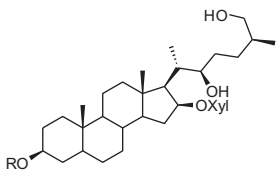


R = {[Gal(1→2)-Glu(1→3)]-Glu(1→4)}-Gal

313

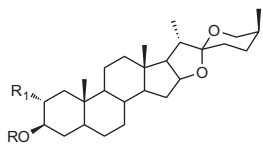
R = {[Glu(1→2)-Glu(1→3)]-Glu(1→4)}-Gal

314



R = {[Glu(1→2)-Glu(1→3)]-Glu(1→4)}-Gal

315



R = {[Gal(1→2)-Glu(1→3)]-Glu(1→4)}-Gal; R_1 = OH

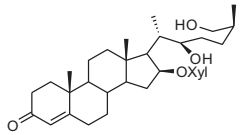
316

R = {[Gal(1→2)-Glu(1→3)]-Glu(1→4)}-Gal; R_1 = H

317

Figure 4.13 (Continued)

◀ (**319**) [123], vernionioside D_2 (**320**) [123], vernionioside D_3 (**321**) [123], vernionioside F_1 (**322**) [123], vernionioside F_2 (**323**) [123], saponin 6 (**324**) [123], saponin 1 (**325**) [107], saponin 2 (**326**) [107], saponin 3 (**327**) [107], saponin 4 (**328**) [107], saponin 5 (**329**) [107], saponin 6 (**330**) [107], saponin 7 (**331**) [107], saponin 8 (**332**) [107], saponin 9 (**333**) [107], saponin 10 (**334**) [107], saponin 11 (**335**) [107], saponin 12 (**336**) [107], saponin 13 (**337**)



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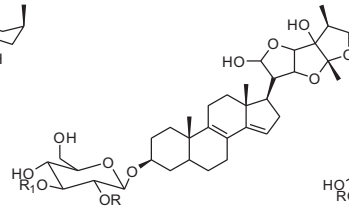
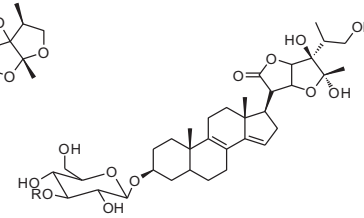


R = R_1 = H **319**

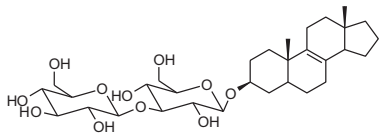
R = H, R_1 = Xyl **320**

R = Glu, R_1 = H **321**

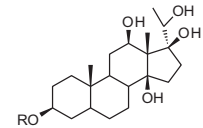


R = H **322**

R = Xyl **323**



324

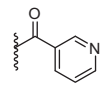


R = The(1→4)-Ole

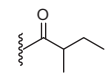
325

Benzoyl (Bz)

Ortho-amino benzoyl *N*-Bz

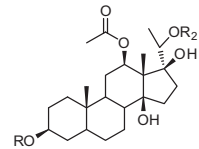


Nicotinoyl (Nic)



2-Methylbutyryl (Mebu)

Isovaleroyl (Isoval)



R = Glu(1→4)-DMAl(1→4)-Ole(1→4)-Cym, R_2 = Bz

326

R = Glu(1→4)-DMAl(1→4)-Ole(1→4)-Cym, R_2 = *N*-Bz

327

R = Glu(1→4)-DMAl(1→4)-Ole(1→4)-Cym, R_2 = Nic

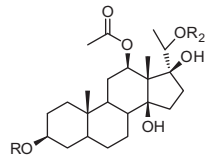
328

R = Glu(1→4)-DMAl(1→4)-Ole(1→4)-Cym, R_2 = Mebu

329

Figure 4.13 (Continued)

◀ [107], saponin 14 (**338**) [107], saponin 15 (**339**) [107], saponin 16 (**340**) [107], saponin 17 (**341**) [107], saponin 18 (**342**) [107], saponin 19 (**343**) [107], saponin 20 (**344**) [107], saponin 21 (**345**) [107], saponin 22 (**346**) [107], saponin 23 (**347**) [107], saponin 24 (**348**) [107], saponin 25 (**349**) [107], saponin 26 (**350**) [107], saponin 27 (**351**) [107], kahiricoside 1 (**352**) [124], 3-*O*-(α-L-arabinopyranosyl)-23-hydroxyursolic acid (**353**) [108], 3-*O*-(β-D-



R = DMAl(1→4)-Ole(1→4)-Cym, R_2 = Bz

330

R = DMAl(1→4)-Ole(1→4)-Cym, R_2 = *N*-Bz

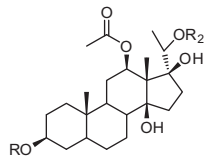
331

R = DMAl(1→4)-Ole(1→4)-Cym, R_2 = Nic

332

R = DMAl(1→4)-Ole(1→4)-Cym, R_2 = Mebu

333



R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Cym, R_2 = Bz

334

R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Cym, R_2 = *N*-Bz

335

R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Cym, R_2 = Nic

336

R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Cym, R_2 = Mebu

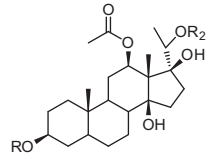
337

R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Cym, R_2 = Isoval

338

Figure 4.13 (Continued)

◀ glucopyranosyl)-23-hydroxyursolic acid (**354**) [108], saponin 1 (**355**) [125], saponin 2 (**356**) [125], saponin 3 (**357**) [125], saponin 4 (**358**) [125], saponin 5 (**359**) [125], bonarienoside A (**360**) [109], bonarienoside B (**361**) [109], bonarienoside C (**362**) [109], bonarienoside D (**363**) [109], bonarienoside E (**364**) [109], kalaic acid (**365**) [126], pursaethoside A (**366**) [127], pursaethoside B (**367**) [127], pursaethoside C (**368**) [127], pursaethoside D (**369**)

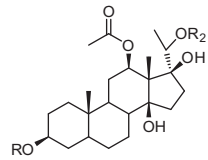


R = Glu(1→4)-Ole(1→4)-Cym, R_2 = Bz

339

R = Glu(1→4)-Ole(1→4)-Cym, R_2 = Mebu

340

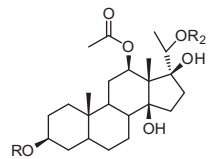


R = Glu(1→4)-Glu(1→4)-Ole(1→4)-Cym, R_2 = Bz

341

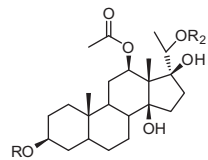
R = Glu(1→4)-Glu(1→4)-Ole(1→4)-Cym, R_2 = Nic

342



The(1→4)-Ole(1→4)-Cym, R_2 = Nic

343



R = Glu(1→6)-Glu(1→4)-The(1→4)-Ole, R_2 = Bz

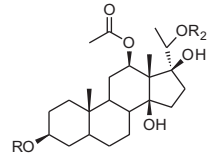
344

R = Glu(1→6)-Glu(1→4)-The(1→4)-Ole, R_2 = Nic

345

Figure 4.13 (Continued)

◀ [127], pursaethoside E (**370**) [127], pallidioside A (**371**) [128], pallidioside B (**372**) [128], pallidioside C (**373**) [128], arboreaside B (**374**) [129], arboreaside A (**375**) [129], arboreaside C (**376**) [129], arboreaside D (**377**) [129], arboreaside E (**378**) [129], saponin 1 (**379**) [110], saponin 2 (**380**) [110], parkioside A (**381**) [130], parkioside B (**382**) [130], parkioside C (**383**) [130], saponin 1 (**384**) [131], saponin 2 (**385**) [131], saponin 3 (**386**) [131], saponin 4

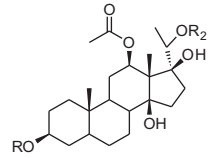


R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Ole, R_2 = Bz

346

R = Glu(1→6)-Glu(1→4)-Ole(1→4)-Ole, R_2 = Nic

347



R = Glu(1→4)-DMA1(1→4)-Cym(1→4)Ole(1→4)-Cym, R_2 = Bz

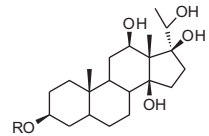
348

R = Glu(1→4)-DMA1(1→4)-Cym(1→4)Ole(1→4)-Cym, R_2 = *N*-Bz

349

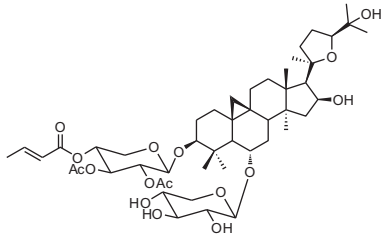
R = Glu(1→4)-DMA1(1→4)-Cym(1→4)Ole(1→4)-Cym, R_2 = Mebu

350



R = Glu(1→4)-DMA1(1→4)-Cym(1→4)Ole(1→4)-Cym

351



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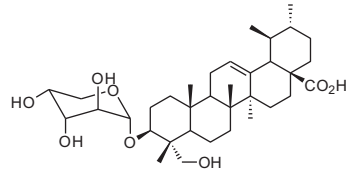
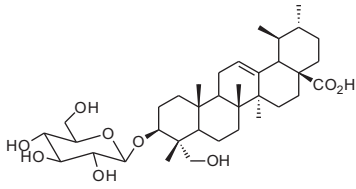


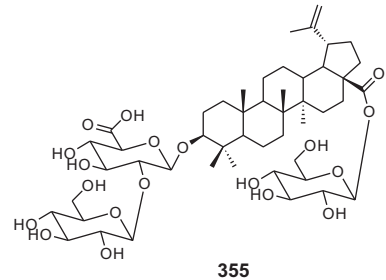
353

Figure 4.13 (Continued)

◀ (**387**) [131], saponin 1 (**388**) [132], saponin 2 (**389**) [132], saponin 3 (**390**) [132], saponin 4 (**391**) [132], saponin 5 (**392**) [132], ardisikivuoside (**393**) [133], compound 2 (**394**) [134], saponin 1 (**395**) [111], saponin 2 (**396**) [111], saponin 3 (**397**) [111], saponin 4 (**398**) [111], saponin 5 (**399**) [111], saponin 6 (**400**) [111], saponin 7 (**401**) [111], saponin 8 (**402**) [111], saponin 9 (**403**) [111], coriarioside A (**404**) [112], coriarioside B (**405**) [112], rheediinoside



354



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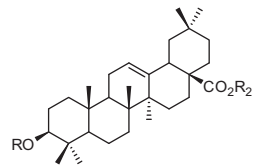


R = Glu(1→2)-Gal(1→3)-GlA, R_2 = H

356

R = Glu(1→3)-GlA, R_2 = Xyl-(1→6)-Glu

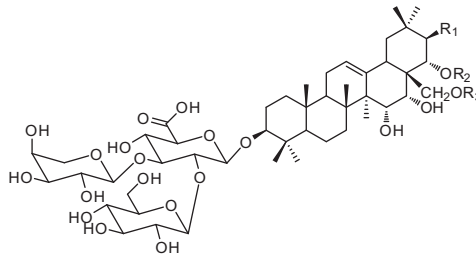
357

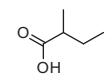
R = Gal(1→3)-GlA, R_2 = Glu-(1→6)-Glu

358

R = Glu(1→3)-Gal(1→3)-GlA, R_2 = Xyl-(1→6)-Glu

359





2-methylbutyroyl (Mb)

R_1 = OMb, R_2 = Ac, R_3 = H **360**

R_1 = OMb, R_2 = H, R_3 = Ac **361**

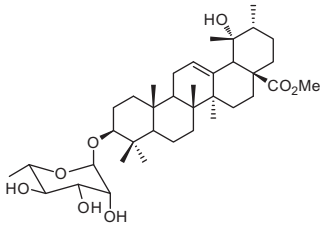
R_1 = OAc, R_2 = H, R_3 = H **362**

R_1 = OH, R_2 = H, R_3 = H **363**

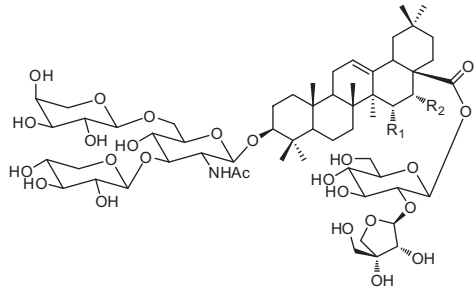
R_1 = H, R_2 = Mb, R_3 = H **364**

Figure 4.13 (Continued)

◀ A (**406**) [113], rheediinoside B (**407**) [113], coriarioside C (**408**) [135], coriarioside D (**409**) [135], coriarioside E (**410**) [135], tetrapteroside A (**411**) [136], tetrapteroside B (**412**) [136], gummiferaoside A (**413**) [114], gummiferaoside B (**414**) [114], gummiferaoside C (**415**) [114], kahiricoside II (**416**) [137], kahiricoside III (**417**) [137], kahiricoside IV (**418**) [137], kahiricoside V (**419**) [137], 6-oxocycloartan-3β,16β-di-*O*-glucoside (**420**) [138],



365



R_1 = H, R_2 = H, R_3 = H, R_4 = H

366

R_1 = H, R_2 = OH, R_3 = H, R_4 = H

367

R_1 = OH, R_2 = OH, R_3 = H, R_4 = H

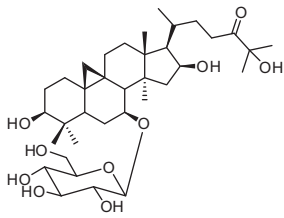
368

R_1 = OH, R_2 = OH, R_3 = Api, R_4 = H

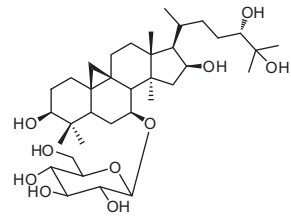
369

R_1 = OH, R_2 = OH, R_3 = Glu, R_4 = Api

370



371



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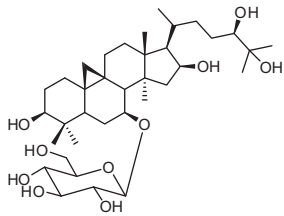
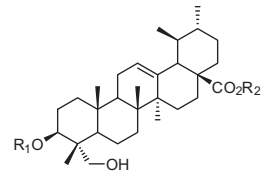


373

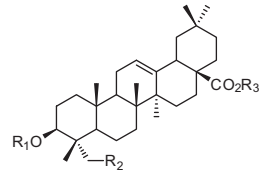


R = Rha(1→4)-Glu, R_2 = Gal(1→6)-Glu

374

Figure 4.13 (Continued)

◀ polysciasoside A (**421**) [139], tomentoside III (**422**) [140], tomentoside IV (**423**) [140], deacetyltomentoside I (**424**) [140], ivorenoside A (**425**) [115], ivorenoside B (**426**) [115], ivorenoside C (**427**) [115], pteleopsoside (**428**) [141], 22α-hydroxyolean-12-en-3β-yl-β-D-galactopyranoside (**429**) [53], 24-hydroxyolean-12-en-3β-yl-β-D-glucopyranoside (**430**) [53], 28β-D-glucopyranosyl-30-methyl-3β-hydroxyolean-12-en-28,30-dioate (**431**) [54],



R = Rha(1→4)-Glu, R_2 = OH, R_3 = Gal(1→6)-Glu

375

R = Glu(1→3)-Xyl(1→2)-aGlu, R_2 = H, R_3 = [Rha(1→4)-Ara(1→6)]Glu

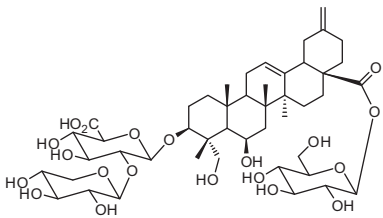
376

R = [Glu(1→2)-Rha(1→4)]Ara, R_2 = H, R_3 = Gal(1→6)Glu

377

R = Glu R_2 = H, R_3 = Rha(1→2)-Glu(1→6)Gal

378



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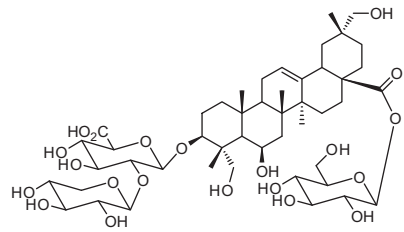

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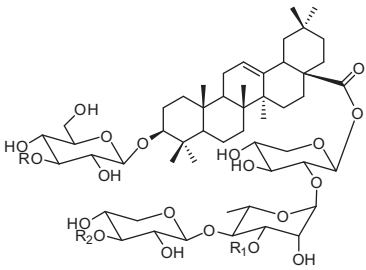
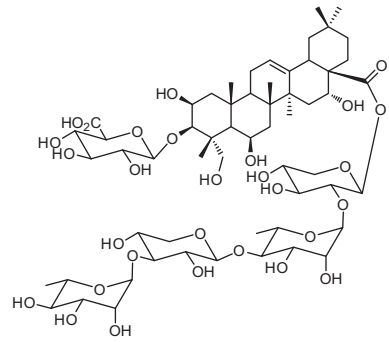


R = H, R_1 = H, R_2 = H

381

R = Api, R_1 = Rha, R_2 = Api

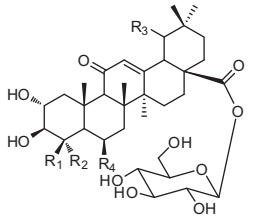
382



383

Figure 4.13 (Continued)

◀ gamboukokoenside A (**432**) [56], gamboukokoenside B (**433**) [56], 3β-hydroxy-29-*O*-(α-L-rhamnopyranosyl)cycloart-24-en-23-on-29-oic acid (**434**) [58], 3β-hydroxy-29-*O*-(α-L-rhamnopyranosyl)-24-methylcycloart-24-(24a)-en-23-on-29-oic acid (**435**) [58], triumfettosaponin (**436**) [95], 1α,23-dihydroxy-12-oleanen-29-oic acid-3β-*O*-2,4-di-acetyl-L-rhamnopyranoside (**437**) [116].



$R_1 = CH_2OH$, $R_2 = CH_2OH$, $R_3 = \alpha$-OH, $R_4 = H$

384

$R_1 = CH_2OH$, $R_2 = CH_2OH$, $R_3 = \beta$-OH, $R_4 = H$

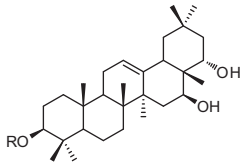
385

$R_1 = CH_3$, $R_2 = CH_2OH$, $R_3 = \alpha$-OH, $R_4 = H$

386

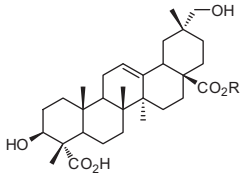
$R_1 = CH_2OH$, $R_2 = CH_3$, $R_3 = \alpha$-OH, $R_4 = OH$

387



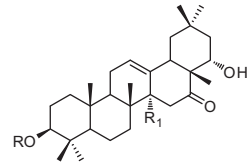
R = Rha(1→2)-Gal(1→2)-GlA

392



R = Gal(1→6)-Glu

394



R = Rha(1→2)-Glu(1→2)-GlA, R_1 = Me

388

R = Rha(1→2)-Xyl(1→2)-GlA, R_1 = Me

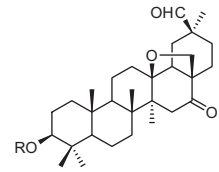
389

R = Rha(1→2)-Gal(1→2)-GlA, R_1 = Me

390

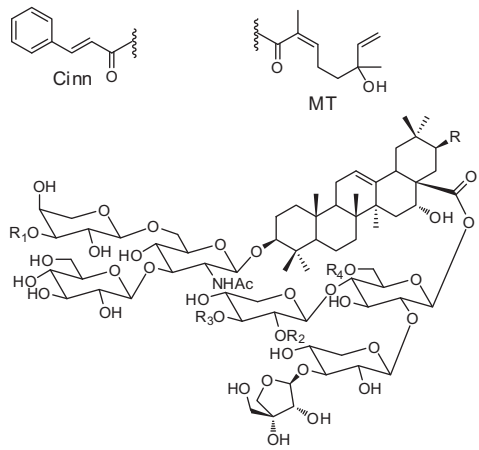
R = Rha(1→2)-Glu(1→2)-GlA, $R_1 = CH_2OH$

391



R = Xyl(1→3)-Glu(1→4)-Xyl

393



R = H, R_1 = Xyl, R_2 = Cinn, R_3 = MT, R_4 = Ac

395

R = H, R_1 = Xyl, R_2 = H, R_3 = MT, R_4 = Ac

396

Figure 4.13 (Continued)

R = OH, R_1 = Xyl, R_2 = H , R_3 = MT, R_4 = Ac

397

R = H, R_1 = Xyl, R_2 = Cinn, R_3 = H, R_4 = Ac

398

R = H, R_1 = Xyl, R_2 = H, R_3 = H, R_4 = Ac

399

R = H, R_1 = Xyl, R_2 = H, R_3 = H, R_4 = Ac

400

R = H, R_1 = Xyl, R_2 = H, R_3 = H, R_4 = Ac

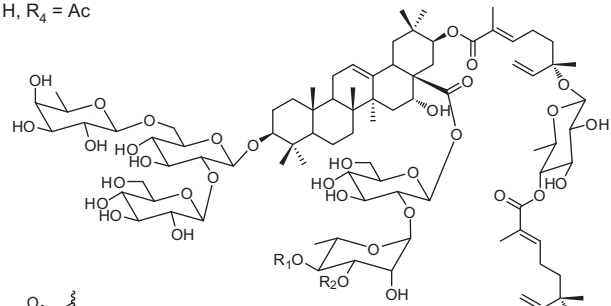
401

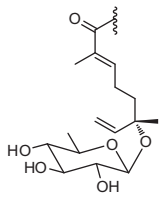
R = H, R_1 = Ara, R_2 = Cinn, R_3 = H, R_4 = Ac

402

R = H, R_1 = Ara, R_2 = H, R_3 = H, R_4 = Ac

403





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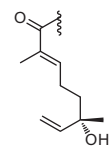
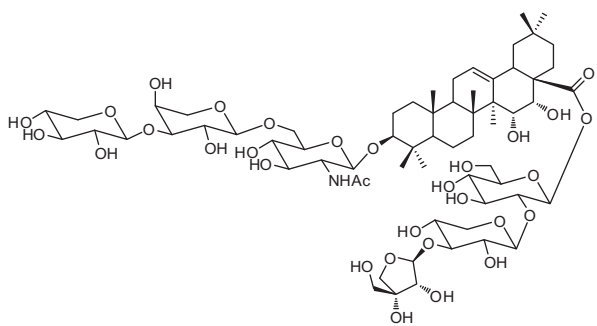


MT

R_1 = Araf, R_2 = Glu, R_3 = S, **404**

R_1 = Xyl, R_2 = H, R_3 = MT, **405**



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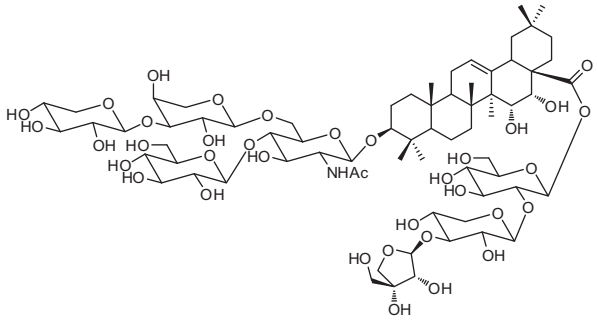

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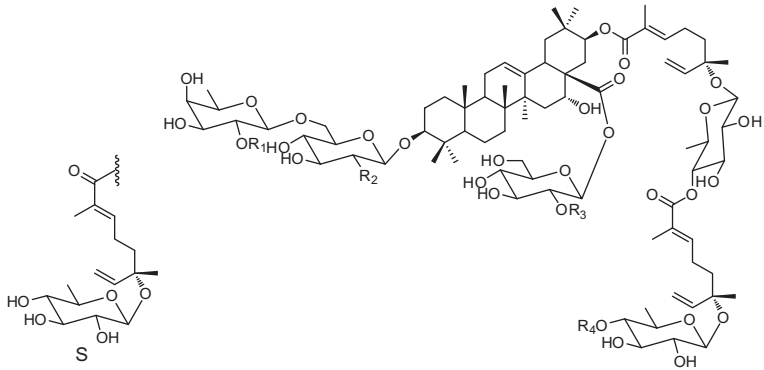
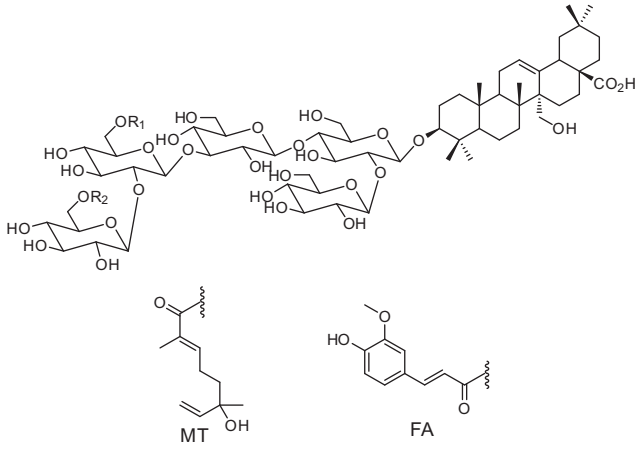


R_1 = Xyl, R_2 = NHAc, R_3 = Xyl (1→4) Rha, R_4 = S, **408**

R_1 = Xyl, R_2 = O-Glu, R_3 = Rha, R_4 = S, **409**

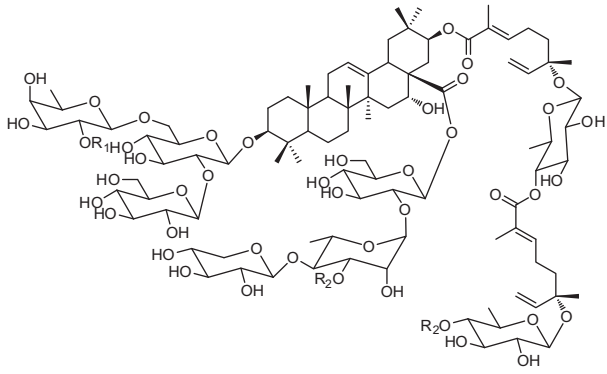
R_1 = H, R_2 = OH, R_3 = H, R_4 = H, **410**



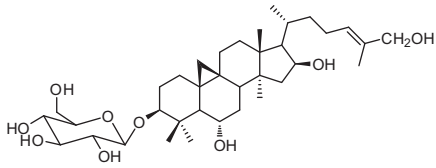
R_1 = H, R_2 = MT, **411**

R_1 = FA, R_2 = H, **412**

Figure 4.13 (Continued)



R_1 = Xyl, R_2 = H, **413**
R_1 = Ara, R_2 = H, **414**
R_1 = H, R_2 = S, **415**



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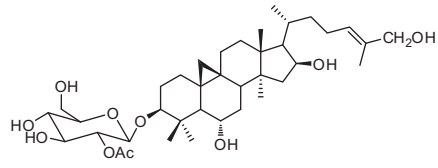

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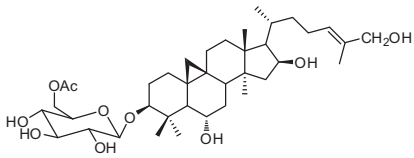

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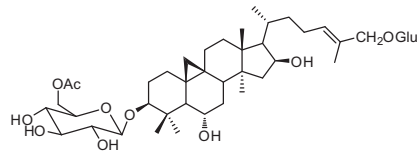

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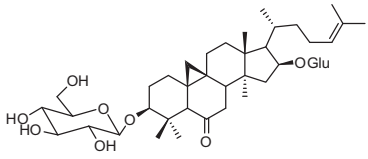

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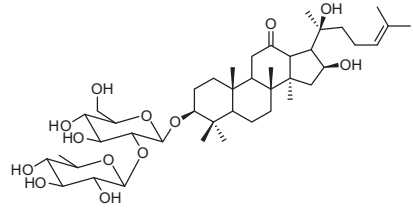

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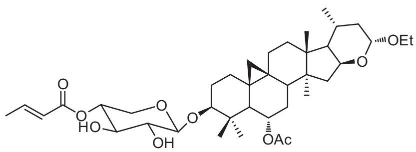

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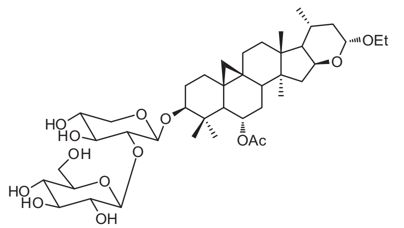

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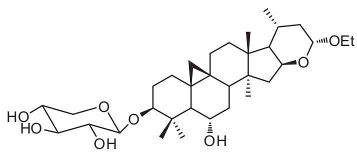

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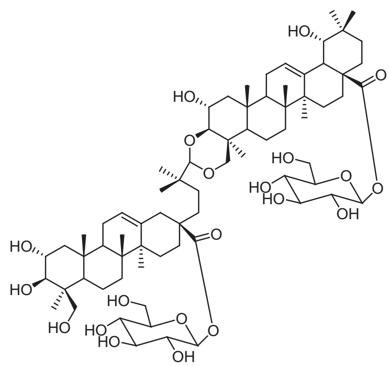

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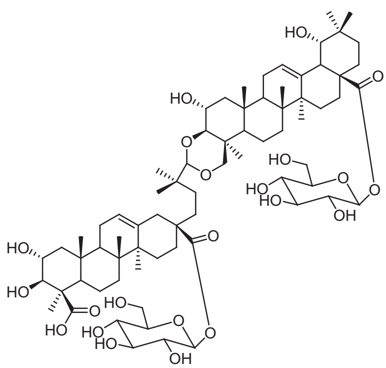

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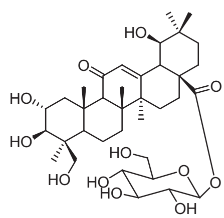

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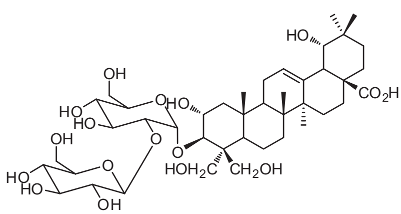

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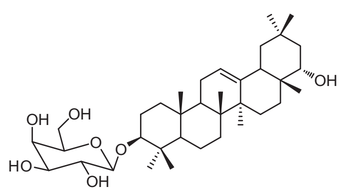

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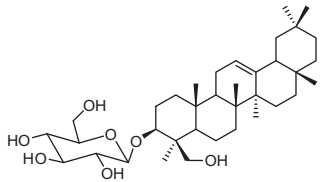

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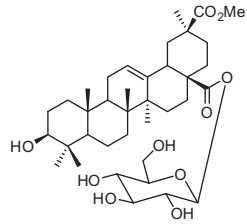

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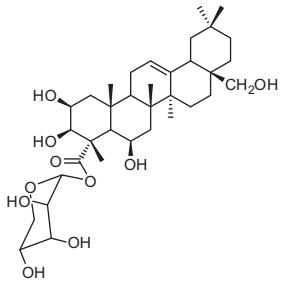

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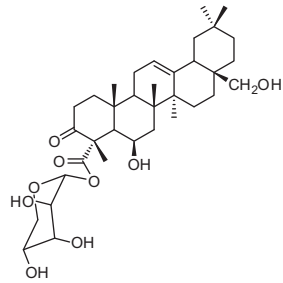

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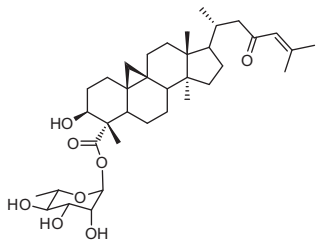

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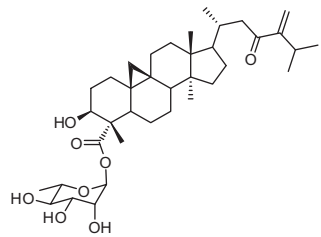

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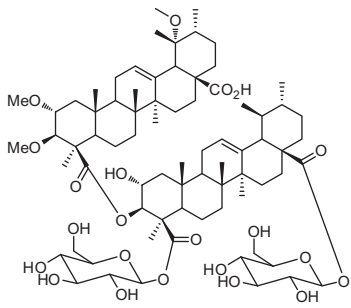

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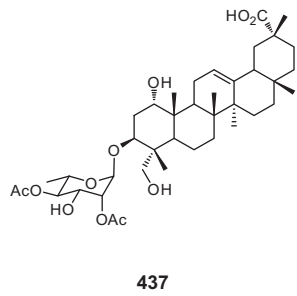


437

Figure 4.13 (Continued).

4.7 Other Triterpenoids from African Medicinal Plants

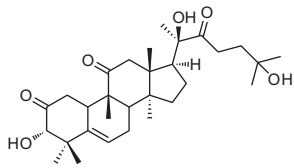
Known terpenoids with different kinds of skeletons, such as steroids, pentacyclic and tetracyclic triterpenes, as well as glycosides and polyhydroxylated triterpenes, have been isolated from African medicinal plants. Some of these molecules have proved to have well-defined biological activity.

Compounds **439** and **440** (Figure 4.14) have shown significant antibacterial activity against six of seven strains tested, namely *Staphylococcus aureus*, *Bacillus subtilis*, *Clostridium sporogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella dysenteriae* and *Clostridium tetani*, with MICs between 15.4 and 37.2 μg/mL, whereas those of gentamicin, used as the reference drug, ranged between 12.1 and 20.7 μg/mL. These natural products were isolated from *Paullinia pinnata*, a Nigerian medicinal plant, lupeyl steryl ether (**440**) being more active than gentamicin against *C. tetani*, with minimal inhibition concentration (MIC) values at 18.4 and 20.7 μg/mL, respectively [40]. Compounds **442**−**445** have been evaluated for their antimicrobial activities against *E. coli*, *S. typhi*, *S. dysenteriae*, *P. aeruginosa*, and *S. aureus*. In the end, compound **445** turned out to be strongly active against *E. coli*, *S. typhi*, and *S. aureus*, with diameters of inhibition at 18, 17, and 21 mm, respectively, while gentamicin, used as the reference drug, had 35, 42, and 34 mm diameters of inhibition. The remaining metabolites (**442**−**444**) were active only against *S. aureus*, with diameters of 11, 10, and 15 mm, respectively [43]. Phytochemistry studies performed on *Boswellia papyrifera*, a Cameroonian medicinal plant, led to the isolation and the identification of β-elemonic acid (**442**), boswellic acid (**448**), and its derivatives (**449**−**451**). These compounds were screened for their ability to inhibit propyl endopeptidase, and all presented significant activity with IC_{50} of 39.74 (**452**), 9.75 (**448**), 36.32 (**449**), 7.89 (**450**), and 114.75 (**451**) μM, while the IC_{50} of the standard drug bacitracin was 129.26 [44]. Known metabolites (**453**−**456**) of *T. ivorensis*, from the littoral region of Cameroon, disclosed weak radical scavenging properties and cytotoxic activities against MDA-MB-231 (human breast cancer cell line), PC3 (human prostatic adenocarcinoma cell line), HCT116 (human colon carcinoma cell line), and T98G (human glioblastoma multiform cell line). Except for PC3, arjunic acid (**455**) showed significant activity against the remaining cancer cell lines, with IC_{50} between 12.6 and 32.8 μM [45]. Ursolic (**458**) and oleanolic acids (**456**), both isolated from Madagascar medicinal plant *Acridocarpus vivy*, have showed significant cytotoxic activity against the A2780 human ovarian cell line, with IC_{50} of 9.2 and 8.0 μg/mL. Moreover, morolic acid (**459**) obtained from the same plant showed moderate antiproliferative activity against the same cancer cell line with an IC_{50} of 13.1 μg/mL [46].

This class of compounds has been widely investigated chemically and biologically, though there is still a lot to do concerning their real role in human health.

4.8 Conclusions

As you can see, triterpenoids are formed from large number of diversified skeletons. Each core can be biosynthetically modified, leading to polyhydroxylated,



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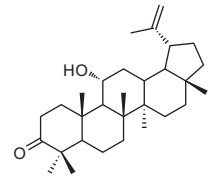

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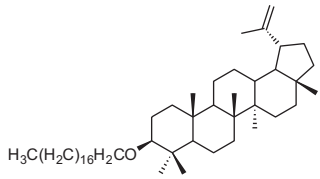

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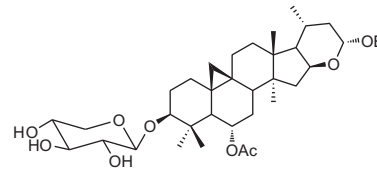

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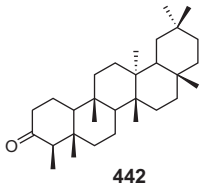

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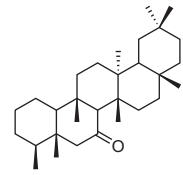

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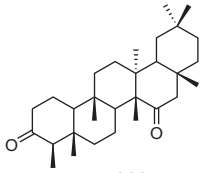

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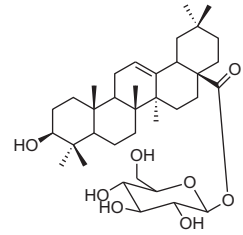

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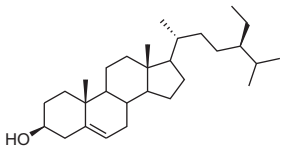

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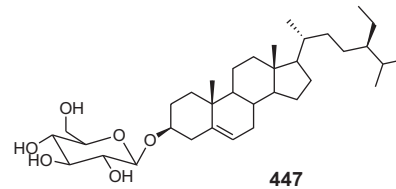


447

Figure 4.14 Some known triterpenoids isolated from African medicinal plants: isocucurbitacin R (**438**) [36], 11α-hydroxy-lup-20(29)-en-3-one (**439**) [40], lupeyl steryl ether (**440**) [40], tomentoside I (**441**) [140], friedelin (**442**) [43], friedelan-7-one (**443**) [43], friedelane-3,15-dione (**444**) [43], 3β-hydroxyolean-12-en-28-β-D-glucopyranosyl ester (**445**) [43], β-sitosterol (**446**) [43], 3-*O*-β-D-glucopyranosyl-β-sitosterol (**447**) [43], β-boswellic acid (**448**) [44], 11-keto-β-boswellic acid (**449**) [44], 3α-acetoxy-11-keto-β-boswellic acid (**450**)

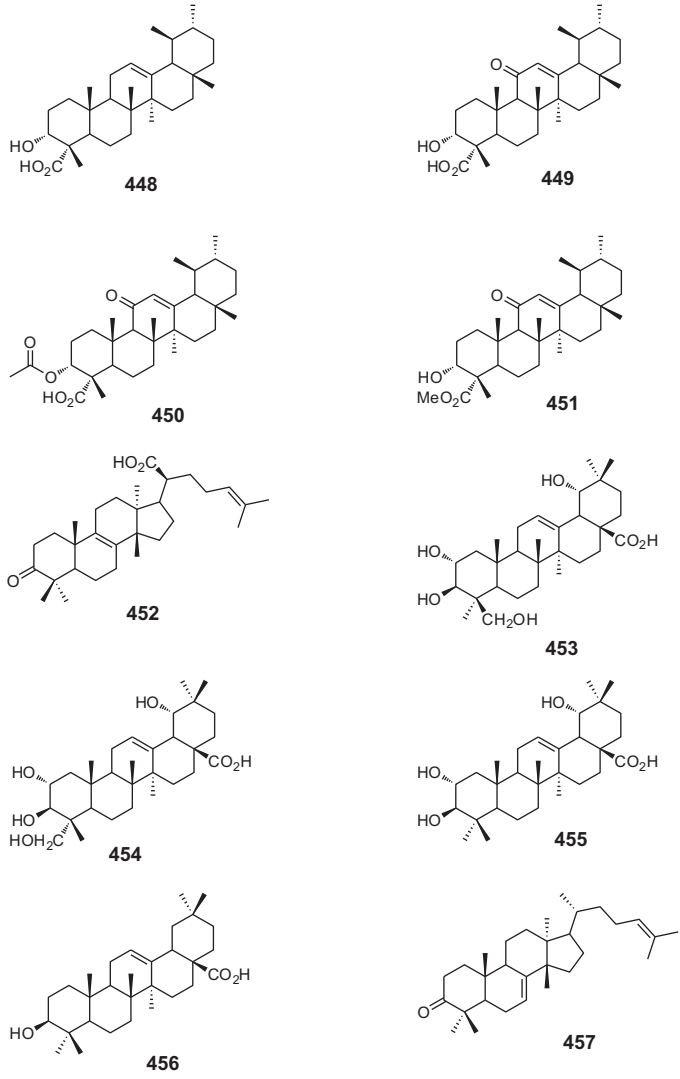
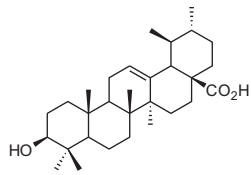


Figure 4.14 (Continued)

◀ [44], methyl ester 11-keto-β-boswellic acid (**451**) [44], β-elemonic acid (**452**) [44], sericic acid (**453**) [45], arjungenin (**454**) [45], arjunic acid (**455**) [45], oleanolic acid (**456**) [45,46], tirucalla-7,24-dien-3-one (**457**) [142], ursolic acid (**458**) [46], moronic acid (**459**) [46], β-amyrin acetate (**460**), β-amyrin arachidate (**461**), β-amyrin behenate (**462**), β-amyrin lignocerate (**463**) [48], erythrodiol (**464**) [48], 28-hydroxy-β-amyrone (**465**) [48], chondrillasterone (**466**) [48], chondrillasterol (**467**) [48], chondrillasterol glucopyranoside



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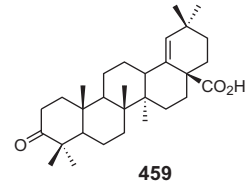

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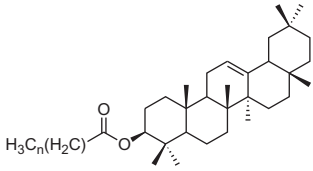
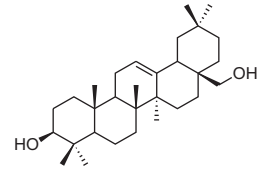


n = 0 **460**, *n* = 18 **461**, *n* = 20 **462**, *n* = 22 **463**



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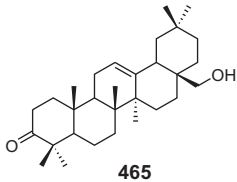

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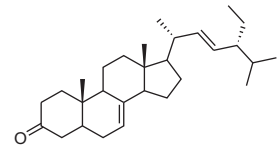

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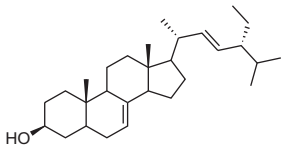

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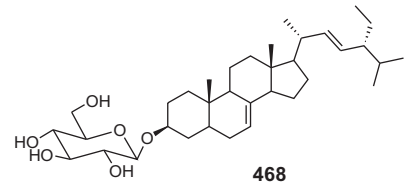

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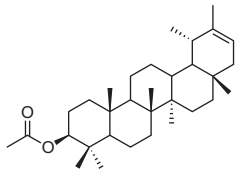

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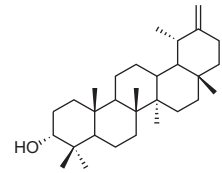

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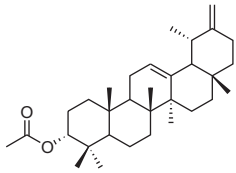
Figure 4.14 (Continued)

◀ (**468**) [48], pseudotaraxasterol acetate (**469**) [51], taraxasterol (**470**) [51], calotropursenyl acetate B (**471**) [51], α-amyrin palmitate (**472**) [62], β-amyrin palmitate (**473**) [62], lupeyl acetate (**474**) [62], lupeol (**475**) [62], 7-deacetylgedunin (**476**) [77], 7-deacetyl-7-oxogedunin (**477**) [77], obacunone (**478**) [78], harrisonin (**479**) [78], 12β-acetoxyharrisonin (**480**) [78], pedonin (**481**) [78], glaucarubinone (**482**) [92].



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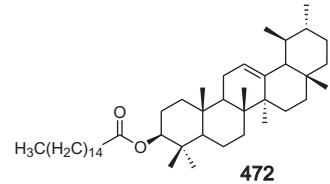

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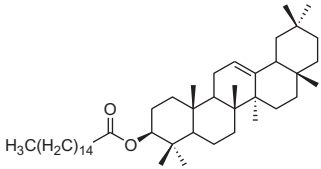

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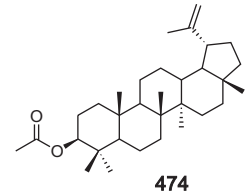

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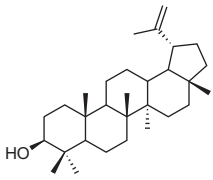

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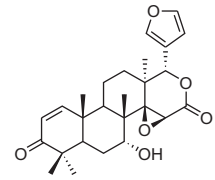

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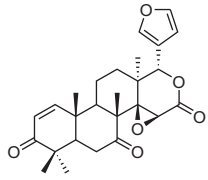

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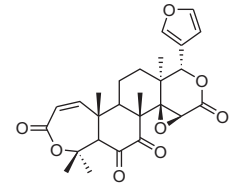

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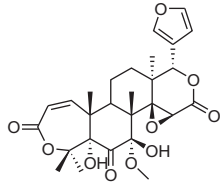

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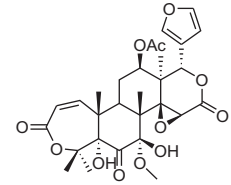

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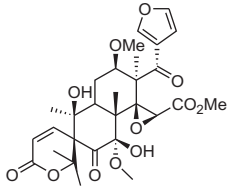

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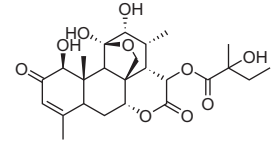

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Figure 4.14 (Continued)

glycosylated, acylated, and esterified, etherified, or oxidized triterpenoids. These compounds are endowed with several biological properties. Some activities are moderate, but others are significant compared to standard drugs, but up to now, only a few of those secondary metabolites have proven more active than the reference drugs. Some compounds like betulinic acid have proved to have strong cytotoxic activity and are drug candidates today. Furthermore, these various structures can offer possibilities as raw material to prepare semisynthetic derivatives for further biological purposes. Finasteride is a drug derived from steroid semisynthesis, and it is used today for the treatment of benign prostatic hyperplasia and men's hair loss [143]. Likewise, this family is the main provider of precursors of human steroidal hormones.

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5 Essential Oils from the Medicinal Plants of Africa

Oladipupo A. Lawal and Isiaka A. Ogunwande

Department of Chemistry, Lagos State University, Lagos, Nigeria

5.1 Introduction

Essential oils involve a large range of plant oils which are highly aromatic. They are found mainly in the flowers, buds, leaves, twigs, bark, wood, roots, rhizomes, bulbs, fruits, peels, seeds, and resin of plants. A few of them are obtained from animal sources or are produced by microorganisms [1−3]. They have well-defined odors, which can be detected at very low concentration. Essential oils, also called oils due to their liquid nature at room temperature, differ entirely in both chemical and physical properties from fixed oils (which are composed of naturally occurring mixtures of lipids), and are composed of a wide variety of natural organic components with different functional groups and molecular structures [1,4]. Essential oils can be considered to be direct metabolites produced in plant organs (such as secretion ducts or glandular trichomes) by intracellular biogenetic pathways; thus, their quality and quantity depends on environmental, genetic, and climatic factors, nutritional status of the plants, and other factors [5−7]. However, investigations on the biosynthesis of plant volatiles have shown that some of the volatiles are actually secondary metabolites not occurring in intact cells [8,9]. Essential oils, also known as essences or volatile oils, are complex mixtures of over 3000 compounds, of which about 300 are of commercial importance [10,11]. The constituents of essential oils include hydrocarbons and their oxygenated derivatives, which consist of alcohols, acids, esters, aldehydes, ketones, amines, and nitrogen and sulfur compounds [1]. The isolation of essential oils from plant materials may be effected by several methods (including hydrodistillation, steam distillation, water and steam distillation, expression, effleurage, maceration, and supercritical, microwave, and solvent extractions, among others), depending on the nature of the material and in accordance with the characteristics of the essential oil [1,2,4]. Since essential oils are complex mixtures of compounds, they are required to comply with some sets of standards. Physicochemical properties/indices have reportedly been used in determining the quality of essential oils [1,12−14]. Also, analyses of essential oils

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have been performed using instrumental techniques such as chromatographic and spectroscopic techniques, or their combinations, for identification and characterization of the constituents of essential oils [1]. Furthermore, different retention index systems based on different stationary phases have been used in determining essential oil constituents; comparison of their retention indices and mass spectra with those of authentic samples and published data has also been pursued [15–18]. Essential oils, like spices, have been used for flavoring, perfumery, and preservative processes since time immemorial [19]. Essential oils gained recognition in the ninth century and become widespread between the sixteenth and twentieth centuries, when their uses for flavor and aroma, as well as in medicine, gradually become known [2]. The greatest uses of essential oils today are in the food, perfumery, cosmetic, cleaning, sanitary, and pharmaceutical industries, as well as in medicine [3,20,21]. The essential oils of many plant species have been reported to possess useful biological, pharmacological, and therapeutic activities, including anti-*Candida*, anti-inflammatory, analgesic, antidiabetic, antidiarrheal, antimutagenic, antimicrobial, antioxidant, antipyretic, anti-inflammatory, cytotoxic, apoptotic, and insecticidal activities, and for inhaling [22–27]. In addition to their traditional uses, various applications (such as massaging and bathing) have also been found in aromatherapy [4,28,29]. Furthermore, some essential oils are valuable alternatives to synthetic compounds [30].

The chemical composition and biological activities of the essential oils from different plant species of African origin have been studied extensively, and reports have shown that many novel compounds with biological and pharmacological activities have been identified, characterized, and isolated [31–33]. However, to the best of our knowledge, no study has reviewed the constituents of essential oils from aromatic and medicinal plants growing in Africa, and no previous information on their biological activity have been reported anywhere, although a review of the chemical composition and biological activity of essential oils of some plants grown in Nigeria has been reported [34]. The aim of this review is to summarize research into the major constituents and biological activities of essential oils from aromatic and medicinal plants of African origin between the years 2007 and 2012.

5.2 Classification of Essential Oils

Most essential oils consist of aliphatic hydrocarbons, monoterpenoids, sesquiterpenoids, and diterpenes, such as α-pinene (Figure 5.1 (**1**)), β-pinene (**2**), myrcene (**3**), α-phellandrene (**4**), *p*-cymene (**5**), limonene (**6**), α-selinene (**7**), β-selinene (**8**), and caryophyllene oxide (**9**). Other groups of compounds include phenylpropanoids, acids, alcohols, ketones, aldehydes, and fatty acids and their esters. In addition, several nitrogen and sulfur compounds, e.g., mintsulfide (**10**), which impart characteristic sensory properties, are also important constituents of many essential oils [4,35,36].

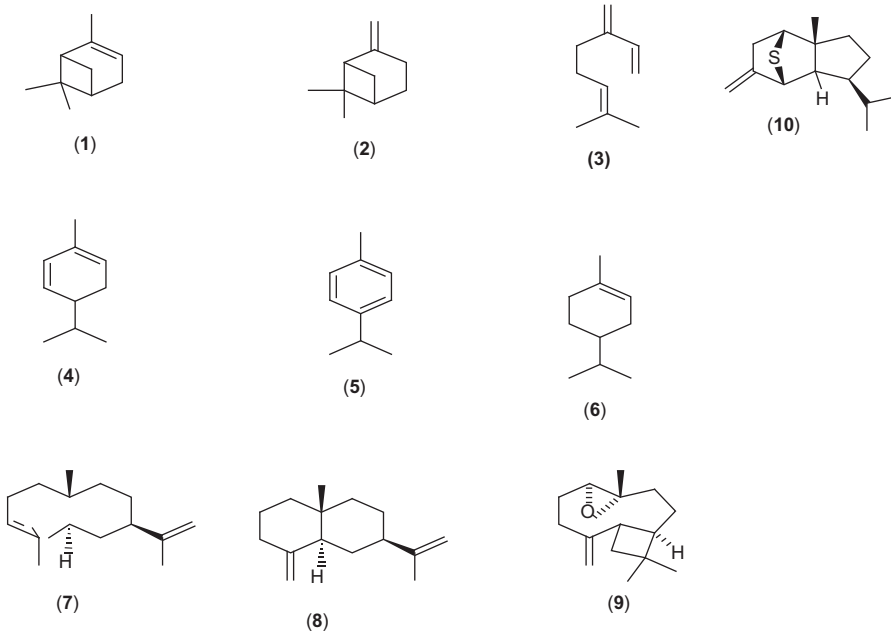

Figure 5.1 Some constituents of essential oils: α-pinene (**1**), β-pinene (**2**), myrcene (**3**), α-phellandrene (**4**), *p*-cymene (**5**), limonene (**6**), α-selinene (**7**), β-selinene (**8**), caryophyllene oxide (**9**), and mintsulfide (**10**).

5.3 Chemical Composition of Essential Oils

Table 5.1 lists the major constituents of the essential oils isolated from some aromatic and medicinal plants from different countries of Africa. In total, 99 plant species from 65 genera and 34 families were identified and reviewed. Literature reports on the composition of the essential oils from these plant species showed that numerous investigations have been reported, and different isolation methods, such as hydrodistillation, steam distillation, microwave extraction, expression, simultaneous distillation−extraction, supercritical extraction, solvent extraction, solid phase microextraction, and headspace solid phase microextraction, among others, have been used for the isolation of essential oils from different parts of these plants [1]. In addition, different techniques such as column chromatography, thin-layer chromatography, high-pressure liquid chromatography, mass spectrometry, nuclear magnetic resonance spectroscopy, gas chromatography/mass spectrometry, liquid chromatography/mass spectrometry, gas chromatography/Fourier-transform infrared spectrophotometry, and gas chromatography/Fourier-transform infrared spectrophotometry/mass have also been used in identification, characterization, and isolation of novel compounds from the essential oils of some plant species [1].

Table 5.1 Major Constituents of Essential Oils of Aromatic and Medicinal Plants of Africa[a]

Family	Family/Plant Species	Constituent	Origin	Reference
Acanthaceae	*Peristrophe bicalyculata*	β-Caryophyllene	Nigeria	[37]
Amaryllidaceae	*Crinum ornatum*	14-Methylpentanedecanoic acid methyl ester	Nigeria	[38]
Anacardiaceae	*Schinus molle*	δ-Cadinene, limonene, α- and β-phellendrene	Tunisia	[39–42]
	Schinus terebinthifolius	δ-3-Cadinene	Tanzania	[43]
		α-Phellandrene	Tunisia	[42]
		Sabinene	Zimbabwe	[44]
	Pistacia lentiscus	α-Pinene and germanicol	Morocco	[45,46]
		Limonene	Tunisia	[47]
Annonaceae	*Monodora myristica*	α-Phellandrene	South Africa	[48]
		p-Cymene	Nigeria	[49]
	Annona senegalensis	Caryophyllene oxide	Egypt	[50]
Asteraceae	*Ageratum conyzoides*	Precocene I	Côte d'Ivoire	[51]
	Blumea perrottetiana	2,5-Dimethoxy-*p*-cymene	Nigeria	[52]
	Chromolaena odorata	α-Pinene	Nigeria	[53]
		Ascaridole	Togo	[54]
	Chrysocoma ciliate	β-Pinene	South Africa	[55]
	Cotula cinerea	*trans*-Thujone	Morocco	[56]
	Felicia muricata	Limonene	South Africa	[57]
	Matricaria pubescens	Isochrysanthemic acid ethyl ester	Algeria	[58]
	Santolina chamaecyparissus	Camphor	Algeria	[59]
	Schistostephium hippifolium	Chrysanthenyl acetate (Su); 1.8-cineole (W)	South Africa	[60]
	Tarchonanthus camphoratus	1,8-Cineole	Kenya	[61]
			South Africa	[62]
	Thelechitonia trilobata	α-Pinene	South Africa	[63]
Apiaceae	*Coriandrum sativum*	2E-Decenal	Kenya	[64]
Aristolochiaceae	*Aristolochia ringens*	Aristolone (R)	Nigeria	[65]
Bignoniaceae	*Tabebuia rosea*	Methyl cyclohexane (L), *n*-amyl ketone (SB)	Nigeria	[66]

Burseraceae	*Aucoumea klaineana*	δ-3-Carene	Burkina Faso	[67]
		α-Phellandrene	Cameroon	[68]
	Canarium schweinfurthii	Limonene	Cameroon	[68]
Caesalpiniaceae	*Mezoneuron benthamianum*	*trans*-Phytofluene	Nigeria	[69]
Chenopodiaceae	*Chenopodium ambrosioides*	α-Terpinene	Benin	[70]
		Ascaridole	Nigeria	[54]
			Togo	[71]
Cupressaceous	*Juniperus phoenicea*	α-Pinene	Algeria	[72,73]
			Tunisia	[74]
	Sabina virginiana	Limonene	Nigeria	[75]
	Tetraclinis articulate	Cedrene	Morocco	[76]
Cyperaceae	*Cyperus articulatus*	*cis*-Calamenene (R)	Egypt	[77]
	Cyperus esculentus	*cis*-Calamenene (R)	Egypt	[77]
	Cyperus rotundus	α-Cyperone (R)	Tunisia	[78]
	Kyllinga erecta	α-Humulene (AP); 1,8-cineole (R)	Nigeria	[79]
Euphorbiaceae	*Acalypha ornata*	Viridiflorene	Nigeria	[80]
	Ricinus communis	α-Thujone	Tunisia	[81]
Fabaceae	*Enterolobium contortisiliquum*	Furfural (S)	Egypt	[82]
	Eriosema englerianum	*o*-Cymene	South Africa	[83]
	Senna alata	ar-Turmerone	Nigeria	[84]
	Senna hirsuta	(*E*)-Phytol	Nigeria	[84]
	Senna occidentalis	(*E*)-Phytol	Nigeria	[84]
	Tetrapleura tetraptera	1,8-Cineole	Nigeria	[85]
Geraniaceae	*Geranium sanguineum*	1-Phenyl butanone (F)	Tunisia	[86]
Hypericaceae	*Psorospermum tenuifolium*	Linlool (L), α-pinene (R)	Nigeria	[87]
Lamiaceae	*Mentha piperita*	Menthol	Burkina Faso	[88]
		Menthone	Morocco	[89]
	Ocimum basilicum	Linalool	Burkina Faso	[88]
		p-Cymene	Morocco	[89]
		1,8-Cineole	Tanzania	[90]

(*Continued*)

Table 5.1 (Continued)

Family	Family/Plant Species	Constituent	Origin	Reference
	Ocimum gratissimum	Thymol	Togo	[91]
	Ocimum kilimandscharicum	Camphor	Tanzania	[90]
	Ocimum lamiifolium	Bornyl acetate	Tanzania	[90]
	Ocimum suave	Germacrene-D	Tanzania	[90]
	Rosemarinus officinalis	α-Pinene	Morocco	[92]
	Salvia officinalis	1,8-Cineole	Tunisia	[41]
	Thymus broussonetii	*p*-Cymene and carvacrol (W & C)	Morocco	[93–95]
	Thymus capitatus	*p*-Cymene	Morocco	[96]
	Thymus maroccanus	Carvacrol (WD & C)	Morocco	[93,94]
	Thymus vulgaris	Camphor	Morocco	[97]
	Thymus satureioides	Carvacrol (WD & C)	Morocco	[93,95]
Malvaceae	*Gossypium barbadense*	Tricyclene	Nigeria	[98]
Moraceae	*Ficus exasperate*	α-Terpineol	Nigeria	[99]
Myrtaceae	*Callistemon citrinus*	1,8-Cineole (L)	South Africa	[100]
	Callistemon viminalis	1,8-Cineole (L)	South Africa	[100]
	Eucalyptus astringens	1,8-Cineole	Tunisia	[101]
	Eucalyptus bicostata	1,8-Cineole	Tunisia	[101]
	Eucalyptus cinerea	1,8-Cineole	Tunisia	[101]
	Eucalyptus globules	Terpiene-4-ol	Nigeria	[102]
	Eucalyptus lahmannii	1,8-Cineole	Tunisia	[101]
	Eucalyptus leucoxylon	1,8-Cineole	Tunisia	[101]
	Eucalyptus maidenii	1,8-Cineole	Tunisia	[101]
	Eucalyptus odorata	Crytone	Tunisia	[101]
	Eucalyptus sideroxylon	1,8-Cineole	Tunisia	[101]
	Melaleuca quinquenervia	1,8-Cineole	Côte d'Ivoire	[51]
Pinaceae	*Pinus caribaea*	β-Phellandrene	Nigeria	[103]
	Pinus halepensis	Caryophyllene oxide	Algeria	[104]
	Pinus patula	α-Pinene	Tunisia	[105]
	Pinus pinea	Limonene	Tunisia	[106]

Piperaceae	*Piper capense*	β-Pinene (L, F)	Cameroon	[107]
	Piper guineense	β-Caryophyllene (F), germacrene B (L)	Cameroon	[107]
	Piper nigrum	Limonene (F), α-selinene (L)	Cameroon	[107]
	Piper umbellatum	β-Pinene (F), β-caryophyllene (L)	Cameroon	[107]
Phyllanthaceae	*Phyllanthus amarus*	Linalool	Nigeria	[108]
Poaceae	*Cymbopogon citratus*	Geranial	Kenya	[109]
			Nigeria	[110]
Ranunculaceae	*Nigella sativa*	*p*-Cymene	Tunisia	[111]
Rubiaceae	*Borreria verticillata*	Phytol	Nigeria	[37]
	Morinda lucida	α-Terpinene	Nigeria	[112]
Rutaceae	*Citrus aurantifolia*	Limonene (L)	Côte d'Ivoire	[58]
	Zanthoxylum leprieurii	Terpinolene (L); *E*-(β)-ocimene (F)	Cameroon	[113]
	Zanthoxylum macrophylla	Limonene (L), thujanol (F)	Cameroon	[113]
	Zanthoxylum xanthoxyloïdes	Mycrene (L), citronellal (F)	Cameroon	[113]
Solanaceae	*Solanum erainthum*	α-Terpinolene (L); α-humulene (F)	Nigeria	[114]
	Solanum macranthum	(*E*)-Phytol (L); α-humulene (F)	Nigeria	[114]
	Datura metel	α-Phellandrene (L); linalool (F); *p*-cymene (F)	Nigeria	[115]
Taxodiaceae	*Taxodium distichum*	α-Pinene (F); thujopsene (L)	Nigeria	[116]
Umbelliferae	*Ferula lutea*	δ-3-Carene	Tunisia	[117]
Verbenaceae	*Lantana camara*	β-Caryophyllene	Algeria	[118]
			Benin	[119]
	Lippia multiflora	*p*-Cymene	Morocco	[89]
		1,8-Cineole	Nigeria	[120]
	Vitex agnus-castus	α-Terpineol	Nigeria	[121]
Zingiberaceae	*Aframomum daniellii*	Limonene (L), 1,8-cineole (S)	Cameroon	[122]
	Aframomum latifolium	β-Pinene (L), β-caryophyllene (S)	Cameroon	[122]
	Aframomum melegueta	β-Pinene (L), α-humulene (S)	Cameroon	[122]
	Zingiber officinale	Zingiberene	Nigeria	[123]

Su, summer; W, winter; WD, wild; C, cultivated.
[a]Plant part—AP, aerial parts; F, flowers; L, leaves; S, stem; SB, stem bark; B, bulbs; R, roots.

The major constituents of essential oils from the plant species reviewed reveal that large numbers of monoterpenes, sesquiterpenes, diterpenes, and fatty acid esters predominate, although the relative composition of the constituents of each oil varies from one plant to the other. In addition, the constituents of oils from the same plant from different countries, or those collected from different locations in same country, vary due to their individual volatile constituents, genotype, growth stage, and geographical and climate conditions [5–7].

5.4 Biological Activity of Essential Oils from African Medicinal Plants

Numerous studies have shown that essential oils and their constituents from a wide variety of plant species from Africa exhibit biological and pharmacological activities such as antifungal, antibacterial, anti-inflammatory, antioxidant, cytotoxicity, and insecticidal activity [23–27]. In addition, effects like allelopathic, antimutagenic, hepatoprotective, and phototoxicity of these essential oils, as well as synergism between their constituents, have also been reported [124–126]. A brief summary of some biological activities is given below, while Table 5.2 lists the activities of the various plant species.

Table 5.2 Biological Activities of Essential Oils from Medicinal Plants of Africa

Plant Species	Activities	Reference
A. ornata	Antioxidant and cytotoxicity	[80]
A. daniellii	Antioxidant and anti-inflammatory	[122]
A. latifolium	Anti-inflammatory	[122]
A. melegueta	Antioxidant and anti-inflammatory	[122]
A. conyzoides	Insecticidal	[58]
A. senegalensis	Cytotoxicity	[56]
A. ringens	Insecticidal	[65]
Aspilia africana	Antimicrobial and cytotoxicity	[59]
A. klaineana	Antimicrobial and antioxidant	[67,68]
B. perrottetiana	Insecticidal	[60]
B. verticillata	Antimicrobial and cytotoxicity	[37]
C. citrinus	Antibacterial	[100]
C. viminalis	Antibacterial	[100]
C. schweinfurthii	Anti-inflammatory	[68]
C. ambrosioides	Antimicrobial, antiradical, cytotoxicity, and anti-inflammatory	[54,70,71]
C. odorata	Antimicrobial and cytotoxicity	[62,63]
C. ciliate	Antimicrobial	[64]
C. aurantifolia	Insecticidal	[58]

(*Continued*)

Table 5.2 (Continued)

Plant Species	Activities	Reference
C. sativum	Antimicrobial	[64]
C. cinerea	Anti-*Candida*	[65]
C. ornatum	Cytotoxicity	[38]
C. citratus	Antifungal, antibacterial	[109,110]
C. esculentus	Hepatoprotective	[77]
C. rotundus	Antioxidant, apoptotic, and cytotoxicity	[78]
D. metel	Antimicrobial and cytotoxicity	[115]
E. contortisiliquum	Antimicrobial	[82]
E. englerianum	Antimicrobial and antioxidant	[83]
E. astringens	Antibacterial, antifungal, and antiviral	[101]
E. bicostata	Antibacterial, antifungal, and antiviral	[101]
E. globules	Antioxidant and cytotoxicity	[102]
E. lahmannii	Antibacterial, antifungal, and antiviral	[101]
E. leucoxylon	Antibacterial, antifungal, and antiviral	[101]
E. maidenii	Antibacterial, antifungal, and antiviral	[101]
E. odorata	Antibacterial, antifungal, and antiviral	[101]
E. sideroxylon	Antibacterial, antifungal, and antiviral	[101]
F. muricata	Antibacterial	[57]
F. lutea	Antimicrobial and antiacetylcholinesterase	[117]
F. exasperate	Anticandidal	[100]
G. sanguineum	Antibacterial and antioxidant	[86]
G. barbadense	Antimicrobial	[98]
J. phoenicea	Antimicrobial and antioxidant	[72−74]
K. erecta	Antimicrobial	[79]
L. camara	Antifungal and insecticidal	[118,119]
L. multiflora	Antioxidant and antibacterial	[89,120]
M. pubescens	Analgesic	[58]
M. quinquenervia	Insecticidal	[51]
M. piperita	Antibacterial and antioxidant	[88,89]
M. benthamianum	Anti-inflammatory	[69]
M. myristica	Antifungal, hypotensive, and insecticidal	[52−54]
M. lucida	Antioxidant	[112]
N. sativa	Antimicrobial and cytotoxicity	[111]
O. basilicum	Antimicrobial	[88]
Ocimum canum	Antimicrobial	[90]
O. gratissimum	Antifungal	[91]
O. kilimandscharicum	Antimicrobial	[90]
O. lamiifolium	Antimicrobial	[90]
O. suave	Antimicrobial	[90]
P. bicalyculata	Antimicrobial and cytotoxicity	[37]
P. amarus	Larvicidal	[108]
P. caribaea	Antibacterial	[103]
P. halepensis	Antifungal	[104]
P. patula	Antifungal and allelopathic	[105]

(*Continued*)

Table 5.2 (Continued)

Plant Species	Activities	Reference
P. pinea	Antifungal and allelopathic	[106]
P. capense	Insecticidal	[107]
P. guineense	Insecticidal	[107]
P. nigrum	Insecticidal	[107]
P. umbellatum	Insecticidal	[107]
P. lentiscus	Antibacterial and insecticidal	[46–50]
P. tenuifolium	Anti-inflammatory	[87]
R. communis	Antioxidant and cytotoxicity	[81]
R. officinalis	Antibacterial	[92]
S. virginiana	Anti-inflammatory	[75]
S. officinalis	Antimicrobial	[41]
S. chamaecyparissus	Antimicrobial	[59]
S. molle	Antimicrobial, anticancer, allelopathic, and insecticidal	[39–42]
S. terebinthifolius	Antimicrobial, anticancer, antioxidant, and insecticidal	[42–44]
S. hippifolium	Antibacterial	[60]
S. alata	Antioxidant and cytotoxicity	[84]
S. hirsuta	Antioxidant and cytotoxicity	[84]
S. occidentalis	Antioxidant and cytotoxicity	[84]
S. erainthum	Antimicrobial and cytotoxicity	[114]
S. macranthum	Antimicrobial and cytotoxicity	[114]
T. rosea	Cytotoxicity	[66]
T. camphoratus	Antimicrobial and larvicidal	[61,62]
T. distichum	Cytotoxicity	[116]
T. articulate	Antibacterial	[76]
T. tetraptera	Antibacterial and cytotoxicity	[85]
T. trilobata	Antitick, repellent, and toxicity	[63]
T. broussonetii	Antimicrobial and insecticidal	[93,94]
T. capitatus	Antioxidant	[95]
T. maroccanus	Antimicrobial and insecticidal	[93,94]
T. satureioides	Antimicrobial and insecticidal	[93,94]
T. vulgaris	Antimicrobial	[97]
V. agnus-castus	Antibacterial and insecticidal	[121]
Z. leprieurii	Antifungal	[113]
Z. macrophylla	Antifungal	[113]
Z. xanthoxyloïdes	Antifungal	[113]
Z. officinale	Antifungal	[123]

5.4.1 Antimicrobial Activity

Plants have been exploited as a source of biologically active compounds since antiquity, and their ability to inhibit the growth of spoilage and food poisoning bacteria, human and animal pathogens, and a number of fungi has been reported to be of immense importance [23,24]. In many plants, the ability to exhibit antimicrobial activity lies within the volatile oil fraction, subject to a number of factors such as

plant maturity, harvesting seasons, the distilled part of the plant, and distillation methods. There are numerous methods (agar well diffusion, agar disk diffusion, broth dilution, and time-kill analysis) aimed at evaluating the antibacterial activity of essential oils and their constituents in inhibiting the growth of bacterial cells. However, many factors, such as the volume of inoculums, growth phase, culture medium used, and the pH of the media, incubation time, and temperature have made comparison of published data more complicated. Despite the differences in methods of assessment, it is apparent that many plant species contain compounds that have been shown to be active against food poisoning and/or spoilage organisms such as *Salmonella enteritidis*, *Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas fluorescens*, and *Clostridium botulinum* [124–128].

5.4.2 Antioxidant Activity

Reactive oxygen species (ROS), which consist of free radicals such as singlet oxygen ($^1O_2$), hydroxyl radicals ($OH^\bullet$), superoxide anion radicals (O_2^-), and nonfree radical species such as hydrogen peroxide (H_2O_2) are different forms of activated oxygen generated as oxidation by-products of biological reactions. They play a major role in many endogenous synthetic pathways and are important in many organic synthetic reactions. On the other hand, they are potentially very toxic to cells, causing a variety of pathophysiological disorders such as aging, arthritis, diabetes, inflammation, and genotoxicity. In addition, ROS can enhance the effects of sunburn, decrease in the ozone layer, skin cancer, high risk of increasing ultraviolet radiation, and other processes that generate ROS in food, such as lipid peroxidation. As a result of this, synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), *tert*-butylhydroquinone, and propylgallate have been widely used as food additives against oxidative degradation of foods by free radicals. However, the synthetic antioxidants BHA and BHT have been suspected of being responsible for several disorders. In recent decades, there has been a growing interest in research concerning essential oils as a source of natural antioxidants [129–134].

5.4.3 Cytotoxicity

Brine shrimp (*Artemia salina*), also known as sea monkey, is a simple zoological organism (marine invertebrate) about 1 mm in size. Their freeze-dried cysts (*A. salina* eggs) can last for several years and can be hatched into larvae without special equipment. The brine shrimp lethality test (BSLT) is a general bioassay that has been used successively for preliminary assessment of cytotoxicity testing of dental materials and marine natural products and antitumor agents, pesticides, and screening of plant extracts for pharmacological activity [135,136]. Reports in the literature have shown a very positive correlation between the lethality to brine shrimp and antitumoral activity in the development of new anticancer drugs from plants. This correlation is considered high quality in relation to brine shrimp and is recommended as an effective prescreening to cytotoxicity and antitumor assays [137]. More recently, it has been shown that there is a very good correlation between the

median lethal concentrations (LC_{50}) and the median lethal doses (LD_{50}) of the same plant extracts to brine shrimp larvae, administered orally in mice [138], although literature on the BSLT for plant essential oils is scanty. However, cytotoxic activities of the essential oils of some plant species have been reported [139–141].

5.4.4 Larvicidal Activity

Mosquito species were among the medically significant insect vectors in the transmission of diseases that have continued to have devastating impacts on human beings. The vector-borne diseases such as dengue, yellow fever, malaria, and filariasis caused by mosquito species and the allergic responses are among the major health problems of many countries around the world [142,143], although the control of mosquito species using synthetic insecticides has been favorable so far because of their speedy action and easy application. However, recent reports have shown that the repeated use of synthetic insecticides has fostered several environmental and health problems, including environmental pollution (soil, water, and air), and undesirable effects on humans and mammals, as well as other nontarget organisms. In addition, increasing resistance of some species of mosquitoes to synthetic insecticides has been observed over the years [144–147].

Plants generally offer an alternative source of insect control agents, because they are available locally, they are cheap, and they contain a wide range of bioactive chemicals that have little or no harmful effect on nontarget organisms and the environment. Thus, much effort has been focused on plant extracts as potential sources of natural insecticidal compounds, due to their lipophilic nature, which facilitates their impeding the behavioral functions of the insects [148–155]. Because of this background, essential oils from many plant species have received much attention as an important natural resource with potentially useful bioactive compounds showing a broad spectrum of activity, including larvicidal, adulticidal, ovicidal, oviposition-deterrent, and repellent activity against mosquito vectors [156–158].

5.5 Conclusion

According to the literature, we can say that the essential oils and their components have many uses, both in pharmacology and in food. In addition, they are endowed with interesting biological activities and have therapeutic potential. For example, essential oils exhibit antimicrobial activities, broad-spectrum antiviral activities, and may be useful as natural remedies; it also seems that essential oils can be used as a suitable therapy for many pathologies. In the cosmetic and food industries, essential oils are an integral part, as they may play different roles. Thus, the economic importance of essential oils is indisputable. It appears imperative, therefore, to preserve our natural, diverse flora and support its protection in order to maintain this inexhaustible source of molecules destined for multiple targets.

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6 Simple Phenols, Phenolic Acids, and Related Esters from the Medicinal Plants of Africa

Guy B. Kougan[a], Turibio Tabopda[a], Victor Kuete[b] and Robert Verpoorte[c]

[a]Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon, [b]Department of Biochemistry, University of Dschang, Dschang, Cameroon, [c]Institute of Biology, Leiden University, Leiden, The Netherlands

6.1 Introduction

Plants synthesize a wide range of organic compounds referred to as secondary metabolites. Among these, phenolic compounds are ubiquitous constituents, generally involved in defense against ultraviolet radiation or aggression by pathogens. Commonly, phenolic compounds are found in a wide range of edible plant foods, such as fruits, vegetables, cereals, and legumes, and in beverages, such as wine, tea, and coffee. Phenolics embrace a wide range of plant substances, possessing in common an aromatic ring with at least one aromatic compound ring substituted by at least one hydroxyl group; they are located in the vacuole and tend to be water soluble as they occur in combined forms with sugars as heterosides [1,2]. Structurally, phenolic compounds can be grouped into two main classes: flavonoids and nonflavonoids, according to their basic structures, and into subclasses, according to specific substituent in basic structure (Figure 6.1) [3–5]. The nonflavonoid phenolics are classified, based on their carbon skeletons, into the following subgroups: simple phenols, phenolic acids and derivatives, phenones, phenylacetic acids and derivatives, hydrolyzable tannins, and stilbenes.

Simple phenols (**1**) are described as compounds having at least one hydroxyl group attached to an aromatic ring as a basic skeleton. Within the class of simple phenols are phenol (**6**), catechol (**7**), resorcinol (**8**), and phloroglucinol (**9**). These phenols are themselves uncommon plant constituents, but phloroglucinol, resorcinol, and catechol may be found in combination with cinnamic acids (**3**) to form various plant flavonoids. Phenolic acids and derivatives (**2**) are major classes of phenolic compounds widely occurring in the plant kingdom [6]. Phenolic acids have a carboxyl group attached to a benzene ring. Depending to their structures,

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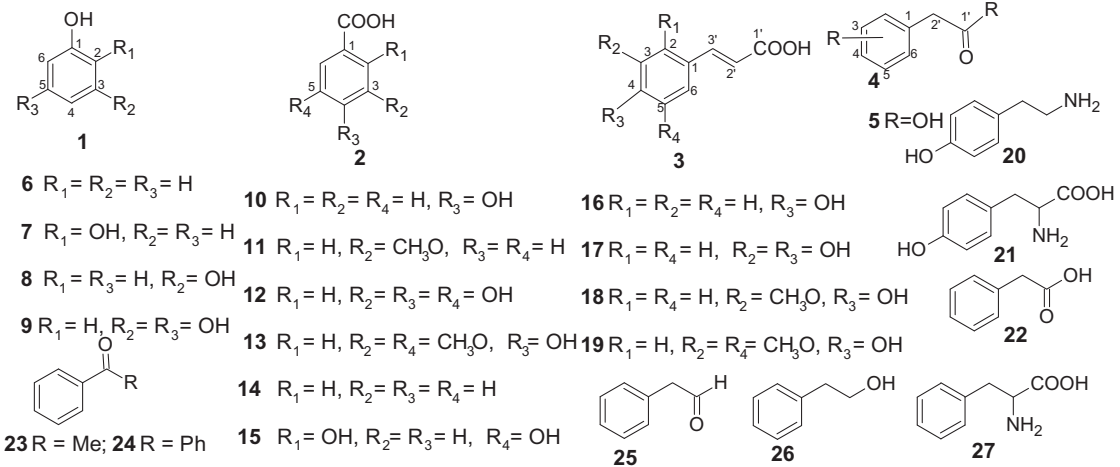


Figure 6.1 Basic structures of phenolic compounds and derivatives: simple phenols (**1**); phenolic acids (**2**); cinnamic acids (**3**); phenylcetone (**4**); phenylacetic acid (**5**); phenol (**6**); catechol (**7**); resorcinol (**8**); phloroglucinol (**9**); protocatechuic acid (**10**); vanillic acid (**11**); gallic acid (**12**); syringic acid (**13**); salicylic acid (**14**); gentisic acid (**15**); *p*-coumaric acid (**16**); caffeic acid (**17**); ferulic acid (**18**); sinapic acid (**19**); tyramine (**20**); tyrosine (**21**); phenylacetic acid (**22**); acetophenone (**23**); benzophenone (**24**); phenylacetaldehyde (**25**); phenylethanol (**26**); phenylamine (**27**).

two main classes of phenolic acids can be distinguished, namely, benzoic acid derivatives and cinnamic acid derivatives [7]. Benzoic acid derivatives with the basic structure C_6-C_1 consist of hydrobenzoic acids, occurring in grapes and wines, including protocatechuic acid (**10**), vanillic acid (**11**), gallic acid (**12**), syringic acid (**13**), salicylic acid (**14**), and gentisic acid (**15**) [8]. Hydroxybenzoic acids are found in common plants such as *Citrus paradisi*, *Olea europaea*, *Daucus carota*, *Fagara macrophylla*, *Mespilus germanica*, *Lonicera japonica*, and *Morus alba* [9–14]. Cinnamic acid derivatives such as hydrocinnamic acids (C_6-C_3) are generated from phenylpropanoids; the most common are *p*-coumaric acid (**16**), caffeic acid (**17**), ferulic acid (**18**), and sinapic acid (**19**) [15]. The phenylpropanoids (C_6-C_3) will be discussed in depth in Chapter 7. The phenolic acids are seldom found in a free state and more often in a combined form such as esters. Other phenolic acids are the alkaloids, namely, tyramine (**20**) and tyrosine (**21**) [16]. The hydroxycinnamic acids and their derivatives are present in various parts of forest trees, as they are direct precursors of the monolignols, which are implicated in lignin biosynthesis [17]. Another source of hydrocinnamic acids is dietary. Good sources of caffeic acid are coffee, blueberries, apples, and cider; *p*-coumaric acid is found in spinach, sugar beets, and cereal brans; sinapic acid is found in broccoli, kale and leafy brassicas, and citrus juices [18,19]. Phenylacetic acid (**22**) and its acetates, acetophenone (**23**), benzophenone (**24**), phenylacetaldehyde (**25**), and phenylethanol (**26**), contain a benzene ring with two side chains and are therefore referred to as the C_6-C_2 class of phenolic compounds, while benzophenone consists of a $C_6-C_1-C_6$ structure [20]. In plants, they are synthesized in response to environmental stresses such as salinity, cold, and heat shock, or as flavors and aromas in fruits, flowers, and tea [21–23]. The class of quinones includes the benzoquinones, napthaquinones, and anthraquinones (see Chapter 10). Ubiquinone, a benzoquinone, is found not only in the plant kingdom but also in the animal kingdom. It functions as an agent in the electron transport system. Betacyanins are often referred to as nitrogenous anthocyanidins, as they are nitrogen-containing phenols having an absorption spectrum resembling that of the anthocyanidins [24]. Phenolic compounds exhibit a wide range of physiological activities. There are a few reviews focusing on the activity of simple phenol, phenolic acids, and derivatives [15,25–27]. Many phenolic acid compounds have displayed antioxidant activity related to the acid moiety and the number and relative positions of hydroxyl groups on the aromatic ring structure [8]. Catechol and pyrogallol, both hydroxylated phenols, were found to be toxic to microorganisms, and their documented antimicrobial activity was due to the site(s) and number of hydroxyl groups on the phenol group. Increased hydroxylation results in increased toxicity [28]. Other activities include anticancer or anticarcinogenic, antimutagenic, antiatherosclerotic, antibacterial, antiviral, and anti-inflammatory activities to a greater or lesser extent; they also exhibit estrogenic, antihepatotoxic, antioxidant, free radical scavenger, chemopreventive and apoptotic, platelet aggregation inhibitor, neuroprotective, low-density lipoprotein (LDL) oxidation inhibitor, and antisickling activities [15,27,29–39].

6.2 Biosynthesis of Phenolic Compounds and Structural Diversity

Phenolic compounds are generally synthesized via two pathways: the shikimic acid pathway and the acetate malonate pathway.

6.2.1 Shikimic Acid Pathway

The shikimic acid pathway is related to the metabolism of carbohydrates and aromatic amino acids. The shikimate pathway consists of seven steps, starting with the condensation of phosphoenolpyruvate and erythrose-4-phosphate (Figure 6.2).

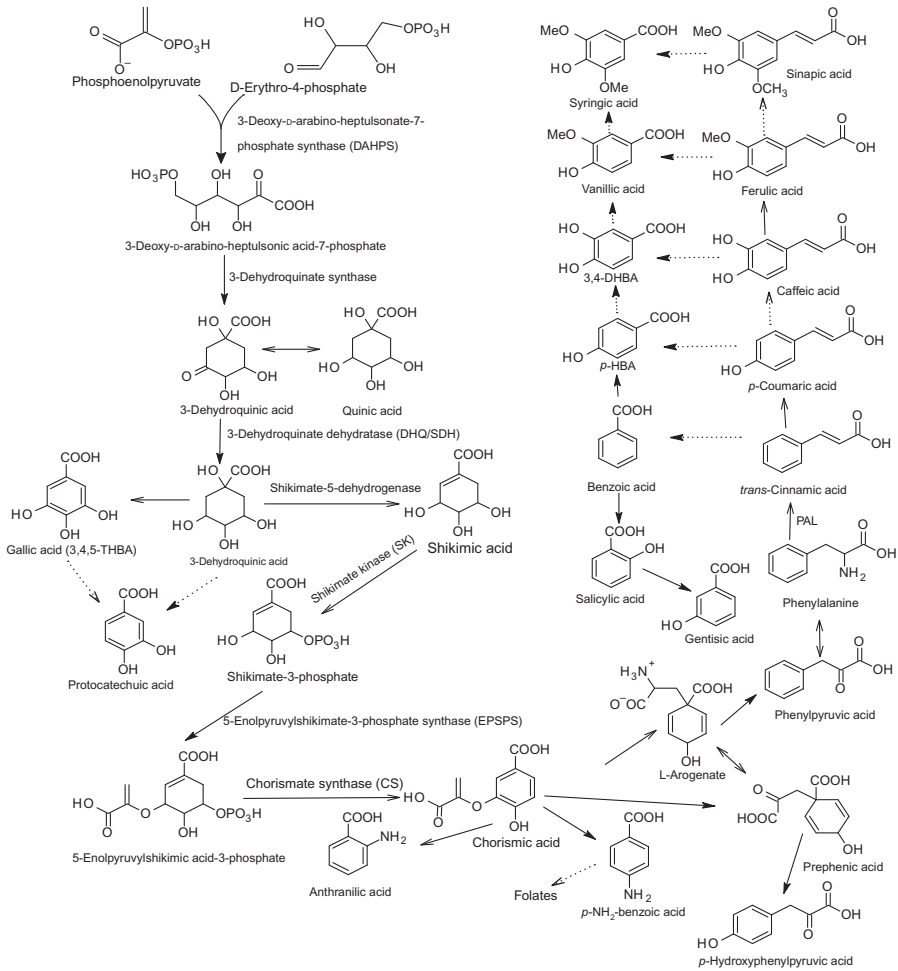


Figure 6.2 Biosynthetic pathways of some phenolic compounds.

Their condensation and cyclization lead to the formation of shikimic acid and end with the synthesis of chorismic acid (Figure 6.2). Active forms of these with coenzyme A (CoA) can access the main classes of phenolic compounds, quoting some transformations to acids of the benzoic acid series (gallic, protocatechuic, etc.) by β-oxidation. Gallic acid itself, in combination with simple sugars, leads to the hydrolyzable tannins (gallic and ellagic tannins), or, after the addition of a molecule of phosphoenolpyruvate and additional series of intermediate stages, followed by amination, gives rise to aromatic amino acids tyrosine (**21**) and phenylalanine (**27**), the starting point of the phenylpropanoid pathway [24,40].

6.2.2 The Phenylpropanoid Pathway

The phenylpropanoid pathway starts with the condensation of phenylalanine to cinnamate via the key enzyme phenylalanine ammonia lyase (PAL). The phenylpropanoid pathway is the precursor for several phenylpropanoids (C_6-C_3 compounds) such as cinnamic acid, caffeic acid, ferulic acid, sinapic acid, and esters of chlorogenic acid by esterification [24,41].

6.3 Simple Phenols, Phenolic Acids, and Related Ethers Isolated from African Medicinal Plants and Their Pharmacological Activities

6.3.1 Simple Phenols and Related Compounds

A survey of the literature and the PubMed, ScienceDirect, SciFinder, Scopus, and Web of Knowledge databases reveals the isolation of some new simple phenols and derivatives from different parts of some species of African plants. The root bark of *Lannea edulis* (Anacardiaceae), a plant used in the traditional medicine of Zimbabwe, was investigated, and the activity-guided isolation of the dichloromethane extract led to the purification of two new isoprenoid long-chain phenols (Figure 6.3), identified as cardonol 17 (**28**) and cardonol 13 (**29**). These two phenols were reported for their radical scavenging properties [42]. Phytochemical investigation of the methylene chloride extract of *Fagara zanthoxyloides* (Rutaceae) from Mali by Chaaib et al. [43] led to the isolation of 4′-(4″-hydroxy-3″-methylbutyloxy)-2-phenylethanol (**30**), a new phenylethanoid derivative, together with known simple phenols identified as dihydrocuspidiol (**31**) [44], cuspidiol (**32**) [43], *cis*-fagaramide (**33**), *trans*-fagaramide (**34**) [45], and 4″-(3″-methylbut-2″-enyloxy)-3-phenylpropanol (**35**) [46]. Dihydrocuspidiol (**31**), cuspidiol (**32**), and 4″-(3″-methylbut-2″-enyloxy)-3-phenylpropanol (**35**) showed potent antifungal activities against *Cladosporium cucumerinum*, with a minimum inhibitory quantity (MIQ) of 0.01, 0.1, and 0.1 μg, respectively, with miconazole used as the reference compound [43]. Cuspidiol (**32**) showed antifungal activity against *Candida albicans* and *Bacillus subtilis*, with an MIQ of 10 μg for both, with miconazole (0.1 μg) and chloramphenicol (1 μg), respectively, as reference compounds [42].

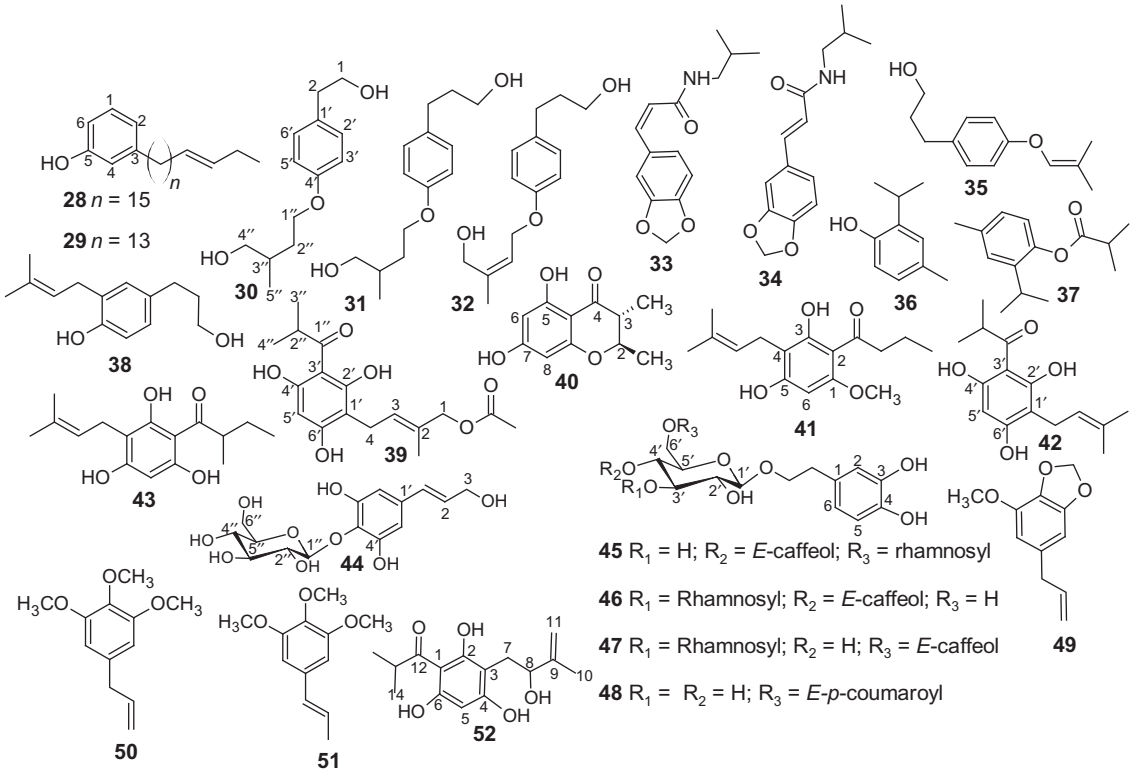


Figure 6.3 Simple phenols, phenolic acids, and related ethers from African medicinal plants: cardonol 17 (**28**); cardonol 13 (**29**); 4′-(4″-hydroxy-3″-methylbutyloxy)-2-phenylethanol (**30**); dihydrocuspidiol (**31**); cuspidiol (**32**); *cis*-fagaramide (**33**); *trans*-fagaramide (**34**); 4″-(3″-methylbut-2″-enyloxy)-3-phenylpropanol (**35**); 2-isopropyl-4-methylphenol (**36**); isobutyric acid 2-isopropyl-4-methylphenylester (**37**); zanthoxylol (**38**); 2-methyl-4-[2′,4′,6′-trihydroxy-3′-(2-methylpropanoyl)phenyl]but-2-enyl acetate (**39**); *trans*-(2*R*,3*R*)-5,7-dihydroxy-2,3-dimethyl-4-chromanone (**40**); 2-butanoyl-4-prenyl-1-methoxy phloroglucinol (**41**); 2-(2-methylpropanoyl)-4-prenylphloroglucinol (**42**); 2-(2-methyl-butanoyl)-4-prenylphloroglucinol (**43**); syringin (**44**); phenylethanoid P1(**45**); phenylethanoid P2 (**46**); phenylethanoid P3 (**47**); phenylethanoid P4 (**48**); myristicin (**49**); elemicin (**50**); isoelemicin (**51**); 2-methyl-1-[2,4,6-trihydroxy-3-(2-hydroxy-3-methyl-3-butenyl)phenyl]-1-propanone (**52**).

cis-Fagaramide (**33**) and *trans*-fagaramide (**34**) showed 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity [43]. One study reported the isolation and identification of essential oil from *Pulicaria odora* (Asteraceae), a Moroccan medicinal plant, and of two major phenol compounds, namely, 2-isopropyl-4-methylphenol (**36**) and isobutyric acid 2-isopropyl-4-methylphenylester (**37**), for the first time; these were examined *in vitro* for their antibacterial and antifungal activities. 2-Isopropyl-4-methylphenol demonstrated the most interesting inhibitory activity, with MIC ranging from 1 to 2 μg/mL (v/v) [47]. The phenol zanthoxylol (**38**), along with hydroxybenzoic acids, was isolated from extracts of *Zanthoxylum zanthoxyloides* (Rutaceae), a well-known local medicinal plant of Nigeria and Cameroon. Zanthoxylol demonstrated *in vitro* antisickling activity [48]. Many phloroglucinols were found from the aerial parts of *Helichrysum* spp. (Asteraceae) [49]. Intensive investigation of compounds in *Helichrysum caespititium* yielded caespitin, which showed interesting antimicrobial activities. An investigation of 27 other South African *Helichrysum* species yielded, in addition to known compounds, 21 new acylphloroglucinol derivatives [50–52]. A new acylated phloroglucinol, 2-methyl-4-[2′,4′,6′-trihydroxy-3′-(2-methylpropanoyl)phenyl]but-2-enyl acetate (**39**), with significant antimicrobial properties, was isolated from the shoots of the South African *H. caespititium* (Asteraceae) [53]. It shows growth inhibition against *Bacillus cereus*, *Bacillus pumilus*, *B. subtilis*, and *Micrococcus kristinae* at the very low concentration of 0.5 μg/mL, and against *Staphylococcus aureus* at 5.0 μg/mL [53]. Six other fungi tested, *Aspergillus flavus*, *A. niger*, *Cladosporium cladosporioides*, *C. cucumerinum*, *Cladosporium sphaerospermum*, and *Phytophthora capsici*, were similarly inhibited at low MICs of 1.0, 1.0, 1.0, 5.0, 0.5, and 1.0 μg/mL, respectively [53]. The investigation of *Helichrysum paronychioides* (Asteraceae), collected in southeastern Botswana, afforded four phloroglucinol derivatives, two of which were novel natural products, *trans*-(2*R*,3*R*)-5,7-dihydroxy-2,3-dimethyl-4-chromanone (**40**) and 2-butanoyl-4-prenyl-1-methoxy phloroglucinol (**41**), and two were known compounds, 2-(2-methylpropanoyl)-4-prenylphloroglucinol (**42**) and 2-(2-methyl-butanoyl)-4-prenylphloroglucinol (**43**) [54]. The four phloroglucinols were screened for antioxidant activity against Cu-induced LDL oxidation, of which 2-(2-methyl-butanoyl)-4-prenylphloroglucinol was found to be the most active at inhibiting LDL oxidation at all concentrations (0.5–10 μM), while the other three showed moderate to no activity [54]. Assay-guided fractionation of the Moroccan *Globularia alypum* (Globulariaceae) by Es-Safi et al. [55] led to the isolation of syringin (**44**) and four phenylethanoid derivatives (**45**–**48**) as the main constituents of the extract, and their antioxidant activity was determined, along with those of flavonoids and six iridoids. The results showed that activity toward the DPPH free radical was mainly due to the phenylethanoid constituents, which were more active than iridoids. Among the tested compounds, all phenylethanoid glycosides showed DPPH radical scavenging properties with an IC_{50} of 11.8, 12.1, 12.2, and 15.5 μmol/L, respectively, values better than butylated hydroxytoluene (BHT) (30.0 μmol/L) [55]. Phytochemical investigation of dichlomethane extract from the leaves of *Diplolophium buchanani* (Umbelliferae), growing in Malawi, yielded three new phenylpropanoids, namely, myristicin (**49**), elemicin (**50**), and isoelemicin (**51**), by means of centrifugal partition chromatography. Myristicin and a mixture of elemicin and isoelemicin showed antifungal activity against

C. cucumerinum, with MIC values of 20 and 8 μg, respectively, in thin-layer chromatography (TLC) bioassay [56]. From the dichloromethane extract of the flowers of *Helichrysum gymnocomum* (Asteraceae), one new acylphloroglucinol and a known acylphloroglucinol (**42**) were isolated for the first time [57]. The new acylphloroglucinol was characterized as 2-methyl-1-[2,4,6-trihydroxy-3-(2-hydroxy-3-methyl-3-butenyl) phenyl]-1-propanone (**52**). This new and the known acylphloroglucinols have shown antimicrobial activity, with MIC values below 64 μg/mL, against a selection of pathogens including *S. aureus*, with the known acylphloroglucinol having the highest sensitivity (6.3−45 μg/mL) for 8 of the 10 pathogens tested, including *S. aureus* (6.3 μg/mL) and the methicillin- and gentamycin-resistant strain of *S. aureus* (7.8 μg/mL) [57].

6.3.2 Phenolic Acids, Phenylacetic Acids, and Phenolic Aldehydes

The study of stem bark from *Terminalia superba* (Combretaceae), used in Cameroon folk medicine for the treatment of gastroenteritis, diabetes, female infertility, and abdominal pain, yielded two new ellagic acid derivatives (Figure 6.4): 3,4-*O*-methylellagic acid, 3′-*O*-β-D-xylopyranoside (**53**), and 4′-*O*-galloy-3,3′-di-*O*-methylellagic acid 4-*O*-β-D-xylopyranoside (**54**), which showed significant α-glucosidase inhibition activity, with IC_{50} of 7.95 and 21.21 μM, respectively [58]. These compounds also showed inhibitory activity using mononuclear cells (50.2% and 86.6%, respectively) at the lower concentration of 3.1 μM/mL tested [58]. An investigation of *Tylosema esculentum* (Fabaceae), collected in Botswana, yielded protocatechuic acid (**10**) and gallic acid (**12**). Both were assayed for DPPH radical scavenging activity and showed activities comparable to the standard (ascorbic acid). Gallic acid showed EC_{50} of 1.85 μg/mL after 30 min of reaction, compared to EC_{50} of 41.08 μg/mL for ascorbic acid, used as the reference compound [59]. Protocatechuic acid (**10**) was also isolated from *Ficus ovata* Vahl (Moraceae), collected in Cameroon, and when tested for antimicrobial activity, it prevented the growth of 80% of organisms tested [60]. An MIC value of 10 μg/mL was observed for protocatechuic acid (**10**) on *Microsporum audouinii* [60]. The phenolic acid derivative 3-hydroxy-4-methoxybenzoic acid (**55**) (isovanillic acid) was isolated from an extract of *Treculia obovoidea* (Moraceae) and tested for antimicrobial activity [61]. Vanillic acid (**11**), isolated from another Cameroonian medicinal plant, *Trilepisium madagascariense*, showed antimicrobial and antioxidant activity [62]. Vanillin and protocatechuic acid (**10**) were isolated from the roots of *Hydnora johannis* (Hydnoraceae), a Sudanese medicinal plant traditionally used for the treatment of dysentery, diarrhea, cholera, and swelling tonsillitis. These compounds showed low cytotoxicity against a selected human mouth epidermoid carcinoma cell line (KB) and the noncancer human fetal lung cell line (MRC-5) [63]. Other new phenolics, *N-p*-coumaroyl tyramine (**56**), 4-nerolidylcatechol (**57**), *N-trans*-feruloyltyramine (**58**), were isolated from *Piper umbellatum* (Piperaceae) collected in Cameroon [64]. *N-p*-Coumaroyl tyramine exhibited potent radical scavenging effects, with an IC_{50} value of 13.7 μM, while 4-nerolidylcatechol showed potent antifungal

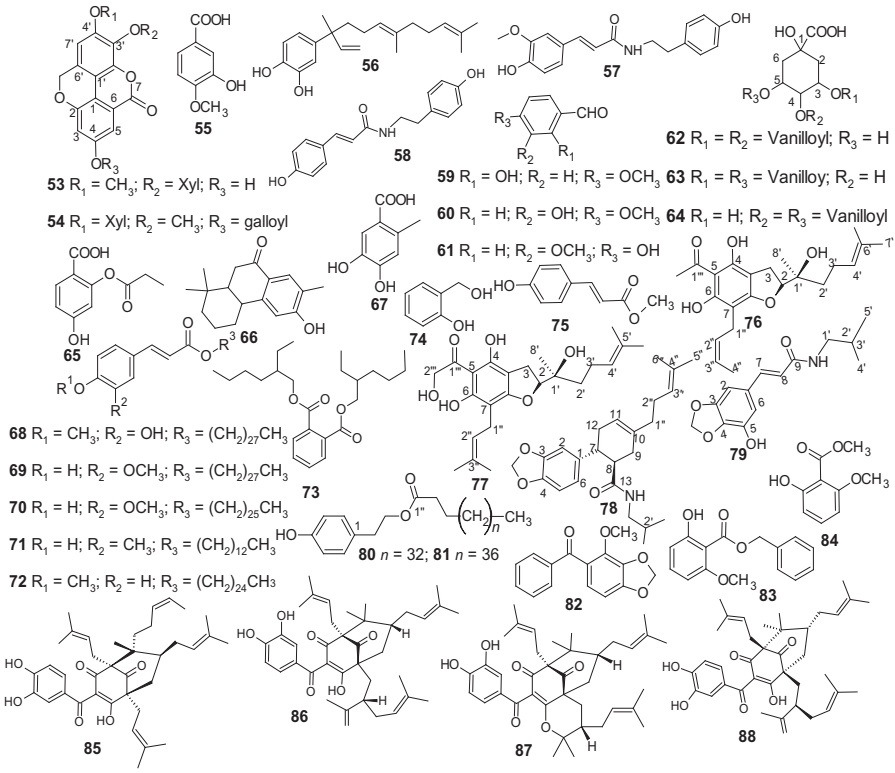


Figure 6.4 Acetophenones and benzophenones and derivatives from African medicinal plants: 3,4-*O*-methylellagic acid 3′-*O*-β-D-xylopyranoside (**53**); 4′-*O*-galloy-3,3′-di-*O*-methylellagic acid 4-*O*-β-D-xylopyranoside (**54**); 3-hydroxy-4-methoxybenzoic acid (**55**); *N*-*p*-coumaroyltyramine (**56**); 4-nerolidylcatechol (**57**); *N*-*trans*-feruloyltyramine (**58**); 2-hydroxy-4-methoxybenzaldehyde (**59**); 3-hydroxy-4-methoxybenzaldehyde (**60**); 4-hydroxy-3-methoxybenzaldehyde (**61**); 3,4-*O*-divanilloylquinic acid (**62**); 3,5-*O*-divanilloylquinic acid (**63**); 4,5-*O*-divanilloylquinic acid (**64**); 2-propionoxy-β-resorcylic acid (**65**); nimbiol (**66**); 2-methylprotocatechuic acid (**67**); erythrinasinate (**68**); erythrinasinate B (**69**); hexacosanyl (*E*)-ferulate (**70**); erythrinasinate C (**71**); erythrinasinate D (**72**); 1,2-benzenedicarboxylic acid bis-(2-ethylhexyl) ester (**73**); saligenin (**74**); 3-(4-hydroxyphenyl)methylpropenoate (**75**); 5-(ethan-1‴-one)-4,6-dihydroxy-7-(3″,3″-dimethylallyl)-2*S*-(1′*S*-hydroxy-1′,5′-dimethylhex-4′-enyl)-2,3-dihydrobenzofuran (**76**); 5-(2‴-hydroxyethan-1‴-one)-4,6-dihydroxy-7-(3″,3″-dimethylallyl)-2*S*-(1′*S*-hydroxy-1′,5′-dimethylhex-4′-enyl)-2,3-dihydrobenzofuran (**77**); heitziamide A (**78**); heitziamide B (**79**); heitziethanoid A (**80**); heitziethanoid B (**81**); (4-methoxy-benzo-[1,3]-dioxol-5-yl)-phenylmethanone (**82**); benzyl-2-hydroxy-6-methoxybenzoate (**83**); methyl-2-hydroxy-6-methoxybenzoate (**84**); guttiferone A (**85**); garcinol (**86**); cambogin (**87**); guttiferone F (**88**).

activity [64]. A bioassay-guided fractionation using mushroom tyrosinase (EC 1.14.18.1) yielded 2-hydroxy-4-methoxybenzaldehyde (**59**) and 3-hydroxy-4-methoxybenzaldehyde (**60**) from *Mondia whitei* Skeels (Asclepiadaceae) [65]. 2-Hydroxy-4-methoxybenzaldehyde was characterized as the principal tyrosinase inhibitor from three East African medicinal plants, the root of *M. whitei* (Hook) Skeels (Asclepiadaceae), the root of *Rhus vulgaris* Meikle (Anacardiaceae), and the bark of *Sclerocarya caffra* Sond (Anacardiaceae). It inhibited the oxidation of L-3,4-dihydroxyphenylalanine (L-DOPA) by mushroom tyrosinase (IC_{50} of 0.03 mM) [65]. 4-Hydroxy-3-methoxybenzaldehyde (**61**) and 4-methoxyphenol, isolated from the twigs of *Dorstenia turbinata* (Moraceae), showed moderate antibacterial activity, their effect being noted against Gram-positive and Gram-negative bacteria species [66]. In another study, 2-hydroxy-4-methoxybenzaldehyde (**59**) showed taste modifying properties [67]. Phytochemical analysis of *F. zanthoxyloides* (Rutaceae), collected in Burkina Faso, yielded three new isomeric divanilloylquinic acid derivatives: 3,4-*O*-divanilloylquinic acid (**62**), 3,5-*O*-divanilloylquinic acid (**63**), and 4,5-*O*-divanilloylquinic acid (**64**), named burkinabins A−C. These compounds play a useful role in sickle cell disease [68]. Phenolic acids, including the new compounds 2-propionoxy-β-resorcylic acid (**65**) and nimbiol (**66**) have been isolated from the Nigerian plant *Trichilia heudelotii* (Meliaceae) leaves, together with known compounds protocatechuic acid (**10**), 4-hydroxybenzoic acid, and 2-methylprotocatechuic acid (**67**). These compounds showed antimicrobial activity [69]. Cinnamate esters are also a class of simple phenolics reported in some African plants. Cinnamate esters have been reported in several African *Erythrina* (Fabaceae) genera. In 1986, a series of ester of cinnamates was isolated from Cameroonian *Erythrina senegalensis*, *Erythrina glauca*, and *Erythrina mildbaedii* [70]. Erythrinasinate (**68**) and erythrinasinate B (**69**) were isolated from *E. senegalensis*, and hexacosanyl (*E*)-ferulate (**70**) was reported from *Erythrina excelsa* [71]. One study reported the isolation of two new esters of ferulic and isoferulic acid, erythrinasinates C (**71**) and D (**72**), from the stem and root bark of *Erythrina sigmoidea* and *Erythrina eriotricha* [72], showing *in vitro* antimicrobial activities. These compounds exhibited central nervous system (CNS), cardiovascular, and metabolic activities [72]. Erythrinasinate B (**69**) showed antiarrhythmic effects (cardiovascular agent) as well as aquaretic properties [72]. Hexacosanyl (*E*)-ferulate (**70**) exhibited reflex depression, behavioral depression, muscle relaxation, cholinergic activation, antiarrhythmic, and aquaretic properties [72]. Erythrinasinate showed reflex depression, behavioral depression, muscle relaxant, cholinergic activation, anti-electric shock, antiarrhythmic, and aquaretic properties [70−72]. A bioguided study of the bark and leaves of *Salix subserrata* (Salicaceae) resulted in the isolation and characterization of 1,2-benzenedicarboxylic acid bis-(2-ethylhexyl) ester (**73**), saligenin (**74**), and catechol. 1,2-Benzenedicarboxylic acid bis-(2-ethylhexyl) ester and saligenin neither showed good activity against the alga *Chlorella fusca* nor antibacterial activity against the Gram-positive bacterium *Bacillus megaterium* or the Gram-negative bacterium *Escherichia coli* [73]. The methanol extract of the fresh Nigerian

plant *Gomphrena celosioides* (Amaranthaceae), commonly used in southern Nigeria for treatment of skin infections and as an abortifacient, yielded 3-(4-hydroxyphenyl) methylpropenoate (**75**), which showed antimicrobial activity against *Salmonella typhi*, *E. coli*, *Pseudomonas aeruginosa*, *B. subtilis*, and *S. aureus*, with inhibition diameter zones varying from 9 to 11 mm at 25 μg/mL [74].

6.3.3 Acetophenones, Benzophenones and their Derivatives

Two new prenylated acetophenones (Figure 6.5), harronin I [5-(ethan-1‴-one)-4,6-dihydroxy-7-(3″,3″-dimethylallyl)-2*S*-(1′*S*-hydroxy-1′,5′-dimethylhex-4′-enyl)-2,3-dihydrobenzofuran] (**76**) and harronin II [5-(2‴-hydroxyethan-1‴-one)-4,6-dihydroxy-7-(3″,3″-dimethylallyl)-2*S*-(1′*S*-hydroxy-1′,5′-dimethylhex-4′-enyl)-2,3-dihydrobenzofuran] (**77**), were isolated from the ripe berries of *Harrisonia abyssinica* (Simaroubaceae) [75]. Harronin I (**76**) showed an MIC of 5 μg/mL against *C. albicans* and 6 μg/mL against *B. cereus*, while harronin II (**77**) was not active (MIC > 100 μg/mL) [75]. Two novel phenylamides, heitziamide A (**78**) and heitziamide B (**79**), and two new phenylethanoids, heitziethanoid A (**80**) and heitziethanoid B (**81**), were isolated from the stem of *Fagara heitzii* (Rutaceae), a Cameroonian rainforest medicinal plant [76]. Heitziamides A (**78**) and B (**79**) were screened for their immunomodulatory potential. Both showed significant effects on the oxidative burst of whole blood, with an IC_{50} of 2.6 and 2.0 μM, respectively, compared to ibuprofen (IC_{50} of 12.1 μM), used as the control [76]. An investigation of the dichloromethane extract of Tanzanian *Securidaca longepedunculata* Fresen (Polygalaceae) yielded (4-methoxy-benzo-[1,3]-dioxol-5-yl)-phenylmethanone (**82**), together with other known compounds, benzyl-2-hydroxy-6-methoxybenzoate (**83**) and methyl-2-hydroxy-6-methoxybenzoate (**84**). (4-Methoxy-benzo-[1,3]-dioxol-5-yl)-phenylmethanone (**82**) exhibited antibacterial activity against *P. aeruginosa*, while benzyl-2-hydroxy-6-methoxybenzoate and methyl 2-hydroxy-6-methoxybenzoate were inactive against all tested bacteria and fungi [77]. Bioguided phytochemical investigation of Cameroonian medicinal plants *Allanblackia monticola* and *Symphonia globulifera* (Clusiaceae) led to the isolation of four known benzophenones: guttiferone A (**85**) from *S. globulifera* leaves, garcinol (**86**), cambogin (**87**), and guttiferone F (**88**) from *A. monticola* fruits (benzophenones are discussed in depth in Chapter 10). Guttiferones A (**84**) and F (**88**) showed particularly strong *in vitro* leishmanicidal activity, with IC_{50} values of 0.2 and 0.16 μM, respectively, comparable to that of the reference compound, miltefosine (0.46 μM) [78]. The four benzophenones showed potent anticholinesterase properties toward acetylcholinesterase (AChE) and butylcholinesterase (BChE). For AChE, the IC_{50} value (0.66 μM) of garcinol was almost equal to that of the reference compound galanthamine (0.50 μM) (Table 6.1). Furthermore, guttiferone A and guttiferone F, with IC_{50} values of 2.77 and 3.50 μM, respectively, were more active than galanthamine (IC_{50} of 8.5 μM) against BChE [78].

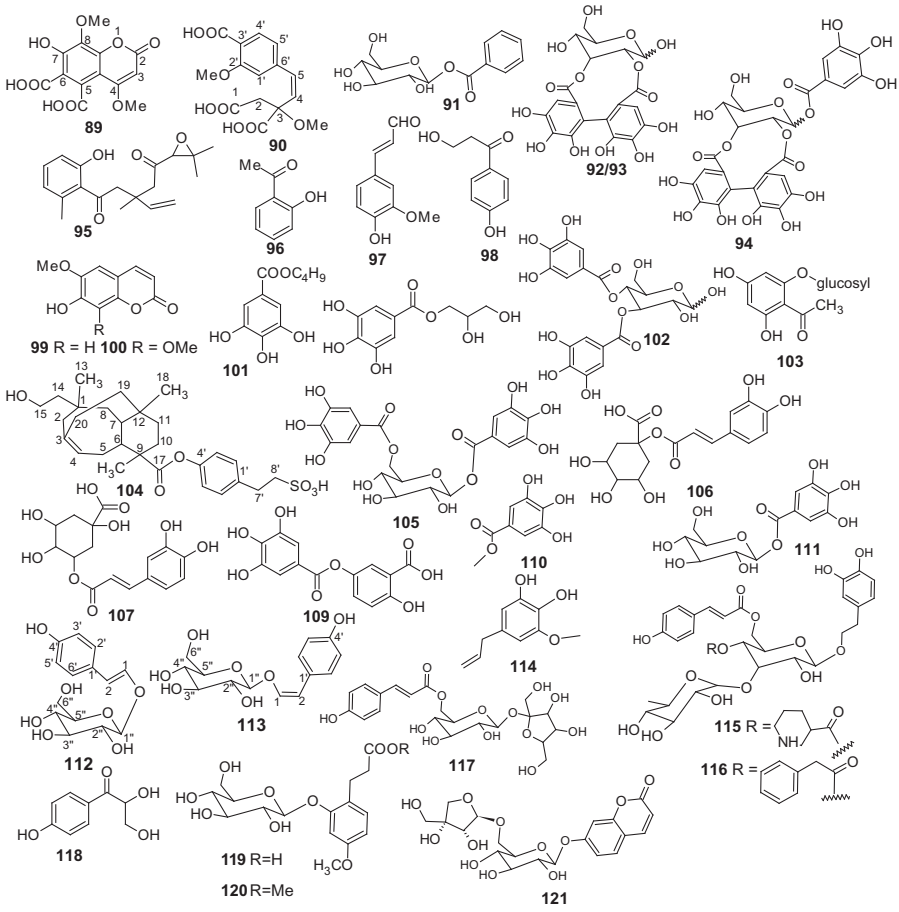


Figure 6.5 New simple phenols, phenolic acids, and related ethers isolated in African medicinal plants: 4,8-dimethoxy-7-hydroxy-2-oxo-2*H*-1-benzopyran-5,6-dicarboxylic acid (**89**); 2-(4-carboxy-3-methoxystyryl)-2-methoxysuccinic acid (**90**); β-glucogallin (**91**); 2,3-hexahydroxydiphenoyl-(α/β)-glucose (**92/93**); 1-galloyl-2,3-hexahydroxydiphenoyl-α-glucose (**94**); ethuliaconyzophenone (**95**); 2-hydroxyacetophenone (**96**); coniferaldehyde (**97**); 4-hydroxy-(3-hydroxypropionyl)-benzene (**98**); scopoletin (**99**); isofraxidin (**100**); gallic acid *n*-butyl ester (**101**); (α,β)-3,4-di-*O*-galloyl-glucopyranoside (**102**); 4,6-dihydroxy-2β-glucopyranosyloxyacetophenone (**103**); 1-*O*-galloylglycerol (**104**); reformin (**105**); 6′-*O*-galloylsalidroside (**106**); 1-caffeoylquinic acid (**107**); 5-caffeoylquinic acid (**109**); 2-hydroxy 5-[(3,4,5-trihydroxyphenyl)carbonyloxy] benzoic acid (**109**); methylgallate (**110**); 1-*O*-galloyl-β-D-glucose (**111**); *trans*-vaginoside (**112**); *cis*-vaginoside (**113**); 2-hydroxy-3-methoxy-5-(2-propenyl)phenol (**114**); 2-(3′,4′-dihydroxyphenyl) ethyl-3-*O*-α-L-rhamnopyranosyl-4-*O*-*p*-hydroxyphenylacetyl-6-*O*-caffeoyl-β-D-glucopyranoside (**115**); 2-(3′,4′-dihydroxyphenyl) ethyl-3-*O*-α-L-rhamnopyranosyl-4-*O*-piperidine-3-carboxylic acid-6-*O*-caffeoyl-β-D-glucopyranoside (**116**); 6-*p*-coumaroyl-sucrose (**117**); schweinfurthinol (**118**); 2-*O*-β-D-glucosyloxy-4-methoxybenzenepropanoic acid (**119/120**); adicardin (**121**).

Table 6.1 Biologically Active Simple Phenols and Related Compounds from African Medicinal Plants

Compounds	Class	Plants (Family)	Pharmacological Activities
Cardonol 17 (**28**); cardonol 13 (**29**)	Simple phenol	*L. edulis* (Anacardiaceae)	Radical scavenging [42]
4′-(4″-Hydroxy-3″-methylbutyloxy)-2-phenylethanol (**30**)	Phenylethanoid	*F. zanthoxyloides* (Rutaceae)	Antifungal; DPPH radical scavenging [43]
Dihydrocuspidiol (**31**); cuspidiol (**32**); *cis*-fagaramide (**33**); *trans*-fagaramide (**34**); 4″-(3″-methylbut-2″-enyloxy)-3-phenylpropanol (**35**)	Simple phenol		
2-Isopropyl-4-methylphenol (**36**); isobutyric acid 2-isopropyl-4-methylphenylester (**37**)	Simple phenol	*P. odora* (Asteraceae)	Antibacterial; antifungal [47]
Zanthoxylol (**38**)	Simple phenol	*Z. zanthoxyloides* (Rutaceae)	*In vitro* antisickling [48]
2-Methyl-4-[2′,4′,6′-trihydroxy-3′-(2-methylpropanoyl) phenyl]but-2-enyl acetate (**39**)	Phloroglucinol	*H. caespititium* (Asteraceae)	Antimicrobial [53]
trans-(2*R*,3*R*)-5,7-Dihydroxy-2,3-dimethyl-4-chromanone (**40**); 2-butanoyl-4-prenyl-1-methoxy phloroglucinol (**41**); 2-(2-methylpropanoyl)-4-prenylphloroglucinol (**42**); 2-(2-methyl-butanoyl)-4-prenylphloroglucinol (**43**)		*H. paronychioides* (Asteraceae)	Antioxidant [54]
Syringin (**44**); phenylethanoid P1 (**45**); phenylethanoid P2 (**46**); phenylethanoid P3 (**47**); phenylethanoid P4 (**48**)	Phenylethanoid	*G. alypum* (Globulariaceae)	DPPH radical scavenging [55]
Myristicin (**49**); elemicin (**50**); isoelemicin (**51**)	Phenylpropanoid	*D. buchanani* (Umbelliferae)	Antifungal [56]
2-Methyl-1-[2,4,6-trihydroxy-3-(2-hydroxy-3-methyl-3-butenyl)phenyl]-1-propanone (**52**)	Phloroglucinol	*H. gymnocomum* (Asteraceae)	Antimicrobial [57]
3,4-*O*-Methylellagic acid 3′-*O*-β-D-xylopyranoside (**53**); 4′-*O*-galloy-3,3′-di-*O*-methylellagic acid 4-*O*-β-D-xylopyranoside (**54**)	Phenolic acid	*T. superba* (Combretaceae)	α-Glucosidase inhibition [58]
Protocatechuic acid (**10**); gallic acid (**12**)	Phenolic acid	*T. esculentum* (Fabaceae); *F. ovata* (Moraceae)	DPPH radical scavenging [59]; antimicrobial [60]
3-Hydroxy-4-methoxybenzoic acid (**55**)	Phenolic acid	*T. obovoidea* (Moraceae)	Antimicrobial [61]
Vanillic acid (**11**); protocatechuic acid (**10**)	Phenolic acid	*T. madagascariense*; *H. johannis* (Hydnoraceae)	Antimicrobial, antioxidant [62]; cytotoxicity [63]

(*Continued*)

Table 6.1 (Continued)

Compounds	Class	Plants (Family)	Pharmacological Activities
N-p-Coumaroyl tyramine (**53**); 4-nerolidylcatechol (**57**); *N-trans*-feruloyltyramine (**58**)	Phenolamine	*P. umbellatum* (Piperaceae)	Radical scavenging; antifungal [64]
2-Hydroxy-4-methoxybenzaldehyde (**59**); 3-hydroxy-4-methoxybenzaldehyde (**60**)	Phenylaldehyde	*M. whitei* (Asclepiadaceae)	Tyrosinase inhibitor [65]
4-Hydroxy-3-methoxybenzaldehyde (**61**)	Phenylaldehyde	*D. turbinata* (Moraceae)	Antibacterial [66]; taste modifying [67]
Burkinabin A (**62**); burkinabin B (**63**); burkinabin C (**64**)	Phenolic acid	*F. zanthoxyloides* (Rutaceae)	Antisickling [68]
2-Propionoxy-β-resorcylic acid (**65**); nimbiol (**66**); protocatechuic acid (**10**); 4-hydroxybenzoic acid; 2-methylprotocatechuic acid (**67**)	Phenolic acid	*T. heudelotii* (Meliaceae)	Antimicrobial [69]
Erythrinasinate (**68**); erythrinasinate B (**69**) Hexacosanyl (*E*)-ferulate (**70**) Erythrinasinate C (**71**);erythrinasinate D (**72**)	Cinnamate	*E. senegalensis*; *E. excelsa*; *E. sigmoidea*; *E. eriotricha* (Fabaceae)	CNS, cardiovascular, muscle relaxation, cholinergic activation, antiarrhythmic, aquaretic properties; metabolic activities [70–72]
1,2-Enzenedicarboxylic acid bis-(2-ethylhexyl) ester (**73**); saligenin (**74**)	Phenolic acid	*S. subserrata* (Salicaceae)	Antifungal; antibacterial [73]
3-(4-Hydroxyphenyl)methylpropenoate (**75**)	Phenylacetate	*G. celosioides* (Amaranthaceae)	Antimicrobial [74]
Harronin I (**76**); harronin II (**77**)	Acetophenone	*H. abyssinica* (Simaroubaceae)	Antimicrobial [75]
Heitziamide A (**78**); heitziamide B (**79**)	Phenylamide	*F. heitzii* (Rutaceae)	Immunomodulatory [76]
Heitziethanoid A (**80**); heitziethanoid B (**81**)	Phenylethanoid		
(4-Methoxy-benzo-[1,3]-dioxol-5-yl)-phenylmethanone (**82**)	Phenylcetone	*S. longepedunculata* (Polygalaceae)	Antibacterial [77]
Garcinol (**86**); cambogin (**87**); guttiferone F (**88**) Guttiferone A (**85**)	Benzophenone	*A. monticola* (Clusiaceae) *S. globulifera* (Clusiaceae)	AChE, BChE inhibition; leishmanicidal [78]

AChE, antiacetylcholinesterase; BChE, antibutylcholinesterase; CNS, central nervous system.

6.4 New Simple Phenols, Phenolic Acids, and Related Ethers Isolated in African Medicinal Plants

Two new phenolic acids, 4,8-dimethoxy-7-hydroxy-2-oxo-2*H*-1-benzopyran-5,6-dicarboxylic acid (**89**) and 2-(4-carboxy-3-methoxystyryl)-2-methoxysuccinic acid (**90**), were isolated from the Egyptian *Sanguisorba minor* (Rosaceae) plant, together with known phenolics gallic acid, ellagic acid, β-glucogallin (**91**), 2,3-hexahydroxydiphenoyl-(α/β)-glucose (**92**, **93**), and 1-galloyl-2,3-hexahydroxydiphenoyl-α-glucose (**94**) with its β-isomer, were also characterized [79]. Reinvestigation of the aerial parts of the Egyptian *Ethulia conyzoides* (Asteraceae) yielded a new monoterpene acetophenone derivative named ethuliaconyzophenone (**95**) [80]. Chromatography of the extract of *Carissa edulis* (Apocynaceae), collected in Ghana, yielded aromatic compounds including 2-hydroxyacetophenone (**96**), vanillin, coniferaldehyde (**97**), 4-hydroxy-(3-hydroxypropionyl)-benzene (**98**), scopoletin (**99**), and isofraxidin (**100**) [81]. Investigation of *Pelargonium reniforme* (Geraniaceae), mainly distributed in coastal regions of Southern Africa, yielded the new gallic acid *n*-butyl ester (**101**), known compounds (α,β)-3,4-di-*O*-galloyl-glucopyranoside (**102**), 4,6-dihydroxy-2β-glucopyranosyloxyacetophenone (**103**), and 1-*O*-galloylglycerol (**104**), a new phenolic compound named reformin (**105**), and 6′-*O*-galloylsalidroside (**106**) [82]. Caffeic acid, 1-caffeoylquinic acid (**107**) and 5-caffeoylquinic acid (**108**) were identified from the leaves of a Tunisian *Morus* species by high-performance liquid chromatography with diode array detector (HPLC-DAD) and HPLC-mass spectrometry (HPLC-MS) [83]. Study of *Uapaca kirkiana* collected in Zimbabwe by Muchuweti et al. [84] yielded *p*-hydroxybenzoic acid in the peel and pulp fruit. The *p*-hydroxybenzoic acid was absent in the seed coat as well as in the embryo. However, the other six phenolic acids were not detected in the peel on the pulp. The seed coat contains ferulic acid, *p*-coumaric acid, and vanillic acid. The phenolic acids detected in embryo were caffeic acid, ferulic acid, *p*-coumaric acid, vanillic acid, and protocatechuic acid [84]. A new phenolic acid was identified and characterized as 2-hydroxyl-5-[(3,4,5-trihydroxyphenyl)carbonyloxy] benzoic acid (**109**) by HPLC-DAD and by HPLC-MS-MS from water extracts of *Delonix regia* (Caesalpiniaceae), together with gallic acid and protocatechuic acid [85]. Activity-guided fractionation of the methanolic extract of Egyptian *Acacia nilotica* pods resulted in the separation of eight phenolic compounds, including methyl gallate (**110**), gallic acid, 1-*O*-galloyl-β-D-glucose (**111**), 1,6-di-*O*-galloyl-β-D-glucose (**105**), digallic acid (**109**), and tannin compound derivatives [86]. Butanol extracts of the flowers of the Egyptian plant *Ononis vaginalis* Vahl. Symb (Fabaceae) yielded two new norphenylpropanoid glucosides, characterized as 1-β-D-glucopyranosyl-2-(4′-hydroxyphenyl) (*E*)-ethene (*trans*-vaginoside) (**112**) and 1-β-D-glucopyranosyl-2-(4′-hydroxyphenyl) (*Z*)-ethene (*cis*-vaginoside) (**113**) [87]. Studies performed on roots and aerial parts of *Bulbine capitata* (Asphodelaceae), an important medicinal plant widely used in Botswana, yielded a novel allyl-substituted pyrogallol derivative, 2-hydroxy-3-methoxy-5-(2-propenyl)phenol (**114**), along with other natural compounds [88]. Two other new natural compounds, characterized as

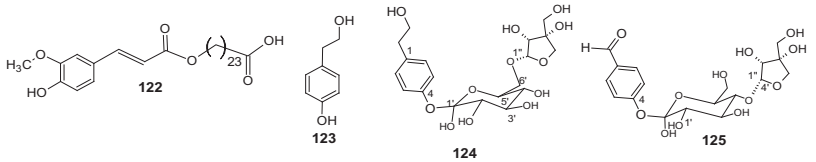
Table 6.2 New Phenolic Acids, Phenylacetic Acids, and Phenolic Aldehydes Isolated from African Plants

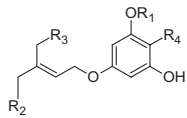
Compounds	Class	Plants	Area of Plant Collection	Plant Part	Physical Properties
4,8-Dimethoxy-7-hydroxy-2-oxo-2*H*-1-benzopyran-5,6-dicarboxylic acid (**89**); 2-(4-carboxy-3-methoxystyryl)-2-methoxysuccinic acid (**90**)	Phenolic acid	*S. minor* (Rosaceae)	Egypt [79]	Whole	–
Ethuliaconyzophenone (**95**)	Acetophenone	*E. conyzoides* (Asteraceae)	Egypt [80]	Aerial parts	$[\alpha]_D$ +32° (*c* 0.125, $CHC1_3$)
2-Hydroxyacetophenone (**96**)	Acetophenone	*C. edulis* (Apocynaceae)	Ghana [81]	Root bark	$[\alpha]_D$ +32° (*c* 0.125, $CHCl_3$)
Reformin (**105**); gallic acid *n*-butyl ester (**101**)	Phenyl ester	*P. reniforme* (Geraniaceae)	South Africa [82]	Aerial parts	$[\alpha]_D$ +33° (*c* 0.03, MeOH)
2-Hydroxy 5-[(3,4,5-trihydroxyphenyl) carbonyloxy] benzoic acid (**109**)	Phenolic acid	*D. regia* (Caesalpiniaceae)	Ivory Coast [85]	Petals	–
trans-Vaginoside (**112**); *cis*-vaginoside (**112**)	Phenylpropanoid	*O. vaginalis* (Fabaceae)	Egypt [87]	Flowers	–
2-Hydroxy-3-methoxy-5-(2-propenyl) phenol (**114**)	Pyrogallol	*B. capitata* (Asphodelaceae)	Botswana [88]	Roots and aerial parts	–
2-(3′,4′-Dihydroxyphenyl) ethyl-3-*O*-α-L-rhamnopyranosyl-4-*O*-*p*-hydroxyphenylacetyl-6-*O*-caffeoyl-β-D-glucopyranoside (**115**); 2-(3′,4′-dihydroxyphenyl) ethyl-3-*O*-α-L-rhamnopyranosyl-4-*O*-piperidine-3-carboxylic acid-6-*O*-caffeoyl-β-D-glucopyranoside (**116**)	Phenylpropanoid	*J. mimosifolia* (Bignoniaceae)	Egypt [89]	Stem bark	–
6-*p*-Coumaroyl-sucrose (**117**)	Phenylpropanoid	*K. pinnata* (Bignoniaceae)	Egypt [90]	Fruits	–
Schweinfurthinol (**118**)	Phenylpropanoid	*C. schweinfurthii* (Burseraceae)	Cameroon [91]	Seeds	mp 210−212°C$[\alpha]_D$ −56,7° (*c* 0.11, MeOH)
2-*O*-β-D-Glucosyloxy-4 methoxybenzenepropanoic acid (**119**)	Phenylpropanoid	*G. polycephala* (Thymelaeaceae)	Botswana [92]	Stem	–

2-(3′,4′-dihydroxyphenyl) ethyl-3-*O*-α-L-rhamnopyranosyl-4-*O*-*p*-hydroxyphenylacetyl-6-*O*-caffeoyl-β-D-glucopyranoside (**115**) and 2-(3′,4′-dihydroxyphenyl) ethyl-3-*O*-α-L-rhamnopyranosyl-4-*O*-piperidine-3-carboxylic acid-6-*O*-caffeoyl-β-D-glucopyranoside (**116**), were isolated from the stem bark of *Jacaranda mimosifolia* (Bignoniaceae) [89]. Further phytochemical investigation of the fruit of *Kigelia pinnata* (Bignoniaceae) yielded a new phenylpropanoid derivative, identified as 6-*p*-coumaroyl-sucrose (**117**), along with 10 known phenylpropanoid and phenylethanoid derivatives. The structures of the isolated compounds were elucidated using various techniques of NMR and mass spectral analysis [90]. The seeds of *Canarium schweinfurthii* (Burseraceae) yielded a new phenylpropanoid, schweinfurthinol (**118**), characterized as 1-(4-hydroxyphenyl)-2,3-dihydroxypropan-1-one [91], and two other new phenylpropanoid glucosides, 2-*O*-β-D-glucosyloxy-4-methoxybenzenepropanoic acid (**119**) and its methyl ester (**120**), together with syringin (**44**) and adicardin (**121**), were isolated from the stem of *Gnidia polycephala* (Thymeleaeceae) and characterized by physical and spectroscopic data (Table 6.2) [92].

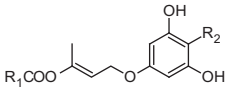
6.5 Other Simple Phenols, Phenolic Acids, and Related Ethers in African Medicinal Plants

Another chemical investigation of the Cameroonian plant *Autranella congolensis* led to the isolation (Figure 6.6) of 24-feruloytetracosanoic acid (**122**) [93]. Continued investigations into the phenolic content of the leaves and stems of *Cyclopia intermedia* yielded tyrosol (**123**), a methoxy analog, 2-[4-[*O*-α-apiofuranosyl-(1″→6′)-β-D-glucopyranosyloxy]phenyl]ethanol (**124**), and 4-[*O*-α-apiofuranosyl-(1″→2′)-β-D-glucopyranosyloxy]benzaldehyde (**125**) [94]. *p*-Hydroxybenzoic acid and phenylethanol esters were isolated from the stem bark of *Spathodea campanulata* [95]. A study of aqueous acetone extract of leaves from 10 Ethiopian browse plant species by HPLC and TLC by Mueller-Harvey et al. [96] allowed the characterization of gallic, ellagic, and chlorogenic acids. In the same study, *trans*- and *cis*-*p*-coumaric and *trans*-ferulic acid were identified after hydrolysis of browse leaves [97]. The large tribe *Inuleae* yielded acylphloroglucinols derivatives. The investigation of several South African species belonging to tribe *Inuleae*, including 27 *Helichrysum* species, namely, *Helichrysum asperum*, *Helichrysum monticola*, *Helichrysum gymnocomum*, *Helichrysum natalitium*, *Helichrysum bellum*, and *Leontonyx-arten*, using high-field NMR-yielded acylphloroglucinol derivatives (**126**–**157**) [98–101]. The hexane-soluble fraction of the methanolic extract of stem bark of *Harungana madagascariensis* (Hypericaceae) yielded methyl-3-formyl-2,4-dihydroxy-6-methylbenzoate (**158**), together with new anthranoids [102]. Phytochemical study of the leaves and twigs of *Dorstenia picta* and the stem bark of *Newbouldia laevis*, two Cameroonian medicinal plants, afforded naringeninic acid (**159**) and 4-(4-hydroxyphenyl)ethyl tricontanoate (**160**), respectively [103]. Further phytochemical investigation of the fruits of *K. pinnata* (Bignoniaceae) yielded 10 known phenylpropanoid and phenylethanoid derivatives (**161**–**170**).

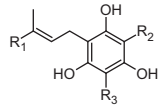




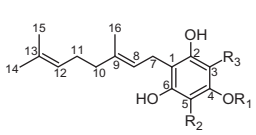
	126	127	128	129	130	131	132	133	134	135	136	137	138
R_1	H	H	H	H	H	H	H	H	H	H	H	H	H
R_2	H	OH	H	OH	OAc	OH	H	Prenyl	OH	OAc	H	OH	OAc
R_3	H	H	H	H	H	OH	H	H	H	H	H	H	H
R_4	PhCO	PhCO	*n*Bu	*n*Bu	*n*Bu	*n*Bu	*i*Bu	*i*Bu	*i*Bu	*i*Bu	MeBu	MeBu	MeBu

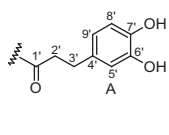


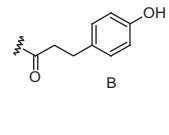
	139	140	141	142	143
R_1	H	H	H	**Me**	**Me**
R_2	*n*Bu	*i*Bu	PhCO	COPh	*i*Bu



	144	145	146	147	148	149	150	151
R_1	Me	Me	Me	Me	Me	CH_2OAc	CH_2OAc	Me
R_2	*n*Bu	*i*Bu	MeBu	PhCO	Ac	*n*Bu	*i*Bu	PhCO
R_3	H	H	H	H	H	H	H	Prenyl







	152	153	154	155	156	157
R_1	H	H	H	**Me**	H	**Me**
R_2	H	H	H	H	OH	H

Figure 6.6 Other simple phenols, phenolic acids, and related ethers in African medicinal plants: 24-feruloytetracosanoic acid (**122**); tyrosol (**123**); 2-[4-[*O*-α-apiofuranosyl-(1″→6′)-β-D-glucopyranosyloxy]phenyl]ethanol (**124**); 4-[*O*-α-apiofuranosyl-(1″→2′)-β-D-glucopyranosyloxy]benzaldehyde (**125**); methyl-3-formyl-2,4-dihydroxy-6-methylbenzoate (**158**); naringeninic acid (**159**); 4-(4-hydroxyphenyl)ethyl tricontanoate (**160**); darendoside A (**161**); 6-*O*-caffeol-β-D-fructofuranoside-(2→1)-α-D-glucopyranoside (**162**); 2-(3-hydroxy-4-methoxyphenol)ethyl *O*-α-L-rhamnopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→6)]-(4-*O*-feruloyl)-β-D-glucopyranoside (**163**); decaffeoylacteoside (**164**); acteoside (**165**); isoacteoside (**166**); jionoside (**167**); echinacoside (**168**); 6-caffeoylglucose (**169**); 6-feruloylsucrose (**170**).

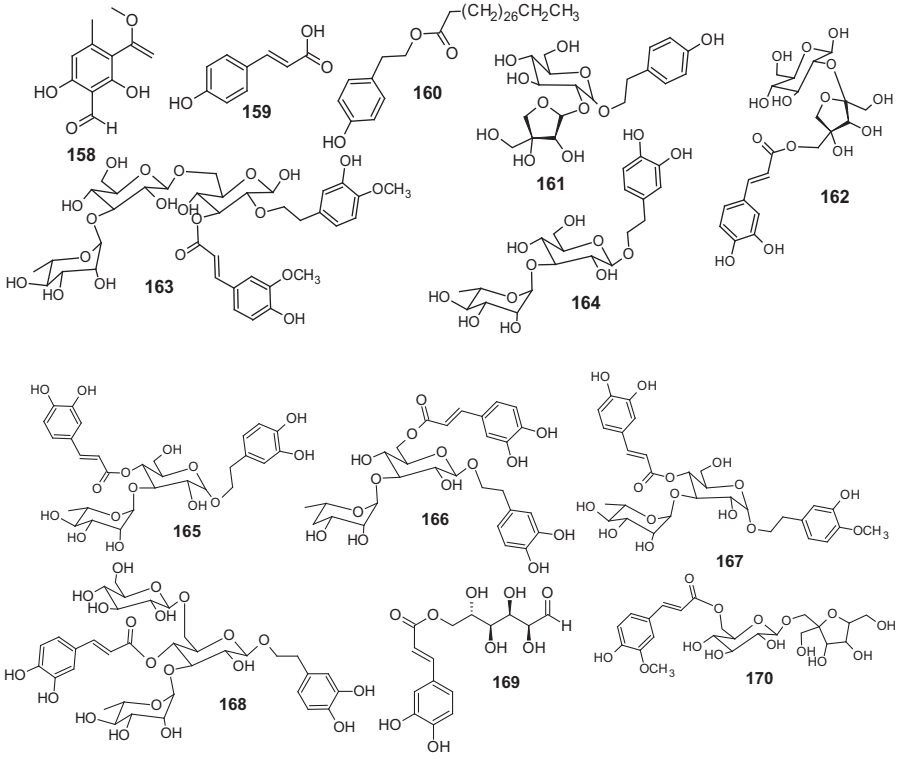


Figure 6.6 (Continued)

The structures of the isolated compounds were elucidated using various techniques of NMR and mass spectral analysis [90].

6.6 Conclusions

The present chapter presents an overview of simple phenols isolated from African plants. When necessary, an overview of phenylpropanoids, phenylethanoids, quinines, and anthranoids was provided. The present chapter shows the richness of African plants as sources of simple phenolic compounds with potent bioactivity.

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7 Phenylpropanoids and Related Compounds from the Medicinal Plants of Africa

Victor Kuete

Department of Biochemistry, University of Dschang, Dschang, Cameroon

7.1 Introduction

Phenylpropanoids occupy a central role in the biosynthesis of phenolic compounds, which are ubiquitous in the plant kingdom. The most frequent pathway for the formation of phenylpropanoids and other phenolics begins with the aromatic amino acids L-phenylalanine and, to a lesser extent, L-tyrosine. Phenylpropanoid metabolism generates an enormous array of secondary metabolites, based on the few intermediates of the shikimate pathway as the core unit [1]. The resulting hydroxycinnamic acids and esters are amplified in several cascades by a combination of reductases, oxygenases, and transferases, resulting in an organ- and developmentally specific pattern of metabolites, characteristic for each plant species [1]. Phenylpropanoid glycosides are widely distributed in the plant kingdom. They are known to exhibit antioxidant, enzyme inhibiting, and immunomodulatory effects [2]. Some antibacterial and antiviral activities have also been mentioned [2], reported mainly in Scrophulariaceae, Oleaceae, Plantaginaceae, and Bignoniaceae [2,3]. This chapter presents a summary of phenylpropanoids, phenylpropanoid esters, and glycosides, as well as other related compounds reported so far in African medicinal plants.

7.2 Biosynthesis of Phenylpropanoids and Structural Diversity

The biosynthesis of phenylpropanoids is accomplished via the so-called phenylpropanoid pathway, as discussed in Chapter 6. Phenylpropanoids are involved in plant responses to biotic and abiotic stimuli, and serve as indicators of plant stress responses upon variation of light or mineral treatment as well as the key mediators of the plants' resistance to pathogenic agents [4]. The biodiversity of phenylpropanoids appears to be the result of the modification and amplification of several basic structures, derived from the shikimate pathway [5]. This biodiversity is also emphasized through the

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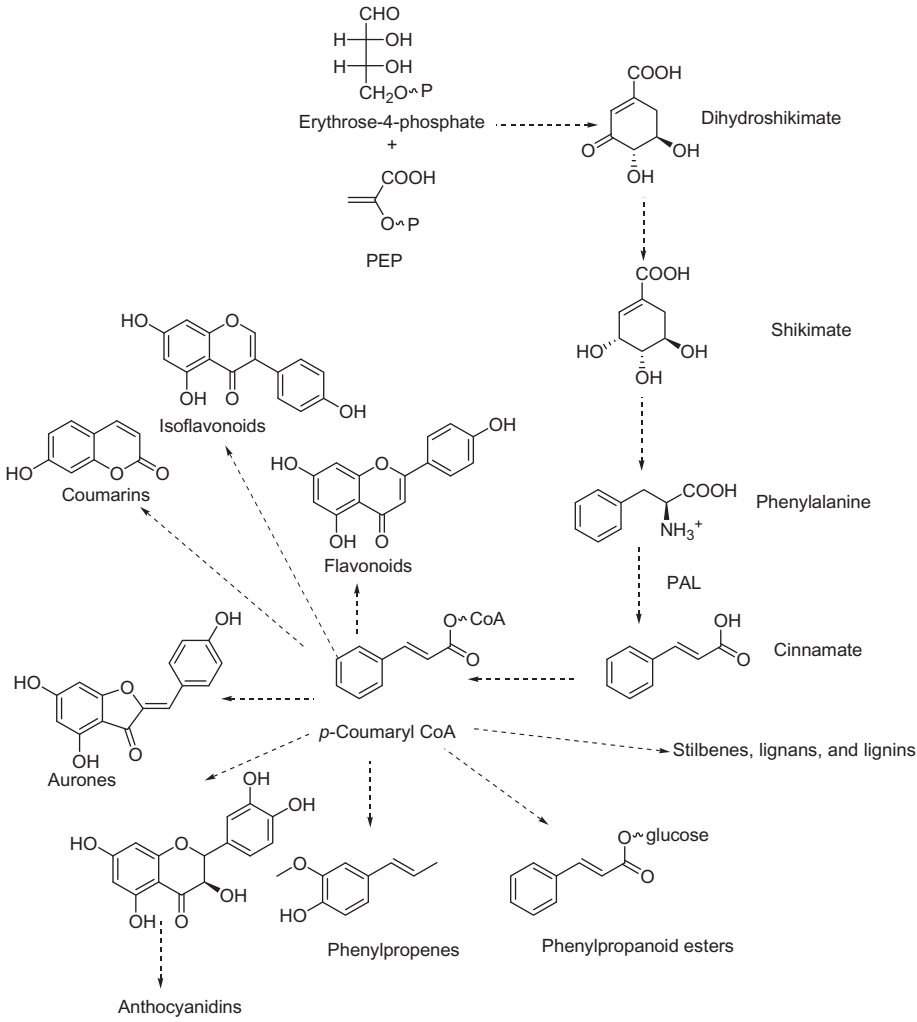

Figure 7.1 Diversification of phenylpropanoids through phenylpropanoid pathway, showing the central role of *p*-coumaryl CoA (PAL: phenylalanine ammonia lyase; PEP: Phosphoenolpyruvic acid).

contribution of a set of enzymes such as oxygenases, ligases, oxidoreductases, and transferases (Figure 7.1) [1].

7.3 Phenylpropanoids Isolated from African Medicinal Plants and Their Pharmacological Activity

Some pharmacological data have been documented on phenylpropanoids identified in African plants. Table 7.1 and Figure 7.2 summarize the known compounds with their

Table 7.1 Biologically Active Phenylpropanoids from African Medicinal Plants

Compounds	Type	Plants (Family)	Pharmacological Activities
2-(4-Hydroxyphenyl)ethyl tricontanoate (**1**)	Phenylpropanoid ester	*Newbouldia laevis* Seem. (Bignoniaceae) [6]	—
4-Hydroxy-(3-hydroxy propionyl)benzene (**2**)	Phenylpropanoid	*Carissa edulis* (Apocynaceae) [7]	—
Caffeic acid (**3**)	Phenylpropanoid ester	*Stereospermum acuminatissimum* K. Schum. (Bignoniaceae) [8]; *Vepris glomerata* (Rutaceae) [9]	Enzyme inhibitor [8]
Coniferaldehyde (**4**)	Phenylpropanoid	*C. edulis* (Apocynaceae) [7]	—
Erythrinassinate B (**5**)	Phenylpropanoid ester	*Erythrina indica* (Leguminosae) [10]	—
Glomeral (**6**)	Phenylpropanoid	*V. glomerata* (Rutaceae) [9]	Antimicrobial [9]
Martynoside (**7**)	Phenylpropanoid glucoside	*N. laevis* Seem. (Bignoniaceae) [3]	—
Methyl caffeate (**8**)	Phenylpropanoid ester	*S. acuminatissimum* K. Schum. (Bignoniaceae) [8]	Enzyme inhibitor [8]
Methyl cinnamate (**9**)	Phenylpropanoid	*V. glomerata* (Rutaceae) [9]	—
p-Coumaric acid (**10**)	Phenylpropanoid ester	*S. acuminatissimum* K. Schum. (Bignoniaceae) [8]; *V. glomerata* (Rutaceae) [9]	Enzyme inhibitor [8]
Psilalic acid (**11**)	Phenylpropanoid ester	*S. acuminatissimum* K. Schum. (Bignoniaceae) [8]	Enzyme inhibitor [8]
Stearyl ferulate (**12**)	Phenylpropanoid ferrulate	*Dorstenia psilurus* (Moraceae) [11]	—
Stearyl-*p*-coumarate (**13**)	Phenylpropanoid cinnamate	*D. psilurus* (Moraceae) [11]	—
Syringin (**14**)	Phenylpropanoid glycoside	*Chlozophora obliqua* Vahl (Euphorbiaceae) [12]; *Gnidia polycephala* (Thymeleaeceae) [13]	Antioxidant [14]; anti-inflammatory [15]
Verbascoside (**15**)	Phenylpropanoid glucoside	*N. laevis* Seem. (Bignoniaceae) [3]	Antioxidant [16]

Table 7.2 New Phenylpropanoids and Some Related Compounds Isolated in African Plants

Compounds	Type	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
2-(4′-Hydroxyphenyl)ethyl dotriacontanoate (**16**)	Phenylethanoid ester	*S. acuminatissimum* K. Schum. (Bignoniaceae) [17]	Cameroon	Stem bark	White powder [17]
2-(4-Hydroxyphenyl)ethyl hentriacontanoate (**17**)	Phenylethanoid ester	*S. acuminatissimum* K. Schum. (Bignoniaceae) [8]	Cameroon	Stem bark	White amorphous powder [8]
2-Hydroxy-3-methoxy-5-(2-propenyl)phenol (**18**)	Phenylpropanoids	*Bulbine capitata* (Asphodelaceae) [18]	Botswana	Roots	Yellow oil [18]
2-*O*-β-D-Glucosyloxy-4-methoxybenzenepropanoic acid (**19**)	Phenylpropanoid glycoside	*G. polycephala* (Thymeleaeceae) [13]	Botswana	Stem	mp 168−169°C $[\alpha]^{22}_{D} = -80°$ (*c* 1.61, MeOH) [13]
4-*O*-Methyl guaiacylglycerol 8-*O*-β-glucopyranoside (**20**)	Phenylpropanoid glucoside	*C. obliqua* Vahl (Euphorbiaceae) [12]	Egypt	Aerial part	White amorphous powder; $[\alpha]^{21}_{D} = -0.42.5°$ (*c* 0.8, MeOH) [12]
4-*O*-Methyl guaiacylglycerol 9-*O*-β-glucopyranoside (**21**)	Phenylpropanoid glucoside	*C. obliqua* Vahl (Euphorbiaceae) [12]	Egypt	Aerial part	White amorphous powder; $[\alpha]^{21}_{D} = -48.8°$ (*c* 0.8, MeOH) [12]
Methyl-2-*O*-β-D-glucosyloxy-4-methoxybenzenepropanoate (**22**)	Phenylpropanoid ester	*G. polycephala* (Thymeleaeceae) [13]	Botswana	Stem	$[\alpha]^{22}_{D} = -8.5°$ (*c* 0.94, MeOH) [13]
Newbouldioside (**23**)	Phenylpropanoid glucoside	*N. laevis* Seem. (Bignoniaceae) [3]	Guinea	Roots	Yellow amorphous powder; $[\alpha]_{D} = -50.7°$ (*c* 1.15, MeOH) [3]

Newbouldioside A (**24**)	Phenylethanoid glycoside	*N. laevis* Seem. (Bignoniaceae) [19]	Nigeria	Stem bark	Yellow amorphous material; $[\alpha]_D = -53.3^\circ$ (*c* 3.15, MeOH) [19]
Newbouldioside B (**25**)	Phenylethanoid glycoside	*N. laevis* Seem. (Bignoniaceae) [19]	Nigeria	Stem bark	Yellow amorphous material; $[\alpha]_D = -50.5^\circ$ (*c* 2.75, MeOH) [19]
Newbouldioside C (**26**)	Phenylethanoid glycoside	*N. laevis* Seem. (Bignoniaceae) [19]	Nigeria	Stem bark	White amorphous material; $[\alpha]_D = -47.9^\circ$ (*c* 2.4, MeOH) [19]
Octacosan-1,28-dioldiferulate and triacontan-1,3′-dioldiferulate (**27**)	Phenylpropanoid ester	*S. acuminatissimum* K. Schum. (Bignoniaceae) [17]	Cameroon	Stem bark	White powder [17]
Trilepisiumic acid (**28**)	Phenylpropanoid ester	*Trilepisium madagascariense* (Moraceae) [20]	Cameroon	Leaves and stem bark	Colorless powder [20]

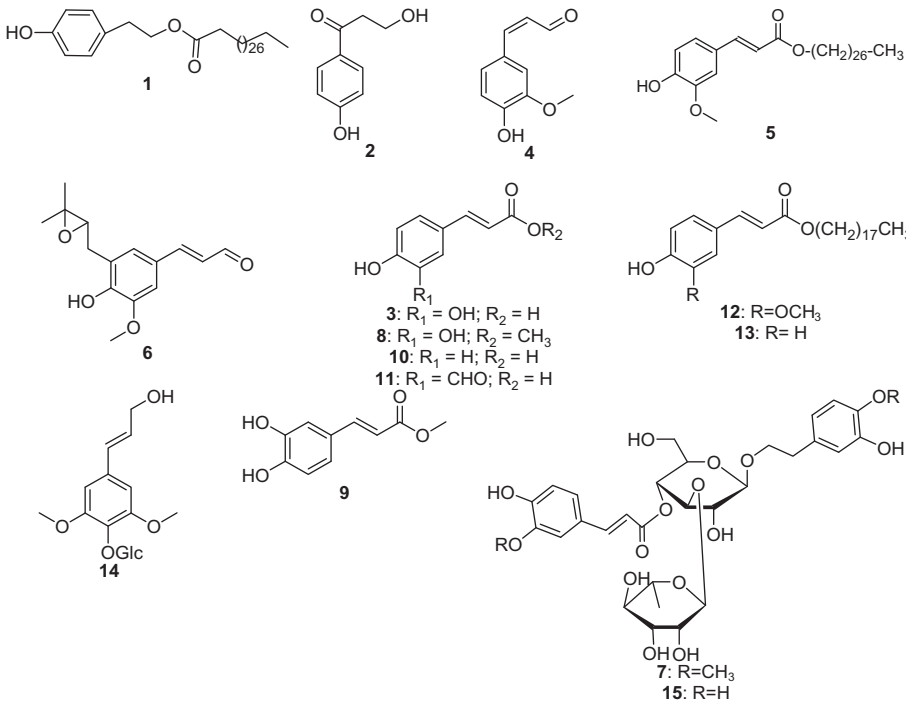

Figure 7.2 Some known phenylpropanoids identified in African plants: 2-(4-hydroxyphenyl) ethyl tricontanoate (**1**), 4-hydroxy-(3-hydroxypropionyl)benzene (**2**), caffeic acid (**3**), coniferaldehyde (**4**), erythrinassinate B (**5**), glomeral (**6**), martynoside (**7**), methyl caffeate (**8**), methyl cinnamate (**9**), *p*-coumaric acid (**10**), psilalic acid (**11**), stearyl ferulate (**12**), stearyl-*p*-coumarate (1**3**), syringin (**14**), and verbascoside (**15**).

pharmacological properties, while new natural products are reported in Table 7.2 and Figure 7.3.

7.3.1 Antimicrobial Activities of Phenylpropanoids and Phenylethanoids Identified in African Medicinal Plants

A few antimicrobial phenylpropanoids and phenylpropanoids classed as C6-C3 or C6-C2 compounds isolated from African plants were reported to show antimicrobial activity. However, the documented effects varied from significant [minimal inhibitory concentration (MIC) below 10 μg/mL], to moderate (10 < MIC < 100 μg/mL), to low (MIC > 100 μg/mL) [10,21].

The phenylethanoid ester 2-(4′-hydroxyphenyl)ethyl dotriacontanoate (**16**) and the phenylpropanoid esters octacosan-1,28-dioldiferulate and triacontan-1,3′-dioldiferulate (**27**), isolated from the Cameroonian plant *S. acuminatissimum*, displayed

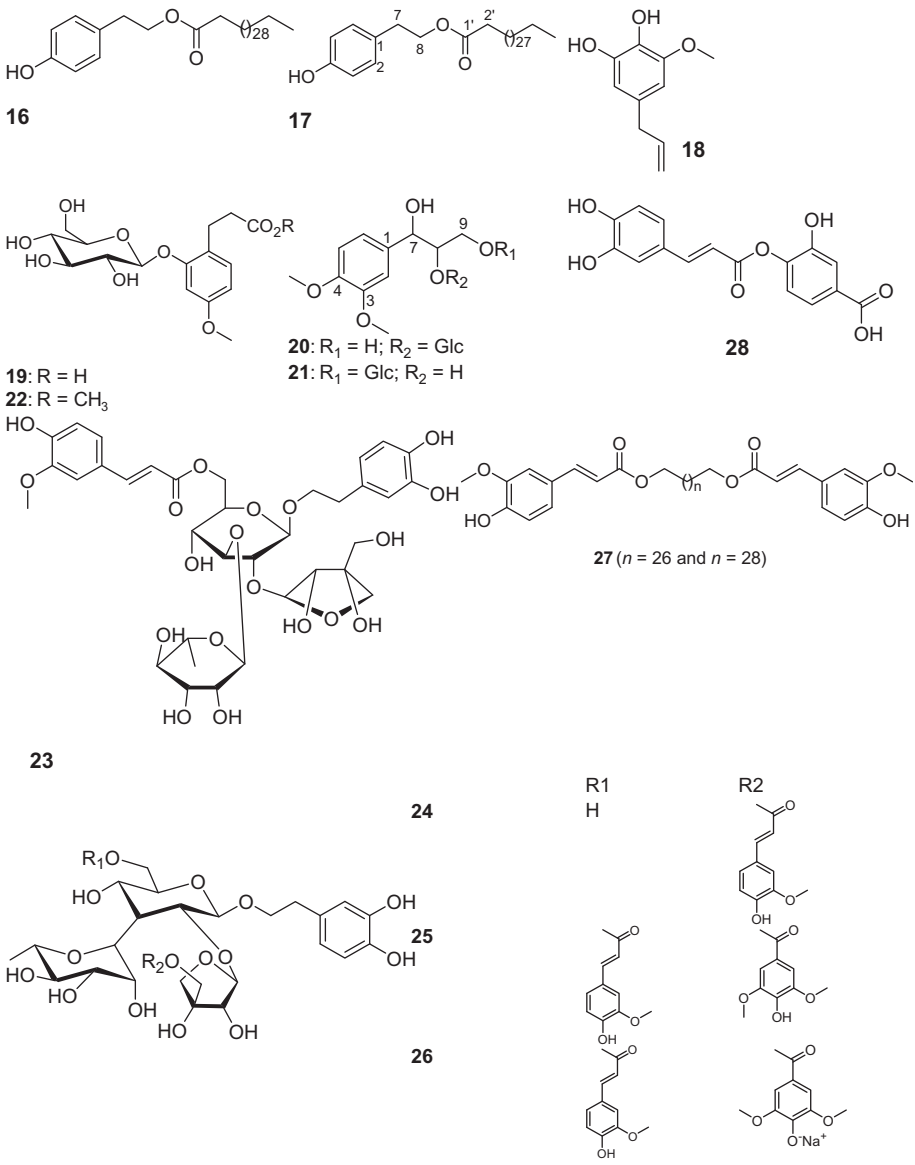

Figure 7.3 Phenylpropanoids and phenylethanoids isolated as new compound in African medicinal plants: 2-(4′-hydroxyphenyl)ethyl dotriacontanoate (**16**), 2-(4-hydroxyphenyl)ethyl hentriacontanoate (**17**), 2-hydroxy-3-methoxy-5-(2-propenyl)phenol (**18**), 2-*O*-β-D-glucosyloxy-4-methoxybenzenepropanoic acid (**19**), 4-*O*-methyl guaiacylglycerol 8-*O*-β-glucopyranoside (**20**), 4-*O*-methyl guaiacylglycerol 9-*O*-β-glucopyranoside (**21**), methyl-2-*O*-β-D-glucosyloxy-4-methoxybenzenepropanoate (**22**), newbouldioside (**23**), newbouldiosides A (**24**), B (**25**), C (**26**), octacosan-1,28-dioldiferulate and triacontan-1,3′-dioldiferulate (**27**), and trilepisiumic acid (**28**).

antimicrobial activities against *C. albicans* (MIC of 50 μg/mL), *Candida glabrata* (MIC of 100 and 50 μg/mL, respectively), *Candida krusei* (MIC of 50 μg/mL), and *Candida parapsilosis* (MIC of 100 μg/mL) [22]. Trilepisiumic acid (**28**), isolated from another Cameroonian plant, *T. madagascariense*, displayed antimicrobial activity against *Pseudomonas aeruginosa*, *Salmonella typhi*, *Escherichia coli* (MIC of 512 μg/mL), and *C. albicans* (MIC of 64 μg/mL) [14]. A prenylated cinnamaldehyde (**6**), together with nine known compounds isolated from the roots and stem bark of *V. glomerata* (Rutaceae), inhibited the growth of *Staphylococcus aureus* and *Shigella dysentriae*, with MIC values of 2.0 and 0.4 μg/mL, respectively [14]. Antibacterial activity of glomeral (**6**) was also reported against *S. aureus* (MIC of 2.0 μg/mL) and *S. dysenteriae* (MIC of 0.4 μg/mL) [12].

7.3.2 Other Activities of Phenylpropanoids Identified in African Medicinal Plants

Other pharmacological activities have been reported for phenylpropanoids identified in African medicinal plants. *p*-Coumaric acid (**10**) (IC_{50} of 265.6 μM) and caffeic acid (**3**) (IC_{50} of 428.2 μM) showed moderate urease inhibitory activities [7]. Syringin (**14**) showed a weak 2,2-diphenyl-1-picrylhydrazyl 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity, with an IC_{50} value of 85.0 μM [16]. Compound **14** also showed superoxide anion scavenging (IC_{50} of 70.88 μM) activity [11], as well as anti-inflammatory properties in human platelets, with up to 69% inhibition of thromboxane A2 release at 50 μM and an IC_{50} value of 29.3 μM, and in mouse peritoneal macrophages stimulated with calcium ionophore A23187 for 2 h (IC_{50} value of 35.5 μM) [6]. The phenylpropanoid glycoside verbascoside (**15**) displayed promising antioxidant activity, with IC_{50} values of 7.18 μg/mL [23].

7.4 New Phenylpropanoids Isolated in African Medicinal Plants

Some phenylpropanoids and phenylethanoids were isolated, mostly as esters or glycosides, in African medicinal plants. They are reported in Table 7.2 and Figure 7.3.

7.5 Conclusion

This chapter shows that phenylpropanoids were isolated, mostly as ester or glycosides, from African medicinal plants. It also highlights biological activities of some of them. Contrary to other classes of phenolics, data on the isolation of free C6-C3 phenylpropanoids are still not sufficient in regard to the structural diversity of the constituents of African medicinal plants.

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8 Coumarins and Related Compounds from the Medicinal Plants of Africa

Hervé Martial Poumale Poumale[a,d], *Rebecca Hamm*[b], *Yanqing Zang*[c], *Yoshihito Shiono*[d] *and Victor Kuete*[e]

[a]Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Yaoundé, Cameroon, [b]Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, University of Mainz, Mainz, Germany, [c]College of Food Science, Heilongjiang Bayi Agricultural University, Daqing, China, [d]Department of Bioresource Engineering, Faculty of Agriculture, Yamagata University, Tsuruoka, Yamagata, Japan, [e]Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon.

8.1 Introduction

Coumarin is a natural product well known for its pleasant vanilla-like odor. It has been reported in many varieties of African plant families including Adoxaceae, Asclepidiaceae, Aspiaceae, Capparidaceae, Compositae, Ebenaceae, Fabaceae, Lauraceae, Meliaceae, Moraceae, Papilionaceae, Ptaeroxylaceae, Rutaceae, etc. Coumarins are benzopyrones, of which the simplest is represented by structure **1** (Figure 8.1). They result from the metabolism of phenylalanine (**2**) via *p*-coumaric acid (**3**) (Figure 8.2) [1,2]. The word coumarin comes from "coumarouna" (*coumaro* in Portuguese), after the South American plant *Dripteryx odorata*, as it was first isolated from the seeds of this plant [1,2]. It has also been found in the form of the glycoside of melilotic acid (hydroxylcoumaric) in various plants (*Anthoxanthum odoratum*, *Melilotus* ssp., *Panicum clandestinum*, etc.). From rotted melilot, a vitamin K antagonist, dicoumarol was isolated, exhibiting anticoagulant activity [1]. *Thamnosma rhodesica*, a perennial woody herb, is used traditionally in Zimbabwe as an ant and flea repellent and smoked for the relief of chest conditions. From this plant, found in Zimbabwe and Botswana, furanocoumarins were isolated [3]. The bark and wood of *Cedrelopsis grevei*, found in Madagascar and South Africa, yielded a range of coumarins and chromones [4,5]. Umbelliferone, or 7-hydroxycoumarine (**4**) (Figure 8.2), initially isolated from distillation products of umbelliferae resins, was also isolated from African plants in free form or as a glycoside [1]. The principal pharmacological activity of coumarins is antiedematous, and their principal mechanism of action would support lymphatic drainage and

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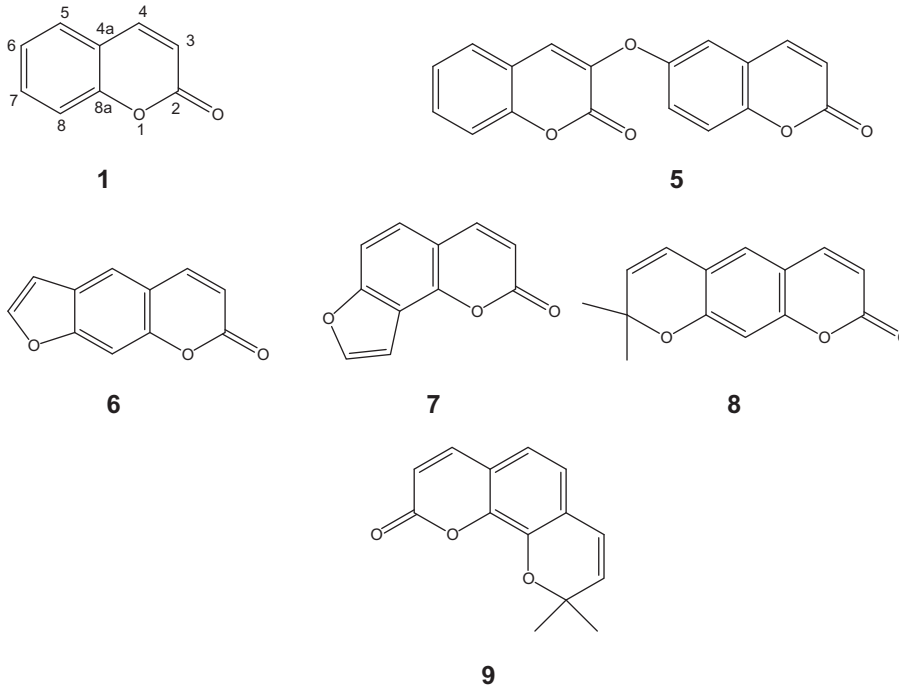


Figure 8.1 Basic skeleton of coumarin and its derivatives.

stimulate the proteolytic activity of macrophages. Coumarins are endowed with antivitamin P (i.e., increase in resistance and reduction in the permeability of the blood capillaries), photosensitizing, and antispasmodic properties. They also stimulate breathing, whereas the dimers exhibit anticoagulant properties [1]. The widespread use of African plants in which coumarins have been isolated in indigenous medicine justified phytochemical and pharmacological search for coumarins in African medicinal plants, as reported in this chapter.

8.2 Biosynthesis and Structural Diversity

Coumarins can be subdivided into simple coumarins (benzo-α-pyrones syn 1,2-benzopyrone) (**1**), dimer coumarins (**5**), furanocoumarins (7-oxygenated coumarins) (**6**, **7**), and pyranocoumarins (**8**, **9**) (Figure 8.1) [6,7]. All subclasses of coumarins derive from the same biosynthetic pathway. The biosynthesis of coumarins has been widely studied during the last 50 years, and their biosynthetic pathways have been established using labeling studies [7,8]. Labeling studies carried out in a plant that produces coumarin as well as 7-hydroxylated coumarins revealed that in the latter instance *para*-hydroxylation preceded the *ortho*-hydroxylation required for

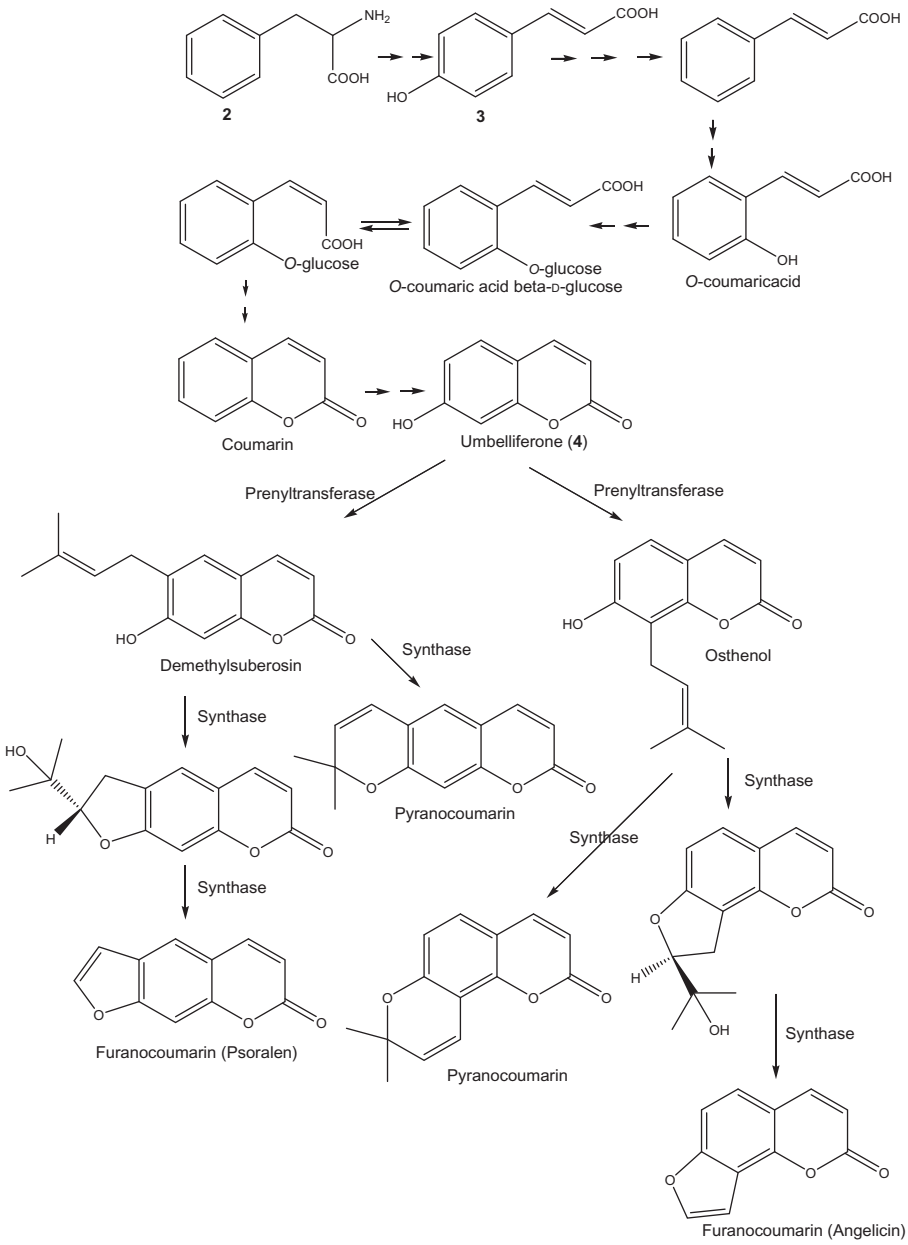


Figure 8.2 Biosynthesis of coumarin and its derivatives.

lactonization [9]. This indicated that umbelliferone (**4**) is derived from *cis*-*p*-coumaric acid, whereas coumarin originates from *cis*-cinnamic acid (Figure 8.2), and may imply different enzymes for the *ortho*-hydroxylation/lactonization of coumarin versus umbelliferone. The *ortho*-hydroxylation is a key step in coumarin biosynthesis that has received insufficient attention. The *trans* form is stable and could not cyclize; therefore, there should be isomerization of some sort, and the enzyme isomerase is implicated. The *cis* form is very unstable and, therefore, will tend to change to the *trans* configuration. Glucose is a good leaving group to assist in the *cis*−*trans* transformation. A specific enzyme found in *Melilotus alba* (Leguminosae) specifically hydrolyzes the *cis*-glucoside (β-glucosidase).

8.3 Detection of Coumarin in Plant Extracts

Coumarins can be detected in plant extract by means a simple chemical test. Take 0.01 g of the extract in a test tube and moisten it with a small amount of water. The mouth of the tube is then covered with filter paper treated with 1 N NaOH solution. The test tube is placed for a few minutes in boiling water, and then the filter paper is removed and examined under UV light. Yellow-green fluorescence indicates the presence of coumarins.

8.4 Pharmacological Activity of Coumarins Isolated from African Medicinal Plants

The presence of biologically active coumarins in many plants seems to be correlated with their ability to act as phytoalexins, as they are produced in response to several environmental stresses as well as pathogen attacks [10]. Thus, they accumulate on the surface of the leaves, fruits, and seeds, inhibiting the growth and sporulation of fungal plant pathogens and acting as repellents against insects and other terrestrial invertebrates [10]. Consequently, coumarins have a variety of bioactivities, including antiinflammatory, antifungal, anticoagulant, estrogenic, dermal photosensitizing, antimicrobial, vasodilatory, molluscacidal, antihelminthic, sedative and hypnotic, analgesic, hypothermic, and calcium antagonistic [11−15]. Several biologically active coumarins have been reported in African medicinal plants.

8.4.1 Antimicrobial Coumarins Isolated from African Medicinal Plants

Coumarins are known to possess a broad range of antimicrobial properties [16−20]. They have been found to stimulate macrophages [18], which could have an indirect negative effect on infections. More specifically, coumarins have been used to prevent the recurrence of cold sores caused by herpes simplex virus type 1 (HSV-1) in humans [16]. Several antimicrobial coumarins have been isolated from African plants. Phytochemicals are routinely classified as antimicrobials on the basis of susceptibility tests that produce minimal inhibitory concentration (MIC) in

the range of 100−1000 mg/mL [21]. Activity is considered to be significant if MIC values are below 10 μg/mL for pure compounds, moderate when 10 < MIC < 100 μg/mL, and weak when MIC > 100 μg/mL [22]. The proposed cutoff points for *in vitro* activity of antimalarial extracts based on their inhibitory concentration 50 (IC_{50}) values can be categorized as follows: $IC_{50} < 0.1$ μg/mL (very good), 0.1−1 μg/mL (good), 1.1−10 μg/mL (good to moderate), 11−25 μg/mL (weak), 26−50 μg/mL (very weak), and >100 μg/mL (inactive) [23]. The following inhibition percentages were proposed for *in vivo* activity of antimalarial compounds at a fixed dose of 250 mg/kg/day: 100−90% (very good activity), 90−50% (good to moderate), 50−10% (moderate to weak), and 0% (inactive) [23]. These criteria will be considered when discussing the antimicrobial activities of known (Figure 8.3, Table 8.1) and new (Figure 8.4, Table 8.2) biologically active coumarins identified in African plants.

The compounds 7-methoxycoumarin (**10**), 7-hydroxycoumarin (**4**), mammea coumarin MAB3 (**11**), and mammeisin (**12**), isolated from *Mammea africana* Sabine collected in Cameroon, showed a reduced and limited activity against bacteria expressing a multidrug resistant (MDR) phenotype [80]. Nevertheless the MIC value of 32 μg/mL was obtained with compound **11** against *Escherichia coli* AG100A [80]. Compounds **10**−**12** were also identified as substrates of efflux pumps of gram-negative bacteria, and their activity against MDR phenotypes significantly increased as a result of the inhibition of AcrAB-TolC and MexAB-OprM efflux pumps [80]. Consequently, MIC values below 10 μg/mL were obtained with compound **11** against MDR *E. coli* AG100 (8 μg/mL), AG100A (4 μg/mL), AG100Atet (8 μg/mL), AG102 (8 μg/mL), and *Enterobacter aerogenes* AE298 (8 μg/mL) [80]. This clearly suggests that a combination of compound **11** with an efflux pump inhibitor could be useful for fighting bacterial infections involving MDR phenotypes. Oughlissi-Dehak et al. [63] demonstrated that two sesquiterpene coumarins, farnesiferol A (**13**) and feselol (**14**), isolated from *Ferula vesceritensis* in Algeria, were able to act as efflux pump inhibitors as they bind to the model recombinant nucleotide-binding site of an MDR-like efflux pump from the enteropathogenic protozoan *Cryptosporidium parvum*.

The compound 6,7-dimethoxylcoumarin (**15**) exhibited good antifungal activity against *Rhizoctonia solani*, with 100% inhibition at 250 μg/mL [31]. Esculetin (6,7-dihydroxycoumarin) (**16**) showed low antimicrobial activity against *Bacillus megaterium* (MIC: 250 μg/mL), *Pseudomonas aeruginosa* PAO1 (MIC: 500 μg/mL), *E. coli* (MIC: 15.62−1000 μg/mL), and *Salmonella enterica serovar typhimurium* ST329 (MIC: 125−1000 μg/mL), and good to moderate activity against *Staphylococcus aureus* (MIC: 3.91−31.25 μg/mL) [26]. Scoparone (6,7-dimethoxycoumarin) (**15**), a coumarin isolated from *C. grevei*, showed low to weak antimicrobial activities against a panel of microorganisms, among which were *Enterococcus faecalis* (MIC: 300 μg/mL), *P. aeruginosa* (MIC: 300 μg/mL), *S. typhi* (MIC: 300 μg/mL), *Shigella sonnei* (MIC: 300 μg/mL), *S. aureus* (MIC of 300 μg/mL), *R. solani* [minimum fungicidal concentration (MFC) of 125 μg/mL and MIC of 31.2 μg/mL], *Rigidoporus microporus* (MIC: 62.5−250 μg/mL), and *Sclerotium oryzae* (MFC: 62.5 μg/mL; MIC: 62.5 μg/mL) [88].

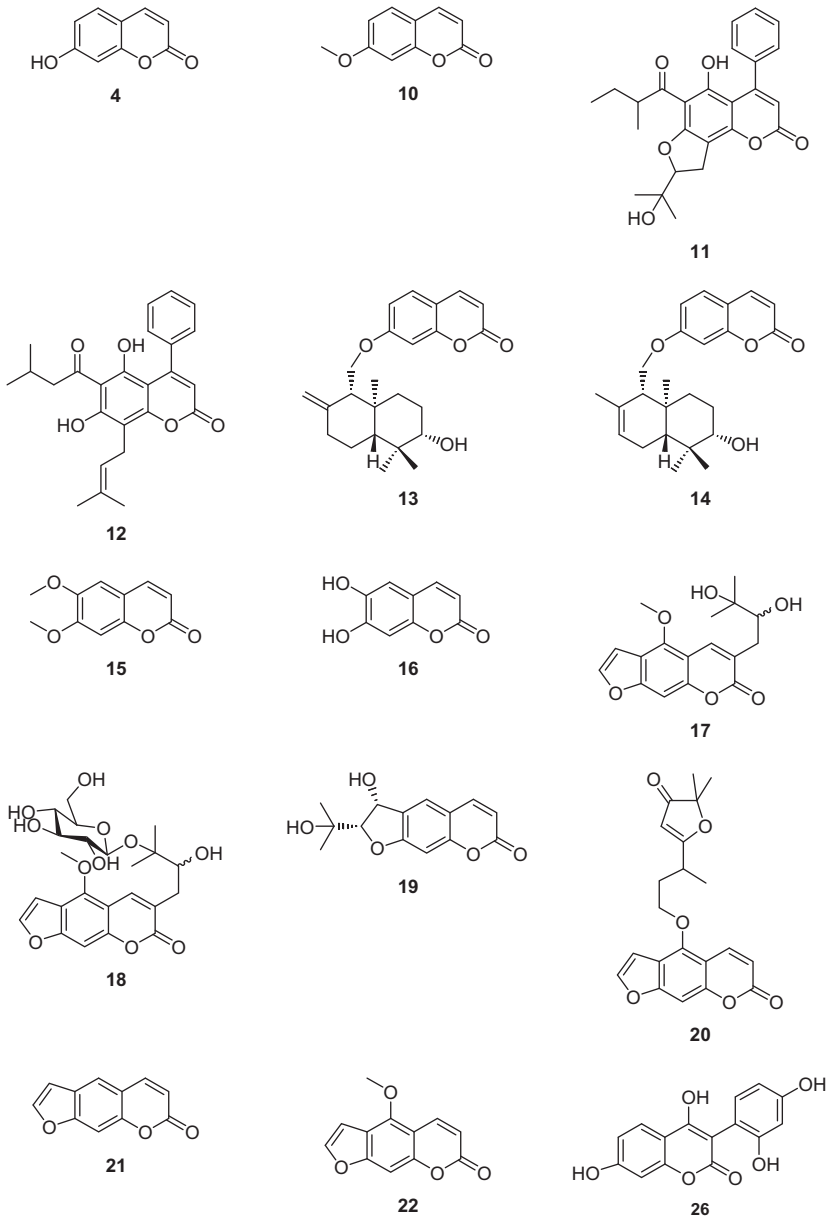


Figure 8.3 Known biologically active compounds from African medicinal plants: 7-hydroxycoumarin (**4**); 7-methoxycoumarin (**10**); MAB3 (**10**); mammeisin (**12**); farnesiferol A (**13**); feselol (**14**); 6,7-dimethoxycoumarin or scoparone (**15**); esculetin (**16**); 5-methoxy-3-(3-methyl-2,3-dihydroxybutyl)psoralen; 5-methoxy-3-[3-(β-glucopyranosyloxy)-2-hydroxy-3-methylbutyl]psoralen (**18**); (2′S, 3′*R*)-3′-Hydroxymarmesin (**19**); *O*-[3-(2,2-dimethyl-3-*oxo*-2*H*-furan-5-yl) butyl]bergaptol (**20**); psoralen (**21**); bergapten (**22**); asphodelin A (**26**);

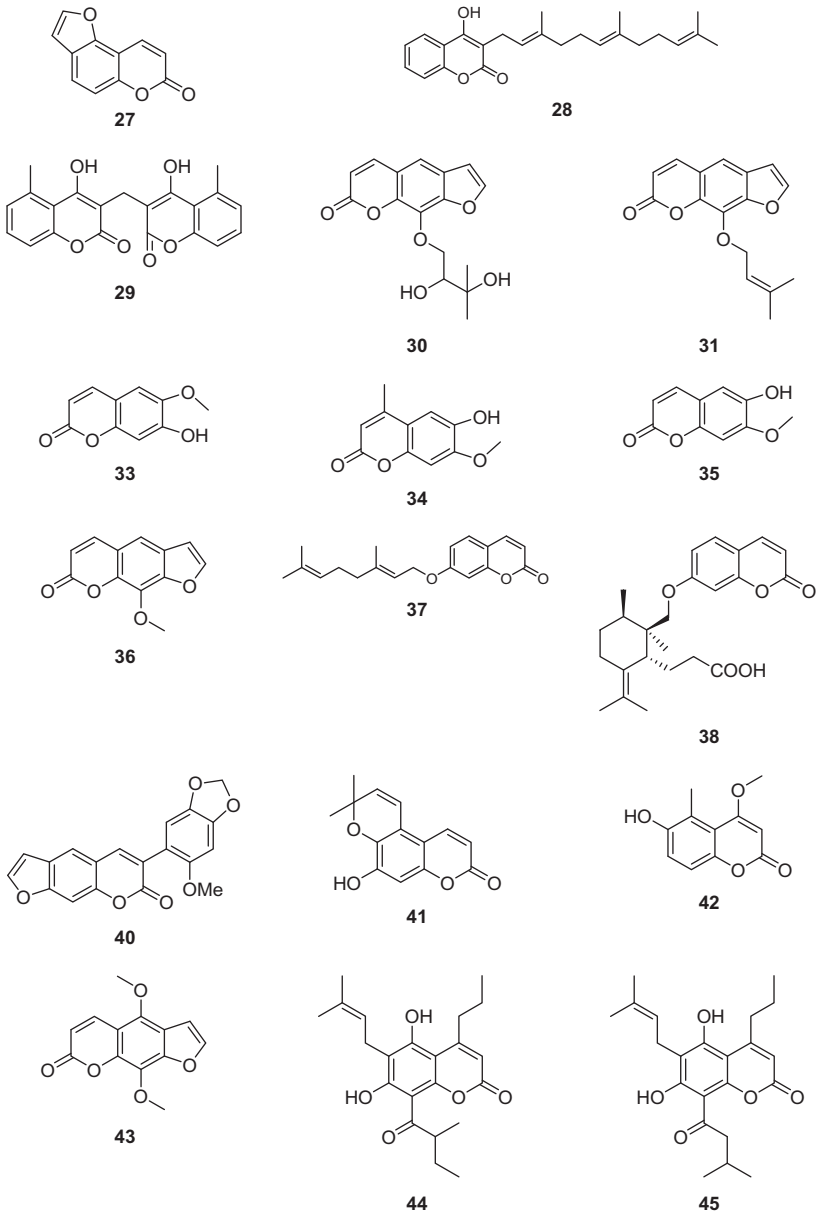


Figure 8.3 (Continued)

◀ bakuchicin (**27**); ferulenol (**28**); gerberinol (**29**); heraclenol (**30**); imperatorin (**31**); scopoletin (**33**); 6-hydroxy-7-methoxy-4-methyl-coumarin (**34**); 6-hydroxy-7-methoxycoumarin (**35**); xanthotoxin (**36**); auraptene or geranyloxycoumarin (**37**); galbanic acid (**38**); achyrrhyzine (**40**); cedrecoumarin A (**41**); 6-hydroxy-4-methoxy-5-methylcoumarin or esculetin (**42**);

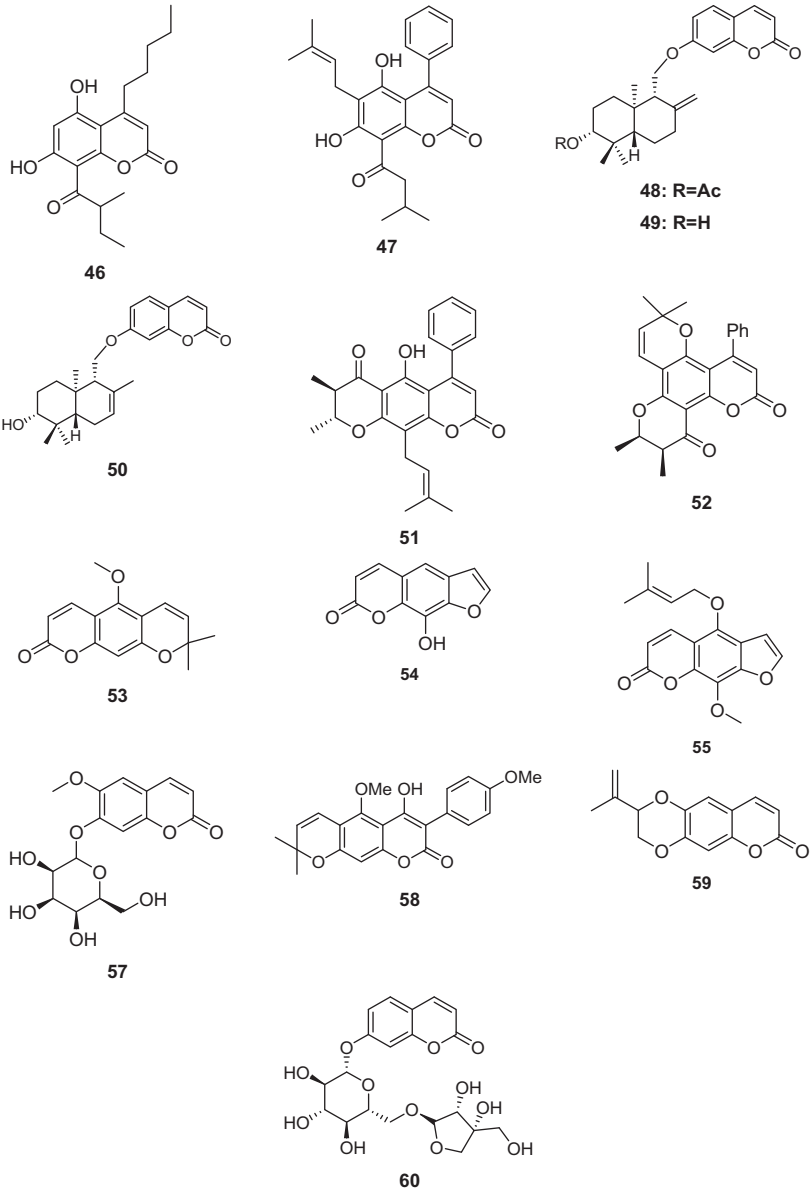


Figure 8.3 (Continued)

◀ isopimpinellin (**43**); mammea B/BB (**44**); mammea B/BA (**45**); mammea C/OB (**46**); mammea A/BA (**47**); coladin (**48**); coladonin (**49**); feselol (**50**); calaustralin (**51**); inophyllum E (**52**); xanthoxyletin (**53**); xanthotoxol (**54**); cnidilin (**55**); scopolin (**57**); robustic acid (**58**); obliquin (**59**); adicardin (**60**).

Table 8.1 Biologically Active Coumarins from African Medicinal Plants

Compounds	Plants (Family)	Pharmacological Activities
(2′S, 3′*R*)-3′-Hydroxymarmesin (**19**)	*D. turbinata* (Moraceae) [20]	Antibacterial, antifungal [24]
5-Methoxy-3-(3-methyl-2,3-dihydroxybutyl)psoralen (**17**)	*D. turbinata* (Moraceae) [24]	Antibacterial, antifungal [24]
5-Methoxy-3-[3-(β-glucopyranosyloxy)-2-hydroxy-3-methylbutyl] psoralen (**18**)	*D. turbinata* (Moraceae) [24]	Antibacterial, antifungal [24]
Esculetin (**42**)	*C. grevei* Baill. (Meliaceae) [25]	Antimicrobial [26], cytotoxic [27], enzyme inhibitor [28]
6,7-Dimethoxylcoumarin (**15**)	*Norantea guianensis* (Marcgraviaceae) [29], *Zanthoxylum leprieurii* Guill. et Perr. (Rutaceae) [30]	Antifungal [31]
6-Hydroxy-4-methoxy-5-methylcoumarin (**42**)	*G. jamesonii* Adlam. (Asteraceae) [32]	Cytotoxic [33]
6-Hydroxy-7-methoxy coumarin or scopoletin (**35**)	*A. majus* L. (Apiaceae) [34], *Scaphopetalum thonneri* (Sterculiaceae) [35], *Artemisia afra* Jacq. ex Willd. (Asteraceae) [36], *Chenopodium murale* L. (Chenopodiaceae) [37], *Dodonaea angustifolia* L.f. (Sapindaceae) [38]	Antiviral and antiinflammatory [34], AChE inhibitor [39], antiinflammatory [40], cytotoxic and antiangiogenic [41–43], antimicrobial [36]
6-Hydroxy-7-methoxy-4 methyl coumarin (**34**)	*A. majus* L. (Apiaceae) [34]	Antiviral and antiinflammatory [34]
7-Hydroxycoumarin (**4**)	*T. obovoidea* (Moraceae) [15]	Antibacterial, antifungal [15]
7-Methoxycoumarin (**10**)	*T. obovoidea* (Moraceae) [15]	Antibacterial, antifungal [15]
Adicardin (**60**)	*G. polycephala* (Thymeleaeceae) [44]	Cytoprotective [45]
Asphodelin A (**26**)	*A. microcarpus* (Asphodelaceae or Liliaceae) [46]	Antimicrobial [46]

(*Continued*)

Table 8.1 (Continued)

Compounds	Plants (Family)	Pharmacological Activities
Auraptene (**37**)	*C. viscosa* (L.) (Capparidaceae) [47]	Antiviral [48], cytotoxic [49], enzyme inhibitor [50]
Bakuchicin (**27**)	*P. plicata* (Leguminosae) [51]	Antifungal [13], enzyme inhibition [52]
Bergapten (**22**)	*T. obovoidea* (Moraceae) [15], *Dorstenia dinklagei* (Moraceae) [53], *P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [54], *Dorstenia picta* Bur. (Moraceae) [53]	Antibacterial, antifungal [15]
Calaustralin (**51**)	*C. inophyllum* L. (Guttiferae) [55], *Allanblackia monticola* Staner L.C. (Guttiferae) [56]	Cytotoxicity [55,56]
Cedrecoumarin A (**41**)	*Cedrelopsis longibracteata* J. F. Leroy. (Ptaeroxylaceae) [4]	Antiinflammatory [57]
Cnidilin (**55**)	*P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [54], *T. rhodesica* (Bak. f.) Mendonça (Rutaceae) [58]	Enzyme inhibitor [59]
Coladin (**48**)	*F. vesceritensis* Coss et Dur (Apiaceae) and *F. sinaica* L. (Apiaceae) [60]	Cytotoxic [32], enzyme inhibitor [61]
Coladonin (**49**)	*F. sinaica* L. (Apiaceae) [60]	Cytotoxic [62], enzyme inhibitor [61]
Farnesiferol A (**13**)	*F. vesceritensis* (Apiaceae) [63]	Efflux pump inhibitor [63]
Ferulenol (**28**)	*Ferula communis var. genuina* (Umbelliferae) [64]	Antimicrobial [65,66]
Feselol (**50**)	*F. vesceritensis* (Apiaceae) [63], *F. sinaica* L. (Apiaceae) [60]	Efflux pump inhibitor [63], cytotoxic [67]
Galbanic acid (**38**)	*F. assa-foetida* (Apiaceae) [68]	Antileishmanial [67]
Gerberinol (**29**)	*D. crassiflora* Hiern (Ebenaceae) [69]	Antimicrobial [69]
Heraclenol (**30**)	*R. montana* (Rutaceae) [70]	Antimycobacterial [70]
Imperatorin (**31**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae) [71], *P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [54], *T. rhodesica* (Bak. f.) Mendonça (Rutaceae) [58]	Anticoagulant [72], antiinflammatory [73], enzyme inhibitor [59,74], cytotoxic [75], antibacterial activity [72,76]
Inophyllum E (**52**)	*C. inophyllum* L. (Guttiferae) [55], *A. monticola* Staner L.C. (Guttiferae) [56]	Cytotoxic [55,56]

Isopimpinellin (**43**)	*R. montana* (Rutaceae) [70], *P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [54], *T. rhodesica* (Bak. f.) Mendonça (Rutaceae) [58]	Cytotoxic [77], relaxing effect [78]
MAB3 (**1**)	*M. africana* Sabine (Guttiferae) [79]	Antibacterial [80]
Mammea A/BA (**47**)	*M. africana* Sabine (Guttiferae) [79]	Cytotoxic [79]
Mammea B/BA (**45**)	*M. africana* Sabine (Guttiferae) [79]	Cytotoxic [79]
Mammea B/BB (**44**)	*M. africana* Sabine (Guttiferae) [79]	Cytotoxic [79]
Mammea C/OB (**46**)	*M. africana* Sabine (Guttiferae) [79]	Cytotoxic [79]
Mammeisin (**12**)	*M. africana* Sabine (Guttiferae) [79], *P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [54], *T. rhodesica* (Bak. f.) Mendonça (Rutaceae) [58]	Antibacterial [15], relaxing effect [81]
O-[3-(2,2-Dimethyl-3-*oxo*-2*H*-furan-5-yl) butyl] bergaptol (**20**)	*T. obovoidea* (Moraceae) [15]	Antibacterial, antifungal [15]
Obliquin (**59**)	*C. grevei* Baill. (Meliaceae) [25]	Antidepressive [82]
Pachyrrhyzine (**40**)	*N. mitis* (A. Rich.) Verdc. (Fabaceae) [83]	Insectivicidal [83]
Psoralen (**21**)	*D. turbinata* (Moraceae) [24], *T. obovoidea* (Moraceae) [15], *Ficus benjamina* (Moraceae) [84], *P. plicata* (Leguminosae) [51]	Antibacterial, antifungal [15]
Robustic acid (**58**)	*M. thonningii* (Schum. & Thonn.) Baker (Fabaceae) [85]	Enzyme inhibition [86]
Scoparone (**7**)	*C. grevei* Baill. (Meliaceae) [25], *Vepris glomerata* [87]	Antimicrobial [88], enzyme inhibitor [89]
Scopolin (**57**)	*S. thonneri* (Sterculiaceae) [35]	AChE inhibitor [39]
Umbelliferone (**4**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae) [90], *F. assa-foetida* [91], *P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [54]	Antimicrobial [80,92−95], cytotoxic [49], enzyme inhibitor [96,97]
Xanthotoxin (**36**)	*A. majus* L. (Apiaceae) [34]	Antiviral and antiinflammatory [34]
Xanthotoxol (**54**)	*P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae) [75]	Antioxidant [98], cytotoxic [99]
Xanthoxyletin (**53**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae) [71]	Cytotoxic [100]

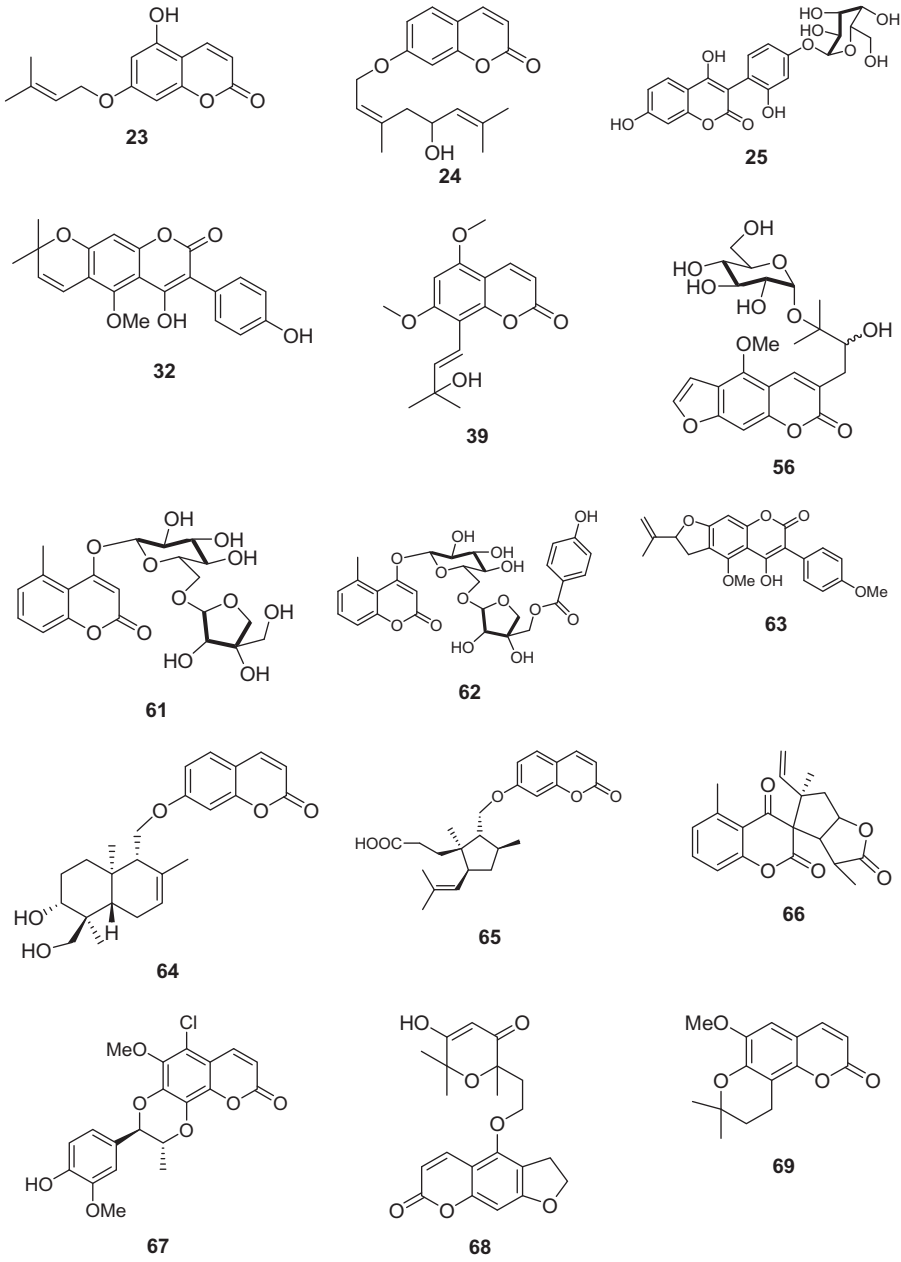
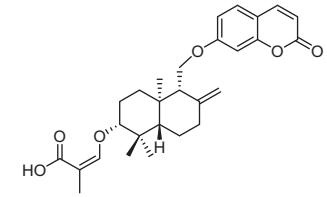


Figure 8.4 Chemical structures of coumarins isolated as new compound in African medicinal plants: anisocoumarin B (**23**); anisocoumarin H (**24**); asphodelin A 4′-*O*-β-D-glucoside (**25**); indicanine B (**32**); 5,7-dimethoxy-8-(3′-hydroxy-3′-methyl-1′-butene)-coumarin (**39**); turbinatocoumarin (**56**); diosfeboside A (**61**); diosfeboside B (**62**); indicanine A (**63**); 13-hydroxyfeselol (**64**); ferulsinaic acid (**65**); spiro-ethuliacoumarin (**66**);



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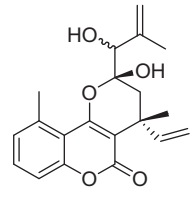

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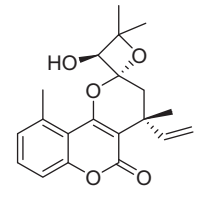

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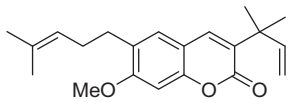

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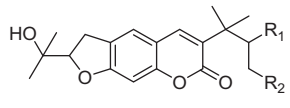
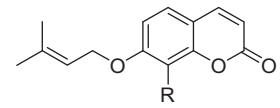
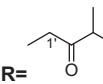


74: R_1+ R_2=O

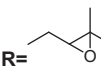
75: R_1=R_2=OH



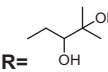
76: R=

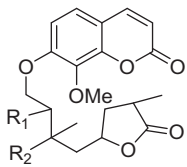


77: R=



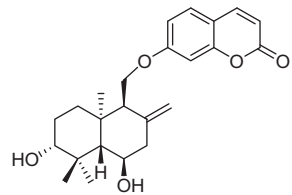
78: R=





79: R_1+ R_2=O

80: R_1=R_2=OH



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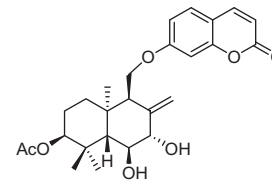

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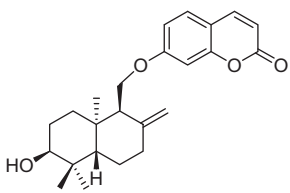

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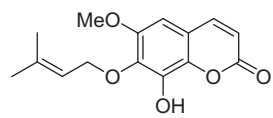

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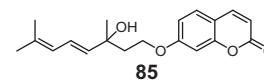

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Figure 8.4 (Continued)

◀ 5-chloropropacin (**67**); 2-*O*-[2-(5-hydroxy-2,6,6-trimethyl-3-*oxo*-2*H*-pyran-2-yl)ethyl] bergaptol (**68**); 3′,4′-dihydrobraylin (**69**); 3-angeloxycoladonin (**70**); 5′-epi-isoethuliacoumarin A (**71**); 5′-epi-isoethuliacoumarin B (**72**); anisocoumarin A (**73**); anisocoumarin C (**74**); anisocoumarin D (**75**); anisocoumarin E (**76**); anisocoumarin F (**77**); anisocoumarin G (**78**); anisocoumarin I (**79**); anisocoumarin J (**80**); assafoetidnol A (**81**);

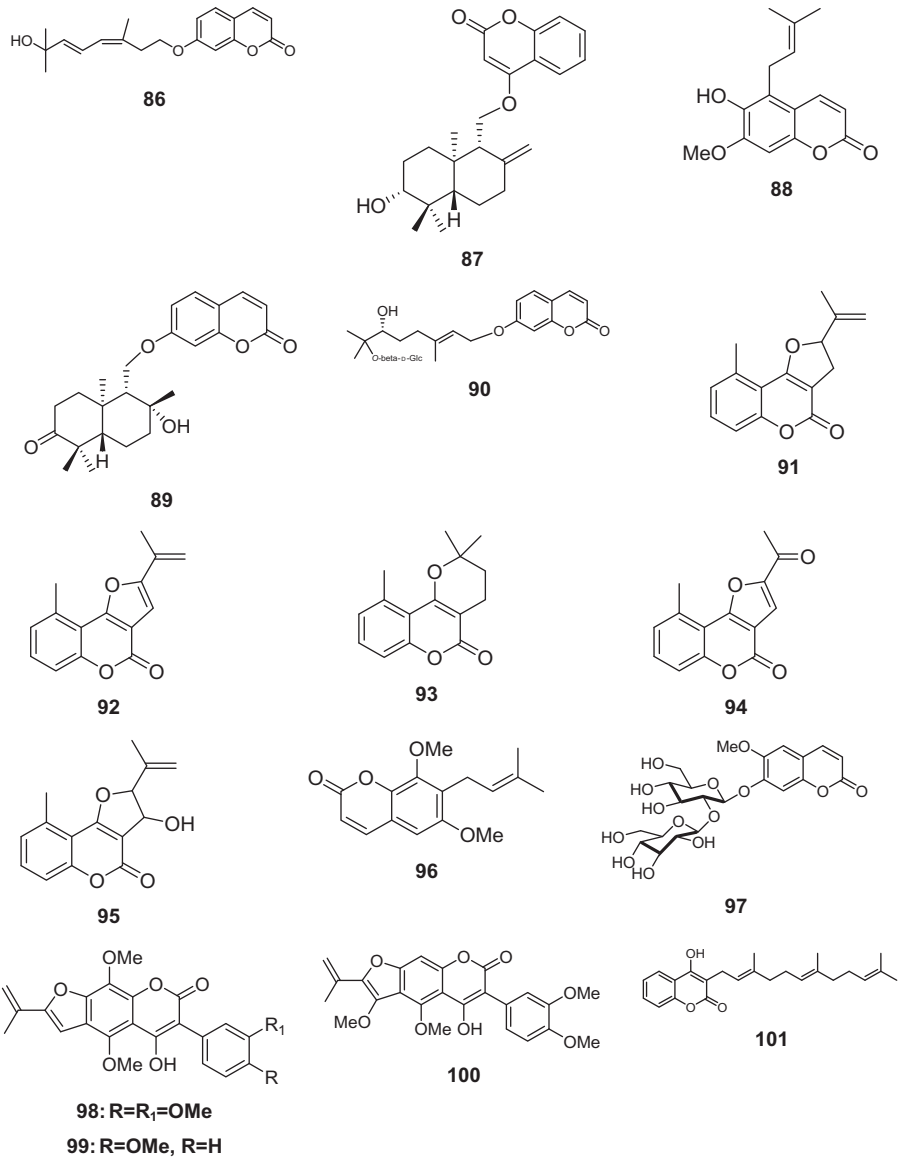

Figure 8.4 (Continued)

◀ assafoetidnol B (**82**); badrakemine (**83**); capensin (**84**); ferulagol A (**85**); ferulagol B (**86**); foetidin (**87**); isocedrelopsin (**88**); neveskone (**89**); pituranthoside (**90**); pterophyllin 1 (**91**); pterophyllin 2 (**92**); pterophyllin 3 (**93**); pterophyllin 4 (**94**); pterophyllin 5 (**95**); puherulin (**96**); scopoletin 7-*O*-β-D-sophoroside (**97**); thonningine A (**98**); thonningine B (**99**); thonningine C (**100**); ω-hydroxyferulenol (**101**).

Table 8.2 New Coumarins Isolated from African Plants

Compounds	Class (Type)	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
13-Hydroxyfeselol (**64**)	Coumarin (sesquiterpene)	*F. vesceritensis* Coss et Dur (Apiaceae)	Algeria [60]	Roots [60]	Yellowish oil; $[\alpha]_D^{25} = -27.5°$ (c 0.02, MeOH) [60]
2-*O*-[2-(5-Hydroxy-2,6,6-trimethyl-3-oxo-2H-pyran-2-yl)ethyl] bergaptol (**68**)	Coumarin (furanocoumarin)	*Dorstenia elliptica* (Moraceae)	Cameroon [101]	Twigs [101]	m.p.: 144−145°C; $[\alpha]_D = -4.1°$ (MeOH; c 0.11) [101]
3′,4′-Dihydrobraylin (**69**)*	Coumarin	*C. grevei* Baill. (Meliaceae)	Madagascar [25]	Trunk bark [25]	–
3-Angeloxycoladonin (**70**)*	Coumarin (sesquiterpene)	*F. vesceritensis* Coss et Dur (Apiaceae)	Algeria [60]	Roots	–
5,7-Dimethoxy-8-(3′-hydroxy-3′methyl-1′-butene)-coumarin (**39**)	Coumarin	*T. asiatica* L. Lam. (Rutaceae)	Kenya [102]	Roots [102]	–
5-Chloropropacin (**67**)*	Coumarin (coumarinolignan)	*M. whitei* (Hook. f.) Skeels (Asclepidiaceae)	Togo [103]	Roots [103]	Amorphous solid; $[\alpha]_D = 0°$ (c 0.7; $CHCl_3$:MeOH 1:1) [103]
5′-Epi-isoethuliacoumarin A (**71**)*	Coumarin (monoterpene acetophenone)	*E. conyzoides* Linn. f. (Compositae)	Egypt [104]	Aerial parts [104]	White powder [104]
5′-Epi-isoethuliacoumarin B (**72**)*	Coumarin (monoterpene acetophenone)	*E. conyzoides* Linn. f. (Compositae)	Egypt [104]	Aerial parts [104]	White powder [104]
Anisocoumarin A (**73**)*	Coumarin	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Combined stem bark and roots [71]	Yellow oil [71]

(*Continued*)

Table 8.2 (Continued)

Compounds	Class (Type)	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Anisocoumarin B (**23**)*	Coumarin	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Combined stem bark and roots [71]	m.p.: 94−95°C [71]
Anisocoumarin C (**74**)*	Coumarin	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Combined stem bark and roots [71]	Colorless oil; $[\alpha]_D^{25} = +15.5°$ ($CHCl_3$; c 1.1) [71]
Anisocoumarin D (**75**)*	Coumarin	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Combined stem bark and roots	m.p.: 210−211°C; $[\alpha]_D^{25} = +20.5°$ (MeOH; c 1.2) [71]
Anisocoumarin E (**76**)*	Coumarin (prenylated)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Leaves	Yellow oil [71]
Anisocoumarin F (**77**)*	Coumarin (prenylated)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Leaves [71]	Yellow oil; $[\alpha]_D^{25} = +27.5°$ ($CHCl_3$; c 1.5) [71]
Anisocoumarin G (**78**)*	Coumarin (prenylated)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Leaves [71]	Yellow oil; $[\alpha]_D^{25} = +32.5$ ($CHCl_3$; c 1.5) [71]
Anisocoumarin H (**24**)	Coumarin (prenylated)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [71]	Leaves [71]	Colorless oil; $[\alpha]_D^{25} = -20.5°$ ($CHCl_3$; c 1.04) [71]
Anisocoumarin I (**79**)*	Coumarin (gerany1ed)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [90]	Leaves [90]	m.p.: 127−128°C; $[\alpha]_D^{20} = +33°$ ($CHCl_3$; c 0.9) [90]
Anisocoumarin J (**80**)*	Coumarin (gerany1ed)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon [90]	Leaves [90]	m.p.: 154°C; $[\alpha]_D^{20} = -125°$ ($CHCl_3$; c 0.2) [90]

Asphodelin A 4′-*O*-β-D-glucoside (**25**)	Coumarin (aryl coumarin glucoside)	*A. microcarpus* (Asphodelaceae or Liliaceae)	Egypt [46]	Bulbs and roots [46]	m.p.: 143−146°C; $[\alpha]_D^{20} = +5.7$ (c 0.05, MeOH) [46]
Assafoetidnol A (**81**)*	Coumarin (sesquiterpene)	*F. assa-foetida* (Apiaceae)	Egypt [68]	Roots [68]	Amorphous solid; $[\alpha]_D = -80°$ (c 0.2, MeOH) [68]
Assafoetidnol B (**82**)*	Coumarin (sesquiterpene)	*F. assa-foetida* (Apiaceae)	Egypt [68]	Roots [68]	Amorphous solid; $[\alpha]_D = +29.4°$ (c 0.2, MeOH) [68]
Badrakemine (**83**)*	Coumarin (sesquiterpene)	*F. assa-foetida* (Apiaceae)	Egypt [68]	Roots [68]	Amorphous solid; $[\alpha]_D = +29.4°$ (c 0.2, MeOH) [68]
Capensin (**84**)*	Coumarin	*Phyllosma capensis* Bolus (Rutaceae)	South Africa [105]	Stem, twigs and leaves [105]	m.p. 135−136°C [105]
Diosfeboside A (**61**)	Coumarin (5-methylcoumarin glycosides)	*D. crassiflora* Hiern (Ebenaceae)	Cameroon [106]	Leaves [106]	m.p.: 202−204°C; $[\alpha]_D^{25} = -1.8°$ (c 0.1, DMSO) [106]
Diosfeboside B (**62**)	Coumarin (5-methylcoumarin glycosides)	*D. crassiflora* Hiern (Ebenaceae)	Cameroon [106]	Leaves [106]	$[\alpha]_D^{20} = -0.6°$ (c 0.1, DMSO) [106]
Ferulagol A (**85**)*	Coumarin (monoterpene)	*Ferula ferulago* (Apiaceae)	Egypt [68]	Roots [68]	–
Ferulagol B (**86**)*	Coumarin (monoterpene)	*F. ferulago* (Apiaceae)	Egypt [68]	Roots [68]	–
Ferulsinaic acid (**65**)*	Coumarin (sesquiterpene)	*F. sinaica* L. (Apiaceae)	Algeria [60]	Root [60]	White amorphous powder; $[\alpha]_D^{25} = -4.5°$ (c 0.02, $CHCl_3$) [60]

(*Continued*)

Table 8.2 (Continued)

Compounds	Class (Type)	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Foetidin (**87**)*	Coumarin (sesquiterpene)	*F. assa-foetida* (Apiaceae)	Egypt [91]	Roots [91]	m.p.: 176−178°C; $[\alpha]_D = -39.8°$ (ethanol) [91]
Indicanine A (**63**)	Coumarin (3-phenylcoumarin)	*E. indica* (Papilionaceae)	Cameroon [107]	Root bark [107]	m.p.: 175−177°C; $[\alpha]_D^{20} = -46°$ (c 1.99, MeOH) [107]
Indicanine B (**23**)	Coumarin (3-phenylcoumarin)	*E. indica* (Papilionaceae)	Cameroon [108]	Root bark [108]	m.p.: 200−201°C [108]
Isocedrelopsin (**88**)*	Coumarin (phenyl)	*C. grevei* Baill. (Meliaceae)	Madagascar [109]	Trunk bark [109]	–
Neveskone (**89**)*	Coumarin (sesquiterpene)	*F. assa-foetida* (Apiaceae)	Egypt [68]	Roots [68]	Amorphous solid; $[\alpha]_D = +29.4°$ (c 0.2, MeOH) [68]
O-[3-(2,2-Dimethyl-3-*oxo*-2H-furan-5-yl)-3-hydroxybutyl]bergaptol (**68**)	Coumarin (furanocoumarin)	*D. elliptica* (Moraceae)	Cameroon [101]	Twigs [101]	m.p.: 168−169°C; $[\alpha]_D = -5.0°$ (MeOH; c 0.12) [101]
Pituranthoside (**90**)*	Coumarin (monoterpene)	*P. triradiatus* (Hochst ex Boiss.) Aschers (Apiaceae)	Egypt [54]	Shoots [54]	m.p.: 185−186°C; $[\alpha]_D^{26} = +12°$ (c 0.5, MeOH) [54]
Pterophyllin 1 (**91**)*	Coumarin	*Ekebergia pterophylla* (C.DC.) Hofmeyr (Meliaceae)	South Africa [110]	Stem bark [110]	m.p.: 61−63°C; $[\alpha]_D^{25} = +44.2°$ (c 0.013, $CHCl_3$) [110]
Pterophyllin 2 (**92**)*	Coumarin	*E. pterophylla* (C.DC.) Hofmeyr (Meliaceae)	South Africa [110]	Stem bark [110]	m.p.: 57−59°C [110]

Pterophyllin 3 (**93**)*	Coumarin	*E. pterophylla* (C.DC.) Hofmeyr (Meliaceae)	South Africa [110]	Stem bark [110]	m.p.: 58−60°C [110]
Pterophyllin 4 (**94**)*	Coumarin	*E. pterophylla* (C.DC.) Hofmeyr (Meliaceae)	South Africa [110]	Stem bark [110]	m.p.: 60−62°C; $[\alpha]_D^{25} = +3.3^\circ$ (c 0.013, $CHCl_3$) [110]
Pterophyllin 5 (**95**)*	Coumarin	*E. pterophylla* (C.DC.) Hofmeyr (Meliaceae)	South Africa [110]	Stem bark [110]	m.p.: 60°C; $[\alpha]_D^{25} = \pm 1.7^\circ$ (c 0.013, $CHCl_3$)
Puherulin (**96**)*	Coumarin	*G. polycephala* (Rutaceae)	South Africa [111]	Aerial parts [111]	m.p.: 90−92°C [111]
Scopoletin 7-*O*-β-D-sophoroside (**97**)*	Coumarin (glycoside)	*Viburnum tinus* (Adoxaceae)	Egypt [112]	Leaves [112]	–
Spiro-ethuliacoumarin (**66**)*	Coumarin (spiro-monoterpene)	*E. conyzoides* Linn. f. (Compositae)	Egypt [113]	Aerial parts [113]	m.p.: 198°C $[\alpha]_D = +167.39$ (c 1.515, $CHCl_3$) [113]
Thonningine A (**98**)*	Coumarin (phenyl)	*M. thonningii* (Schum. & Thonn.) Baker (Fabaceae)	Ghana [114]	Seeds [114]	m.p.: 205−208°C [114]
Thonningine B (**99**)*	Coumarin (phenyl)	*M. thonningii* (Schum. & Thonn.) Baker (Fabaceae)	Ghana [114]	Seeds [114]	–
Thonningine C (**100**)*	Coumarin (phenyl)	*M. thonningii* (Schum. & Thonn.) Baker (Fabaceae)	Ghana [115]	Root wood	m.p.: 199−200°C [115]
Turbinatocoumarin (**56**)	Coumarin (furanocoumarin glycoside)	*D. turbinata* (Moraceae)	Cameroon [116]	Twigs [116]	Amorphous solid; $[\alpha]_D^{20} = -10.6$ (c 1, $CHCl_3$ + MeOH 1:1) [116]
ω-Hydroxyferulenol (**101**)*	Coumarin (isoprenyl)	*F. communis var. genuina* (Umbelliferae)	Morocco [64]	Root sap [64]	–

m.p.: melting point; (−): not reported: (*): no reported pharmacological activity.

The coumarins 5-methoxy-3-(3-methyl-2,3-dihydroxybutyl)psoralen (**17**), 5-methoxy-3-[3-(β-glucopyranosyloxy)-2-hydroxy-3-methylbutyl]psoralen (**18**), and (2′S,3′R)-3′-hydroxymarmesin (**19**), isolated from the Cameroonian plant *Dorstenia turbinata*, exhibited significant antifungal activities, with MICs close to those of the reference antifungal drug nystatin [24]. *O*-[3-(2,2-dimethyl-3-*oxo*-2H-furan-5-yl) butyl]bergaptol (**20**) also showed good but selective antimicrobial activity against yeasts of the genus *Candida*, as well as gram-positive and gram-negative bacteria [15]. Compounds **17**−**20** prevented the growth of a panel of microorganisms with MICs ranging from 9.76 to 78.12 μg/mL. These microorganisms include bacteria, such as *S. aureus* (MIC > 78.12 for **19** and **20**), *E. coli*, *Shigella dysenteriae*, *Klebsiella pneumoniae*, *P. aeruginosa*, *S. typhi*, *Citrobacter freundii*, and fungi, namely *Candida albicans*, *Candida glabrata*, *Microsporum audouinii*, and *Trichophyton rubrum* [24]. Under similar experimental conditions, compounds **17** and **18** were as active as the nystatin against the previously mentioned fungal species [24]. The coumarins (**10**, **4**, **20**), psoralen (**21**), and bergapten (**22**), isolated from *Treculia obovoidea* collected in Cameroon, were reported to exhibit antibacterial and antifungal activities [15]. The inhibitory effects of these coumarins were selective, with the active compounds exhibiting MIC values ranging from 4.88 to 78.12 μg/mL [15]. However, they all were active against *C. albicans*, *C. glabrata*, and *Candida krusei*, with the lowest MIC value of 4.88 μg/mL obtained with **20** being only twofold greater than that of nystatin under similar experimental conditions [15]. Antibacterial activity (MIC around or below 78.12 μg/mL) was reported for **20**, **21**, and **22** against *E. coli* (**22** not active in this case), *Enterobacter cloacae*, *Shigella flexneri*, *S. aureus* (**22** not active in this case), *Streptococcus faecalis*, *B. megaterium*, and *Bacillus subtilis* [15]. Regarding the structure−activity relationship of the above coumarins, it has been observed that the additional furo-cycle generally increases the antimicrobial activity, as three cyclic coumarins, such as **20**, **21**, and **22**, showed better inhibitory effects than coumarins with two cyclic systems, such as **10** and **4**[15]. It has also been shown that compound **10** (7-methoxycoumarin) is generally more active than **4** (7-hydroxycoumarin) against MDR gram-negative bacteria [80]. Additionally, among the three cyclic coumarins, it has been demonstrated that the substitution of the 5-methoxy (−OCH_3) group of compound **22** by the *O*-[3-(2,2-dimethyl-3-*oxo*-2*H*-furan-5-yl) butyl] group leading to **20** also increases antimicrobial activity [15]. The activity of psoralen (**21**) and its derivatives has been widely discussed [15,24,109,117]. Generally, psoralens are a group of photobiologically active compounds currently employed in the treatment of vitiligo, psoriasis, and other skin diseases, as well as viral infections involving the HSV-1 [109,117]. The molecular basis for their action consists of an intercalation into the DNA double helix, followed by a C4 photo-cyclo addition to the pyrimidine bases of nucleic acid, yielding a covalently bound drug polynucleotide complex [118]. However, the presence of this compound does not necessarily guarantee the activity of the plant, although it has been noted that African plants containing compound **22** were generally active against various types of bacteria and fungi [15,24].

Anisocoumarin B (**23**), isolated as a new compound in the Cameroonian plant *Clausena anisata* [90], showed an anti-HIV activity, inhibiting reverse transcriptase

production with an IC_{50} value of 18.3 μM [48]. Another coumarin from *C. anisata*, anisocoumarin H (**24**), exhibited selective antifungal activities, with no effect observed against *C. albicans*, *C. tropicalis*, or *Saccharomyces cerevisiae*, though moderate effects were noted against *Cryptococcus neoformans* (MIC: 125 μg/mL) and *Trichophyton mentagrophytes*, *T. rubrum*, and *Microsporum gypseum* (MIC: 62.5 μg/mL) [119].

Asphodelin A 4′-*O*-β-D-glucoside (**25**), isolated from the Egyptian plant *Asphodelus microcarpus*, showed moderate antimicrobial activity against *S. aureus* (MIC: 128 μg/mL), *E. coli* (MIC: 128 μg/mL), *P. aeruginosa* (MIC: 256 μg/mL), *C. albicans* (MIC: 512 μg/mL), and *Botrytis cinerea* (MIC: 1204 μg/mL) [46]. Its aglycone asphodelin A (**26**) generally exhibited better activity on the same microbial species, namely *S. aureus* (MIC: 16 μg/mL), *E. coli* (MIC: 4 μg/mL), *P. aeruginosa* (MIC: 8 μg/mL), *C. albicans* (MIC: 512 μg/mL), and *B. cinerea* (MIC: 128 μg/mL) [46].

The antifungal activity of bakuchicin (**27**), one of the constituents of the Egyptian plant *Psoralea plicata* [51], was reported to be active against *Aspergillus niger* (MIC: 62.5 μg/mL) and *S. cerevisiae* (MIC: 125 μg/mL) [13]. Ferulenol (**28**) exhibited a low but broad spectrum of antimicrobial activity against bacteria and fungi, such as *S. aureus* (MIC: 2.4 mg/mL), *Streptomyces scabies* (MIC: 2.2 mg/mL), *B. subtilis* (MIC: 2.0 mg/mL), *Bacillus cereus* (MIC: 2.1 mg/mL), *P. aeruginosa* (MIC: 2.3 mg/mL), *E. coli* (MIC: 4.8 mg/mL), *A. niger* (MIC: 4.7 mg/mL), and *Fusarium oxysporum* (MIC: 4.6 mg/mL) [65]. Compound **28** showed good activity against mycobacteria, such as *Mycobacterium aurum* (MIC: 2 μg/mL), *Mycobacterium smegmatis* (MIC: 0.5 μg/mL), *M. phlei* (MIC: 2 μg/mL), and *M. fortuitum* (MIC: 2 μg/mL) [120].

The bicoumarin gerberinol (**29**) is active against fungi of the genus *Candida*, namely *C. albicans* (MIC: 39.06 μg/mL), *C. krusei* (MIC: 39.06 μg/mL), as well as *E. coli* (MIC: 19.53 μg/mL), *S. dysenteriae* (MIC: 4.88 μg/mL), *S. typhi* (MIC: 4.88 μg/mL), and *S. aureus* (19.53 μg/mL) [69].

The furocoumarin heraclenol (**30**), isolated from the Algerian plant *Ruta montana* [70], inhibited the growth of *Mycobacterium tuberculosis* and *M. avium*, with an MIC of 100 μg/mL [121]. At 200 μg/disc, the inhibitory activity of **30** was also documented on *B. subtilis*, with the diameter of inhibition zone (IZ) obtained being 19 mm, against *B. cereus* (IZ: 23.5 mm), and *Staphylococcus epidermidis* (IZ: 20.5 mm) [20]. Poor inhibitory activity was reported for **30** against *S. aureus* (MIC: 0.68 mg/mL), *S. epidermidis* (MIC: 0.64 mg/mL), *P. aeruginosa* (MIC: 0.7 mg/mL), and *Streptococcus viridans* (MIC: 0.5 mg/mL) [76]. In an *in vitro* test, no antifungal activity was observed for **30** against *C. albicans* or *C. tropicalis* [76].

The antibacterial activity of imperatorin (**31**) was found to be moderate against *B. subtilis* (MIC: 128 μg/mL), *Proteus mirabilis* (MIC: 32 μg/mL), *S. typhi* (MIC: 64 μg/mL) [72], *S. aureus* (MIC: 45 μg/mL), *S. epidermidis* (MIC: 35 μg/mL), *P. aeruginosa* (MIC: 70 μg/mL), *E. cloacae* (MIC: 28 μg/mL), *K. pneumoniae* (MIC: 30 μg/mL), *E. coli* (MIC: 25 μg/mL), *Streptococcus mutans* (MIC: 18 μg/mL), *S. viridans* (MIC: 15 μg/mL) [76], and *Mycobacterium intracellulare* (IC_{50}: 50 μg/mL) [72]. This compound is also active against fungi like *C. neoformans* (IC_{50} of 20 μg/mL), though no antifungal activity was observed against *C. albicans*, *C. tropicalis*, *C. glabrata* [76], or *Aspergillus fumigatus* [72].

The phenylcoumarin indicanine B (**32**), isolated from *Erythrina indica* of Cameroon, showed significant antibacterial activity against *S. aureus* (MIC: 9.7 μg/mL) and moderate activity against *E. coli* (MIC: 18.5 μg/mL), but was found to be inactive against *M. smegmatis* [108]. Scopoletin (**33**) exhibited low activity against gram-positive bacteria *Actinomyces israelii* (MIC: 0.25 mg/mL), *Actinomyces naeslundii* (MIC: 1 mg/mL), and gram-negative bacteria *Prevotella intermedia* (MIC: 0.5 mg/mL) [36].

The common coumarin umbelliferone (**4**) exhibited low antimicrobial activity against MDR *E. coli* AG100A (MIC: 256 μg/mL), *E. coli* AG100ATet (MIC: 128 μg/mL), *E. aerogenes* EA294 (MIC: 256 μg/mL), *E. aerogenes* EA294 (MIC: 256 μg/mL) [80], *M. tuberculosis* H37Rv (MIC: 150 μg/mL [92] or 58.3 μg/mL) [93]. It is worth noting that the activity of **4** improved when it was combined with an efflux pump inhibitor against MDR gram-negative bacteria, clearly indicating that the compound is a substrate of efflux pumps [80]. Its antiamoebic activity was also documented, as an IC_{50} value of 6.380 μM was observed against trophozoites of *Entamoeba histolytica* [94]. This compound also showed antiprotozoal activity against *Leishmania donovani* (IC_{50}: 27.9 μg/mL) and *Trypanosoma brucei rhodesiense* (IC_{50}: 51.8 μg/mL) [95].

The three coumarins 6-hydroxy-7-methoxy-4 methyl coumarin (**34**), 6-hydroxy-7-methoxy coumarin (**35**), and xanthotoxin (**36**), isolated from the Egyptian plant *Ammi majus*, showed a dose-dependent antiviral activity against the vesicular stomatitis virus (VSV) [34]. Unfortunately, the work of Selim and Ouf [34] did not provide the activity parameters and the data remain mainly informative. However, the antimicrobial activity of *A. majus* can be attributed to the presence of well-known active constituents like compound **36**. Auraptene (**37**), a constituent of the Sudanese plant *Cleome viscosa* [47], showed anti-HIV properties in C8166 cells infected with HIV-1IIIB (IC_{50}: 59.7 μM) [48].

Galbanic acid (**38**) is one of the constituents of the Egyptian plant *Ferula assa-foetida* [68]. Antileishmanial activity (IC_{50}: 164.8 μM) was reported against the promastigotes of *Leishmania major* [67]. This compound also showed protection against influenza A H1N1 virus (IC_{90}: 0.88 μg/mL) when tested on Madin−Darby canine kidney cells [122]. In an *in vitro* antibacterial test, compound **38** did not exhibit activity against *S. aureus* (at >120 μg/mL); however, it potentiates the antimicrobial actions of penicillin G and cephalexin [123]. In the presence of 100 μg/mL of this compound, the MIC of penicillin G for *S. aureus* decreased from 64 to 1 μg/mL and for cephalexin from 128 to 1 μg/mL [123]. A new coumarin, 5,7-dimethoxy-8-(3′-hydroxy-3′-methyl-1′-butene)-coumarin (**39**), isolated from *Toddalia asiatica*, showed moderate antiplasmodial activity against chloroquine-sensitive (IC_{50}: 16.2 μg/mL) and chloroquine-resistant (IC_{50}: 8.8 μg/mL) strains [102]. Pachyrrhizine (**40**), also isolated from the Tanzanian plant *Neorautanenia mitis*, showed insecticidal activity against *Anopheles gambiae* (IC_{50}: 7 μg/mL) [83].

8.4.2 Antiinflammatory Coumarins from African Medicinal Plants

Pain is a common health problems with substantial socioeconomic impact because of its high incidence. It is a symptom of many diseases, and it is estimated that

80−100% of the population experience back pain at least once in their lifetime [124]. The treatment of pain requires analgesics including antiinflammatory products. Hence, most of the nonsteroidal antiinflammatory agents also have analgesic activity. The inhibition of prostaglandin E2 (PGE2) and nitric oxide (NO) production has been proposed as a potential therapy for different inflammatory disorders [125]. Although many analgesics and antiinflammatory agents are present in the market, modern drug therapy is associated with some adverse effects, such as gastrointestinal irritation [124,126], fluid retention, bronchospasm, and prolongation of bleeding time. Plant products have been used in the development of new drugs, and they continue to play an invaluable role in the progress of drug discovery [127]. They can be an important source of safer drugs for the treatment of pain and inflammation. Some coumarins identified in African plants are known to have antiinflammatory activity.

At a dose level of 0.01 mg/100 g, compounds **34**, **35**, and **36** (Figure 8.3) exhibited an appreciable inhibition of carrageenan-induced rat paw edema—37.81%, 36.80%, and 28.17%, respectively. These values were comparable to that of the standard drug indomethacin (60.50%) under similar experimental conditions [34]. Cedrecoumarin A (**41**) showed antiinflammatory activity, inhibiting luminol-enhanced chemiluminescence of reactive oxygen metabolites and scavenging the superoxide anions in human polymorphonuclear leukocytes (IC_{50}: 3.0 μg/mL) [57].

The vasodilatative properties of imperatorin (**31**) were reported for concentrations ranging from 10^{-6} to 0.001 M on the mesenteric arterial ring (from Sprague-Dawley rat) and on human omental artery segments [128]. Antiinflammatory activity was also observed on ddY mouse macrophages with an IC_{50} value of 60 μM [73]. Compound **30** also showed antiinflammatory activity on tetradecanoylphorbol acetate (TPA)-induced ear edema in mice [129]. Compound **33** (scopoletin) has a remarkable antiinflammatory effect in both croton oil- and carrageenan-induced inflammatory models involving the inhibition of PGE2 and tumor necrosis factor-α (TNF-α) overproduction, as well as neutrophil infiltration [40]. It has been demonstrated that **33** ameliorates the clinical symptoms of rat adjuvant-induced arthritis, partially by preventing synovial angiogenesis and inducing apoptosis of fibroblast-like synoviocytes [41−43].

8.4.3 Cytotoxic Coumarins Identified from African Medicinal Plants

The cytotoxicity of several coumarins found in African plants (Figures 8.3 and 8.4, Tables 8.1 and 8.2) was documented on a variety of cancer cell lines, and the modes of action of some of these molecules have also been studied. However, the activity of the majority of coumarins identified in African plants was observed to be moderate with $IC_{50} > 10$ μM or $IC_{50} > 4$ μg/mL [130,131].

The coumarin (**31**) (imperatorin) inhibited the proliferation of human cancer cells, with an IC_{50} of 9.6 μg/mL obtained against oral epidermal carcinoma KB cells, 37.62 μg/mL against breast cancer MCF7 cells, and 28.58 μg/mL against small-cell lung cancer NCI-H187 cells [75]. This compound induced apoptosis in Jurkat leukemia cells at a concentration of 25 μg/mL, causing DNA fragmentation mainly at the

G1/S transition phase [66]. Low cytotoxicity has been reported for **30** (heraclenol) against HeLa cells (IC_{50}: 0.27 mg/mL) and the prostate carcinoma LNCaP (IC_{50}: 0.411 mg/mL) [132]. Compound **4** (umbelliferone) was also tested on several cancer cell lines, but only a very few of them were sensitive to it, with an IC_{50} value of 97 μM against the colon cancer LoVo cell line [49]. Compound **36** (xanthotoxin) showed activity against HeLa cells (IC_{50}: 7.6 μg/mL) [133], immortalized keratinocytes (IC_{50}: 5.5 μM), LoVo cells (IC_{50}: 1.1 μM), T-cell leukemia Jurkat cells (IC_{50}: 1.2 μM) [134], and cervix adenocarcinoma HeLa cells (IC_{50}: 10 μM) [135].

A constituent of the Egyptian plant *Gerbera jamesonii* [32], 6-hydroxy-4-methoxy-5-methylcoumarin (**42**), is cytotoxic against the human KB carcinoma cell line ($IC_{50:}$ 4.8 mg/L) [33]. The antiproliferative activity of **42** was also documented against the cervix adenocarcinoma HeLa cell line (IC_{50}: 37.8 μM); the compound showed an apoptosis-like morphological change and increased cell population in the sub-G1 phase [27]. This compound was also reported to be cytotoxic against EPG85-257RDB cells (IC_{50}: 16 μM) and HT-29P cells (IC_{50}: 24 μM) [136], as well as against promonocytic leukemia U-937 cells (IC_{50}: 31.33 μM) [137]. Unfortunately, compound **42** also showed a high cytotoxicity against normal kidney cells (Vero cells) in the African green monkey, the maximal noncytotoxic concentration (MNCC) being as low as 0.14 mM [138].

The coumarin (**23**) (anisocoumarin B) exhibited a low cytotoxicity against leukemia C8166 cells with an IC_{50} value of 813 μM [48]. Compound **37** (auraptene) also showed antiproliferative effects on a panel of cancer cell lines, such as human glioblastoma U373 cells (IC_{50}: 82 μM), esophageal carcinoma OE21 (IC_{50}: 58 μM), non-small-cell lung cancer A549 (IC_{50}: 82 μM), prostate cancer cells PC-3 (IC_{50}: 65 μM), melanoma cancer cells SKMEL-28 (IC_{50}: 87 μM), Jurkat T-cell clone E6.1 (IC_{50}: 16.5 μg/mL), and colon cancer cells LoVo (IC_{50}: 66 μM) [49]. At 50 μM, compound **37** induced G0−G1 phase cell cycle arrest in breast cancer MDA-MB-231 cells. Compound **22** (bergapten) was reported to be cytotoxic against cancer cell lines, with IC_{50} values of 36.6 μg/mL against the murine leukemia cell line P-388, 40.8 μg/mL against human colon adenocarcinoma cell line Colo-205, and 24.7 μg/mL against HeLa cells [77]. Isopimpinellin (**43**) exhibited a moderate cytotoxicity against Colo-205 with an IC_{50} value of 39.2 μg/mL [77]. Some coumarins from *M. africana*, such as compounds **11** (MAB3), B/BB (**44**), B/BA (**45**), C/OB (**46**), and A/BA (**47**), showed a low cytotoxicity against the human 9-KB cell line [79].

The cytotoxicity of three coumarins—coladin (**48**), coladonin (**49**), and feselol (**50**)—identified in the extract of the Algerian plant *Ferula sinaica* [60] on cancer cell lines has been documented. The antiproliferative activity of compound **48** was reported against colorectal cancer HCT 116 cells (IC_{50}: 3.7 μM) and colorectal cancer HT-29 cells (IC_{50}: 5.4 μM) [62]. Compound **49** also showed a moderate cytotoxicity against HCT 116 cells (IC_{50}: 15.1 μM) and HT-29 cells (IC_{50}: 13.3 μM) [62], whereas **50** has been reported to be active against leukemic monocyte lymphoma U-937 cells (IC_{50}: 8 μM) and Raji cells (IC_{50}: 14.3 nM) [139].

A moderate cytotoxic effect against KB cells was reported for calaustralin (**51**) (IC_{50}: 42.0 μg/mL) and inophyllum E (**52**) (IC_{50}: 36.1 μg/mL), isolated from the Cameroon plant *Calophyllum inophyllum* [55].

The coumarin xanthoxyletin (**53**) showed low cytotoxicity on cancer cells; however, antiproliferative effects were reported against KB cells (IC_{50}: 133.12 μM) and the Jurkat cell line (IC_{50}: 77.5 μM) [140]. The cytotoxicity of xanthotoxol (**54**), a compound newly isolated from the Egyptian plant *Pituranthos triradiatus* [54], was documented on KB cells (IC_{50}: 26.97 μg/mL), MCF7 cells (IC_{50}: 11.92 μg/mL), and small-cell lung cancer NCI-H187 cells (IC_{50}: 40.41 μg/mL) [99].

8.4.4 Enzyme Inhibitory Coumarins Isolated from African Medicinal Plants

Many coumarins isolated from Cameroonian plants showed enzyme inhibitory activities. This includes compound **31** (imperatorin), known as an inhibitor of several enzymes, including human recombinant β-secretase (BACE; EC 3.4.23.46), with an IC_{50} value of 91.8 μM [50]. Beta-secretase is an aspartic acid protease important in the formation of myelin sheaths in peripheral nerve cells [141]. Therefore, drugs to block this enzyme (BACE inhibitors) in theory would prevent the buildup of beta-amyloid and may help to slow or stop Alzheimer's disease (AD). The inhibition of β-secretase BACE1 has also been documented for compound **37** (auraptene) (IC_{50}: 345.1 μM) and cnidilin (**55**) (IC_{50}: 344 μM) [59]. At a concentration of 5 μM, **31** also inhibited the activity of enoyl−acyl carrier protein reductase (or ENR, EC 1.3.1.9) isolated from *E. coli* [74]. ENR is a key enzyme of the type II fatty acid synthesis (FAS) system [142] and is an attractive target for narrow-spectrum antibacterial drug discovery because of its essential role in metabolism and its sequence conservation among many bacterial species. In addition, the bacterial ENR sequence and structural organization are distinctly different from those of mammalian fatty acid biosynthesis enzymes [143]. Other enzymatic activities of compound **31** include the inhibition of human P450 1B1 and P450 reductase supersomes, with an IC_{50} value of 0.71 μM, as well as the human P450 1A2 and P450 reductase supersomes (IC_{50}: 0.38 μM) [144]. Umbelliferone (**4**) inhibited recombinant aldose reductase 2 with an IC_{50} of 85.7 μM, aldose reductase 1 (IC_{50}: 22.9 μM), and sorbitol dehydrogenase (IC_{50}: 120 μM) [28]. Aldose reductase (or aldehyde reductase, EC 1.1.1.21) is an nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidoreductase that catalyzes the reduction of a variety of aldehydes and carbonyls, including monosaccharides. Aldose reductase inhibitors are potential drugs to fight diabetes mellitus [96]. Esculetin (**42**) has been reported to inhibit the activity (IC_{50}: 82.9 μM) [28] of the enzymes sorbitol dehydrogenase (EC 1.1.1.14) and aldose reductase (IC_{50}: 36.5 μM) [97], whereas scoparone (**15**) potentially inhibits the activity of α-glucosidase (IC_{50}: 0.45 μM) [89], suggesting that this compound could be a possible antidiabetic drug to control diabetes mellitus type 2.

At the concentration range of 0.025−250 μM, turbinatocoumarin (**56**), isolated from *D. turbinata*, showed concentration-dependent inhibition of matrix metalloproteinase-2 (MMP-2) secretion in human U87 glioblastoma cells [116]. Proteins of the MMP family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis. The enzyme plays a role in endometrial menstrual breakdown, regulation of vascularization, and inflammatory response [145].

Doxycycline, a member of the tetracycline antibiotics group, is a well-known MMP inhibitor.

The coumarin (**36**) (xanthotoxin) was reported to be an inhibitor of the calf thymus topoisomerase I (IC_{50} of 28 μM) [146]. Topoisomerases (type I: EC 5.99.1.2, type II: EC 5.99.1.3) are enzymes that regulate the overwinding or underwinding of DNA. Topoisomerase inhibitors work by interfering with mammalian-type eukaryotic topoisomerases in cancer cells [147], probably explaining the cytotoxic effect of compound **36**. Compound **27** (bakuchicin) also inhibited the activity of topoisomerase II (IC_{50} of 404 μM) [52]. This inhibition can induce breaks in the DNA that ultimately lead to apoptosis, the well-known programmed cell death [147]. Topoisomerase I is the antigen recognized by anti-Scl-70 antibodies in scleroderma [147].

Coladin (**48**) and coladonin (**49**) inhibited acetylcholinesterase (AChE) activity, with IC_{50} values of 602 μM and 1171.1 μM, respectively [61]. The coumarins glycoside scopolin (**57**) and scopoletin (**33**) are also known to act as AChE inhibitors [39]. The two compounds showed dose-dependent and long-lasting AChE inhibitory activities. Rollinger et al. [39] demonstrated in an *in vivo* experiment that the application of 2 μmol of **57** and **33** increased the extracellular acetylcholine (ACh) concentration in the rat brain to about 170% and 300%, compared to basal release, respectively. It was also shown that, at the same concentration, the positive control galanthamine increased ACh concentration to about the same level as **57**[39], clearly highlighting the role of this compound as an AchE inhibitor [39]. In fact, cholinesterase inhibition is the mainstay of treatment for AD and also serves as a promising strategy for the treatment of senile dementia, ataxia, myasthenia gravis, and Parkinson's disease [39]. AChE inhibitor drugs increase the effectiveness of cholinergic transmissions by inhibiting the metabolic hydrolysis of ACh [148,149].

The 4-methoxy-3-phenyl-coumarin robustic acid (**58**) (one of the constituents of the seeds of the Ghanean plant *Milletia thonningii*) [85], inhibited (IC_{50}: 10 μM) the rat liver cyclic adenosine monophosphate (AMP)-dependent protein kinase (PKA or protein kinase A) catalytic subunit [86], showing its ability to alter many physiological functions, as PKA (EC 2.7.11.11) has several functions in the cell, including the regulation of glycogen, sugar, and lipid metabolism.

8.4.5 Antioxidant Coumarins Identified in African Medicinal Plants

The common link between oxidants and inflammatory reactions, infections, cancer, and other disorders has been well established [150,151]. However, this may not really be of therapeutic relevance, but more related to preventive medicine. In chronic infections and inflammation, as well as in other disorders, release of leukocytes and other phagocytic cells readily defends the organism from further injury. The cells do this by releasing free oxidant radicals, and these by-products are generally reactive oxygen species (ROS), such as superoxide anion, hydroxyl radical, NO, and hydrogen peroxide, that result from cellular redox processes [150,152]. At low or moderate concentrations, ROS exert beneficial effects on cellular responses and immune function. At high levels, however, free radicals and oxidants generate oxidative stress, a deleterious process that can damage cell structures, including

lipids, proteins, and DNA [153]. Oxidative stress plays a major role in the development of chronic and degenerative ailments, such as cancer, autoimmune disorders, rheumatoid arthritis, cataracts, aging, and cardiovascular and neurodegenerative diseases [153,154]. Antioxidants act as free radical scavengers by preventing and repairing damage caused by ROS and, therefore, can enhance the immune defense and lower the risk of cancer and degenerative disease [150,154]. In recent years, there has been increasing interest in finding antioxidant phytochemicals, because they can inhibit the propagation of free radical reactions, and thereby protect the human body from disease [155]. Some coumarins identified in African medicinal plants have been reported for their antioxidant properties. Omisore et al. [156] considered the cutoff point for antioxidant activity as 50 μg/mL. Samples with $IC_{50} > 50$ μg/mL were classified as moderately active, whereas samples with $IC_{50} < 50$ μg/mL were judged as having high antioxidant capacity. Another ranking threshold proposed $IC_{50} < 10$ μg/mL for compounds with significant antioxidant capacity, $10 < IC_{50} < 20$ μg/mL for moderate antioxidant capacity, and $IC_{50} > 20$ μg/mL for low antioxidant capacity [157]. However, no ranking was proposed for compounds using their IC_{50} values in micromolar, a unit often found in many scientific reports. Therefore, in the present chapter, we will also randomly consider compounds with $IC_{50} < 50$ μM as being significantly active and $IC_{50} > 50$ μM as moderately active.

The coumarin (**42**) (esculetin) showed antioxidant activities, such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging (IC_{50}: 69.1 μM) [158], 2,2′-azinobis-(3-ethylbenzothiazine-6-sulfonic acid) (ABTS) radical scavenging (IC_{50}: 22 μM), ferric reducing (FRAP, IC_{50}: 24.5 μM), NO radical scavenging (IC_{50}: 53.1 μM), hypochlorite (HOCl) scavenging (IC_{50}: 182.13 μM), and inhibition of 2,2′-azobis(2-amidinopropane) hydrochloride (AAPH)-induced peroxidation (IC_{50}: 10.35 μM) [159]. Heraclenol (**30**) exhibited a low DPPH scavenging activity (IC_{50}: 0.54 mg/mL) [132], whereas scopoletin (**33**) has been reported to possess DPPH radical scavenging activity (IC_{50}: 1.24 μg/mL), with an inhibiting potential equal to the reference compound vitamin C (IC_{50}: 1.22 μg/mL) under similar experimental conditions [36]. Compound **54** (xanthotoxol) showed a variety of antioxidant activities, such as DPPH radical scavenging (IC_{50}: 69.6 μM), ABTS radical scavenging (IC_{50}: 10.3 μM), and galvinoxyl radical scavenging (IC_{50}: 188.3 μM) [98].

8.4.6 Other Activities Associated with Coumarins Identified in African Medicinal Plants

Compound **43** (isopimpinellin) was found to strongly inhibit insulin-stimulated lipogenesis, indicating that it might activate the actions of lipolytic hormones and selectively inhibit the effects of antilipolytic hormones [160]. In phenylephrine (PE)-precontracted endothelium-intact rabbit corpus cavernosum, **43** exhibited a relaxing effect, with an IC_{50} value of 18.4 μM [78].

The 4-*n*-propylcoumarin (**44**) (mammea B/BB) and 4-phenylcoumarins (**12**) (mammeisin), and (**45**) (B/BA) were reported as having vasorelaxant effects via endothelium dependence and the liberation of Ca^{2+} into muscle cells [81].

Obliquin (**59**), a coumarin of the Madagascan plant *C. grevei* [25], showed antidepressive activity in mice, decreasing the immobility time from 176.2 to 132.1 s at 0−80 mg/kg [82]. Compound **31** (imperatorin) also showed anticoagulant activity with a prolonged prothrombin time at the doses of 3 and 10 mg/kg on the Wistar rat [72]. It also exhibited anticonvulsant activity in a concentration range of 20−50 mg/kg in the Swiss mouse [161], and NO production in the murine macrophage cells RAW 264.7 (IC_{50}: 17.7 μg/mL) [162].

The cytoprotective effect of adicardin (**60**), identified in the stem bark of *Gnidia polycephala* [44], was reported on Wistar rat hepatocytes when studied in a concentration range of 1−100 μM [45].

8.5 New Coumarins Isolated in African Medicinal Plants

Several coumarins were isolated as new compounds for the first time in African plants (Figure 8.4, Table 8.2). Their biological activities either were not significant (**23**, **24**, **25**, **32**, **39**, and **56**) or have not been reported at all. Two new 5-methylcoumarin glycosides, diosfebosides A (**61**) and B (**62**), were isolated from the leaves of the Cameroonian plant *Diospyros crassiflora* (Hiern). The *in vitro* cytotoxic activity of the new compounds against human carcinoma cell lines (HL-60, Bel-7402, BGC-823, and KB) was evaluated and were found inactive [106]. Similarly, the 3-phenylcoumarin indicanine A (**63**), isolated from the Cameroonian plant *D. crassiflora* [107], was tested for antimicrobial activity against *S. aureus*, *M. smegmatis*, and *E. coli*, but no activity was observed [107].

The compound 13-hydroxyfeselol (**64**), isolated for the first time from the Algerian plant *F. vesceritensis*, is a first sesquiterpene coumarin ether of the hydroxymethyl type from the genus *Ferula*; similarly, ferulsinaic acid (**65**) is the first member of a new, rearranged class of sesquiterpene coumarins from this genus [60].

Spiro-ethuliacoumarin (**66**) was reported for the first time in the Egyptian plant *Ethulia conyzoides*, with a spiro moiety between the monoterpene and the 5-methylcoumarin both fused at C-3 through the central carbon [113]. Before this finding, the monoterpenoid part was usually known to be connected to oxygen at C-3 or C-4 in the monoterpen-5-methylcoumarin [113]. Also, when reported for the first time from the African plant *Mondia whitei*, 5-chloropropacin (**67**) was the first chlorinated compound of the coumarinolignan family [103].

8.6 Other Coumarins in African Medicinal Plants

Though the biological activity of coumarins is well established, many of them have not yet been subjected to any pharmacological study. Also, some of them did not show any potential therapeutic effect. Coumarins which are either not yet studied for their pharmacological potencies or which are inactive are summarized in Table 8.3.

Table 8.3 Known Coumarins with No Reported Pharmacological Activity Isolated from African Plants

Compounds	Plants (Family)	Area of Plant Collection	Plant Part	References
3-(1,1-Dimethylallyl)xanthyletin (**102**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Combined stem bark and roots	[71]
4′-Acetylrobustic acid (**103**)	*M. thonningii* (Schum. & Thonn.) Baker (Fabaceae)	Ghana	Seeds	[85]
6′-Hydroxy-β-cycloauraptene (**104**)	*C. viscosa* (L.) (Capparidaceae)	Sudan	Roots	[47]
8-Methoxyobliquin (**105**)	*C. grevei* Baill. (Meliaceae)	Madagascar	Trunk bark	[25]
Braylin (**106**)	*C. longibracteata* J. F. Leroy. (Ptaeroxylaceae)	Madagascar	Stem bark	[4]
Byakangelicin (**107**)	*T. rhodesica* (Bak. f.) Mendonça (Rutaceae)	Zimbabwe	Roots	[58]
Capnolactone (**108**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Leaves	[90]
Cycloethuliacoumarin (**109**)	*E. conyzoides* Linn. f. (Compositae)	Egypt	Aerial parts	[104]
Ethuliacoumarin (**110**)	*E. conyzoides* Linn. f. (Compositae)	Egypt	Aerial parts	[104]
Gravelliferone methyl ether (**111**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Combined stem bark and roots	[71]
Gummosin (**112**)	*F. assa-foetida* (Apiaceae)	Egypt	Roots	[68]
Heliettin (**113**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Combined stem bark and roots	[71]
Isoponcimarin (**114**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Leaves	[90]
Microfolicoumarin (**115**)	*C. grevei* Baill. (Meliaceae)	Madagascar	Trunk bark	[25]
Norbraylin (**116**)	*C. longibracteata* J.F. Leroy. (Ptaeroxylaceae)	Madagascar	Stem bark	[4]
Pervilleanine (**117**)	*Millettia pervilleana* Viguier (Leguminosae)	Madagascar	Root bark	[163]
Polyathin (**118**)	*F. assa-foetida* (Apiaceae)	Egypt	Roots	[68]
Propacin (**119**)	*M. whitei* (Hook. f.) Skeels (Asclepidiaceae)	Togo	Roots	[103]
Robustic acid methyl ether (**120**)	*M. thonningii* (Schum. & Thonn.) Baker (Fabaceae)	Ghana	Seeds	[85]
Swietenocoumarin I (**121**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Combined stem bark and roots	[71]
Triphasiol (**122**)	*C. anisata* (Will) Hook. f. ex Benth. (Rutaceae)	Cameroon	Leaves	[90]

8.7 Coumarin-Related Compounds from African Medicinal Plants

The isocoumarin typharin (**123**, Figure 8.5) was isolated as a new natural product from the rhizome of the South African plant *Typha capensis* [164]. However, no pharmacological activity has been reported on this compound yet.

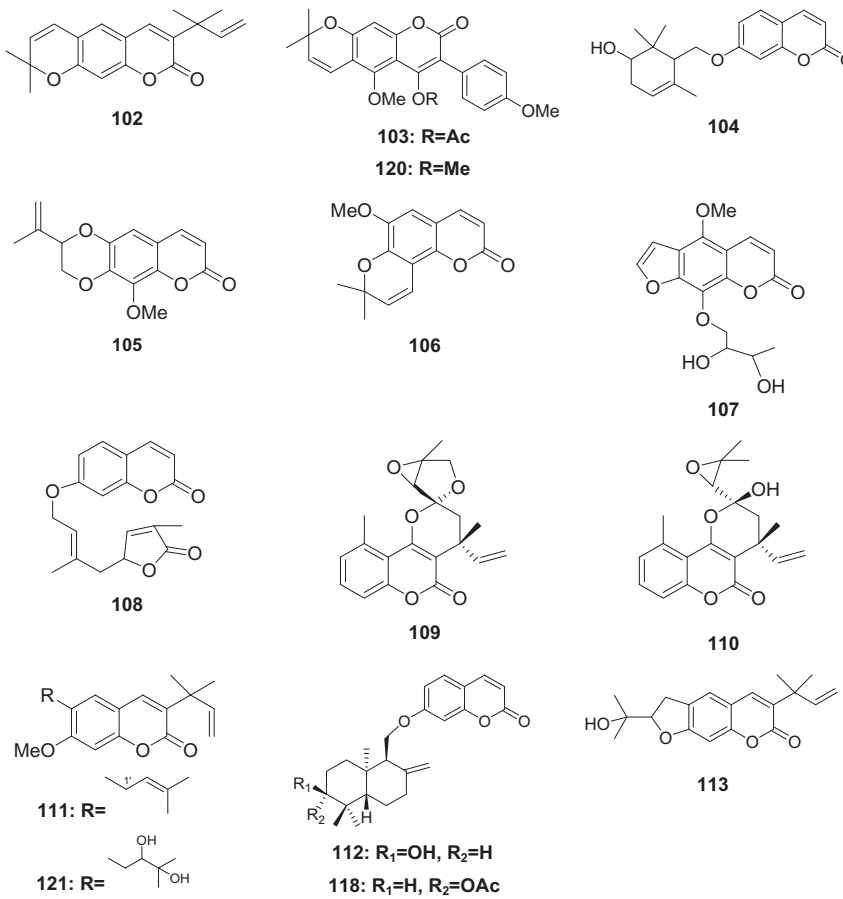

Figure 8.5 Chemical structures of coumarins isolated in African medicinal plants without any activity or known to be pharmacologically inactive: 3-(1,1-dimethylallyl)xanthyletin (**102**); 4′-acetylrobustic acid (**103**); 6′-hydroxy-β-cycloauraptene (**104**); 8-methoxyobliquin (**105**); braylin (**106**); byakangelicin (**107**); capnolactone (**108**); cycloethuliacoumarin (**109**); ethuliacoumarin (**110**); gravelliferone methyl ether (**111**); gummosin (**112**); heliettin (**113**); isoponcimarin (**114**); microfolicoumarin (**115**); norbraylin (**116**); pervilleanine (**117**); polyathin (**118**); propacin (**119**); R = Me: robustic acid methyl ether (**120**); swietenocoumarin I (**121**); triphasiol (**122**); typharin (**123**).

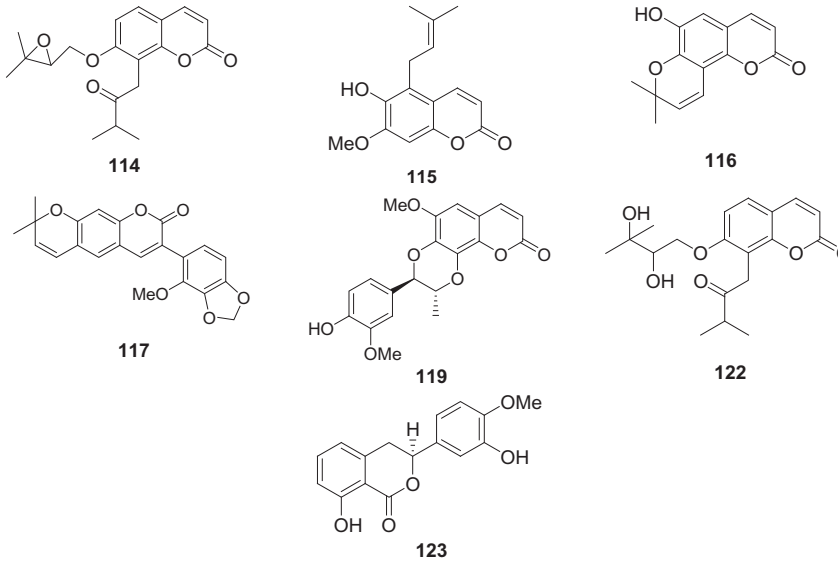

Figure 8.5 (Continued)

8.8 Conclusion

This chapter shows not only the amount of work done by researchers around the world to isolate coumarins from African plants but also highlights the structural diversity of these compounds and their pharmacological potential. The overview embodied in this chapter describes the role and importance of African plants in enhancing the economy of the community and opening an international trade by exporting these plants. However, this chapter also shows some limitations in the pharmacological research concerning newly isolated coumarins in Africa. Indeed, many of the coumarins, isolated as new products for the first time from the African plants, have not yet been subjected to pharmacological study. However, it has been noted that such ignorance was common only until year 2000, whereas the recent interest of African researchers in the discovery of bioactive substances is the reality today.

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9 Flavonoids and Related Compounds from the Medicinal Plants of Africa

Bathelemy Ngameni[a], *Ghislain W. Fotso*[b], *Justin Kamga*[b], *Pantaleon Ambassa*[b], *Tchoukoua Abdou*[b], *Aimé G. Fankam*[c], *Igor K. Voukeng*[c], *Bonaventure T. Ngadjui*[b], *Berhanu M. Abegaz*[d] *and Victor Kuete*[c]

[a]Department of Pharmaceutical Sciences and Traditional Pharmacopoeia, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon; [b]Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Cameroon; [c]Department of Biochemistry, Faculty of Science, University of Dschang, Cameroon; [d]African Academic of Sciences, Nairobi, Kenya

9.1 Introduction

The phenolic compounds of the plant world comprise a body of organic compounds of extraordinary variety and interest, and the flavonoids, one of the most numerous and widespread groups of natural products, occupy a prominent position among the plant phenols. The role of flavonoids as the major red, blue, and purple pigments in plants has gained these secondary products a great deal of attention over the years. Interest in flavonoid compounds, mainly because of the conspicuous, vivid, and beautiful colors these pigments impart to various parts of plants, can be traced as far back as the period of Robert Boyle in 1664 [1]. The importance of these compounds in the tanning of leather, the fermentation of tea, the manufacture of cocoa, and the flavor quality of foodstuffs has led to many investigations into the chemistry of these compounds. Furthermore, the universal distribution of these compounds in vascular plants, their relatively stable chemical nature, and the rapidity with which they can be identified using the relatively simple methods available have made them important taxonomic markers in plant classification. They now occupy a preeminent position as the most favored of all plant constituents as taxonomic markers.

The known structural variations of flavonoid compounds can be divided into no fewer than 15 classes; some of the principal ones are shown in Figure 9.1. The myriad individual compounds within each class are distinguished from one another by the number and

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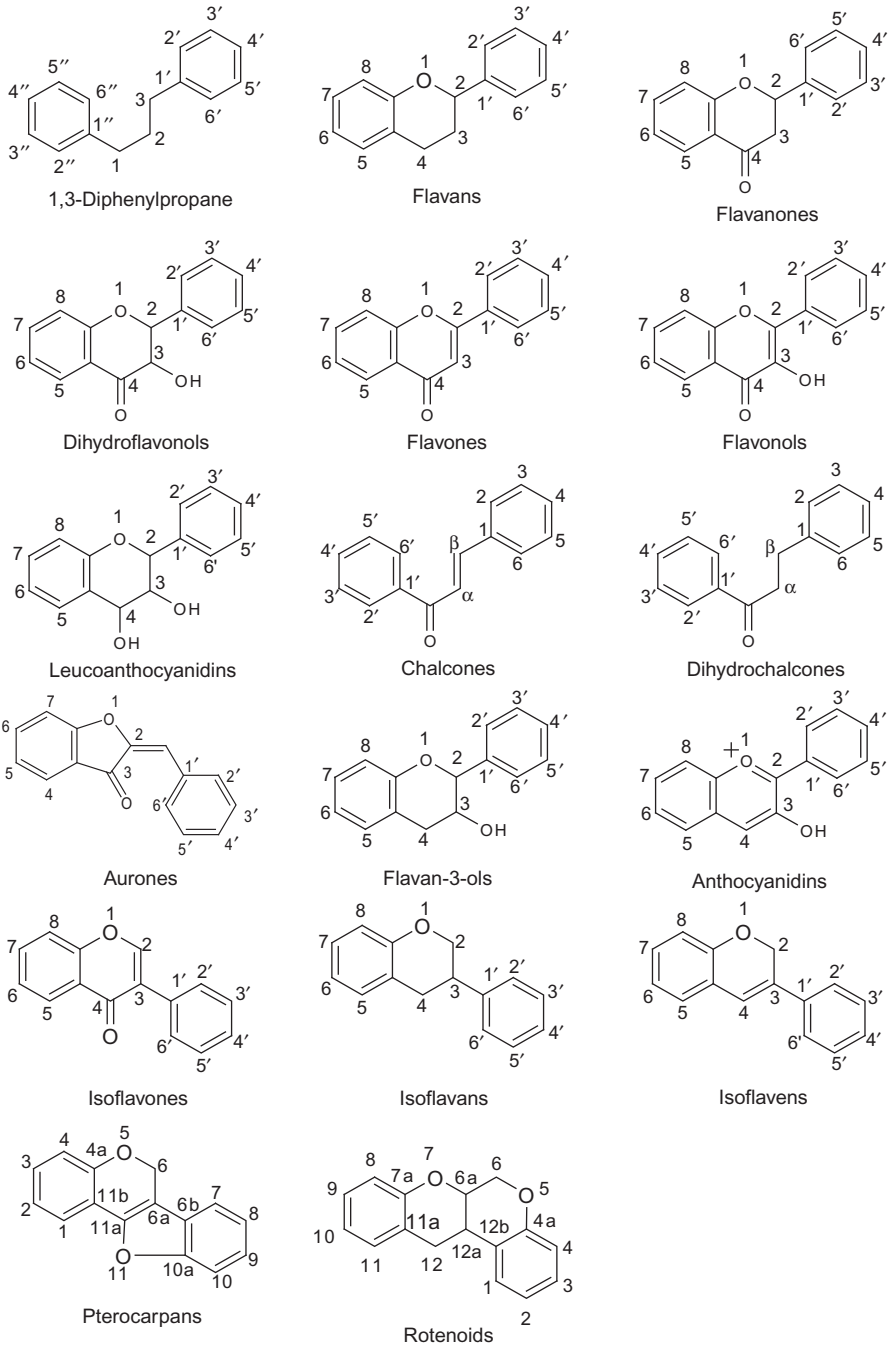


Figure 9.1 Basic skeleton of some flavonoid compounds.

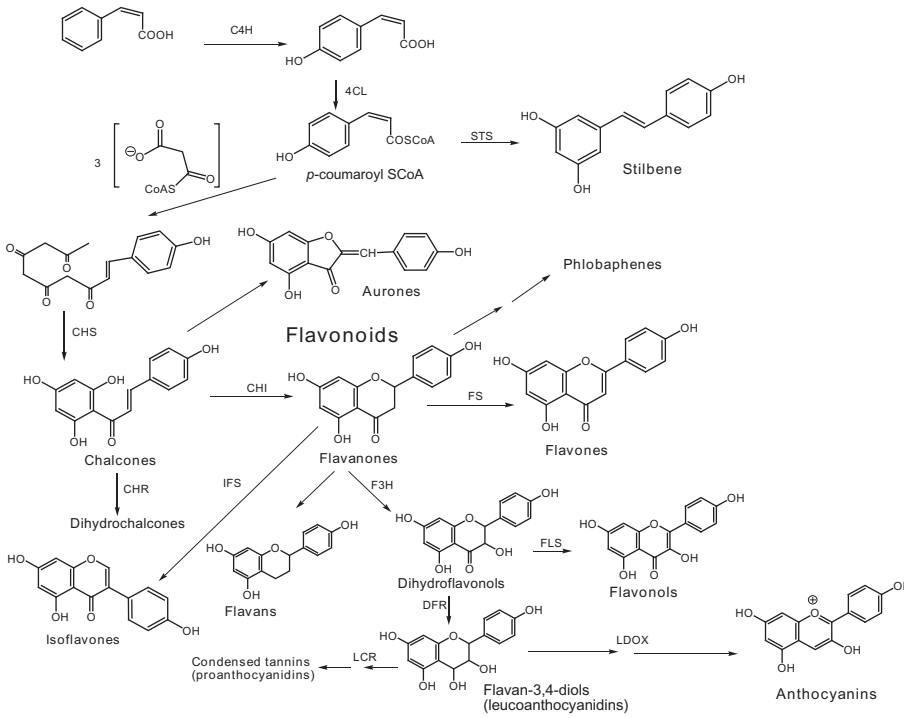


Figure 9.2 General biosynthetic pathway of flavonoids. Schematic of the major branch pathways of flavonoid biosynthesis, starting with general phenylpropanoid metabolism and leading to the nine major subgroups: the colorless chalcones, aurones, isoflavonoids, flavones, flavonols, flavandiols, anthocyanins, condensed tannins, and phlobaphene pigments. The first committed step is catalyzed by chalcone synthase (CHS), which uses malonyl-CoA and 4-coumaroyl-CoA as substrates. Enzyme names are abbreviated as follows: cinnamate-4-hydroxylase (C4H), chalcone isomerase (CHI), chalcone reductase (CHR), chalcone synthase (CHS), 4-coumaroyl:CoA-ligase (4CL), dihydroflavonol 4-reductase (DFR), flavonol synthase (FLS), flavanone 3-hydroxylase (F3H), flavone synthase (FS), isoflavone synthase (IFS), leucoanthocyanidin dioxygenase (LDOX), leucoanthocyanidin reductase (LCR), and stilbene synthase (STS).

orientation of hydroxyl groups and by the degree these groups can be modified by methyl, isoprenyl, and glycosyl substituents. The simple structures of these compounds and the close structural and biosynthetic relationships among the various classes of this group, as shown in Figure 9.2, make the structural elucidation of this group of natural products comparatively easier, even to the beginner in natural products chemistry.

Flavonoids also have key roles in signaling between plants and microbes, in male fertility of some species, in defense as antimicrobial agents and feeding deterrents, and in UV protection [1,2]. The "early" steps in the pathway are found even in the bryophytes (mosses), and it has been suggested that synthesis of flavones, flavanones, and flavonols may have evolved first to provide chemical messengers and then UV

sunscreens [3]. Flavonoids also have significant activities when ingested by animals, and there is great interest in their potential health benefits, particularly for compounds such as isoflavonoids, which have been linked to the anticancer benefits of soy-based foods [2]. Much attention is currently being paid to flavonoids, which are found in seeds, herbs, flowers, olive oil, tea, and red wine. They exhibit several biological effects such as anti-inflammatory, antimicrobial, antiviral, antiulcer, hepatoprotective, antitumor, and antioxidant activities [2]. Many biological properties of flavonoids may be related to their capacity to penetrate into cell membranes and thus to affect their biological activity. In this chapter, an attempt is made to review the flavonoids and related compounds from the medicinal plants of Africa.

9.2 Biosynthesis and Structural Diversity

In recent years, more effort has been directed at elucidating the flavonoid biosynthetic pathway from a molecular genetics point of view. Mutants affecting flavonoid synthesis have been isolated in a variety of plant species based on alterations in flower and seed pigmentation. Maize, snapdragon (*Antirrhinum majus*), and petunia (*Petunia hybrida*) were established as the first major experimental models in this system, and work on these species led to the isolation of many flavonoid structural and regulatory genes [4,5]. Arabidopsis more recently helped to facilitate analysis of the regulation and subcellular organization of the flavonoid pathway. Flavonoid biosynthesis can conveniently be divided into three stages: (i) the formation of the $C_6{-}C_3{-}C_6$ skeleton; (ii) the biosynthesis of the different classes of flavonoids; and (iii) the biosynthesis of the individual compounds within each flavonoid class. Flavonoids are synthesized by the phenylpropanoid metabolic pathway, in which the amino acid phenylalanine is used to produce 4-coumaroyl-CoA [6]. This can be combined with malonyl-CoA to yield the true backbone of flavonoids, a group of compounds called chalcones, which contain two phenyl rings. The conjugate ring closure of chalcones results in the familiar form of flavonoids, the three-ringed structure of a flavone. The metabolic pathway continues through a series of enzymatic modifications to yield flavanones, dihydroflavonols, and anthocyanins. It has, however, been established by Wallace and Grisebach [7] that chalcones are the more direct precursors to flavonoid compounds such as flavanes, flavanones, flavones, flavonols, isoflavones, anthocyanins, proanthocyanidins (tannins), and a host of other polyphenolics (Figure 9.2). Flavanoids can possess chiral carbons. Methods of analysis should take this element into account [8], especially with respect to bioactivity or enzyme stereospecificity [9]. A well-known physiological function of the anthocyanin pigments and flavonol copigments is the recruitment of pollinators and seed dispersers. These compounds also have figured into some of the major scientific breakthroughs of the past 150 years, including Mendel's elucidation of genetics, seed coat color being one of the major characters followed in his experiments with peas (*Pisum sativum*), and McClintock's discovery of transposable elements that moved in and out of flavonoid biosynthetic genes expressed in maize kernels. Anthocyanins more recently have aided in understanding the phenomenon of co-suppression, particularly in the petunia (*P. hybrida*).

Some plant species also synthesize specialized forms of flavonoids, such as the isoflavonoids that are found in legumes and a small number of nonlegume plants. Similarly, sorghum (*Sorghum bicolor*), maize (*Zea mays*), and gloxinia (*Sinningia cardinalis*) are among the few species known to synthesize 3-deoxyanthocyanins (or phlobaphenes in the polymerized form). The stilbenes, which are closely related to flavonoids, are synthesized by another group of unrelated species that includes grapes (*Vitis vinifera*), peanuts (*Arachis hypogaea*), and pines (*Pinus sylvestris*). Thus, it appears that branches in this pathway have evolved multiple times or been lost from specific plant lineages over the course of evolution [1].

9.3 Characterization of Flavonoids in Plant Extracts

9.3.1 Ferric Chloride Test

About 5 mg of the compound is dissolved in ethanol (2 mL). A few drops of 10% ferric chloride solution are added. A green-blue coloration indicates the presence of a phenolic hydroxyl group.

9.3.2 Shinoda's Test

Four pieces of magnesium filings are added to the ethanolic extract, followed by a few drops of concentrated hydrochloric acid. A pink or red color indicates the presence of flavonoids.

9.3.3 Sodium Hydroxide Test

About 5 mg of the compound is dissolved in water, then warmed, and filtered. Ten percent aqueous sodium hydroxide is added to 2 mL of this solution. This produces a yellow coloration. A change in color from yellow to colorless on addition of diluted hydrochloric acid is an indication for the presence of flavonoids.

9.3.4 Quantification

Lamaison and Carnet (1990) have designed a test for the determination of the total flavonoid content of a sample ($AlCI_3$ method). After proper mixing of equal volume of the sample and the reagent (2% $AlCl_3$, $6H_2O$ in methanol), the mixture is incubated for 10 min at ambient temperature, and the absorbance of the solution is read at 440 nm. Flavonoid content is expressed in mg/g of quercetin.

9.3.5 Test for Flavonoid Glycosides

The ether extract (5 mL) from the hydrolyzed alcohol extract is evaporated to dryness. The residue is dissolved in 2 mL of 50% methanol by heating. A small piece of magnesium ribbon is added, followed by 5−6 drops of concentrated hydrochloric acid. A red solution indicates the presence of flavonoid glycosides.

9.4 Pharmacological Activities of Flavonoids and Related Compounds Isolated from African Medicinal Plants

Flavonoids are a large class of secondary metabolites, produced by plants for protection against photosynthetic stress, reactive oxygen species, and wounds. A number of them exhibit significant inhibition of cancer development in various animal models, as well as antioxidant, antimicrobial, and anti-inflammatory activities [2]. In this section, we emphasize some of the well-known pharmacological flavonoids reported in African plants. An overview of biologically active African flavonoids is given in Table 9.1.

9.4.1 Antimicrobial Flavonoids Isolated from African Medicinal Plants

The conquest of natural antimicrobial substances is a domain that has witnessed significant expansion in Africa for the last two decades. Significant progress has been noted both in the quality and quantity of scientific reports, available on scientific websites such as Web of Knowledge, ScienceDirect, Scirus, Scopus, and PubMed. Stringent endpoint criteria for anti-infective activities of medicinal plants have been developed. Fabry et al. [83] set the bar for significant antimicrobial activity of plant extracts to a minimal inhibitory concentration (MIC) below 8 mg/mL. In a review paper of Gibbons [84] covering research data from 1995 to 2003, criticisms were made of literature that claims natural products and extracts displaying antibiotic activity with MIC values over 1 mg/mL; this author set a bar at 64 μg/mL or 0.25% v/v for liquids. Many researchers on the continent still report plant extracts with MIC $>$ 1 mg/mL as active. Nonetheless, African authors pace more emphasis on the cutoff point criteria. However, the cutoff points most often used for promising antimicrobial extracts and compounds are MIC values below 100 and 10 μg/mL, respectively [85,86]. Hit molecules with significant activities (MIC $<$ 10 μg/mL) include flavonoids (Figure 9.3) such as isobavachalcone (**18**), 4-hydroxylonchocarpin (**20**), and kanzonol C (**23**) [85,86], with antibacterial and antifungal inhibitory effects better than or close to that of gentamicin and nystatin on most of the tested microbial species.

However, several flavonoids isolated from African medicinal plants have been reported as having antimicrobial activities (Figure 9.1). Such compounds mainly include chalcones, flavones, and isoflavones. Chalcones were isolated primarily from plants of the family Moraceae and the genus *Dorstenia*, such as *Dorstenia angusticornis* [19], *Dorstenia elliptica* [87], *Dorstenia turbinata* [12], and *Dorstenia barteri*[18,23]. Among the chalcones, diprenylated compounds such as angusticornin B (**15**) and bartericin A (**14**) were reported to be very active vis-à-vis many Gram-positive and Gram-negative bacteria, as well as yeasts such as *Candida albicans*, *Candida glabrata*, and *Candida krusei* [19]. Gancaonin Q (**82**), stipulin (**19**), compound **15**, and bartericin C (Figure 9.4) displayed antimicrobial activities against *Citrobacter freundii* (MIC of 0.31 μg/mL for **189** and 0.61 μg/mL for **15**), *Enterobacter aerogenes* (MIC of 1.22 μg/mL for **82**, 78.12 μg/mL for **189**, and 39.06 μg/mL for **15**), *Escherichia coli* (MIC of 1.22 μg/mL for **189** and 0.61 μg/mL

Table 9.1 Biologically Active Flavonoids and Related Compounds Isolated in African Medicinal Plants

Class and Compounds	Plants (Family)	Pharmacological Activities
Biflavanols		
Beilschmieflavonoids A (**1**); B (**2**)	*B. zenkeri* (Lauraceae)	Antibacterial, antiplasmodial [10]
Agasthisflavone (**3**)	Cashew plant(*A. occidentale* L.) (Anacardiaceae)	Cytotoxic [11]
Amentoflavone (**4**)	*D. barteri* Bureau var. *multiradiata* (Moraceae); *Garcinia livingstonei* (Guttiferae)	Antimicrobial [12]
4′-Methoxy amentoflavone (**5**)	*G. livingstonei* (Guttiferae)	Antimicrobial [12]
Chalcones		
Praecansone A (**6**); praecansone B (**7**); demethylpraecansone A (**8**)	*Tephrosia aequilata* (Fabaceae)	Antimicrobial [13]
4′-*O*-Geranylisoliquiritigenin (**9**)	*Millettia usaramensis* subsp. *usaramensis*	Antiplasmodial [14]
Licoagrochalcone A (**10**); abyssinone VI (**11**); 5′-prenylbutein (**12**)	*E. addisoniae* (Fabaceae)	Enzyme inhibition [15,16]
Cedrediprenone (**13**)	*Cedrelopsis grevei* (Ptaeroxylaceae)	Anti-inflammatory [17]
Bartericin A (**14**)	*D. barteri* var. *subtriangularis* (Moraceae)	Antimicrobial [18]
Angusticornin B (**15**)	*D. angusticornis* (Moraceae)	Antimicrobial [19,20]
Candidachalcone (**16**)	*T. candida* (Fabaceae)	Estrogenic [21]
Abyssinone-VI-4-*O*-methyl ether (**17**)	*E. mildbraedii* (Fabaceae)	Antidiabetic, antiobesity [22]
Isobavachalcone (**18**); stipulin (**19**)	*D. barteri* Bureau var. *multiradiata*; *D. barteri* Bureau var. *multiradiata*; *D. angusticornis* Engl.; *Dorstenia dinklagei* (Moraceae)	Antibacterial [18−20,23−27], antireverse transcriptase [18]
4-Hydroxylonchocarpin (**20**)	*D. barteri* Bureau var. *multiradiata*; *Lonchocarpus sericeus*; *D. mannii*; *D. dinklagei; D. turbinata* (Moraceae)	Antibacterial [18,23], antireverse transcriptase [28], cytotoxicity [12,20,24]
Kanzanol (**21**)	*D. barteri* Bureau var. *multiradiata* (Moraceae); *G. livingstonei* (Guttiferae)	Antibacterial [18]

(*Continued*)

Table 9.1 (Continued)

Class and Compounds	Plants (Family)	Pharmacological Activities
2′-Hydroxy-4′-glucoside-6′-methoxychalcone (**22**)	*Helichrysum gymnocomum* (Asteraceae)	Antimicrobial [29]
Kanzonol C (**23**)	*D. turbinata* (Moraceae); *D. barteri* (Moraceae)	Antimicrobial [23]
4,2′,4′-Trihydroxy-3′-δ,δ-dimethylallylchalcone (**24**)	*E. latissima* (Fabaceae)	Antimicrobial, antioxidant [30]
Cardamonin (**25**)	*C. apiculatum* subsp. *apiculatum*	Weak activity [31]
Isoliquiritigenin (**26**)	*Trilepisium madagascariense* (Moraceae); *Agapanthus africanus* (Liliaceae)	Antimicrobial [32], antioxidant [33]
(*E*)-3,2′,4′-Trihydroxychalcone (**27**); (*E*)-2′,4′-dihydroxychalcone (**28**)	*Galenia africana* (Aizoaceae)	Antimycobacterial [34]
Homobutein (**29**); licoagrochalcone A (**30**)	*Erythrina abyssinica* (Fabaceae)	Antiplasmodial [35,36]
2′,4′,6′-Trihydroxydihydrochalcone (**31**)	*Greyia flanaganii* (Bolus) (Greyiaceae)	Antityrosinase [37]
Flavan-3-ols		
Epigallocatechin gallate (**32**)	*Sideroxylon inerme* L. (Sapotaceae)	Antioxidant, tyrosinase inhibitor [38,39]
(−)-Epicatechin (**33**)	*Ficus gnaphalocarpa* (Miq.) Steud. ex A. Rich (Moraceae)	Antioxidant, hepatoprotective [39,40]
(−)-Epicatechin-3-gallate (**34**); epigallocatechin (**35**)	*F. gnaphalocarpa* (Miq.) Steud. ex A. Rich (Moraceae)	Antioxidant [39]
Daidzein (**36**)	*E. latissima* (Fabaceae); *E. indica* (Papilionaceae)	Antioxidant [30], antimicrobial [41]
Flavanols		
(2*S*,4*R*)-5,6,7-Trimethoxyflavan-4-ol (**37**)	*B. zenkeri* (Lauraceae)	Antibacterial, antiplasmodial [10]
(2*S*,4*R*)-4,5,6,7-Tetramethoxyflavan (**38**)	*B. zenkeri* (Lauraceae)	Antibacterial, antiplasmodial [10]
Dorsmanin F (**39**)	*D. mannii* (Moraceae)	Antioxidant [42]
Catechin (**40**)	*Ficus cordata* (Moraceae); *Acacia mearnsii*; *F. gnaphalocarpa* (Miq.) Steud. ex A. Rich (Moraceae); *Aframomum letestuianum* (Zingiberaceae)	Antimicrobial (not active) [43], antioxidant [39,44], antioxidant and hepatoprotective [40,45]
Epiafzelechin (**41**)	*F. cordata* (Moraceae)	Antimicrobial [43]

Flavanones

7-Hydroxy-4′-methoxy-3′-(3-hydroxy-3-methyl-*trans*-but-1-enyl)-5′-(3-methylbut-2-enyl) flavanone (**42**)	*E. mildbraedii* (Fabaceae)	Antidiabetic, antiobesity [22]
5,7-Dihydroxyflavanone (pinocembrin) (**43**)	*C. apiculatum* (Combretaceae); *G. flanaganii* (Bolus) (Greyiaceae)	Antibacterial [31,37,46]
ent-Naringeninyl-(I-3*R*,II-8)-4′-*O*-methylnaringenin	*G. livingstonei* (Clusiaceae)	Moderate activity against *P. falciparum* (IC_{50} of 6.7 μM) [47]
Eriodictyol 7-*O*-sophoroside (**44**)	*Globularia alypum* (Globulariaceae)	Antioxidative activity [48]
Abyssinone V (**45**)	*E. burttii* (Fabaceae)	Antiplasmodial, radical scavenging [36,49,50]
Abyssinone V methyl ether (**46**); 4-*O*-methylsigmoidin B (**47**)	*E. burttii* (Fabaceae)	Antiplasmodial [49]
Abyssinin III (**48**); abyssinone IV (**49**); abyssinone V 4′-methyl ether (**50**); sigmoidins A (**51**); B (**52**); 5-deoxysigmoidin B-4′-methyl ether or erylatissin C (**53**); sigmoidins C (**54**); E (**55**)	*E. abyssinica* (Fabaceae)	Antiplasmodial [35,36]
Nitidulin (**106**)	*Berchemia discolor* (Rhamnaceae)	Cytotoxic [51]
Garcinia biflavanones I (**56**); II (**57**); kolaflavanone (**58**)	*Garcinia kola* (Guttiferae)	Protective effect to gamma radiation [52]
Sigmoidins A (**51**); B (**52**)	*E. sigmoidea* (Fabaceae)	Antibacterial [53,54]
Tephrocandidin A (**59**); B (**60**)	*T. candida* (Fabaceae)	Estrogenic [21]
Licoflavanone-4′-*O*-methyl ether (**61**); abyssinone-IV-4′-*O*-methyl ether (**62**)	*E. mildbraedii* (Fabaceae)	Antidiabetic, antiobesity [22]
(*S*)-Naringenin (**63**)	*M. aquatica* L. (Lamiaceae)	GABA-benzodiazepine assay [55]
Burttinone (**65**)	*Erythrina caffra* Thunb (Fabaceae)	Antimycobacterial [56]
(2*S*)-5,7,2′-Trihydroxyflavanone (**66**)	*G. africana* (Aizoaceae)	Antimycobacterial [34]

(*Continued*)

Table 9.1 (Continued)

Class and Compounds	Plants (Family)	Pharmacological Activities
Flavones		
Apigenin (**67**)	*C. erythrophyllum* (Combretaceae); *Helichrysum foetidum* (Compositae)	Antimicrobial [57,58]
R═H═(+)-Volkensiflavone (**68**); R═OH═(+)-morelloflavone (**69**)	*G. livingstonei* (Clusiaceae)	Antiprotozoal, cytotoxicity [47]
Quercetin-3-*O*-rutinoside (**70**)	*Pavetta crassipes* (Rubiaceae)	Antimicrobial [59]
6-Hydroxyluteolin 7-*O*-laminaribioside (**71**)	*G. alypum* (Globulariaceae)	Antioxidative [48]
5,7-Dihydroxy-3,6,4′-trimethoxy-3′-(4-hydroxy-3-methyl-but-2-enyl)flavone (**72**); 3,6-dimethoxy-5,7,4′-trihydroxyflavone (**73**)	*D. viscosa* (Sapindaceae)	Anti-inflammatory [60]
Griffonianone E (**74**)	*M. griffoniana* (Fabaceae)	Estrogenic properties [61]
Luteolin 6,8-di-C-β-glucopyranoside (lucenin 1) (**75**); luteolin 8-C-β-glucoside (orientin) (**76**); isorhamnetin (**77**); quercetin 7-*O*-β-glucopyranoside (**78**)	*Erucaria hispanica* (Brassicaceae)	Cytotoxic [62]
Genkwanin (**79**); 5-hydroxy-7,4′-dimethoxy flavone (**80**); quercetin-5,3′-dimethylether (**81**)	*C. erythrophyllum* (Combretaceae)	Antimicrobial, anti-inflammatory, antioxidant [57]
Lupiwighteone	*Bolusanthus speciosus* (Fabaceae)	Antimicrobial [63]
Gancaonin Q (**82**)	*D. angusticornis* Engl. (Moraceae)	Antimicrobial [19], cytotoxicity [20]
Flavonols		
3,5,7-Trihydroxyflavone (galangin) (**83**)	*Helichrysum aureonitens* Sch. Bip. (Asteraceae)	Antimicrobial [64,65]
Dorsilurins F (**84**); G (**85**); H (**86**); I (**87**); J (**88**); K (**89**); C (**90**)	*D. psilurus* (Moraceae)	α-Glucosidase inhibition [66]
Dorsmanin C (**91**)	*D. mannii* (Moraceae)	Antioxidant [42]

Kaempferol (**92**)	*C. erythrophyllum*; *C. apiculatum* subsp. *apiculatum* (Combretaceae); *H. caffrum* (Anacardiaceae); *D. viscosa* Jacq. var. *angustifolia* (Sapindaceae)	Antimicrobial, antioxidant [31,57,67]
3-Methoxyquercetin (**93**)	*H. gymnocomum* (Asteraceae); *F. gnaphalocarpa* (Miq.) Steud. ex A. Rich (Moraceae)	Antimicrobial [29], antioxidant and hepatoprotective [40]
Quercitrin (**94**)	*A. mearnsii*; *C. apiculatum* subsp. *apiculatum* (Combretaceae); *F. gnaphalocarpa* (Miq.) Steud. ex A. Rich (Moraceae)	Antioxidant [31,44], hepatoprotective [40]
3,5,7-Trihydroxy-4′-methoxyflavone (**95**)	*D. viscosa* Jacq. var. *angustifolia*	Antioxidant [67]
5-Hydroxy-7,4′-dimethoxyflavone (**96**)	*C. erythrophyllum* (Combretaceae)	Antimicrobial [57]
Rhamnocitrin (**97**); rhamnazin (**98**); quercetin-5,3′-dimethylether (**99**)	*C. erythrophyllum* (Combretaceae)	Antimicrobial, antioxidant, anti-inflammatory [57]
Isoflav-3-enes		
Burttinols A (**100**); B (**101**); C (**102**); H (**103**)	*E. burttii* (Fabaceae)	Antiplasmodial, radical scavenging [49]
Isoflavan		
(3*R*)-2,7-Dihydroxy-3′-(3-methylbut-2-enyl)-2‴,2‴-dimethylpyrano[5‴,6‴: 4′,5′]isoflavan (**104**)	*E. mildbraedii* (Fabaceae)	Antidiabetic, antiobesity [22]
Isoflavane		
Discoloranone B (**105**)	*B. discolor* (Rhamnaceae)	Cytotoxic activity in a small panel of human cancer cells [51]
Isoflavanones		
Nitidulin (**106**); amorphigenin (**107**); dabinol (**108**)	*B. discolor* (Rhamnaceae)	Cytotoxic activity in a small panel of human cancer cells [51]
Bidwillon A (**109**)	*E. burttii* (Fabaceae)	Antimicrobial [50]
Prostratol C (**110**); saclenone (**111**)	*Erythrina sacleuxii* (Fabaceae)	Antiplasmodial [68]
Isodiscoloranones A (**112**); B (**113**)	*B. discolor* (Rhamnaceae)	Cytotoxic [51]

(*Continued*)

Table 9.1 (Continued)

Class and Compounds	Plants (Family)	Pharmacological Activities
Lysisteisoflavanone (**114**)	*Erythrina lysistemon* (Fabaceae)	Cytotoxic [69]
Isoflavones		
6,8-Diprenylgenistein (**115**)	*E. caffra* Thunb (Fabaceae)	Antimycobacterial [56]
Genistein (**116**)	*B. speciosus* (Fabaceae); *Ficus chlamydocarpa* (Moraceae); *E. latissima* (Fabaceae); *E. indica* (Fabaceae)	Antimicrobial [30,43,63,70,71]
6,7-Dimethoxy-3′,4′-methylenedioxyisoflavone (**117**); 7,2′-dimethoxy-4′,5′-methylenedioxyisoflavone (**118**)	*Tephrosia fulvinervis* (Fabaceae)	Antileishmanial [72]
Barbigerone (**119**)	*M. usaramensis* subsp. *usaramensis*	Antiplasmodial [14]
Corylin (**120**)	*E. sacleuxii* (Fabaceae)	Enzyme inhibition [15,16], antiplasmodial [68]
Erysubin F (**121**); 7-demethylrobustigenin (**122**); 2,3-dehydrokeivetone (**123**)	*E. sacleuxii* (Fabaceae)	Antiplasmodial [68]
Isoelliptol (**124**)	*E. sacleuxii* (Fabaceae)	Cytotoxic [73]
Erythraddison A (**125**)	*E. addisoniae* (Fabaceae)	Enzyme inhibition [15,16]
Isowighteone (**126**)	*E. addisoniae* (Fabaceae)	Enzyme inhibition [15,16]
Wighteone (**127**)	*E. addisoniae* (Fabaceae)	Enzyme inhibition [15,16], antimicrobial [63], cytotoxicity [70,74]
7-*O*-Geranylformononetin (**128**); 4′-methoxy-7-*O*-[(*E*)-3-methyl-7-hydroxymethyl-2,6-octadienyl] isoflavone (**129**); 4′-*O*-geranylisoliquiritigenin (**130**); 3′,4′-dihydroxy-7-*O*-[(*E*)-3,7-dimethyl-2,6-octadienyl]isoflavone (**131**); griffonianone C (**132**)	*M. griffoniana* (Fabaceae)	Estrogenic properties [61]
Griffonianone D (**133**)	*M. griffoniana* (Fabaceae)	Anti-inflammatory [75]

5,4′-di-*O*-Methylalpiummisoflavone (**134**)	*E. indica* (Fabaceae)	Antimicrobial [76]
Jacanin (**135**)	*E. indica* (Fabaceae)	Antimicrobial [76]
Lachnoisoflavones A (**136**); B (**137**)	*C. lachnophora* (Fabaceae)	Antimicrobial [77]
2,7-Dihydroxy-4′-methoxy-5′-(3-methylbut-2-enyl)isoflavone (**138**)	*E. mildbraedii* (Fabaceae)	Antidiabetic, antiobesity [22]
Indicanine D (**139**)	*E. indica* (Fabaceae)	Cytotoxicity [70]
7-Hydroxy-4′-methoxyisoflavone (**140**); 7,3′-dihydroxy-4′-methoxyisoflavone (**141**)	*B. speciosus* (Fabaceae); *E. indica* (Fabaceae)	Antimicrobial [63], cytotoxicity [70,74]
Alpium isoflavone (**142**)	*F. chlamydocarpa*; *E. caffra* Thunb (Fabaceae); *E. mildbraedii* (Fabaceae); *E. indica* (Fabaceae)	Antimicrobial [43,56], antidiabetic and antiobesity [78], cytotoxicity [70,79]
Laburnetin (**143**)	*F. chlamydocarpa* (Moraceae)	Antimicrobial [43]
2′-Hydroxyisoprunetin (**144**); cajanin (**145**); 6,7-(2-isopropenyl furo)-5,2′,4′-trihydroxyisoflavone (**146**)	*Ficus ovata* (Moraceae)	Antimicrobial [80]
Isopterocarpan		
3-Hydroxy-9-methoxy-10-prenylpterocarpene (**147**)	*E. abyssinica* (Fabaceae)	Antiplasmodial [36]
Pterocarpans		
(−)-Maackiain (**148**)	*T. fulvinervis* (Fabaceae)	Moderate cytotoxicity (IC_{50} of 43 μM on MRC-5 cells) [72]
Calopocarpin (**149**)	*E. burttii* (Fabaceae)	Antiplasmodial [49]
Cristacarpin (**150**)	*E. lysistemon* (Fabaceae)	Antimicrobial [30], effects on protein tyrosine phosphatase 1B [81]
Erybraedin A (**152**); orientanol C (**153**); erysubin D (**154**); eryvarin D (**155**)		Effects on protein tyrosine phosphatase 1B [81]
Erystagallin A (**156**)		Effects on protein tyrosine phosphatase 1B [81], cytotoxic, PTP1B inhibitory [82]

(*Continued*)

Table 9.1 (Continued)

Class and Compounds	Plants (Family)	Pharmacological Activities
Erythribyssins A (**157**); B (**158**); C (**159**); eryvarin K (**160**); neorautenol (**161**); erybreadin B (**162**); 3,9-dihydroxy-4-prenyl-[6a*R*;11a*R*] pterocarpan (**163**); folitenol (**164**); erybreadin D (**165**); erysubin E (**166**); erybreadin C (**167**); phaseollidin (**168**)	*E. abyssinica* (Fabaceae)	Cytotoxic and PTP1B inhibitory [82], antioxidant [30, 82]
Sophorapterocarpan A (**169**); erythrabyssin II (**170**)		Cytotoxic, PTP1B inhibitory [82]
Erythribyssin O (**171**)		Neuraminidase [16]
Erythribyssin L (**172**); erythribyssin D (**173**); erythribyssin M (**174**); 3,9-dihydroxy-10-δ,δ-dimethylallylpterocarpan (phaseollidin) (**168**)	*E. abyssinica* (Fabaceae)	Neuraminidase [16]
Rotenoids		
Usararotenoid A (**175**); 12-dihydrousararotenoid A (**176**); 12a-epimillettosin (**177**); 6a,12a-dehydromillettone (**178**)	*M. usaramensis* subsp. *usaramensis* (Fabaceae)	Antiplasmodial [14]

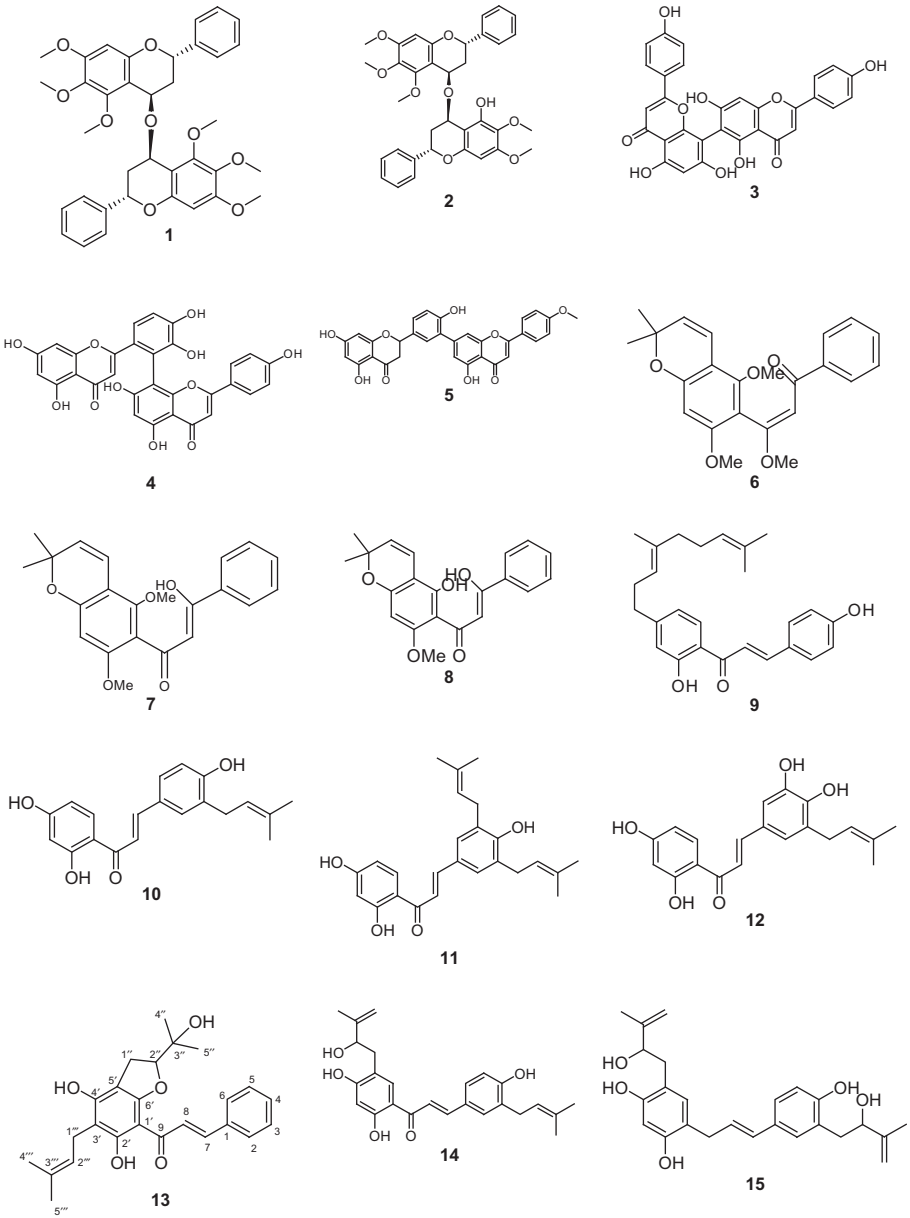


Figure 9.3 Bioactive biflavonoids and chalcones identified in African medicinal plants: beilschmieflavonoid A (**1**); beilschmieflavonoid B (**2**); agasthisflavone (**3**); amentoflavone (**4**); 4′-methoxy amentoflavone (**5**); praecansone A (**6**); praecansone B (**7**); demethylpraecansone A (**8**); 4′-*O*-geranylisoliquiritigenin (**9**); licoagrochalcone A (**10**); abyssinone VI (**11**); 5′-prenylbutein (**12**); cedrediprenone (**13**); bartericin A (**14**); angusticornin B (**15**); candidachalcone (**16**); abyssinone-VI-4-*O*-methyl ether (**17**);

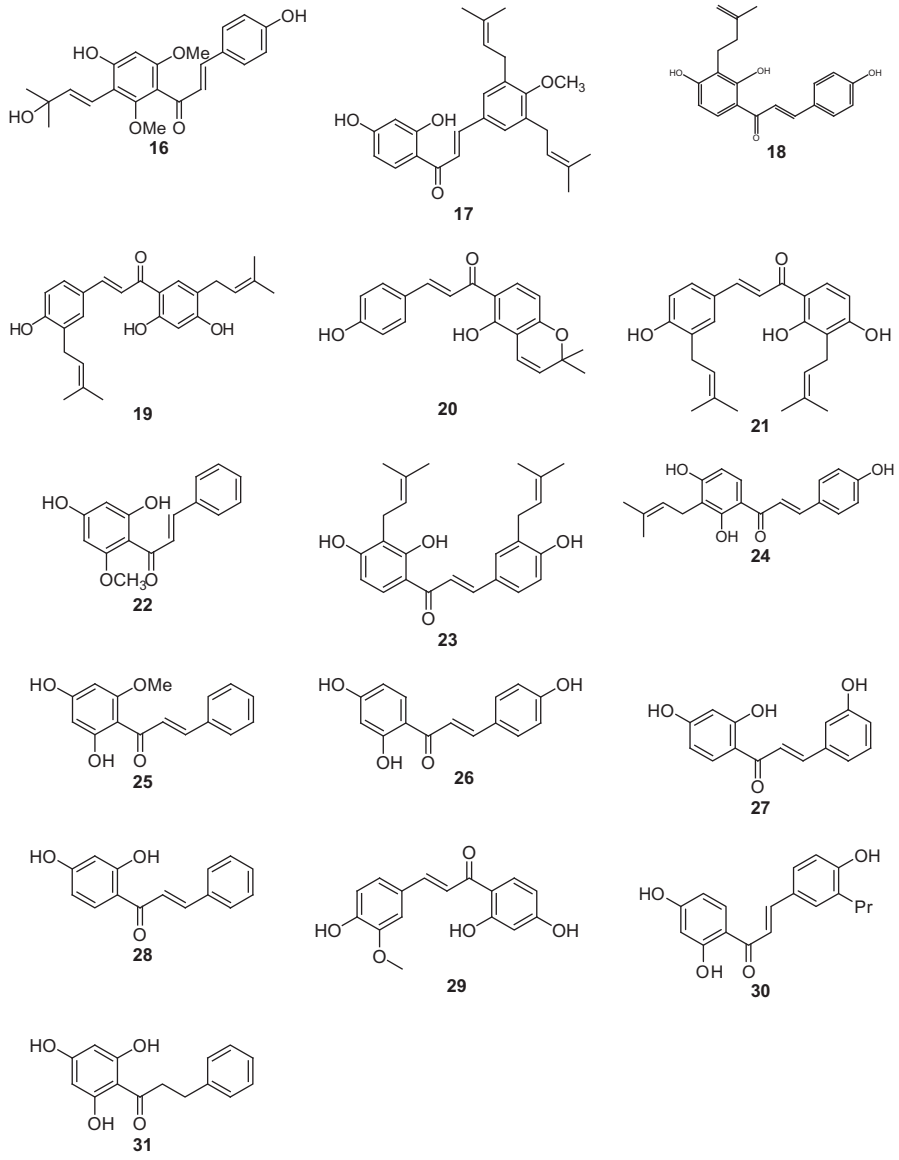


Figure 9.3 (Continued)

◀ isobavachalcone (**18**); stipulin (**19**); 4-hydroxylonchocarpin (**20**); kanzanol (**21**); 2′-hydroxy-4′-glucoside-6′-methoxychalcone (**22**); kanzonol C (**23**); 4,2′,4′-trihydroxy-3′-δ,δ-dimethylallylchalcone (**24**); cardamonin (**25**); isoliquiritigenin (**26**); (*E*)-3,2′,4′-trihydroxychalcone (**27**); (*E*)-2′,4′-dihydroxychalcone (**28**); homobutein (**29**); licoagrochalcone A (**30**); 2′,4′,6′-trihydroxydihydrochalcone (**31**).

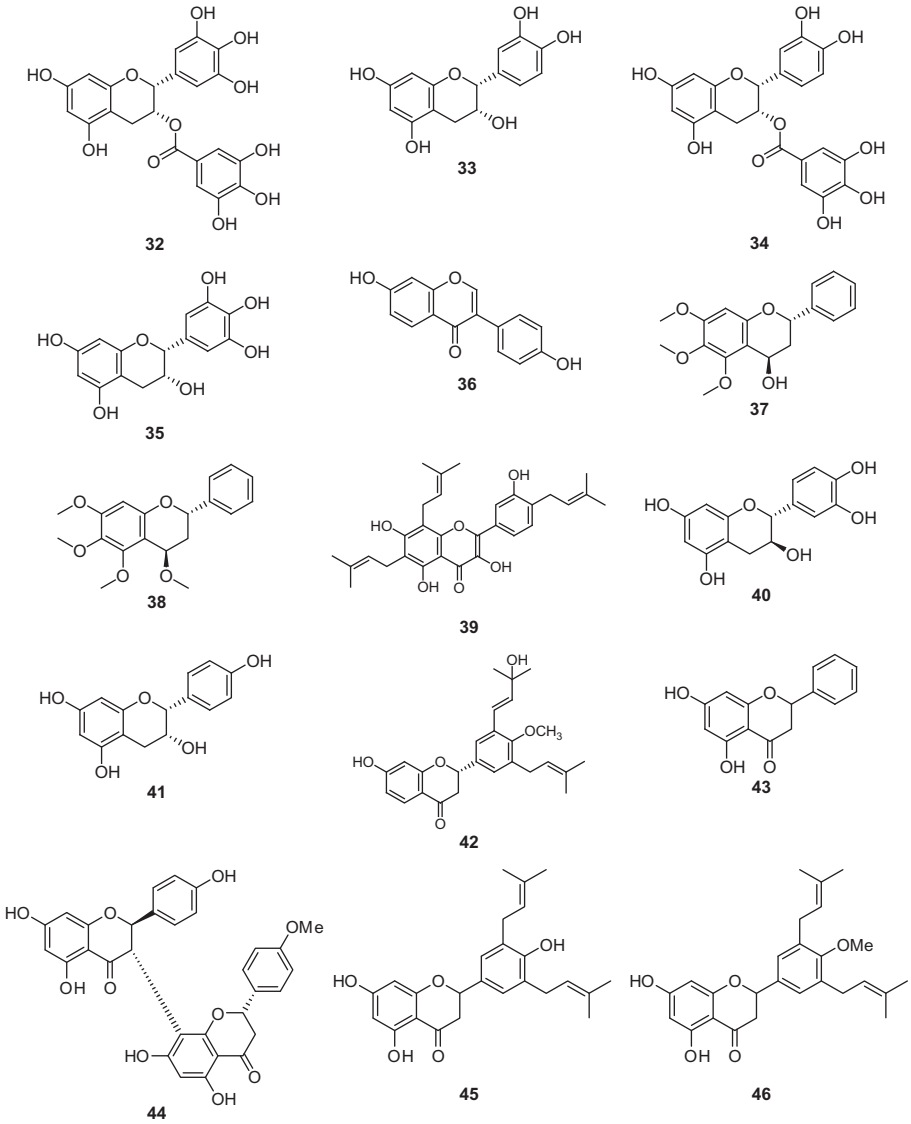


Figure 9.4 Bioactive flavan-3-ol, flavanol, flavanone, flavones, and flavonol identified in African medicinal plants: epigallocatechin gallate (**32**); (−)-epicatechin (**33**); (−)-epicatechin-3-gallate (**34**); epigallocatechin (**35**); daidzein (**36**); (2*S*,4*R*)-5,6,7-trimethoxyflavan-4-ol (**37**); (2*S*,4*R*)-4,5,6,7-tetramethoxyflavan (**38**); dorsmanin F (**39**); catechin (**40**); epiafzelechin (**41**); 7-hydroxy-4′-methoxy-3′-(3-hydroxy-3-methyl-*trans*-but-1-enyl)-5′-(3-methylbut-2-enyl)flavanone (**42**); 5,7-dihydroxyflavanone (or pinocembrin) (**43**); *ent*-naringeninyl-(I-3*R*,II-8)-4′-*O*-methylnaringenin eriodictyol 7-*O*-sophoroside (**44**); abyssinone V (**45**); abyssinone V methyl ether (**46**); 4-*O*-methylsigmoidin B (**47**); abyssinin III (**48**); abyssinone IV (**49**); abyssinone V 4′-methyl ether (**50**); sigmoidin A (**51**); sigmoidin B (**52**); 5-deoxysigmoidin B-4′-methyl ether or erylatissin C (**53**); sigmoidin C (**54**);

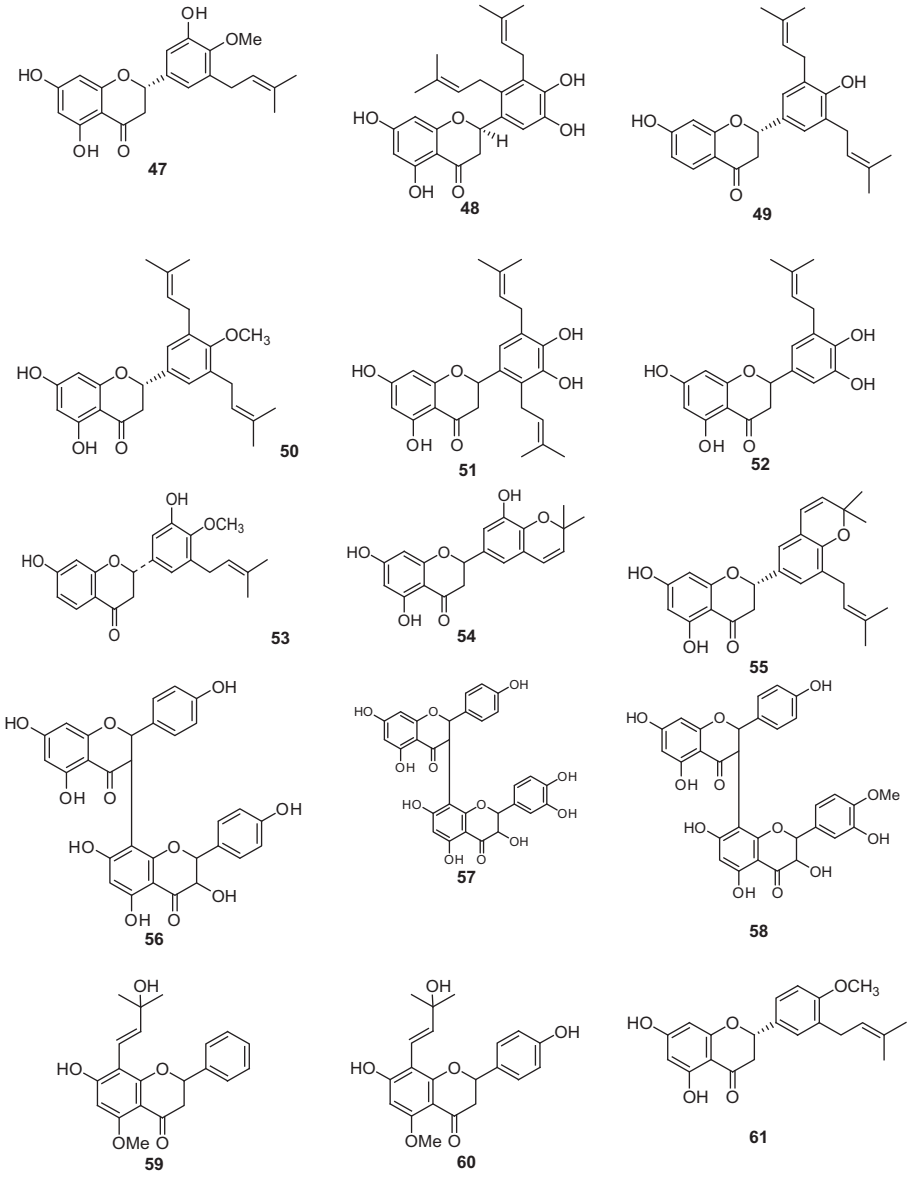


Figure 9.4 (Continued)

◀ sigmoidin E (**55**); garcinia biflavanone I (**56**); garcinia biflavanone II (**57**); kolaflavanone (**58**); tephrocandidin A (**59**); tephrocandidin B (**60**); licoflavanone-4′-*O*-methyl ether (**61**); abyssinone-IV-4′-*O*-methyl ether (**62**); (*S*)-naringenin (**63**); abyssinone-V-4′-*O*-methyl ether (**64**); burttinone (**65**); (2*S*)-5,7,2′-trihydroxyflavanone (**66**); apigenin (**67**); (+)-volkensiflavone (**68**); (+)-morelloflavone (**69**); quercetin-3-*O*-rutinoside (**70**); 6-hydroxyluteolin 7-*O*-laminaribioside (**71**); 5,7-dihydroxy-3,6,4′-trimethoxy-3′-

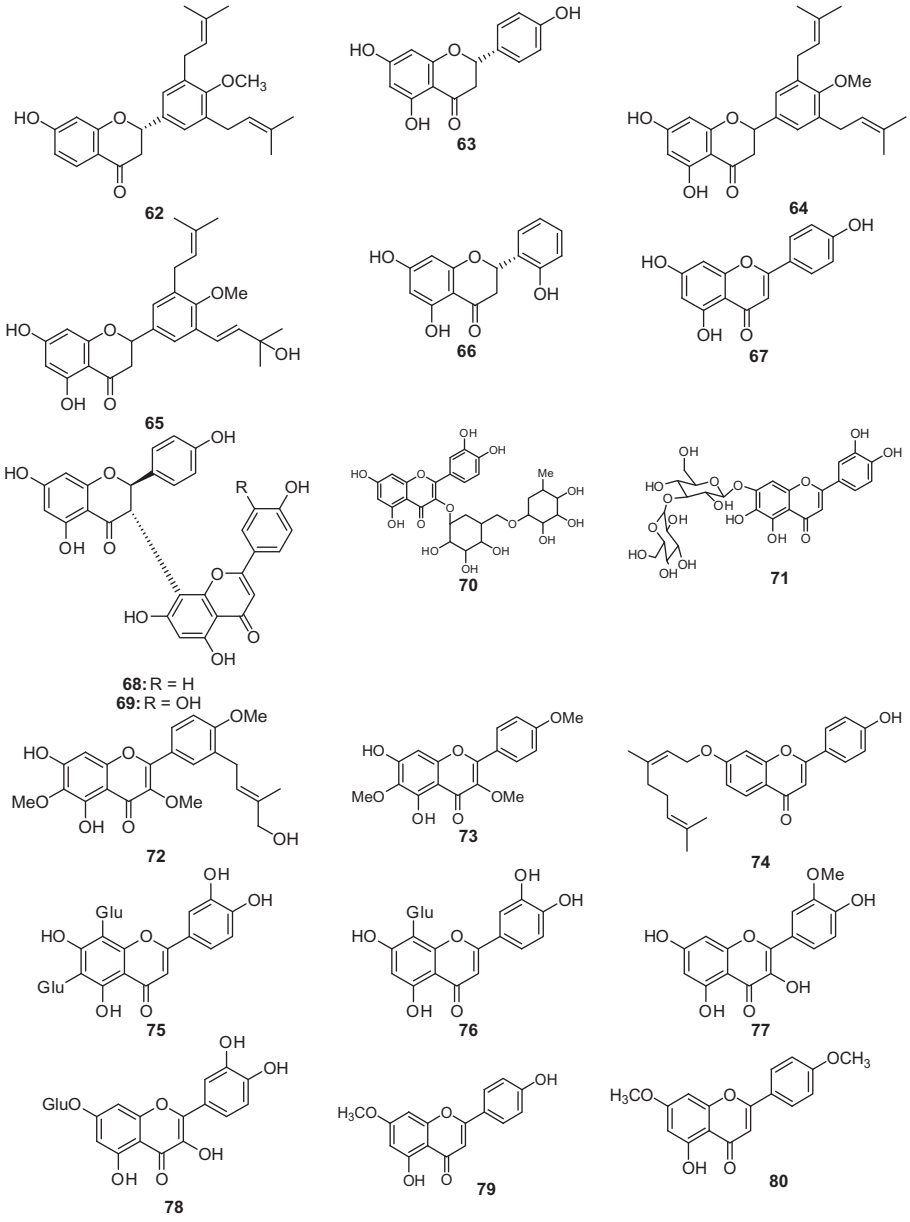


Figure 9.4 (Continued)

◀ (4-hydroxy-3-methyl-but-2-enyl)flavone (**72**); 3,6-dimethoxy-5,7,4′-trihydroxyflavone (**73**); griffonianone E (**74**); luteolin 6,8-di-C-β-glucopyranoside (lucenin 1) (**75**); luteolin 8-C-β-glucoside (orientin) (**76**); isorhamnetin (**77**); quercetin 7-*O*-β-glucopyranoside (**78**); genkwanin (**79**); 5-hydroxy-7,4′-dimethoxyflavone (**80**); quercetin-5,3′- dimethylether (**81**); gancaonin Q (**82**); 3,5,7-trihydroxyflavone (galangin) (**83**); dorsilurin F (**84**); dorsilurin G (**85**); dorsilurin H (**86**); dorsilurin I (**87**); dorsilurin J (**88**); dorsilurin K (**89**);

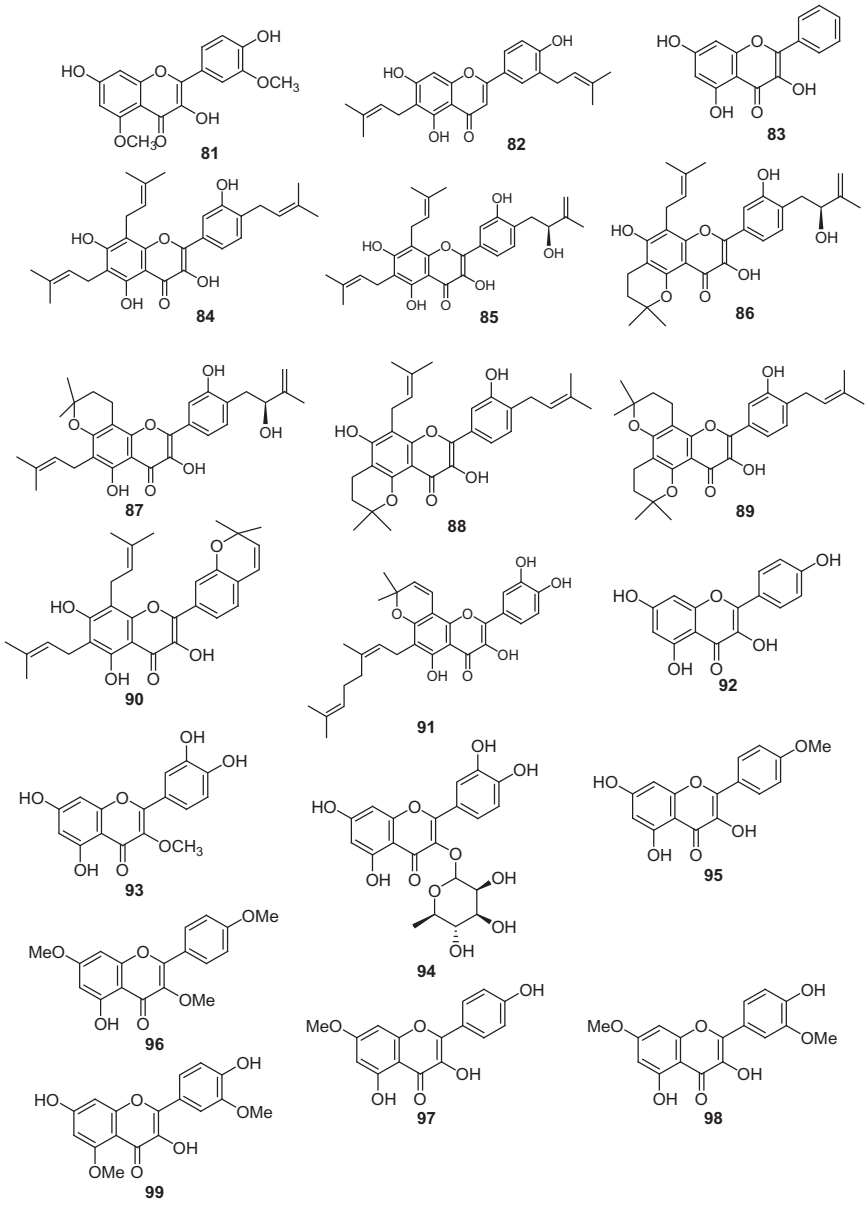


Figure 9.4 (Continued)

◀ dorsilurin C (**90**); dorsmanin C (**91**); kaempferol (**92**); 3-methoxyquercetin (**93**); quercitrin (**94**); 3,5,7-trihydroxy-4′-methoxyflavone (**95**); 5-hydroxy-7,4′-dimethoxyflavone (**96**); rhamnocitrin (**97**); rhamnazin (**98**); quercetin-5,3′-dimethylether (**99**).

for **15**), *Klebsiella pneumoniae* (MIC of 39.06 μg/mL for **82** and 19.53 μg/mL for **19**, **15**, and **189**), *Morganella morganii* (MIC of 39.06 μg/mL for **82**, 1.22 μg/mL for **189**, and 0.61 μg/mL for **15**), *Proteus mirabilis* (MIC of 39.06 μg/mL for **82**, 78.12 μg/mL for **19**, and 2.44 μg/mL for **189** and **15**), *Pseudomonas aeruginosa* (MIC of 39.06 μg/mL for **82**, 19.53 μg/mL for **19**, 9.76 μg/mL for **189**, and below 0.31 μg/mL for **15**), *Shigella dysenteriae* (MIC of 19.53 μg/mL for **19**, 2.44 μg/mL for **82** and **189**, and 0.61 μg/mL for **15**), *Salmonella typhi* (MIC of 39.06 μg/mL for **82**, 78.12 μg/mL for **19** and **189**, and 19.53 μg/mL for **15**), *Bacillus cereus* (MIC of 4.88 μg/mL for **19**, 1.22 μg/mL for **189**, and 0.61 μg/mL for **82** and **15**), *Staphylococcus aureus* (MIC of 2.44 μg/mL for **189** and 0.61 μg/mL for **15**), *Streptococcus faecalis* (MIC of 2.44 μg/mL for **19**, 1.22 μg/mL for **189**, and 0.61 μg/mL for **82** and **15**), *C. albicans* and *C. glabrata* (MIC of 0.61 μg/mL for **189** and **15**), and *C. krusei* (MIC of 1.22 μg/mL for **189** and **15**) [19].

Isobavachalcone (**18**) displayed significant antimicrobial activities against *P. mirabilis*, *Proteus vulgaris*, *Microsporum audouinii*, and *Trichophyton rubrum* (MIC of 1.2 μg/mL); *E. aerogenes*, *M. morganii*, *Shigella flexneri*, *Bacillus subtilis*, *Bacillus megaterium*, and *B. cereus* (MIC of 0.6 μg/mL); *Enterobacter cloacae*, *S. faecalis*, *S. aureus*, *C. albicans*, and *C. glabrata* (MIC of 0.3 μg/mL) [23]; *Mycobacterium tuberculosis* ATCC700084 and *M. tuberculosis* H37Rv (MIC of 2.44 μg/mL); and *Neisseria gonorrhoeae* (MIC range of 0.61−9.76 μg/mL) [18].

4-Hydroxylonchocarpin (**20**) also displayed significant activity against *M. audouinii* (MIC of 9.8 μg/mL); *E. aerogenes*, *S. flexneri*, *S. faecalis*, *S. aureus*, *B. cereus*, *B. subtilis C. albicans*, *C. glabrata*, and *T. rubrum* (MIC of 4.9 μg/mL); *E. cloacae*, *M. morganii*, *B. megaterium*, and *Bacillus stearothermophilus* (MIC of 1.2 μg/mL) [5]; *M. tuberculosis* ATCC700084 (MIC of 9.76 μg/mL); and *N. gonorrhoeae* ATCC49226 (MIC of 9.76 μg/mL) [18].

Kanzonol C (**23**) showed good activity against *P. mirabilis*, *P. vulgaris*, *B. cereus*, *B. subtilis*, and *M. audouinii* (MIC of 9.8 μg/mL); *E. aerogenes*, *E. cloacae*, *M. morganii*, *S. flexneri*, *S. faecalis*, *B. stearothermophilus*, *C. albicans*, and *C. glabrata* (MIC of 4.9 μg/mL) [5]; *M. tuberculosis* ATCC700084 (MIC of 9.76 μg/mL); and *N. gonorrhoeae* ATCC49226 (MIC of 9.76 μg/mL) [18].

It has been demonstrated that hydroxylation of the prenyl groups of **19** leads to compounds **18** and **20**, inducing a significant increase in antimicrobial activity [19]. Mbaveng et al. [23] also demonstrated that transposition of prenyl from 5′ (stipulin) to 3′ leads to kanzonol C (**23**), inducing an increase of antimicrobial activity. Compound **23** exhibits significant antimicrobial activity against *M. morganii* and *S. flexneri*, while **19** is not so active. A monoprenylated chalcone (**18**) was more active than most of the diprenylated chalcones tested so far, with significant inhibitory effects observed on several bacteria and fungi [23]. Cyclization of this molecule leading to **20** induced a significant reduction of the activity [23]. Kuete et al. [88] also demonstrated that the shift of a prenyl group from C3 of **18** to position 3′ (4,2′,4′-trihydroxy-3-prenylchacone; (**24**)) reduced the specificity of **24** against Gram-negative bacteria, while the activity remained significant on Gram-positive bacteria and yeasts.

Several other flavonoids have shown moderate antimicrobial activity. This includes catechin (**40**), epiafzelechin (**41**), amentoflavone (**4**), and others [19,23,43,88,89]. Many bioactive isoflavonoids have been isolated from Cameroonian medicinal plants. Although isoflavonoids such as laburnetin (**143**) [43] showed significant activity against *M. tuberculosis* (MIC of 0.61 μg/mL) (Figure 9.5), its activities against Gram-positive and Gram-negative bacteria and fungi, as well as those of genistein (**116**), alpium isoflavone (**42**), 2′-hydroxyisoprunetin (**144**), 6,7-(2-isopropenyl furo)-5,2′,4′-trihydroxyisoflavone (**146**), and cajanin (**145**), were found to be selective, moderate, or negligible (MIC > 10 μg/mL) [43,89]. Similar to chalcones, it has been demonstrated that the cyclization of flavones (e.g., artocarpesin to cycloartocarpesin) reduced antimicrobial activity [89].

Other flavonoids with antimicrobial activity are listed in Table 9.1; some of them, including 3-methoxyquercetin (**93**), showed moderate inhibitory effects (MIC > 63 μg/mL) against *Enterococcus faecalis*, *S. aureus*, *B. cereus*, *E. coli*, *K. pneumoniae*, *Cryptococcus neoformans*, and *C. albicans* [29]. Using the Thin Layer Chromatography (TLC) bioautographic assay, it was demonstrated that compound **24** had antimicrobial effects against *E. coli* and *Candida mycoderma* (minimal inhibitory amount (MIA) of 0.5 μg), *S. aureus*, and *B. subtilis* (MIA of 0.01 μg) [30]. 5-Deoxysigmoidin B-4′-methyl ether or erylatissin C (**53**), 3,6a-dihydroxy-9-methoxy-10-δ,δ-dimethylallylpterocarpan or cristacarpin (**150**), also tested using TLC bioautographic assay, displayed antimicrobial activities against *E. coli* (MIA of 0.5 and 0.1 μg, respectively), *S. aureus* (MIA of 0.1 μg for both compounds), *B. subtilis* (MIA of 0.01 μg for both compounds), and *C. mycoderma* (MIA of 0.01 and 0.5 μg, respectively) [30]. Antimicrobial activity of the chalcone isoliquiritigenin (**9**) was also reported against *E. faecalis* ATCC 10541 (MIC range of 60−780 μg/mL) and *Candida guilliermondii* (MIC range of 0.01−190 μg/mL) (Figure 9.6) [32].

Flavones such as 5-hydroxy-7,4′-dimethoxyflavone (**80**) and genkwanin (**79**), isolated from the South African medicinal plant *Combretum erythrophyllum*, showed moderate to low activity against *Micrococcus luteus* (MIC of 100 and 50 μg/mL, respectively), *E. coli* (MIC of 50 and 100 μg/mL, respectively), *Shigella sonnei* (MIC of 50 and 25 μg/mL, respectively), *Vibrio cholerae* (MIC of 25 and 50 μg/mL, respectively), *P. aeruginosa* (MIC of 100 μg/mL for both compounds), and *E. faecalis* (MIC of 50 μg/mL for both compounds) [57]. The flavonols quercetin-5,3′-dimethylether (**81**), rhamnazin (**98**), and rhamnocitrin (**97**) also displayed moderate to low activity against *M. luteus* (MIC of 50 μg/mL for **81** and **98** and 50 μg/mL for **97**), *E. coli* (MIC of 50 μg/mL for **81** and **97** and 100 μg/mL for **98**), *S. sonnei* (MIC of 25 μg/mL for **81** and **97** and >100 μg/mL for **98**), *V. cholerae* (MIC of 50 μg/mL for **81** and **98** and 25 μg/mL for **97**), *P. aeruginosa* (MIC of 100 μg/mL for the three compounds), and *E. faecalis* (MIC of 100 μg/mL for the three compounds) [57]. One of the most common flavonols, kaempferol (**92**), isolated from several African plants such as *C. erythrophyllum*, *Combretum apiculatum* subsp. *apiculatum*, *Harpephyllum caffrum*, *Dodonaea viscosa* Jacq. var. *angustifolia*, and *Vismia laurentii* [31,57,67,90,91] displayed significant antimicrobial activity against *S. typhi*, *S. aureus*, *B. cereus*, *B. megaterium* (MIC of 9.76 μg/mL), *S. dysenteriae* (MIC of 4.88 μg/mL), *B. subtilis*, and *C. glabrata* (MIC of 2.44 μg/mL) [90]. 5,7-

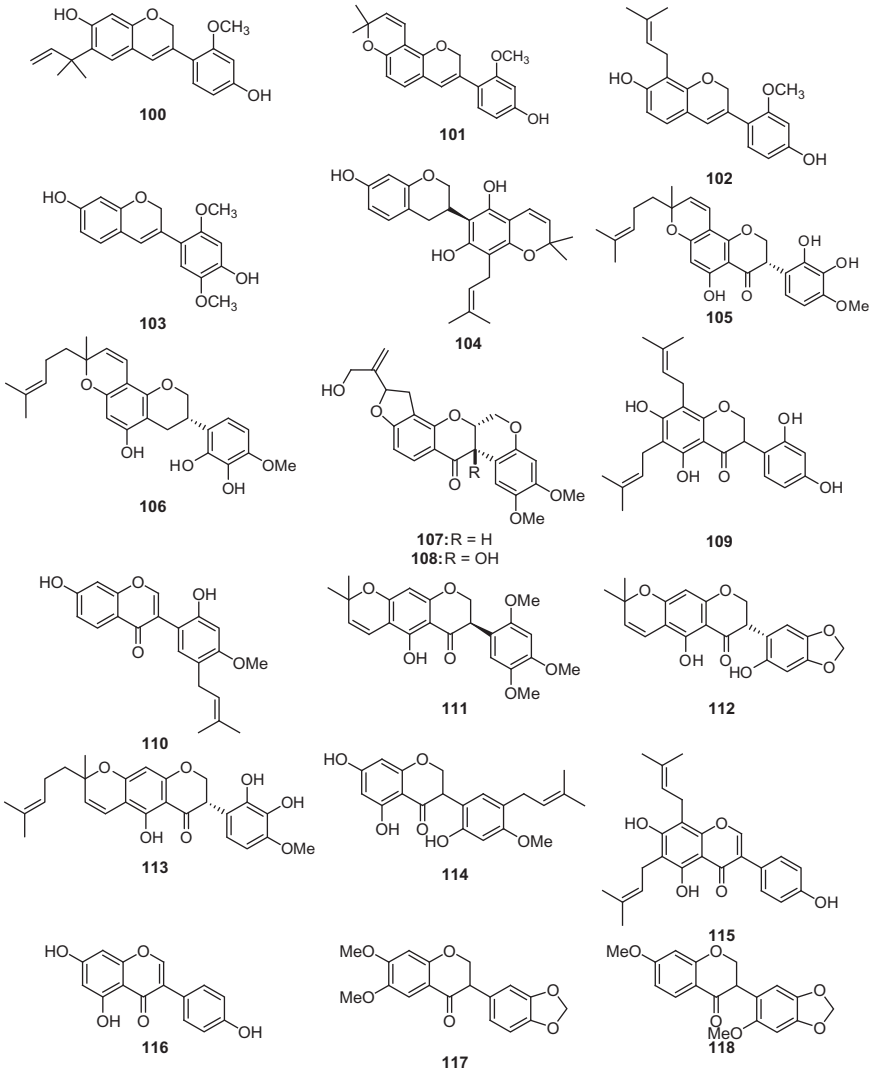


Figure 9.5 Bioactive isoflanoids identified in African medicinal plants: burttinol A (**100**); burttinol B (**101**); burttinol C (**102**); eryvarin H (**103**); (3*R*)-2,7-dihydroxy-3′-(3-methylbut-2-enyl)-2‴,2‴-dimethylpyrano[5‴,6‴:4′,5′]isoflavan (**104**); discoloranone B (**105**); nitidulin (**106**); amorphigenin (**107**); dabinol (**108**); bidwillon A (**109**); prostratol C (**110**); saclenone (**111**); isodiscoloranone A (**112**); isodiscoloranone B (**113**); lysisteisoflavanone (**114**); 6,8-diprenylgenistein (**115**); genistein (**116**); 6,7-dimethoxy-3′,4′-methylenedioxyisoflavone (**117**); 7,2′-dimethoxy-4′,5′-methylenedioxyisoflavone (**118**); barbigerone (**119**); corylin (**120**); erysubin F (**121**); 7-demethylrobustigenin (**122**); 2,3-dehydrokeivetone (**123**); isoelliptol (**124**); erythraddison A (**125**); isowighteone (**126**); wighteone (**127**); 7-*O*-geranylformononetin (**128**); 4′-methoxy-7-*O*-[(*E*)-3-methyl-7-hydroxymethyl 2,6-octadienyl] isoflavone (**129**); 4′-*O*-geranylisoliquiritigenin (**130**); 3′,4′-dihydroxy-7-*O*-[(*E*)-3,7-dimethyl-

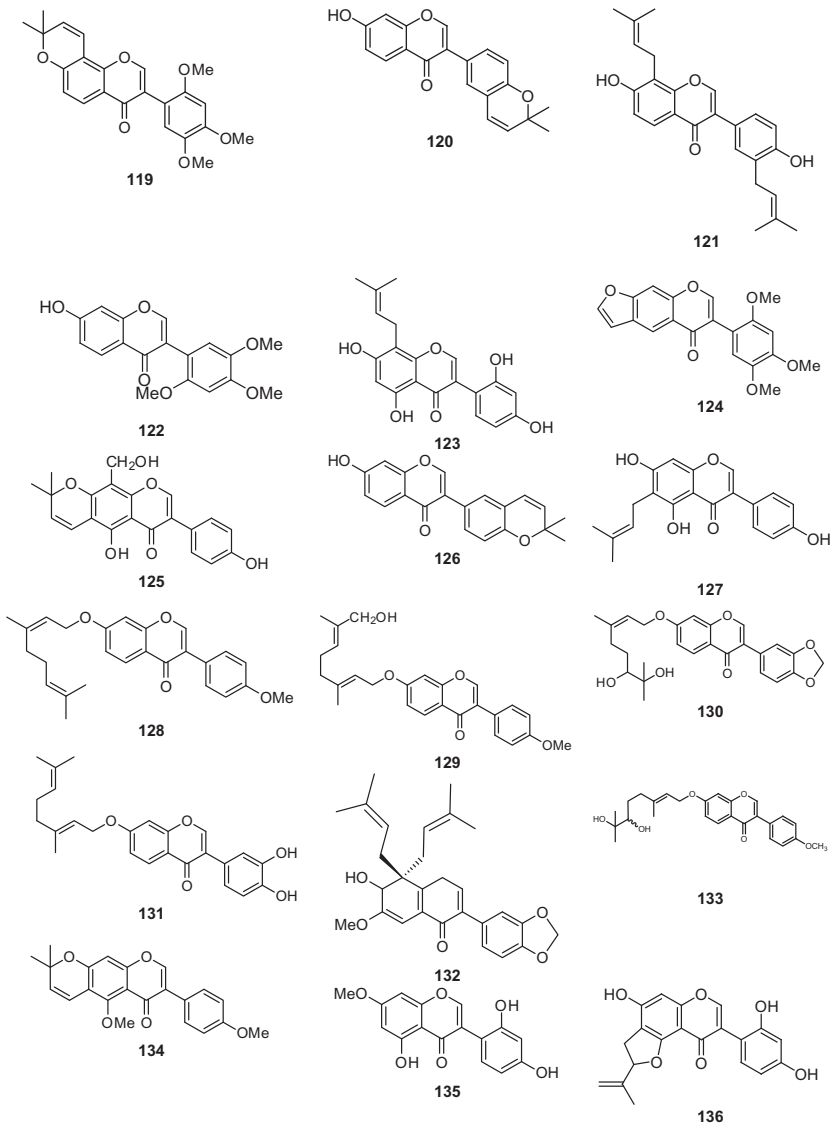
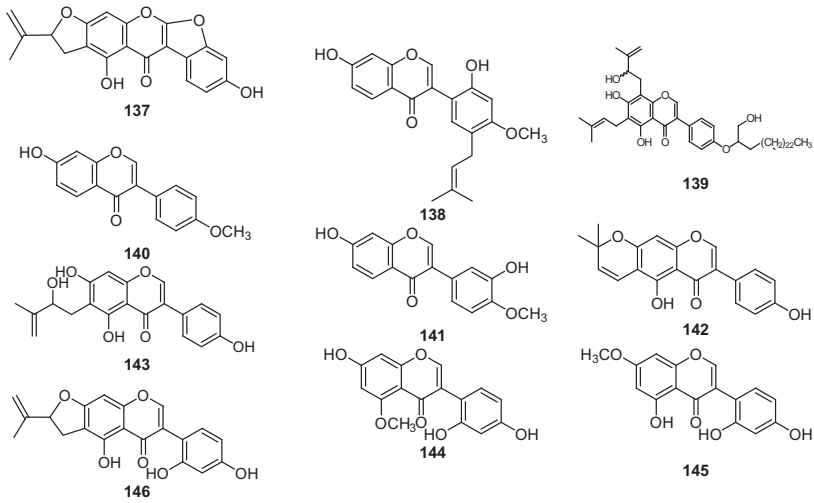


Figure 9.5 (Continued)

◀ 2,6-octadienyl]isoflavone (**131**); griffonianone C (**132**); griffonianone D (**133**); 5,4′-di-*O*-methylalpiummisoflavone (**134**); jacanin (**135**); lachnoisoflavone A (**136**); lachnoisoflavone B (**137**); 2,7-dihydroxy-4′-methoxy-5′-(3-methylbut-2-enyl)isoflavone (**138**); indicanine D (**139**); 7-hydroxy-4′-methoxyisoflavone (**140**); 7,3′-dihydroxy-4′-methoxyisoflavone (**141**); alpium isoflavone (**142**); laburnetin (**143**); 2′-hydroxyisoprunetin (**144**); cajanin (**145**); 6,7-(2-isopropenyl furo)-5,2′,4′-trihydroxyisoflavone (**146**).



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Dihydroxyflavanone or pinocembrin (**43**), isolated from the root bark of the South African medicinal plant *Erythrina indica*, displayed antibacterial activity against *S. aureus* (MIC of 12.5 μg/mL) and *C. albicans* (MIC of 6.25 μg/mL) [46].

Erycristagallin (**151**), a pterocarpene isolated from the Cameroonian medicinal plant *Erythrina mildbraedii*, displayed antimicrobial activity against *S. aureus*, *Mycobacterium smegmatis*, *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Actinobacillus actinomycetemcomitans* [92–96].

Based on qualitative assays using disk diffusion, the new isoflavones lachnoisoflavones A and B, as well as luteolin-7-*O*-α-L-rhamnoside, 2′-hydroxygenistein, 3′-*O*-methylorobol, 7-*O*-methyltectorigenin, prunetin, licoagroisoflavone, and cajanin (**145**), isolated from the Cameroonian medicinal plant *Crotalaria lachnophora*, showed moderate inhibitory activity against *E. coli* and *K. pneumoniae*, with the inhibition zone diameters varying from 7 to 10.7 mm [77].

Few studies are observed in the search for anti-HIV drugs from medicinal plants. This is obviously the consequence of the low income of most of the African countries, which reduces their ability to create new standard screening laboratories, most effort being spent on how to afford available therapies. However, some data reporting anti-HIV properties of African medicinal plants are available. Kuete et al. [18] reported a good *in vitro* anti-HIV reverse transcriptase activity for *D. barteri* and its two main flavonoids, isobavachalcone (**18**) and 4-hydroxylonchocarpin (**20**), with 59.37% and 56.26% inhibition percentage at 100 μg/mL. However, such reports on the medicinal value of plants as potential anti-HIV drugs from studies performed in Africa constitute a great progress today, and let us expect more progress in the future in anti-HIV research on the continent.

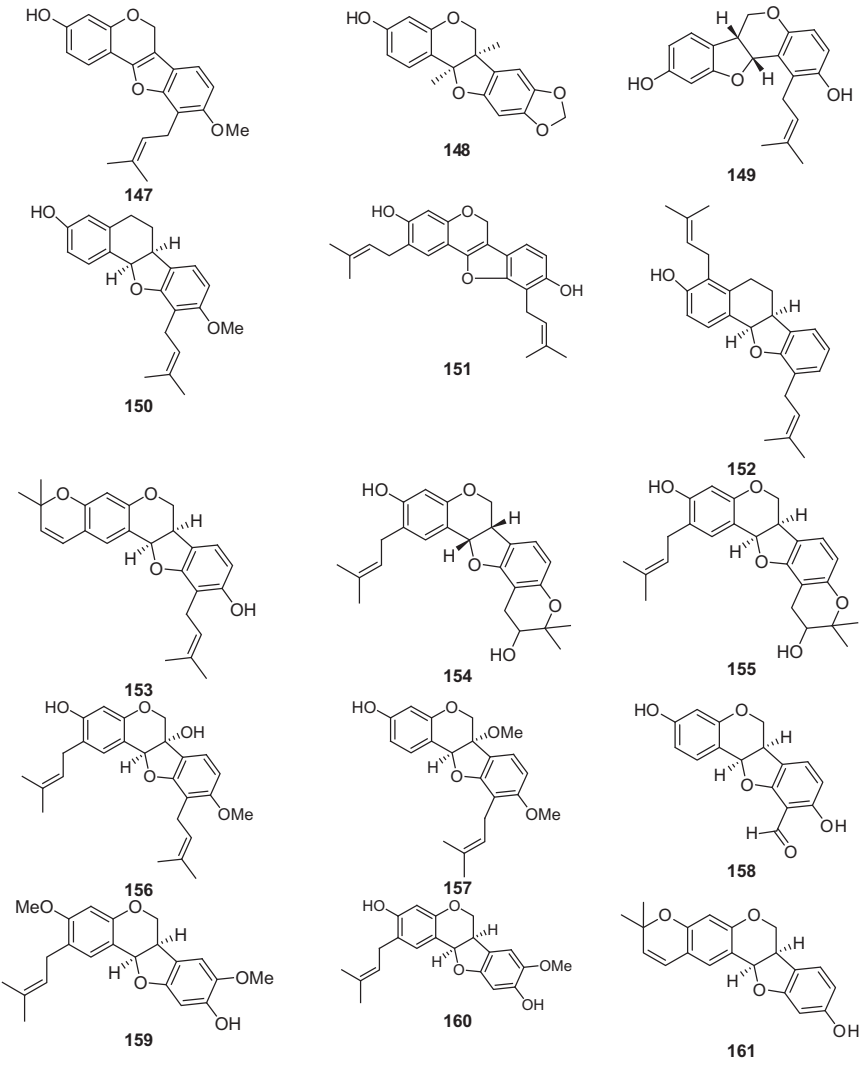
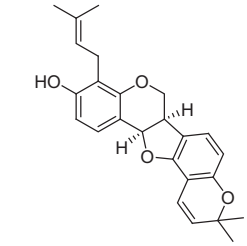


Figure 9.6 Bioactive pterocarpan, proanthocyanidins, and rotenoids identified in African medicinal plants: 3-hydroxy-9-methoxy-10-prenylpterocarpene (**147**); (−)-maackiain (**148**); calopocarpin (**149**); cristacarpin (**150**); erycristagallin (**151**); erybraedin A (**152**); orientanol C (**153**); erysubin D (**154**); eryvarin D (**155**); erybreadin A (**156**); erythribyssin A (**157**); erythribyssin B (**158**); erythribyssin C (**159**); eryvarin K (**160**); neorautenol (**161**); erybreadin B (**162**); 3,9-dihydroxy-4-prenyl-[6a*R*;11a*R*] pterocarpan (**163**); folitenol (**164**); erybreadin D (**165**); erysubin E (**166**); erybreadin C (**167**); phaseollidin (**168**); sophorapterocarpan A (**169**); erythrabyssin II (**170**); erythribyssin O (**171**); erythribyssin L (**172**); erythribyssin D (**173**); erythribyssin M (**174**); usararotenoid A (**175**); 12-dihydrousararotenoid A (**176**); 12a-epimillettosin (**177**); 6a,12a-dehydromillettone (**178**).



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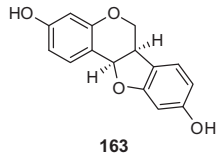

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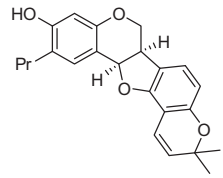

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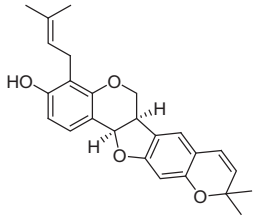

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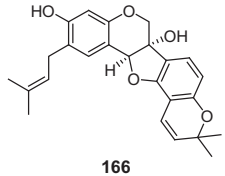

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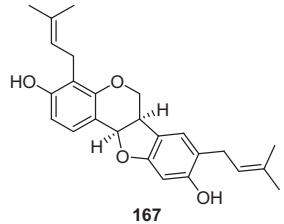

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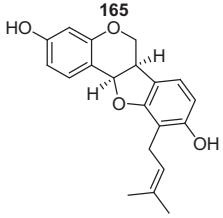

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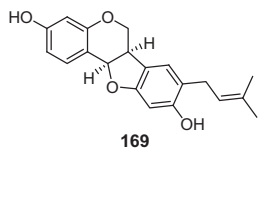

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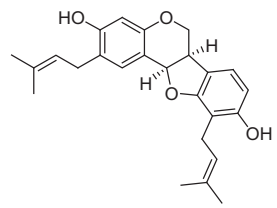

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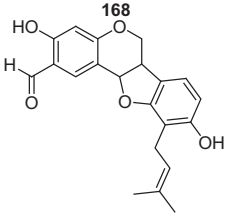

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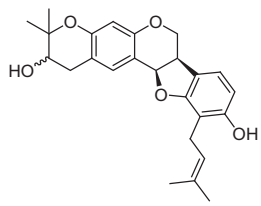

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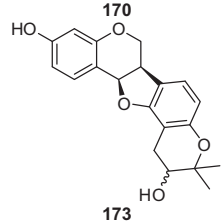

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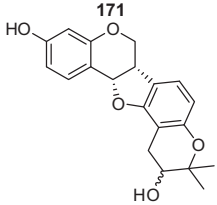

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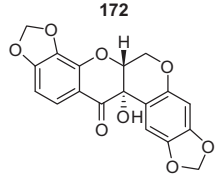

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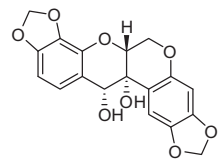

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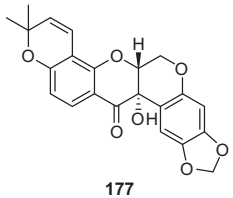

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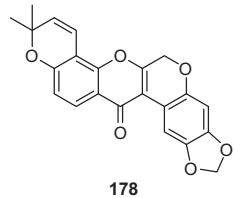

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Figure 9.6 (Continued)

Several flavonoids identified in African plants were also screened for antiparasitic properties. Flavonoids with considerable antimalarial activity reported from African plants include joziknipholone A (IC_{50} of 0.14 μg/mL on *Plasmodium falciparum* K1 strain) and joziknipholone B, isolated from *Bulbine frutescens* [97]. The isoflavones burttinols A (IC_{50} of 7.6 and 8.5 μM, respectively), C (IC_{50} of 9.3 and 9.1 μM, respectively), B (IC_{50} of 19.1 and 21.1 μM, respectively), and eryvarin H (IC_{50} of 9.3 and 9.1 μM, respectively), as well as the flavanones 4′-*O*-methylsigmoidin B (IC_{50} of 12.4 and 12.7 μM, respectively), abyssinone V (IC_{50} of 5.7 and 6.6 μM, respectively) and abyssinone V methyl ether (IC_{50} of 10.7 and 11.9 μM, respectively), isolated from the root bark of *Erythrina burttii* harvested in Kenya, showed *in vitro* antiplasmodial activity against the chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *P. falciparum*, respectively [49]. 5-ydroxy-7,8-dimethoxyflavanone, isolated from the Cameroonian plant *Beilschmiedia zenkeri*, showed an IC_{50} value of 9.3 μM [10].

9.4.2 Cytotoxicity of Flavonoids Isolated from African Medicinal Plants

Many flavonoids isolated from African plants have displayed cytotoxic activities against various type of human cancer cells (Table 9.1). Some hit compounds include isobavachalcone (**18**), gancaonin Q (**82**), 6-prenylapigenin, 6,8-diprenyleriodictyol, 4-hydroxylonchocarpin (**20**), and agasthisflavone (these are discussed in Chapter 18). Isobavachalcone (**18**), isolated from *D. barteri* [24] and *D. turbinata* [98], exhibited a cytotoxicity against many tumor cell lines, including ovarian carcinoma OVCAR-8 cells, prostate carcinoma PC-3 cells, breast carcinoma MCF-7 cells, and lung carcinoma A549 cells [99]. Compound **3** significantly ablated Akt phosphorylation at Ser-473 and Akt kinase activity in cells, which subsequently led to inhibition of Akt downstream substrates and caused significant increases in the mitochondrial pathway leading to apoptosis [99]. Nishimura et al. [100] demonstrated that compound **3** induced apoptotic cell death with caspase-3 and caspase-9 activation and Bax upregulation in neuroblastoma cell lines. Compound **3** also inhibited MMP-2 secretion from U87 glioblastoma cells [24]. Flavonoids from the genus *Dorstenia*, gancaonin Q (**82**), 6-prenylapigenin, 6,8-diprenyleriodictyol, and 4-hydroxylonchocarpin (**20**), also displayed antiproliferative activities against a panel of human cancer cells (see Chapter 18) [20]. It was found that the biflavonoid agasthisflavone, isolated from the cashew plant (*Anacardium occidentale*), has antiproliferative activity against Jurkat cells (IC_{50} of 4.45 μM), and the induction of apoptosis was proposed as its likely mode of action in this cell line [11]. However, agasthisflavone showed a low cytotoxic effect on the acute promyelocytic leukemia cell line HL60, Burkitt lymphoma Raji cells, and Hep-2 laryngeal carcinoma cells [11].

9.4.3 Anti-Inflammatory Flavonoids Identified in African Medicinal Plants

Several flavonoids isolated from Cameroonian plants have been reported as highly active anti-inflammatory compounds (Figure 9.2). Warangalone, isolated from the

bark of *Erythrina addisoniae*, showed significant inhibition of phospholipase A_2 (PLA_2)-acute mouse paw edema (68% at 5 mg/kg bw), while the reference compound cyproheptadine, under the same conditions, showed 63% inhibition [101]. Erycristagallin (**151**), isolated from the root of *E. mildbraedii*, exhibited a strong effect when assayed in the 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced acute ear edema test (mice), inhibiting the edema by 94% at a dose of 0.25 mg/ear, while the reference drug indomethacin produced an 82% inhibition at 0.5 mg/ear [102]. Flavonoid sigmoidins A (**51**) and B (**52**), isolated from *Erythrina sigmoidea*, were also effective against TPA-induced ear edema, showing 89% and 83% inhibition, respectively, at 0.25 mg/ear, almost as good as the reference compound indomethacin (83%), tested at 0.5 mg/ear [103]. Griffonianone D (**133**), isolated from *Millettia griffoniana*, showed 77% inhibition of TPA-induced ear edema (at 0.25 mg/ear; mice), and was almost as good as the reference compound indomethacin (81%), tested at 0.5 mg/ear [75]. The chalcone cedrediprenone (**13**) was found to be active in inhibiting the luminol-enhanced chemiluminescence of reactive oxygen metabolites generated by human polymorphonuclear leucocytes activated with opsonized zymosan (IC_{50} of 8.1 μg/mL) and in scavenging superoxide anions in a cell free system (IC_{50} of 0.2 μg/mL), suggesting an anti-inflammatory activity [17].

In vivo, erycristagallin significantly inhibited the phospholipase A2-induced mouse paw edema, as well as the mouse ear edema induced by TPA ($IC_{50} < 10$ mg/ear) and also significantly reduced the chronic inflammation and leukocyte infiltration induced by repeated application of TPA [102]. *In vitro*, erycristagallin inhibited the arachidonic acid metabolism via the 5-lipoxygenase pathway in rat polymorphonuclear leukocytes (IC_{50} of 23.4 μM) but had no effect on cyclooxygenase-1 metabolism in human platelets [102]. As with other phenolics, it was suggested that the anti-inflammatory activity of erycristagallin may be based on its capacity to inhibit the arachidonic acid metabolism via the 5-lipoxygenase pathway [102].

9.4.4 Antidiabetes Flavonoids Isolated in African Medicinal Plants

Several medicinal plants are used in Africa to treat diabetes mellitus; their antihyperglycemic effects were attributed to their ability to restore the function of pancreatic tissues by increasing insulin output, inhibiting the intestinal absorption of glucose, or enhancing metabolism of insulin-dependent processes. In the last two decades, there has been an increase in the popularity among researchers in Africa of the search for antidiabetic drugs from medicinal plants. A good number of plant extracts have successfully undergone *in vitro* screening, and the hit samples involved both crude drugs and compounds. Investigation for new antidiabetes compounds in Africa also involved the search of new α-glucosidase inhibitors. In effect, α-glucosidase inhibitors are oral antidiabetic drugs used for diabetes mellitus type 2 that work by preventing the digestion of carbohydrates, reducing the impact of carbohydrates on blood sugar. Hit antidiabetes products from Africa thus include plant extracts with direct effect *in vivo* on the decrease of blood glucose levels and samples acting *in vitro* as α-glucosidase inhibitors. Flavonoids isolated from African plants with good α-glucosidase inhibitory activity include dorsilurins C (**90**)

(IC_{50} of 11.17 μM), F (**84**) (IC_{50} of 4.13 μM), G (**85**) (IC_{50} of 7.51 μM), and J (**88**) (IC_{50} of 16.91 μM) isolated from *Dorstenia psilurus* [66].

The inhibition of protein tyrosine phosphatase 1B (PTP1B) has been proposed as a therapy for treatment of type 2 diabetes and obesity. In fact, the binding of insulin to the extracellular R-subunit of the insulin receptor (IR) triggers a conformational change that activates the intrinsic tyrosine kinase activity of the α-subunit via autophosphorylation of specific tyrosine residues. This results in the phosphorylation of IR substrates (IRSs), which then activates several signaling cascades, leading to biological responses such as glucose transport into the cell and glycogen synthesis [78]. Protein tyrosine phosphatases (PTPs) are responsible for the dephosphorylation of tyrosine residues and are considered negative regulators of insulin signaling. Although several PTPs such as PTP-R, leukocyte antigen-related tyrosine phosphatase (LAR), and SH2-domain-containing phosphotyrosine phosphatase (SHP2) have been implicated in the regulation of insulin signaling, there is substantial evidence supporting PTP1B as the critical PTP-controlling insulin signaling pathway [78]. PTP1B can interact with and dephosphorylate the activated insulin receptor as well as IRS proteins [78]. Its overexpression has been shown to inhibit the IR signaling cascade, and increased expression of PTP1B occurs in the insulin-resistant states. Furthermore, recent genetic evidence has shown that PTP1B gene variants are associated with changes in insulin sensitivity [78]. As with the insulin signaling pathway, the leptin signaling pathway can be attenuated by PTPs, and there is compelling evidence that PTP1B is also involved in this process. Therefore, it has been suggested that compounds that reduce PTP1B activity or expression levels can be used for treating not only type 2 diabetes but also obesity [78]. Several flavonoids isolated from *E. mildbraedii*, such as alpium isoflavone (**142**) (IC_{50} of 4.5 μM), abyssinone-VI-4-*O*-methyl ether (**17**) (IC_{50} of 14.8 μM), abyssinone IV (**49**) (IC_{50} of 16 μM), abyssinone-IV-4′-*O*-methyl ether (**62**) (IC_{50} of 21.2 μM), abyssinone-V-4′-*O*-methyl ether (**64**) (IC_{50} of 26.3 μM), sigmoidin E (**55**) (IC_{50} of 39.2 μM), abyssinone V (**45**) (IC_{50} of 39.7 μM) [78], (3*R*)-2′,7-dihydroxy-3′-(3-methylbut-2-enyl)-2‴,2‴-dimethylpyrano[5‴,6‴:4′,5′]isoflavan (IC_{50} of 5.5 μM), 2′,7-dihydroxy-4′-methoxy-5′-(3-methylbut-2-enyl)isoflavone (IC_{50} of 21.3 μM), licoflavanone-4′-*O*-methyl ether (IC_{50} of 29.6 μM), parvisoflavone B (IC_{50} of 39.7 μM), and abyssinin II (IC_{50} of 42.6 μM) [22], inhibited PTP1B activity, suggesting their possible role in diabetes therapy.

9.4.5 Antioxidant Flavonoids Isolated from African Medicinal Plants

The search for antioxidant drugs from natural sources has received much attention, and many studies have been published by researchers from institutes in Africa in the past two decades. The experimental methods used include both *in vitro* techniques (such as the 1,1-diphenyl-2-picryl hydrazyl radical scavenging (DPPH) test, scavenging of hydrogen peroxide, assay of nitric oxide scavenging activity, assay of ferrous ion metal chelating activity, determination of antioxidant activity by

the ferric thiocyanate (FTC) method) and *in vivo* enzymatic techniques (such as catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD) assays, and nonenzymatic methods, namely, ferric reducing ability of plasma (FRAP) assay and total radical trapping parameter (TRAP) assay). Compounds are considered to have high or significant antioxidant capacity when $IC_{50} < 10$ μg/mL, moderate antioxidant capacity when $10 < IC_{50} < 20$ μg/mL, and low antioxidant capacity when $IC_{50} > 20$ μg/mL for compounds [86].

Several flavonoids with significant antioxidant activity were reported from African medicinal plants. 4,2′,4′-Trihydroxy-3′-δ,δ-dimethylallylchalcone (**24**) and 3,9-dihydroxy-10-δ,δ-dimethylallylpterocarpan or phaseollidin (**168**), isolated from *Erythrina latissima* harvested in Cameroon, showed 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity, with IC_{50} values of 160 and 671 μg/mL, respectively [30]. Compounds such as burttinols A (**100**) (IC_{50} of 9.8 μM), C (**102**) (IC_{50} of 10.6 μM), B (**101**) (IC_{50} of 75.6 μM), eryvarin H (**103**) (IC_{50} of 62 μM), and abyssinone V (**45**) (IC_{50} of 31.3 μM) also showed DPPH radical scavenging activity [49]. The prenylated flavonoids 6,8-diprenyleriodictyol and dorsmanins C (**91**) and F (**39**), isolated from the Cameroonian plant *Dorstenia mannii*, were found to be potent scavengers of the stable free radical DPPH when they were tested in a concentration range of 1−100 μM [42]. Under similar experimental conditions, they were more potent than butylated hydroxy toluene (BHT), a common antioxidant used as a food additive [42]. They also inhibited Cu^{2+}-mediated oxidation of human low-density lipoprotein (LDL) in a dose-dependent manner [42].

9.4.6 Other Activities

The antityrosinase activity of 2′,4′,6′-trihydroxydihydrochalcone (**31**) was reported, with an IC_{50} value of 69.15 μM [37]. Another chalcone (**26**) also showed DPPH radical activity (IC_{50} of 28.73 μg/mL) [32]. Candidachalcone (**16**) and the flavanones tephrocandidin A (**59**) and tephrocandidin B (**60**), isolated from *Tephrosia candida*, showed estrogenic activity, with IC_{50} values of 80, 3500, and 1000 μM, respectively [21]. The flavanone (*S*)-naringenin (**63**), isolated from the South African plant *Mentha aquatica*, showed binding activity to the GABA-benzodiazepine site [55].

9.5 Flavonoids and Related Compounds Newly Identified in African Medicinal Plants

Several flavonoids and isoflavonoids were reported as new compounds in African plants. They were identified in plants found in various parts of the continent. Table 9.2 and Figure 9.7 summarize these compounds as well as their origin.

Table 9.2 Chemical Structures of Some Newly Identified Compounds in African Medicinal Plants

Class and Compounds	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Biflavonoids				
Dorstenone (**179**)	*D. barteri* (Moraceae)	Cameroon	Whole plant	[25]
Lophirones L (**180**); M (**181**)	*Lophira alata* Banks ex Gaertn (Ochnaceae)	Cameroon	Leaves	[104]
Chalcones				
(*E*)-3,2′,4′-Trihydroxy-3′-methoxychalcone (**182**)	*G. africana* (Aizoaceae)	South Africa	Leaves	[34]
2-Hydroxy-3,4,6-trimethoxychalcone (**183**)	*Uvaria dependens* (Annonaceae) [105]	Tanzania	Root bark	mp 138−139°C [105]
3′,4′-(3-Hydroxy-2,2-dimethyldihydropyrano)-4,2′-dihydroxychalcone (**184**)	*Dorstenia zenkeri* and *Dorstenia prorepens* (Moraceae)	Cameroon	Twigs	[106]
Abyssinone-VI-4-*O*-methyl ether (**17**)	*E. mildbraedii* (Fabaceae)	Cameroon	Root bark	[22]
5-Prenylbutein (**185**)	*E. abyssinica* (Fabaceae)	Kenya	Stem bark	[36]
Angusticornins A (**186**); B (**15**); C (**187**)	*D. angusticornis* (Moraceae)	Cameroon	Twigs	[25]
Bartericin A (**14**); B (**188**); C (**189**); D (**190**)	*D. barteri* var. *subtriangularis* (Moraceae)	Cameroon	Twigs	[25]
Calodenin A (**191**); B (**192**)	*Ochna calodendron* (Ochnaceae)	Cameroon	Stem bark	[107]
Candidachalcone (**16**)	*T. candida* (Fabaceae)	Cameroon	Aerial parts	[21]
Cedrediprenone (**13**); cedreprenone (**193**)	*C. grevei* (Ptaeroxylaceae)	South Africa	Seeds	[17]
Dihydrolophirone C (**194**); isolophirone C (**195**)	*Ochna afzelii* (Ochnaceae)	Cameroon	Stem bark	[108]
Lophirone B (**196**)	*Lophira lanceolata* (Ochnaceae)	Cameroon	Stem bark	mp 251−253°C [109]
Lophirone C (**197**)	*L. lanceolata* (Ochnaceae)	Cameroon	Stem bark	mp 191−193°C [108,109]
Lophirone K (**198**)	*O. calodendron* (Ochnaceae)	Cameroon	Stem bark	[107]
Prorepensin (**199**)	*D. zenkeri*; *D. prorepens*; *Dorstenia picta* (Moraceae)	Cameroon	Twigs and leaves	[106]

l-(1β,2α)-di-(2,4-Dihydroxybenzoyl)-rel-(3β,4α)-di-(4-hydroxyphenyl)-cyclobutane	*A. africanus* (Liliaceae)	South Africa	Roots	[33]
Rhuschalcone 1 (**200**)	*Rhus pyroides* (Anacardiaceae)	Botswana	Twigs	[110]
Coumestan				
Sigmoidin J (**201**)	*E. sigmoidea* (Leguminoseae)	Cameroon	Root bark	[111]
Flavanols				
7-*O*-β-Xylopyranosyl-epicatechin (**202**)	*Guibourtia coleosperma* (Caesalpiniodeae)	Egypt	Bark	[112,113]
Beilschmieflavonoids A (**1**); B (**2**)	*B. zenkeri* (Lauraceae)	Cameroon	Stem bark	[10]
Epicatechin-(7,8-bc)-9β-(3-methoxy-4-acetoxyphenyl)-dihydro-2(3*H*)-pyranone (**203**); hepta-*O*-acetyl-7-β-xylopyranosyl-epicatechin (**204**); tetra-*O*-acetyl-tri-*O*-methyl-7-β-xylopyranosyl-epicatechin (**205**)	*G. coleosperma* (Caesalpiniodeae)	Egypt	Bark	[113]
Flavan				
(+)-7′,7′-Dimethyl-5-hydroxy-2*R*,3*S*-*trans*-pubeschin (**206**)	*Entandrophragma cylindricum*	Cameroon	Heartwood	[114]
Flavanones				
4′-*O*-Methylsigmoidin B (**207**)	*E. burttii* (Fabaceae)	Kenya	Root bark	[49]
5-Deoxyabyssinin II (**208**)	*E. abyssinica* (Fabaceae)	Kenya	Stem bark	$[\alpha]_D = 0°C$ [36]
7-Hydroxy-4′-methoxy-3′-(3-hydroxy-3-methyl-*trans*-but-1-enyl)-5′-(3-methylbut-2-enyl)flavanone (**42**)	*E. mildbraedii* (Fabaceae)	Cameroon	Root bark	[22]
Abyssinone V (**45**); abyssinone V methyl ether (**46**)	*E. burttii* (Fabaceae)	Kenya	Root bark	[49]
Abyssinone-IV-4′-*O*-methyl ether (**62**)	*E. mildbraedii* (Fabaceae)	Cameroon	Root bark	[22]
Dinklagin A (**209**)	*D. dinklagei* (Moraceae)	Cameroon	Twigs	[24]
Dorsmanins E (**210**); F (**211**); G (**212**); H (**213**)	*D. mannii* (Moraceae)	Cameroon	Twigs	[37,115]
Eriodictyol 7-*O*-sophoroside (**44**)	*G. alypum* (Globulariaceae) [48]	Morocco	Aerial parts	$[\alpha]_D^{20} = -35.6°$ [48]
Erylatissin C (**53**)	*E. latissima* (Fabaceae)	Botswana	Stem wood	[116]
Erythrisenegalone (**214**)	*Erythrina senegalensis*	Cameroon	Stem bark	mp 122−124°C [117]
Licoflavanone-4′-*O*-methyl ether (**61**)	*E. mildbraedii* (Fabaceae)	Cameroon	Root bark	[22]

(*Continued*)

Table 9.2 (Continued)

Class and Compounds	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Sigmoidins A (**51**); B (**52**)	*E. sigmoidea* (Fabaceae)	Cameroon	Stem bark	[53]
Tephrocandidins A (**59**); B (**60**)	*T. candida* (Fabaceae)	Cameroon	Aerial parts	[21]
Flavonols				
(2*S*,4*R*)-5,6,7-Trimethoxyflavan-4-ol (**37**); (2*S*,4*R*)-4,5,6,7-tetramethoxyflavan (**38**)	*B. zenkeri*(Lauraceae)	Cameroon	Stem bark	[10]
3,7,8,3′,4′-Pentahydroxyflavanone (**215**)	*Albizia adianthifolia* (Fabaceae)	South Africa	Wood	[118]
6,8-di-C-Methylquercetin-3,3′,7-trimethyl ether (**216**); 6,8-di-C-methylquercetin-3,3′-dimethyl ether (**217**); 6-C-methylquercetin-3-methyl ether (**218**)	*Piliostigma reticulatum* (Caesalpiniaceae)	South Africa	Leaves	[119]
6-Methoxykaempferol 7,4′-dimethylether 3-sulfate (**219**)	*Brickellia longifolia* (Asteraceae)	Egypt	Aerial parts	[120]
Dorsilurins C (**90**); F (**84**); G (**85**); I (**87**); J (**88**); K (**89**)	*D. psilurus* (Moraceae)	Cameroon	Twigs	[66]
Dorsmanin C (**91**)	*D. mannii* (Moraceae)	Cameroon	Twigs and leaves	[42]
Piliostigmol (**220**)	*P. reticulatum* (Caesalpiniaceae)	South Africa	Leaves	[119]
Flavones				
3′,4′,5,7-Tetrahydroxyflavone-3-glucoside (**221**)	*A. mearnsii* (Fabaceae)	South Africa	Leaves	[44]
3′,6,8,-Tri-C-methylquercetin-3,7-dimethyl ether (**222**)	*P. reticulatum* (Caesalpiniaceae)	South Africa	Leaves	[119]
5,7-Dihydroxy-3,6,4′-trimethoxy-3′-(4-hydroxy-3-methyl-but-2-enyl)flavone (**72**)	*D. viscosa* (Sapindaceae)	Cameroon	Aerial parts	[60]
6-Hydroxyluteolin 7-*O*-laminaribioside (**71**)	*G. alypum* (Globulariaceae) [48]	Morocco	Aerial parts	$[\alpha]^{20}_{D}$ −45.3° [48]
Dinklagin B (**223**); C (**224**)	*D. dinklagei* (Moraceae)	Cameroon	Twigs	[24]
Isoflavans				
(3*R*)-2,7-Dihydroxy-3′-(3-methylbut-2-enyl)-2‴,2‴-dimethylpyrano[5‴,6‴: 4′,5′]isoflavan (**104**)	*E. mildbraedii* (Fabaceae)	Cameroon	Root bark	[22]
Bolusanthol A (**225**)	*B. speciosus* (Fabaceae)	Botswana	Stem bark	[121]
Isoflavones				
7-*O*-Methylluteone (**226**)	*E. burttii* (Fabaceae)	Kenya	Stem bark	[35]

2,7-Dihydroxy-4′-methoxy-5′-(3-methylbut-2-enyl) isoflavone (**138**)	*E. mildbraedii* (Fabaceae)	Cameroon	Root bark	[22]
Isoflav-3-enes				
7,4′-Dihydroxy-2′,5′-dimethoxyisoflav-3-ene (**227**)	*E. abyssinica* (Fabaceae)	Kenya	Root bark	[35]
Bolusanthin III (**228**)	*B. speciosus* (Fabaceae)	Botswana	Root wood	[63]
Burttinol A (**100**); B (**101**); C (**102**)	*E. burttii* (Fabaceae)	Kenya	Root bark	[112]
Isoflavanones				
Bolusanthol B (**229**); C (**230**)	*B. speciosus* (Fabaceae)	Botswana	Stem bark	[121]
Eriotrichin B (**231**)	*Erythrina eriotricha* (Fabaceae)	Cameroon	Root bark	[113]
Lysisteisoflavanone (**232**)	*E. lysistemon* (Fabaceae)	Egypt	Stem bark	[69]
Isoflavene				
Dimethoxytrihydroxyisoflavene	*Baphia nitida* (Fabaceae)	Sierra Leone	Wood	[122]
Isoflavone				
4′,5′,7-Triacetoxy-2′-methoxyisoflavone (**233**); 4′,5′,7-trihydroxy-2′-methoxyisoflavone (**234**)	*Dalbergia nitidula* (Fabaceae)	South Africa	Heartwood	[113]
5,4′-Dimethoxy-3′-prenylbiochanin A (**235**)	*Erythrina eriotriocha* (Leguminoseae)	Cameroon	Stem bark	[123]
5-Deoxy-3′-prenylbiochanin A (**236**)	*E. sacleuxii* (Fabaceae)	Kenya	Root bark	mp 190−192°C [68]
8-Prenylluteone (**237**)	*Erythrina eriotriocha* (Fabaceae)	Cameroon	Stem bark	[124]
Eriotriochin (**238**)	*Erythrina eriotriocha* (Fabaceae)	Stem bark	Cameroon	[123]
Erylatissins A (**239**); B (**240**)	*E. latissima* (Fabaceae)	Botswana	Stem wood	[116]
Erysenegalenseins D (**241**); E (**242**); F (**243**); G (**244**); L (**245**); M (**246**)	*E. senegalensis* (Fabaceae)	Cameroon	Stem bark	[125]
Erythraddison A (**125**)	*E. addisoniae* (Fabaceae)	Cameroon	Root bark	[15]
Griffonianones A (**247**); B (**248**); C (**132**); D (**133**)	*M. griffoniana* (Fabaceae)	Cameroon	Root bark	[75,115]
Indicanine C (**249**)	*E. indica* (Fabaceae)	Cameroon	Root bark	mp 195°C [76]
Indicanines D (**139**); E (**250**)	*E. indica* (Fabaceae)	Cameroon	Stem bark	[70]
Isoerysenegalensein E (**251**)	*E. lysistemon* (Fabaceae)	Egypt	Stem bark	[69]
Isogancaonin C (**252**)	*B. speciosus* (Fabaceae)	Botswana	Root wood	[63]

(*Continued*)

Table 9.2 (Continued)

Class and Compounds	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Isosenegalensein (**253**)	*E. lysistemon* (Fabaceae)	Egypt	Stem bark	[69]
Kraussianones 1 (**254**); 2 (**255**); 3 (**256**); 4 (**257**); 5 (**258**)	*Eriosema kraussianum* N. E. Br (Papilionaceae)	South Africa	Roots	[126,127]
Lachnoisoflavones A (**136**); B (**137**)	*C. lachnophora* (Fabaceae)	Cameroon	Whole plant	[77]
Pentandrin (**259**); pentandrin glucoside (**260**)	*Ceiba pentandra* (Malvaceae)	Cameroon	Stem bark	[128]
Proanthocyanidins				
Epicatechin-(4β→8)-7-*O*-β-xylopyranosyl-epicatechin (**261**); dodeca-*O*-acetyl-epicatechin-(4β→8)-7-*O*-β-xylopyranosyl-epicatechin (**262**); hepta-*O*-acetyl-hexa-*O*-methyl-epicatechin-(4β→8)-7-*O*-β-xylopyranosyl-epicatechin (**263**)	*G. coleosperma* (Caesalpiniodeae)	Egypt	Bark	[113]
Pterocarpans				
3,4:8,9-Dimethylenedioxypterocarpan (**264**)	*T. aequilata* (Papilionaceae)	Kenya	Roots	mp 154−156°C [13]
3-Hydroxy-9-methoxy-10-(3,3-dimethylallyl) pterocapene (**265**)	*E. abyssinica* (Fabaceae)	Kenya	Root bark	[35]
Erythribyssin A (**157**); B (**158**); C (**159**); D (**173**); L (**172**); M (**174**); O (**171**)	*E. abyssinica* (Fabaceae)	Cameroon	Stem bark	[16,81]
Erythribyssin O (**171**)	*E. abyssinica* (Fabaceae)	Cameroon	Stem bark	[16]
Rotenoids				
6-Acetoxydihydrostemonal (**266**)	*Tephrosia pentaphylla* (Fabaceae)	Ethiopia	Leaves and roots	[129]
9-Demethyldihydrostemonal (**267**)	*T. pentaphylla* (Fabaceae)	Ethiopia	Pods	[129]
Dihydrostemonal (**268**)	*T. pentaphylla* (Fabaceae)	Ethiopia	Pods, leaves, and roots	[129]
Triflavoids				
Caloflavans A (**269**); B (**270**)	*O. calodendron* (Ochnaceae)	Cameroon	Leaves	[130]

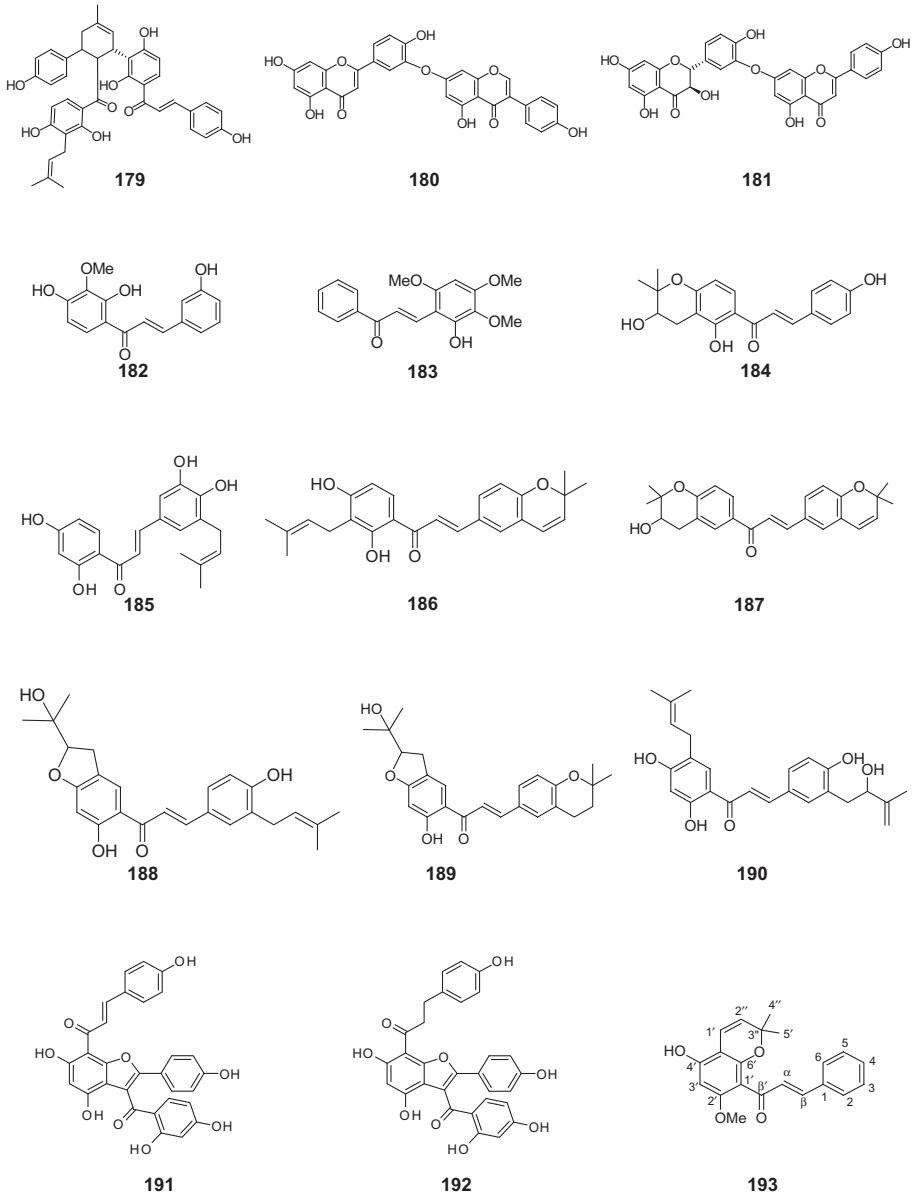


Figure 9.7 New flavonoids and related compounds identified in African plants: dorstenone (**179**); lophirone L (**180**); lophirone M (**181**); (*E*)-3,2′,4′-trihydroxy-3′-methoxychalcone (**182**); 2-hydroxy-3,4,6-trimethoxychalcone (**183**); 3′,4′-(3-hydroxy-2,2-dimethyldihydropyrano)-4,2′-dihydroxychalcone (**184**); 5-prenylbutein (**185**); angusticornin A (**186**); angusticornin C (**187**); bartericin B (**188**); bartericin C (**189**); bartericin D (**190**); calodenin A (**191**); calodenin B (**192**); cedreprenone (**193**); dihydrolophirone C (**194**);

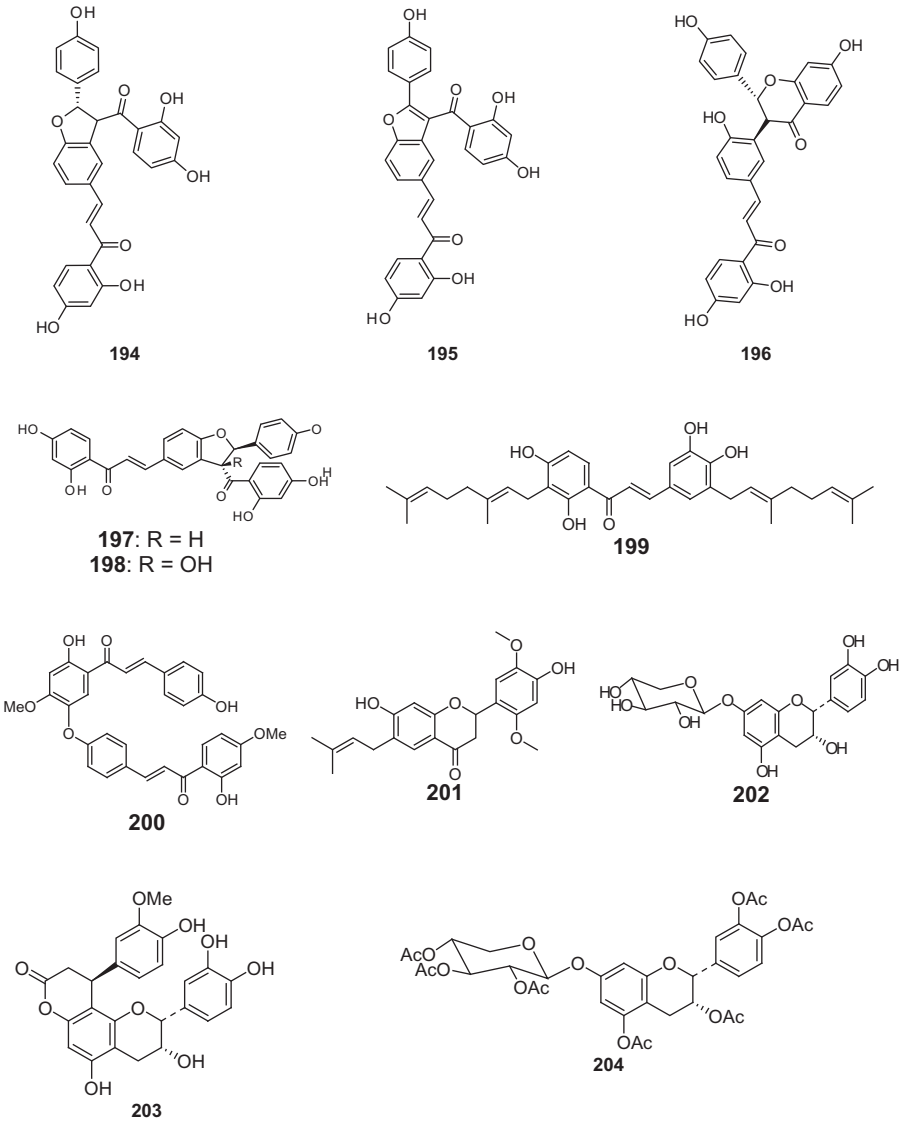
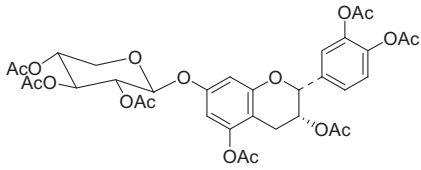


Figure 9.7 (Continued)

◀ isolophirone C (**195**); lophirone B (**196**); lophirone C (**197**); lophirone K (**198**); prorepensin (**199**); rhuschalcone 1 (**200**); sigmoidin J (**201**); 7-*O*-β-xylopyranosyl-epicatechin (**202**); epicatechin-(7,8-bc)-9β-(3-methoxy-4-acetoxyphenyl)-dihydro-2(3*H*)-pyranone (**203**); hepta-*O*-acetyl-7-β-xylopyranosyl-epicatechin (**204**); tetra-*O*-acetyl-tri-*O*-methyl-7-β-xylopyranosyl-epicatechin (**205**); (+)-7′,7′-dimethyl-5-hydroxy-2*R*,3*S*-*trans*-pubeschin (**206**); 4′-*O*-methylsigmoidin B (**207**); 5-deoxyabyssinin II (**208**); dinklagin A (**209**);



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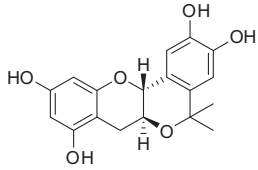

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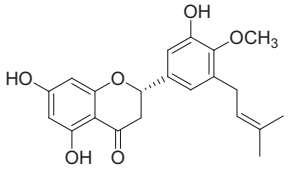

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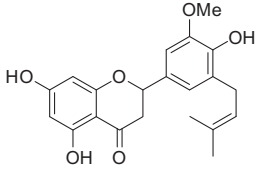

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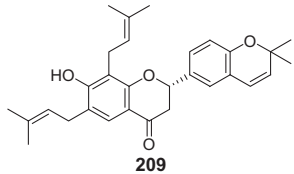

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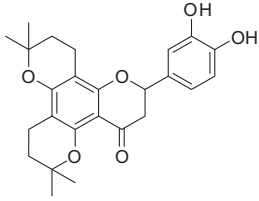

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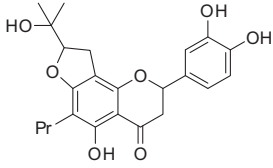

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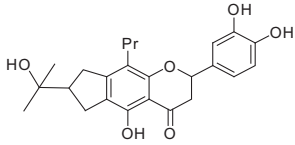

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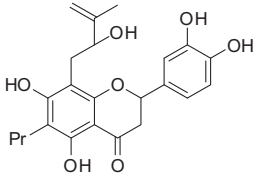

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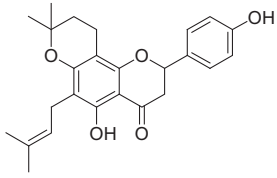

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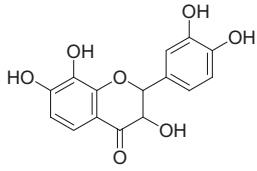

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Figure 9.7 (Continued)

◀ dorsmanin E (**210**); dorsmanin F (**211**); dorsmanin G (**212**); dorsmanin H (**213**); erythrisenegalone (**214**); 3,7,8,3′,4′-pentahydroxyflavanone (**215**); 6,8-di-C-methylquercetin-3,3′,7-trimethyl ether (**216**); 6,8-di-C-methylquercetin-3,3′-dimethyl ether (**217**); 6-C-methylquercetin-3-methyl ether (**218**); 6-methoxykaempferol 7,4′-dimethylether 3-sulfate (**219**); piliostigmol (**220**); 3′,4′,5,7-tetrahydroxyflavone-3-glucoside (**221**); 3′,6,8,-tri-C-methylquercetin-3,7-dimethyl ether (**222**); dinklagin B (**223**); dinklagin C (**224**);

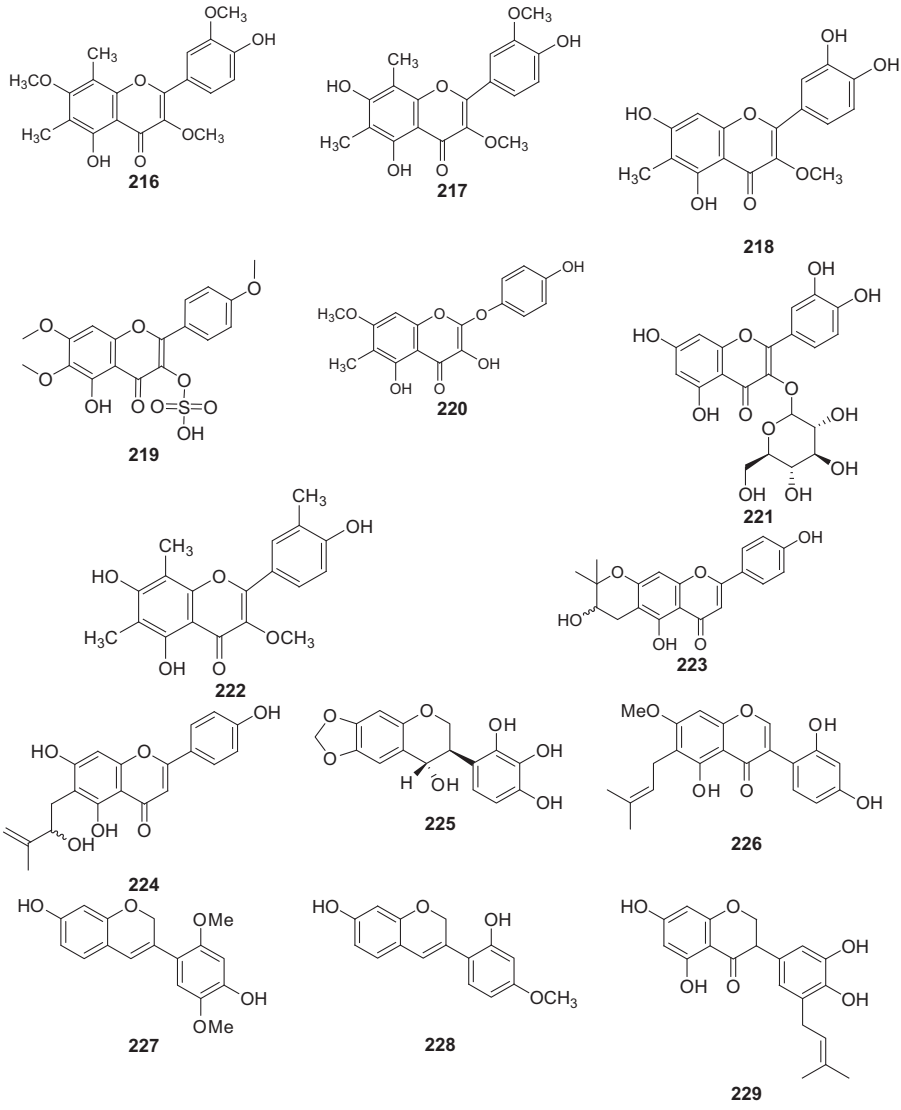


Figure 9.7 (Continued)

◀ bolusanthol A (**225**); 7-*O*-methylluteone (**226**); 7,4′-dihydroxy-2′,5′-dimethoxyisoflav-3-ene (**227**); bolusanthin III (**228**); bolusanthol B (**229**); bolusanthol C (**230**); eriotrichin B (**231**); lysisteisoflavanone (**232**); 4′,5′,7-triacetoxy-2′-methoxyisoflavone (**233**); 4′,5′,7-trihydroxy-2′-methoxyisoflavone (**234**); 5,4′-dimethoxy-3′-prenylbiochanin A (**235**); 5-deoxy-3′-prenylbiochanin A (**236**); 8-prenylluteone (**237**); eriotriochin (**238**); erylatissin A (**239**); erylatissin B (**240**); erysenegalensein D (**241**); erysenegalensein E (**242**); erysenegalensein

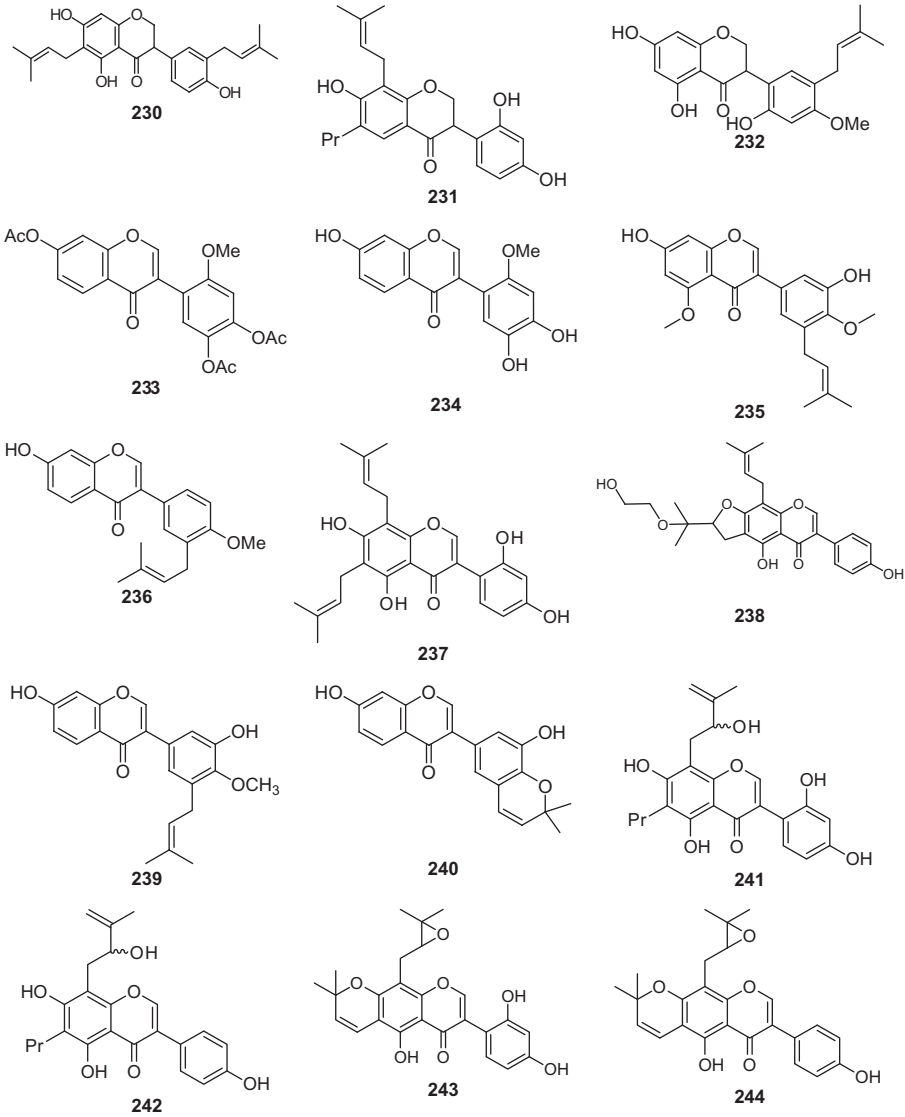
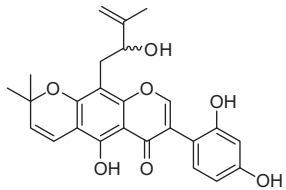


Figure 9.7 (Continued)

◀ F (**243**); erysenegalensein G (**244**); erysenegalensein L (**245**); erysenegalensein M (**246**); griffonianone A (**247**); griffonianone B (**248**); indicanine C (**249**); indicanine E (**250**); isoerysenegalensein E (**251**); isogancaonin C (**252**); isosenegalensein (**253**); kraussianone 1 (**254**); kraussianone 2 (**255**); kraussianone 3 (**256**); kraussianone 4 (**257**); kraussianone 5 (**258**); pentandrin (**259**); pentandrin glucoside (**260**); epicatechin-(4β→8)-7-*O*-β-xylopyranosyl-epicatechin (**261**); dodeca-*O*-acetyl-epicatechin-(4β→8)-7-*O*-



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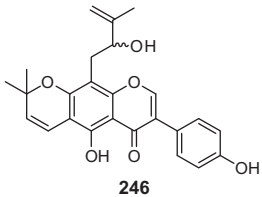

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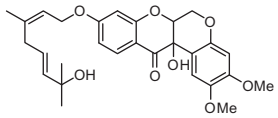

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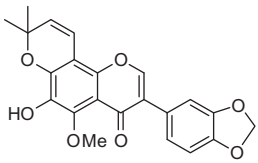

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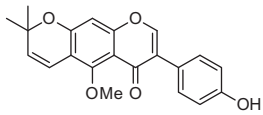

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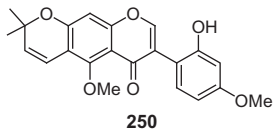

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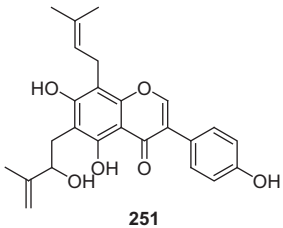

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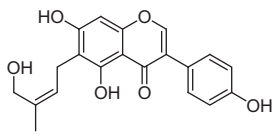

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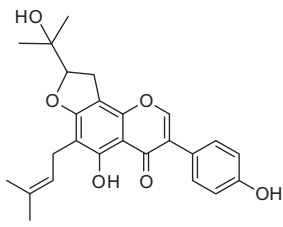

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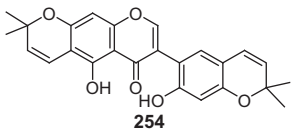

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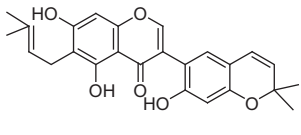

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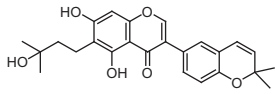

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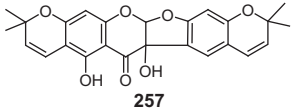

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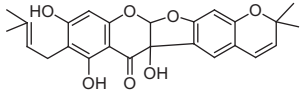

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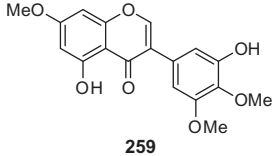

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Figure 9.7 (Continued)

◀ β-xylopyranosyl-epicatechin (**262**); hepta-*O*-acetyl-hexa-*O*-methyl-epicatechin-(4β→8)-7-*O*-β-xylopyranosyl-epicatechin (**263**); 3,4:8,9-dimethylenedioxypterocarpan (**264**); 3-hydroxy-9-methoxy-10-(3,3-dimethylallyl)pterocapene (**265**); 6-acetoxydihydrostemonal (**266**); 9-demethyldihydrostemonal (**267**); dihydrostemonal (**268**); caloflavan A (**269**); caloflavan B (**270**).

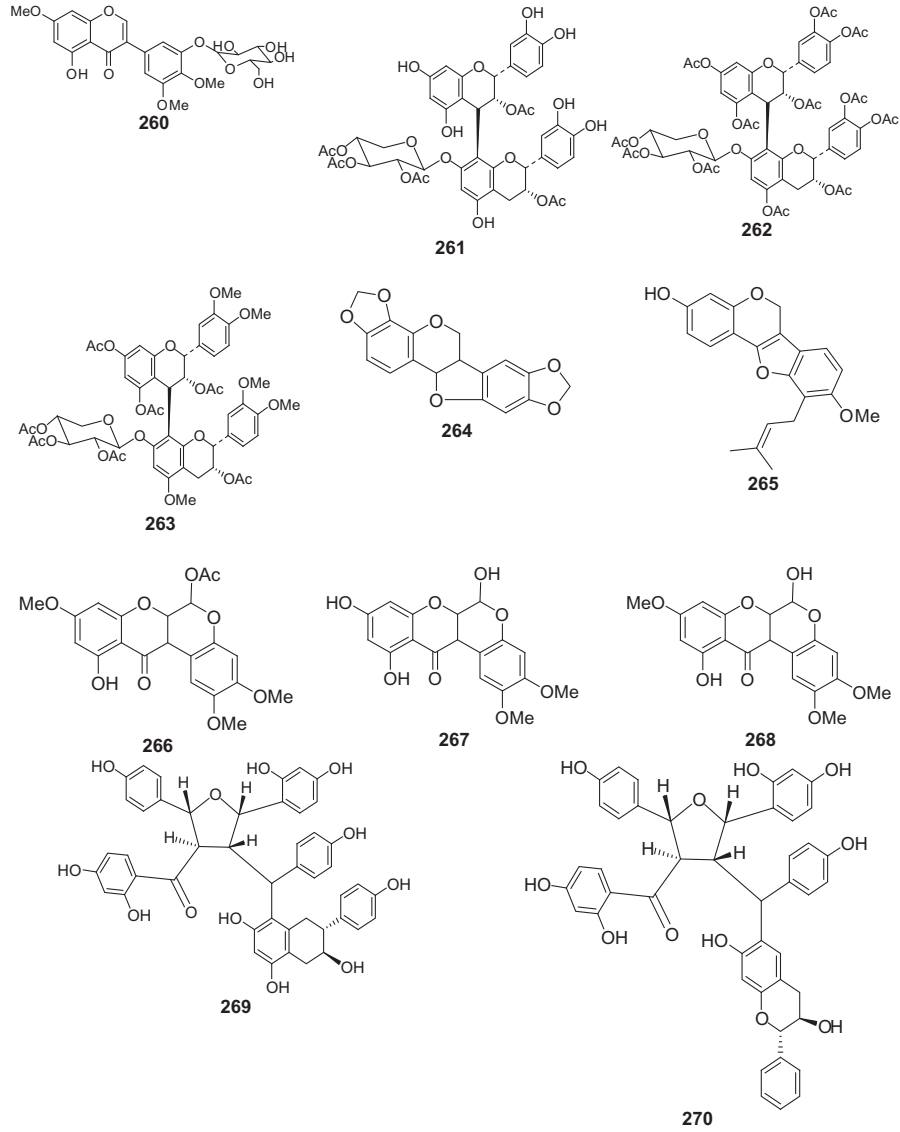

Figure 9.7 (Continued)

9.6 Conclusions

This chapter has given insights into the flavonoids identified in medicinal plants of Africa. It clearly shows the rich diversity of flavonoid structures in African plants and their enormous pharmacological activity. The most represented families include flavonoids of the family Moraceae such as isobavachalcone, 4-hydroxylonchocarpin, kanzonol C, and dorsilurin C.

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10 Quinones and Benzophenones from the Medicinal Plants of Africa

Kenneth O. Eyong[a], *Victor Kuete*[b,c] *and Thomas Efferth*[c]

[a]Department of Organic Chemistry, University of Yaounde 1, Yaounde, Cameroon, [b]Department of Biochemistry, University of Dschang, Dschang, Cameroon, [c]Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, University of Mainz, Mainz, Germany

10.1 Introduction

Quinones are secondary metabolites isolated principally from plants and having an aromatic (hexacyclic saturated) di-one or di-ketone system. They are generally derived from the oxidation of hydroquinones. Naturally occurring quinones are widely distributed and include benzoquinones, naphthoquinones, anthraquinones, and polyquinones [1–3].

1. Benzoquinones: These are groups of compounds containing two carbonyl groups on a saturated hexacyclic aromatic ring system (benzene ring), usually at *ortho* or *para* positions (monocyclic).
2. Naphthoquinones: These occur to some extent in fungi and are extremely common in higher plants; they contain the naphthalene nucleus with two carbonyl groups on one nucleus, usually at the *ortho* or *para* position (bicyclic).
3. Anthraquinones: These are common fungal metabolites and also occur in higher plants. They are compounds containing the anthracene nucleus with two carbonyl groups, usually on ring B at *para* positions (tricyclic).
4. Polyquinones: These are dimers of the different types of quinones. Some polyquinones are of mixed origin. Inter- or intramolecular oxidative coupling can occur with formation of carbon–carbon or carbon–oxygen bonds.

In naming quinones, preference is given to the carbonyl functions, and each is given the smallest possible number. This numbering applies mainly to benzo- and naphthoquinones. In anthraquinones, the two side rings (A and C) are numbered first, followed by the quinoid carbonyl groups. However, in the presence of a furano- or pyrano-ring system, these systems are numbered first, with the oxygen

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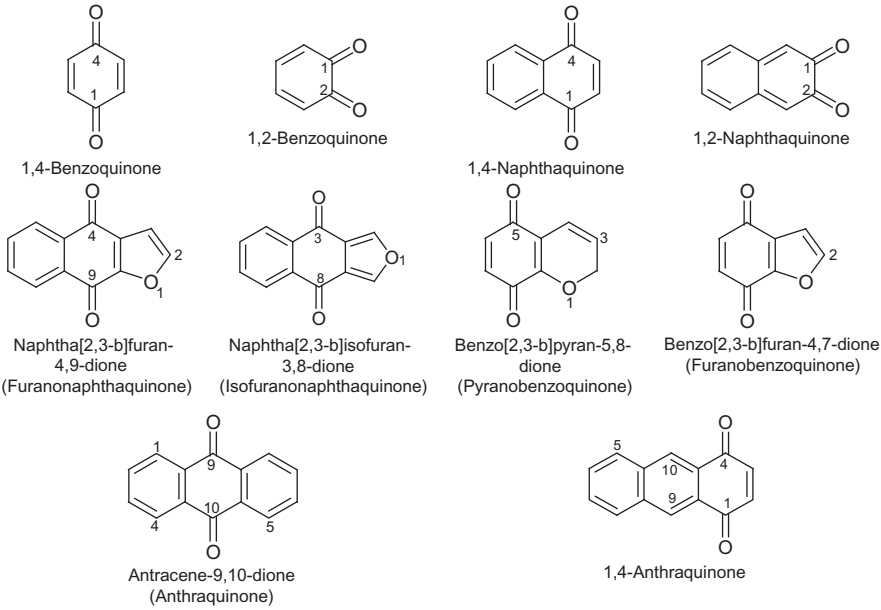
atom given preference. The compounds described below summarize the naming of quinones.



There are, however, several types of side chains in the quinoid nucleus, the majority of which are isoprenyl or multiple isoprenyl units called phytyl or derived phytyl, phenyl, terphenyl, or quinone units as in dimeric quinones.

In designating the length of side chains, the position of the side chain relative to the quinone nucleus is given first, followed by the naming of the side chain in parenthesis, and finally the quinone nucleus, as indicated in Figure 10.1.

On reduction, the 2-prenylquinones yield the corresponding hydroquinones, and each of these has an isomer formed by ring closure; these are known as chromenols and chromanols, respectively, as summarized in Scheme 10.1.

It should be noted that it is very difficult to exhaust the nomenclature of quinones since they constitute veritable vitamins and coenzymes; hence trivial names and even abbreviations are given to represent them. The corresponding hydroquinones, chromenols, and chromanols are named by replacing the suffix "quinon" with "quinol," "chromenol," and "chromanol," respectively.

Quinones exhibit numerous biological activities such as neurological, antibacterial, antiplasmodial, antioxidantal, trypanocidal, antitumor, and anti-HIV, and these activities have been proven to be related to the redox properties of their carbonyl functions [4,5]. The isoprenoid quinones—e.g., the ubiquinones—are essential metabolites, being involved in electron transport in living systems [6].

Quinones, in general, and naphthoquinones, in particular, are well known for antibacterial, antifungal, and antitumoral activities; lapachol (**3**) has been especially

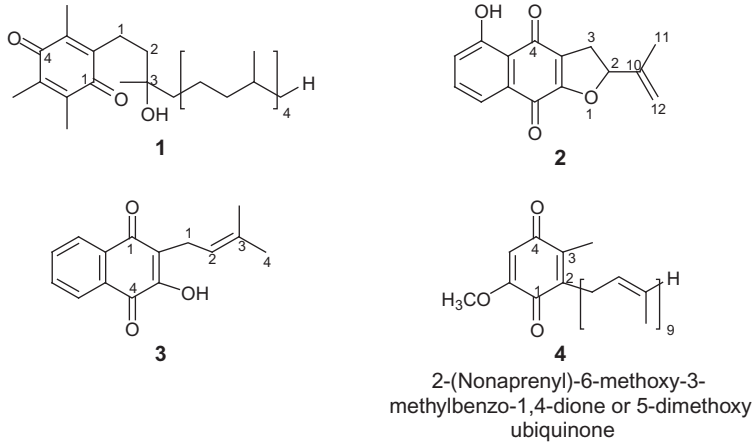
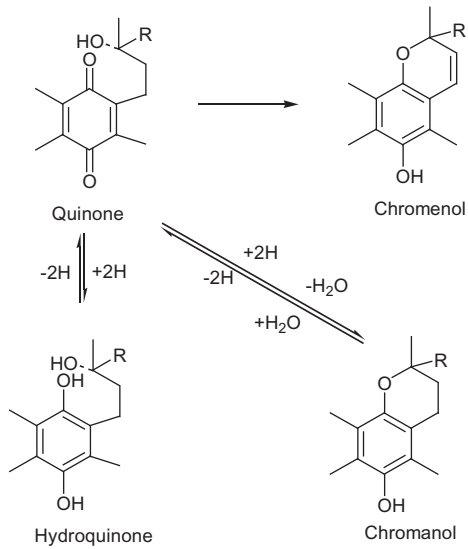


Figure 10.1 Nomenclature of quinones with side chain [1–3]: 2-(3-hdroxy-3,7,11,15-tetramethylhexadecanyl)-3,5,6-trimethylbenzo-1,4-dione or α-tocopherol quinone (**1**); 2-(1′-methylethenyl)-5-hydroxynaphtha[2,3-b]furan-4,9-dione or lapachone (**2**); 2-(3′-methyl-2-butenyl)-3-hydroxynaphtha-1,4-dione or lapachol (**3**); 2-(nonaprenyl)-6-methoxy-3-methylbenzo-1,4-dione or 5-dimethoxy ubiquinone (**4**).



Scheme 10.1 The interrelationships between quinones, hydroquinones, chromenols, and chromanols [2].

Table 10.1 Antifungal and Antibacterial Activities of Naphthoquinones and Reference Drugs from *N. laevis* [7]

Compounds and Reference Drugs (*)	*C. cucumerinum*	*C. albicans*	*B. subtilis*	*E. coli*
5-Hydroxy-dehydro-iso-α-lapachone (**5**)	0.02[a]	10[b]	1.25[b]	0.06[a]
Dehydro-iso-α-lapachone (**6**)	0.06[a]	20[b]	40[b]	0.2[a]
5-Methoxy-dehydro-iso-α-lapachone (**7**)	0.2	80[b]	40[b]	0.6[a]
7-Hydro-dehydro-iso-α-lapachone (**8**)	4	n.d.	10[b]	0.2[a]
5,7-Dihydroxy-dehydro-iso-α-lapachone (**9**)	0.01	10[b]	1.25[b]	0.1[a]
3-Hydroxy-dehydro-iso-α-lapachone (**10**)	0.1[a]	40[b]	20[b]	2[a]
2-Isopropenyl-8-hydroxynaphtho[2,3-b] furan-4,9-quinone (**11**)	0.2[a]	40[b]	1.25[b]	0.1[a]
Lapachol (**3**)	0.6[a]	n.d.	n.d.	2[a]
Propiconazole*	0.1[a]	n.d.	n.d.	n.d.
Amphotericin*	1[a]	1[b]	n.d.	n.d.
Chloramphenicol*	n.d.	n.d.	1[b]	0.1[a]

n.d. = MIC of compound not determined.
[a]Minimal amount (μg) of compound to inhibit growth on silica gel TLC plate.
[b]Minimal inhibition concentration MIC (μg/mL) of compound in agar-dilution assays.

widely tested in various pharmacological studies [7]. The antifungal and antibacterial activities of some naphthoquinones isolated from *Newbouldia laevis* (Table 10.1) have been documented against *Candida albicans*, *Cladosporium cucumerinum*, *Bacillus subtilis*, and *Escherichia coli* [7]. In spite of strong bioactivity, the medical use of naphthoquinones is limited. Owing to their supposed mechanisms of action, the compounds are likely to be toxic for all living organisms [7].

Novel phenyl anthraquinones and isofuranonaphthoquinones isolated from *Bulbine* spp. were found to exhibit antiparasitic and antioxidant properties [3], while polyhalogenated benzo- and naphthoquinones were found to be potent inhibitors of pure ureases from *Bacillus pasteurii* and *Canavalia ensiformis*. They also inhibited ureases in whole cells of *Helicobacter pylori*, *Klebsiella axytoca*, and *Proteus mirabilis* [8]. Juglone (**12**) is used against cutaneous infections, while lawsone (**13**), from henna, is used in tinting. Anthraquinones are antifungal, and some are used as purgatives. Some tetracyclic quinones have antitumoral properties.

10.2 Biosynthesis and Structural Diversity

10.2.1 Biosynthesis of Quinones

At least two pathways are known for the biosynthesis of quinones (anthraquinones) in higher plants: the acetate−malonate pathway and the shikimate or *o*-succinoyl benzoic acid (OSB) pathway [9−11].

10.2.1.1 Acetate–Malonate Pathway

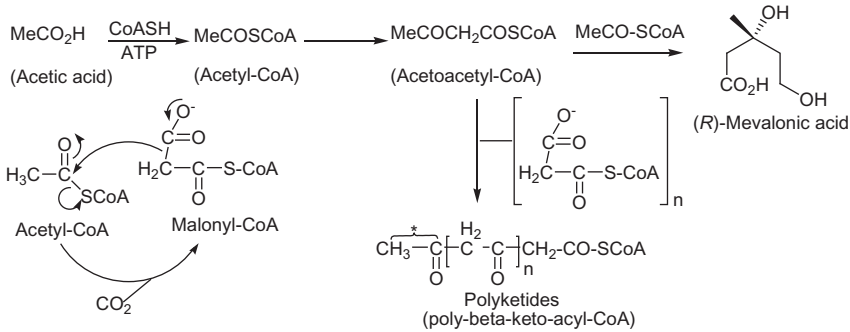
A very large number of natural products are derived by condensation of acetyl-coenzyme A, which itself is derived from acetate, with malonyl-CoA, which is generally derived by carboxylation of acetyl-SCoA. Three of these acetyl-SCoA units condense to form mevalonic acid in the acetate–malonate pathway. One of the principal pathways is one that proceeds by a "linear polyketide" chain that is subsequently modified by reduction and cyclization to produce fatty acids and derivatives or polyphenols. These are sometimes collectively called acetogenins (Scheme 10.2). The polyketide origin from acetate can be rationalized by the classic folding of a poly-β-keto chain [6].

Incorporation of [1-^{14}C] acetate into a polyketide metabolite gives labeling throughout the chain of alternate carbon atoms, which are, of course, the normally oxygenated ones. Labeled malonate, on the other hand, tends to label the second and successive acetate-derived units more heavily than the first, which derives directly from acetate and not from malonate. Because of this, the first acetate unit, called "starter" acetate, tends to be more heavily labeled by labeled acetate than the other units [6].

This differential labeling may be used to detect starter units, i.e., the acetate unit at the beginning of a polyketide chain. Incorporation of up to three deuterium atoms from [$^{2}H_3$] acetate on a methyl group in a metabolite similarly indicates starter acetate; malonate units can only have a maximum of two deuterium atoms. The assembly of poly-β-keto-acyl-CoA and subsequent modification yield the different quinones in stable form.

10.2.1.1.1 Tetraketides

Tetraketides are formed from four acetate/malonate units (four C_2 units) and involves open-chain compounds (compounds containing no carbon ring) and compounds containing carbon rings. Most tetraketides result from this mode of cyclization, often with subsequent modification of the initial aromatic product. Indeed, this is the largest class of polyketide-derived compounds and has probably

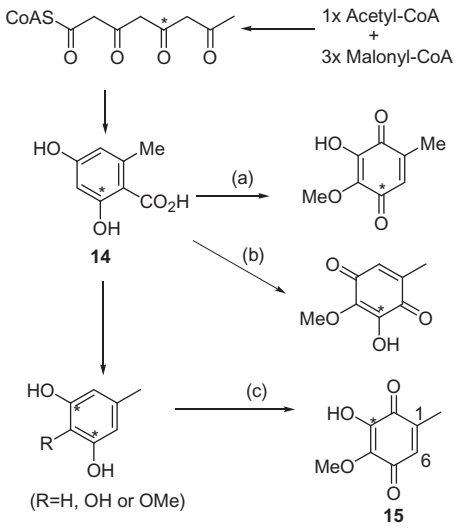


Scheme 10.2 Acetate–malonate pathway for the synthesis of polyketides [6].

received the greatest attention from the point of view of the biosynthesis and interrelationship of its members [9]. The majority of the quinones in this class are benzoquinones and their dimers. Orsellinic acid (6-methyl salicylic acid) (**14**) is the parent compound derived by this cyclization since it retains all the carbon and oxygen atoms of the polyketide precursor. Fumigatin (**15**) is an example of a quinone of tetraketide origin, as summarized in Scheme 10.3 [9].

10.2.1.1.2 Pentaketides

Pentaketides are five C_2 units and, like tetraketides, they involve various mode of cyclization, as shown in Figure 10.2. For the most part, naphthaquinones are obtained from pentaketides. Each structural unit could give rise to the observed oxygenation patterns. Examples include compounds **12** and **13** (Figure 10.3) [9].



Scheme 10.3 Alternative routes for the formation of fumigatin (**15**) from orsellinic acid (**14**) [6,9]. (*): As demonstrated by labeled experiments.

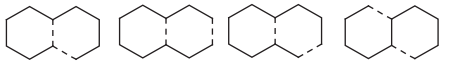


Figure 10.2 Alternative cyclizations of a pentaketide to give naphthaquinones [9].

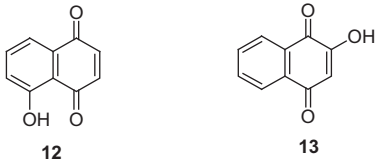


Figure 10.3 Chemical structures of juglone (**12**) and lawsone (**13**).

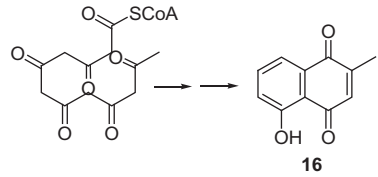
10.2.1.1.3 Hexaketides

Hexaketides are six C_2 units and are somewhat rare. Some of the compounds included in this group are tentatively classified by inspection of their structures without the support of tracer experiments and may belong elsewhere. An example is plumbagin (**16**) (Scheme 10.4) [9].

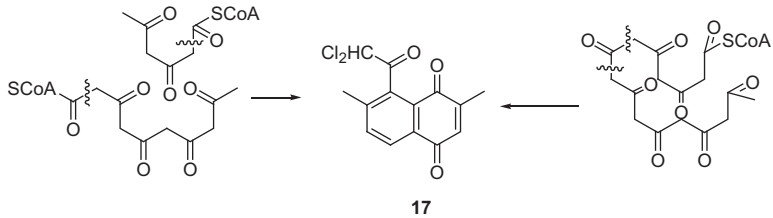
Another, and probably unique, pathway for the generation of the naphthaquinone skeleton is exemplified by mollisin (**17**), a secondary metabolite from the fungus *Mollisia caesia*. Mollisin may be derived from two distinct polyketide chains, where each of the terminal carbonyl groups is lost; however, an alternative and realistic scenario exists in which a carbonyl has been carved from the loop of a continuous polyketide chain folding back on itself, as summarized in Scheme 10.5 [10].

10.2.1.1.4 Heptaketides

Heptaketides are seven C_2 units. Marticin (**18**) (Figure 10.4), a naphthaquinone from *Fusarium martii*, provides a pathway for the generation of this structural



Scheme 10.4 Plumbagin (**16**), possibly derived from hexaketide.



Scheme 10.5 Mollisin (**17**), possibly derived from a hexaketide.

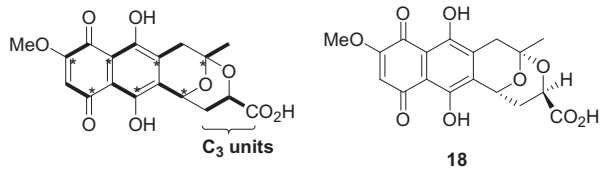
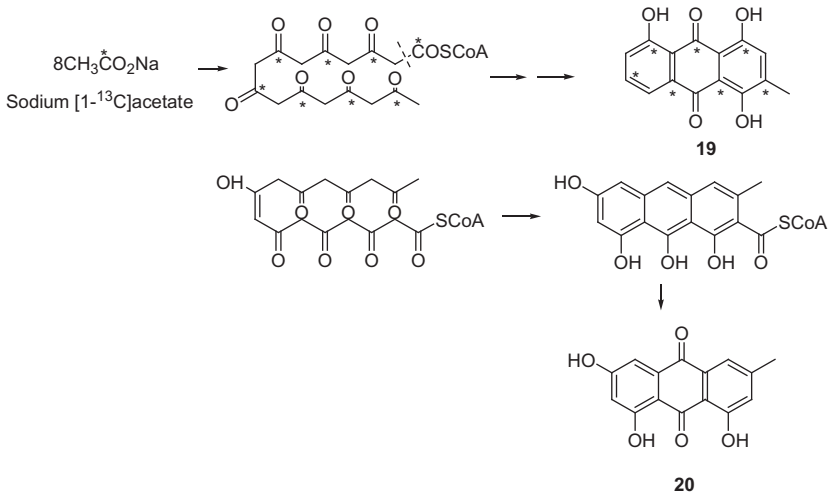


Figure 10.4 Marticin (**18**), possibly derived from a heptaketide [10]. (*): As demonstrated by labeled experiments.



Scheme 10.6 Islandicin (**19**) and emodin (**20**), possibly derived from an octaketide.

group. Marticin is of mixed biosynthetic origin, derived from a heptaketide and a C_3 unit from the citric acid cycle [10].

10.2.1.1.5 Octaketides

Octaketides are eight C_2 units, and the common structural type here are the anthraquinones and related compounds such as islandicin (**19**) [9] and emodin (**20**) [10], summarized in Scheme 10.6.

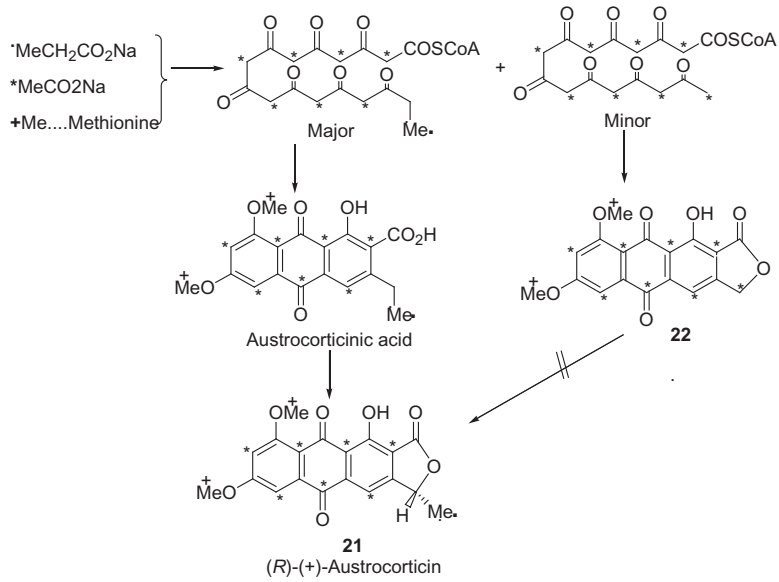
It has also been confirmed that most anthraquinone cometabolites arise by way of a conventional acetate-triggered octaketide pathway that must operate in the organism in tandem with the predominant propionate/methionine-initiated pathway, as demonstrated in the synthesis of austrocorticin (**21**) (Scheme 10.7) and noraustrocorticin (**22**) [12].

10.2.1.1.6 Nonaketides

Nonaketides are nine C_2 units, and there are relatively few nonaketides. The largest group comprises the aflatoxins and related compounds, though there is still some controversy over the origin of these compounds. Versicolin A (**23**) (Figure 10.5) and deoxyversicolin A (**24**) are examples of aflatoxins isolated from *Aspergillus versicolor* [9].

10.2.1.1.7 Decaketides

Decaketides are ten C_2 units and include the anthracyclines, which are a group of antibiotic gycosides produced by *Streptomyces* spp. The aglycone consists of an anthraquinone chromophore with a fourth (saturated) ring fused on; from a biosynthetic point of view, three main structural variations may be discerned. They include ε-pyrromycinone (rutilantinone) (**25**), β-rhodomycinone (**26**), and daunomycinone (**27**). Compound **25** has been shown to arise by the condensation of a propionyl with nine acetyl (malonyl) units, as shown in Scheme 10.8 [9].



Scheme 10.7 Acetate-triggered octaketide pathway in tandem with propionate−methionine pathway. (*): As demonstrated by labeled experiments.

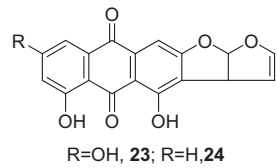
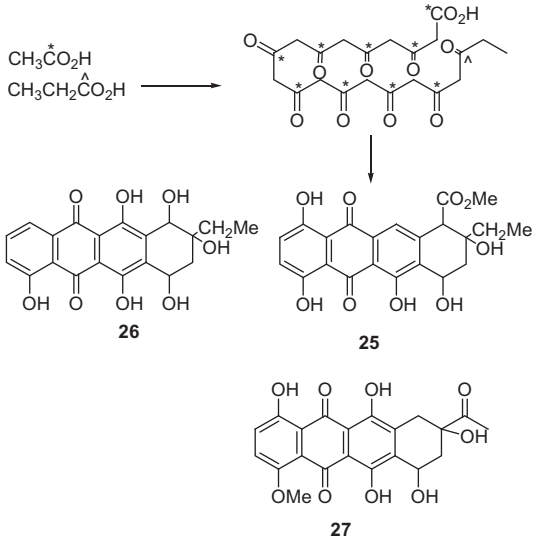


Figure 10.5 Chemical structures of versicolin A (**23**) and deoxyversicolin (**24**).

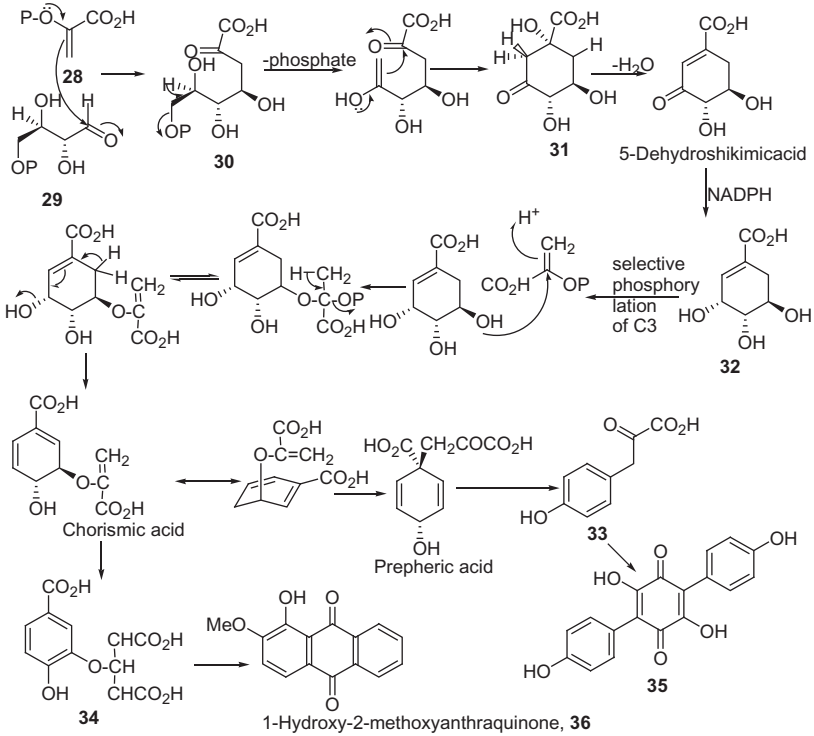
10.2.1.2 Shikimate Pathway

10.2.1.2.1 Shikimic Acid Pathway

A very large number of compounds show a C_6 aromatic−C_3 side chain. The biosynthesis of these compounds and/or precursors such as aromatic amino acids, L-phenylalanine, L-tyrosine, and L-tryptophan has been derived from shikimic acid—hence the shikimic acid pathway. This pathway has its origins in carbohydrate metabolism and involves the condensation of phosphoenol pyruvate (C_3 unit) (**28**) with a tetrose(D-erythrose-4-phosphate) (**29**) to yield 3-deoxy-D-arabinoheptulosonic acid (DAHP) (**30**), a seven-carbon sugar. This undergoes an aldol cyclization to dehydroquinic acid (**31**), which is then transformed into shikimic acid (**32**). The shikimic acid in turn undergoes selective phosphorylation of a C_3 unit to give *p*-OH-phenylpyruvic acid (**33**) and *O*-succinoyl benzoic acid (**34**), which have been found to be the source of terphenyl quinones (**35**) and anthraquinones (**36**), as summarized in Scheme 10.9 [6,11].



Scheme 10.8 Incorporation of acetate and propionate into ε-pyrromycinone (**25**). (*): As demonstrated by labeled experiments.



Scheme 10.9 The shikimic acid pathway.

10.2.1.2.2 Shikimic–α-Ketoglutaric Acids Pathway

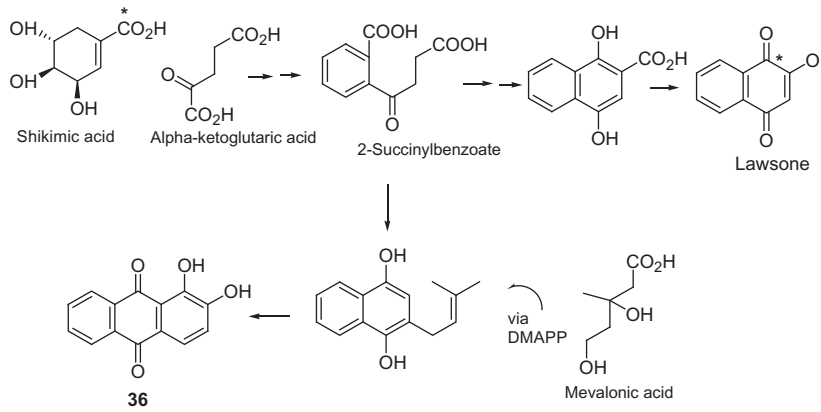
In higher plants, an alternative and predominant pathway to anthraquinones involves shikimic and α-ketoglutaric acids and dimethyl allyl pyrophosphate (DMAPP), derived from mevalonic acid. The orange pigment alizarin (**36**), from *Rubia tinctorum* L. (madder plant), is a well-known example, and its biosynthesis has been studied in detail [6,10], as shown in Scheme 10.10.

10.2.1.2.3 Quinones Derived from Shikimate and Mevalonate Pathway

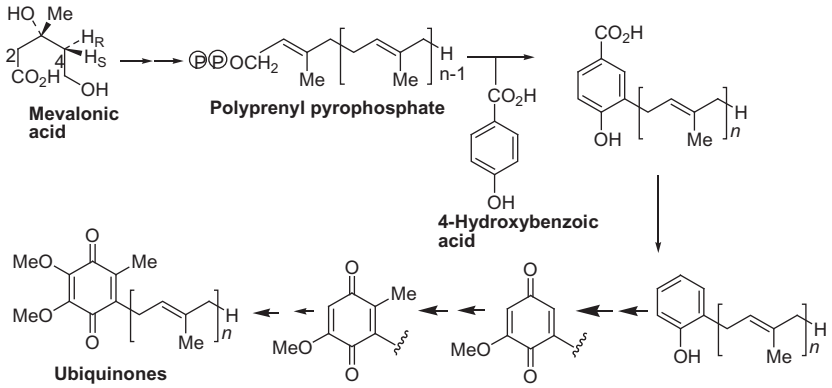
The isoprenoid quinines, including ubiquinones, plastoquinones, and tocopherols, make up a large group of metabolites, being involved in electron transport in living systems. Mevalonic acid is well established as the source of polyprenyl side chains in these metabolites. It is probable that the side chain is assembled as a polyprenyl pyrophosphate, which then couples the aromatic fragment from shikimic acid. In the ubiquinones, a particular chain length is favored, from $n = 6$ in certain microorganisms to $n = 10$ in most mammals [6]. Ubiquinones are found in bacteria and are involved in redox reactions in these organisms (Scheme 10.11).

Plastoquinones (**38**) (Figure 10.6) and tocopherols (**39**) are biosynthesized only in higher plants and algae; they differ from ubiquinones in having a variety of side chain modifications, and they function in photosynthetic electron transport [6]. They include methyl substituents on the quinone ring instead of methoxy groups, as seen in the ubiquinones.

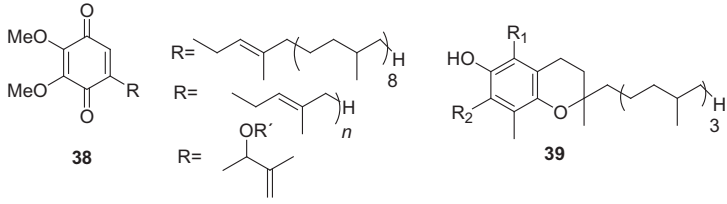
Alpha-tocopherol is the main active principle of vitamin E (β- and γ-tocopherols are also present but are less potent). Vitamin E (**39**) deficiency is associated with muscular disorders in animals but not in humans. It is associated with the maintenance of sexual potency. Compound **39** is possibly biosynthesized as shown in Figure 10.7 [6]. Phylloquinones [vitamins K_1 (**40**) and K_2 (**41**)] are produced in higher plants and are essential for blood clotting (Figure 10.8).



Scheme 10.10 Possible biosynthetic pathway for the synthesis of alizarin (**36**).



Scheme 10.11 The shikimic acid and mevalonate pathway.



(**39**) where, $R^1=R^2$ =Me ; α-tocopherol; R^1=Me R^2 =H ; β-tocopherol; R^1=H R^2 =Me ; γ-tocopherol

Figure 10.6 Chemical structures of plastoquinones (**38**) and tocopherols (**39**).

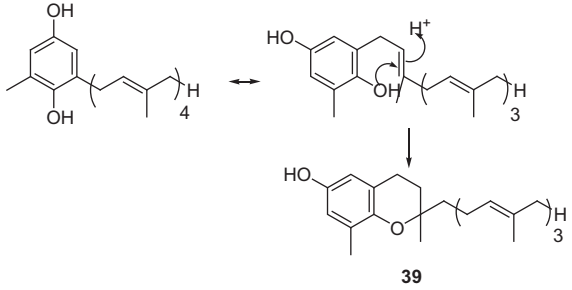


Figure 10.7 Possible biosynthetic pathway of vitamin E (**39**).

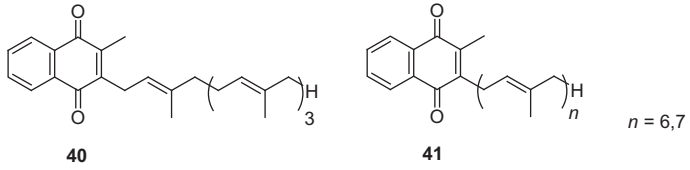


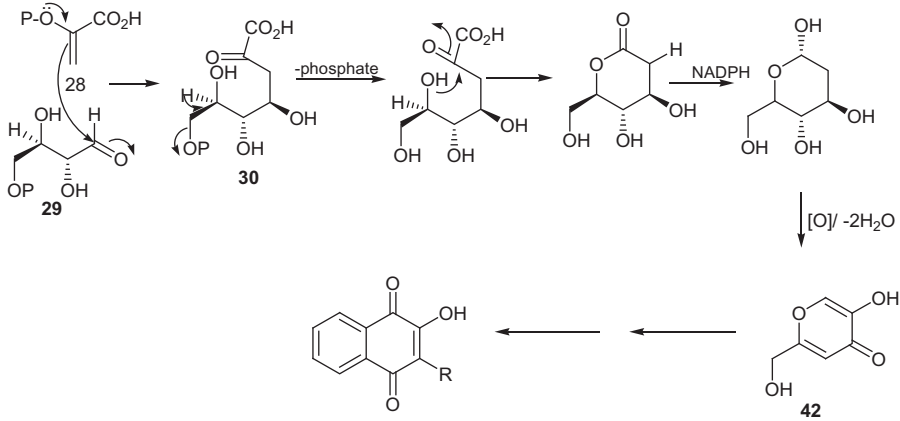
Figure 10.8 Chemical structures of vitamins K_1 (**40**) and K_2 (**41**).

10.2.1.3 Kojic Acid Pathway

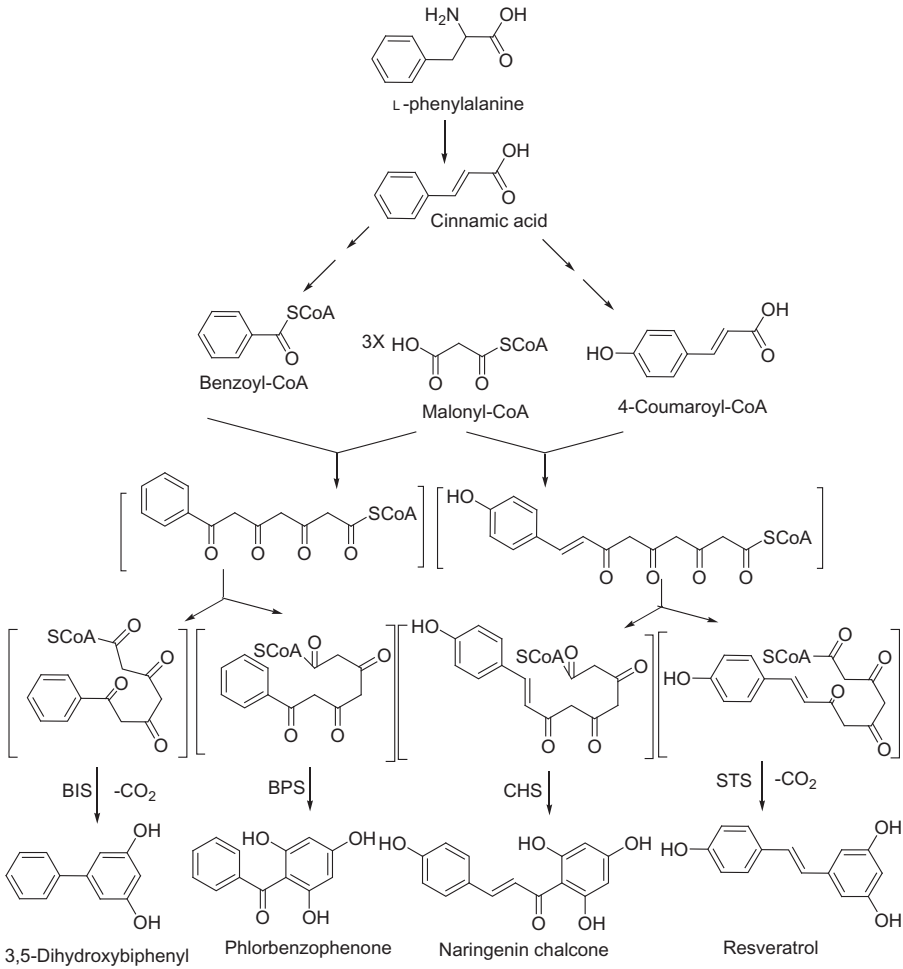
Kojic acid (**42**) (Scheme 10.12), a fungal metabolite whose structure was unambiguously confirmed by single-crystal X-ray studies, was isolated for the first time from the African plant *Kigelia africana* and is a possible intermediate in the shikimic acid (**32**) pathway [6,11]. This is a key pathway in the biosynthesis of quinones, suggesting that kojic acid is a possible taxonomic marker in the biogenesis of the quinone skeleton. This pathway involves the condensation of phosphoenol pyruvate (C_3 unit) (**28**) with a tetrose (D-erythrose-4-phosphate) (**29**) to yield DAHP (**30**), a seven-carbon sugar. The seven-carbon sugar undergoes intramolecular condensation and subsequent dehydration to yield compound **42**. Further investigation is needed for the conversion of **42** to naphthoquinones.

10.2.2 Biosynthesis of Benzophenones

Benzophenone is an example of a group of secondary metabolites derived from type III polyketide synthases (PKSs) generated by varying the starter substrate, the number of condensation reactions, and the mechanism of ring closure. Among the starter substrates, benzoyl-CoA is a rare starter molecule. Benzophenone synthase (BPS) catalyzes the formation of identical linear tetraketide intermediates from benzoyl-CoA and three molecules of malonyl-CoA via intramolecular cyclization reactions to form 2,4,6-trihydroxybenzophenone. The functionally diverse PKSs, which include biphenyl synthase (BIS), BPS, stilbene synthase (STS), and the ubiquitously distributed chalcone synthases (CHSs), form separate clusters, which originate from a gene duplication event prior to the speciation of the angiosperms (Scheme 10.13) [13]. Polyprenylated benzophenone derivatives with bridged polycyclic skeletons are widely distributed in the Clusiaceae (Guttiferae). Xanthones are regioselectively cyclized benzophenone derivatives.



Scheme 10.12 The kojic acid pathway (R = isoprene or alkyl unit).



Scheme 10.13 Reactions catalyzed by type III polyketide synthases and biogenic relationship of their starter substrates.

10.3 Quinones and Benzophenones Isolated from African Medicinal Plants

10.3.1 Naphthoquinones

Naphthaquinones form a group of compounds, the majority of which occur in the plant kingdom. Most natural furanonaphthaquinones obtained from plants are presumably derived from lapachol (**3**), the main constituent of the family Bignoniaceae [1]. A summary of some naphthaquinones that have been obtained from African medicinal plants is presented in Table 10.2 and Figure 10.9.

Table 10.2 Naphthaquinones from Some African Medicinal Plants

Compounds	Plants (Family)	Parts
Lapachol (**3**)	*N. laevis* (Bignoniaceae)	Roots [7,14] and stem bark [15]
5-Hydroxy-dehydro-iso-α-lapachone (**5**)* Dehydro-iso-α-lapachone (**6**)* 5-Methoxydehydro-iso-α-lapachone (**7**)* 7-Hydroxydehydro-iso-α-lapachone (**8**)* 5,7 or 6,8-Dihydroxydehydro-iso-α-lapachone (**9**)* 3-Hydroxydehydro-iso-α-lapachone (**10**)* 5-Hydroxy-7-methoxydehydroiso-α-lapachone (**43**)* 3,7-Dihydroxydehydroiso-α-lapachone (**44**) 6-Hydroxydehydro-iso-α-lapachone (**45**)* 3-Hydroxy-8-methoxydehydro-iso-α-lapachone or 3-hydroxy-5-methoxydehydro-iso-α-lapachone (**46**)*	*N. laevis* and *Markhamia stipulata* (Bignoniaceae)	Root bark [1,14,16] and stem bark [17]
2-Acetyl-5-hydroxynaphtha[2,3-b]furan-4,9-dione (**47**)* 2-Acetylfuronaphthoquinone (Figure 10.9 (**48**))* 2-Acetyl-7-methoxylfuronaphthoquinone (**49**) 2-Acetyl-7-methoxylfuronaphthoquinone (**50**)*	*N. laevis* (Bignoniaceae), *K. africana* (Bignoniaceae) and *Millettia versicolor* (Fabaceae)	Root bark [1,14,16] and stem bark [18]
2-(1′-Methylethenyl)-naphtha[2,3-b]furan-4,9-dione (**51**)* 2-(1′-Methylethenyl)-7-hydroxynaphtha[2,3-b]-furan-4,9-dione (**52**)* 2-(1′-Methylethenyl)-5-hydroxynaphtha[2,3-b]-furan-4,9-dione (**53**)* 2-Isopropenyl-8-hydroxynaphtho[2,3-b] furan-4,9-quinone (**11**)	*N. laevis* (Bignoniaceae)	Root bark [1,14,16] and stem bark [17,18]
Dehydro-α-lapachone (**54**)	*M. stipulata* (Bignoniaceae)	Stem bark [15]
β-Lapachone (**55**)	*M. stipulata* (Bignoniaceae)	[15]
α-Lapachone (**56**) 9-Hydroxy-α-lapachone (**57**) Kigelinone (**58**)*, 2-(1-hydroxyethyl)naphtho [2,3-b]furan-4,9-dione (**59**)* 2,3-Dihydro-2-(1-hydroxyethyl)naphtho[2,3-b] furan-4,9-dione (**60**)*	*K. africana* (Bignoniaceae)	[17,19]
Avicequinone D (**61**)* Avicequinone C (**62**)* Avicequinone E (**63**)* Stenocarpoquinone B (**64**)	*Mendoncia cowanii* (Fabaceae)	Stem and roots [20]

(*Continued*)

Table 10.2 (Continued)

Compounds	Plants (Family)	Parts
Plumbagin (**16**)	*D. crassiflora* and *D. canaliculata* (Ebenaceae)	Roots [21]
7-Methyljuglone (**65**)* 5-Hydroxy-3,6-dimethoxy-2-methylnaphthalene-1,4-dione (**66**)* 5,8-Dihydroxy-3-methoxy-2-methylnaphthalene-1,4-dione (**67**)* 3-Hydroxy-5,6-dimethoxy-2-methylnaphthalene-1,4-dione (**68**)	*E. natalensis* (Ebenaceae) and *Aloe secundiflora* (Aloeaceae)	Roots [22−24]
Diospyrin (**69**)* Isodiospyrin (**70**)* Mamegakinone (**71**)* Neodiospyrin (**72**)*	*E. natalensis* (Ebenaceae)	Roots [25,26]
Crassiflorone (**73**)* Diospyrone (**74**)*	*D. canaliculata* and *D. crassiflora* (Ebenaceae)	Stem bark [27,28]
Canaliculatin (**75**)* Cyclocanaliculatin (**76**)*	*D. canaliculata* (Ebenaceae)	[28,29]
Pycnanthuquinone C (**77**)*	*Pycnanthus angolensis* (Myristicaceae)	Stem bark [30]
Pentalongin (**78**)* Psychorubrin (**79**)*	*Pentas longiflora* and *Pentas lanceolata* (Rubiaceae)	Stem [31]
(3α,3′α,4β,4′β)-3,3′-Dimethoxy-*cis*-[4,4′-bis(3,4,5,10-tetrahydro-1*H*-naphtho[2,3−c]pyran)]-5,5′,10,10′-tetraone (**80**)*	*P. longiflora* (Rubiaceae)	Roots [32]

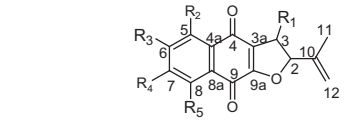
*Novel derivatives.

10.3.2 Benzoquinones

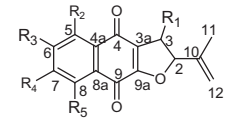
Benzoquinones are tetraketides derived by the cyclization of 6-methyl salicylic acid (**14**) since it retains all the carbon and oxygen atoms of the polyketide precursor. A summary of some of the benzoquinones that have been obtained from some African medicinal plants is presented in Table 10.3 and Figure 10.10.

10.3.3 Anthraquinones

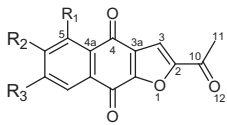
Anthraquinones are formed mainly via the acetate and the shikimic acid pathways. In some cases, plant anthraquinones may derive from 2-succinylbenzioc acid (Scheme 10.7). A summary of some of the anthraquinones that have been obtained from some African medicinal plants is presented in Table 10.4 and Figure 10.11.



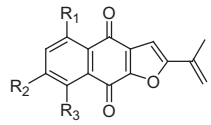
5: $R_1=R_3=R_4=R_5=H$, $R_2=OH$
6: $R_1=R_2=R_3=R_4=R_5=H$
7: $R_1=R_3=R_4=R_5=H$; $R_2=OCH_3$
43: $R_1=R_3=R_5=H$; $R_2=OH$; $R_4=OMe$
44: $R_1=OH$; $R_2=R_3=R_4=H$; $R_5=OH$



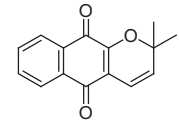
8: $R_1=R_2=R_3=R_5=H$; $R_4=OH$
9: $R_1=R_3=R_5=H$; $R_2=R_4=OH$
10: $R_2=R_3=R_4=R_5=H$; $R_1=OH$
45: $R_1=R_2=R_4=R_5=H$; $R_3=OH$
46: $R_3=R_4=R_5=H$; $R_1=OH$; $R_2=OCH_3$



47: $R_1=OH$; $R_2=R_3=H$
48: $R_1=H$; $R_2=R_3=H$
49: $R_1=R_2=H$; $R_3=OMe$
50: $R_1=R_3=H$; $R_2=OMe$



51: $R_1=R_2=R_3=H$
52: $R_1=R_3=H$; $R_2=OH$
53: $R_1=R_2=H$; $R_3=OH$



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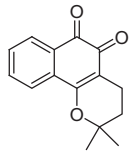

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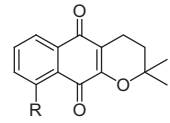
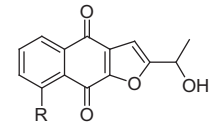
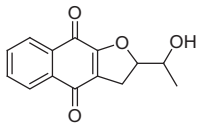


56: R=H
57: R=OH



58: R=OH
59: R=H



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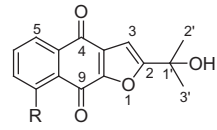
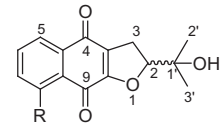
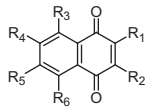


61: R=OH
62: R=H

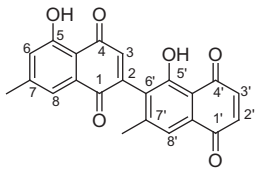


63: R=OH
64: R=H

Figure 10.9 Chemical structures of naphthaquinones from some African medicinal plants [(*): new derivative]: 5-hydroxy-dehydro-iso-α-lapachone (**5***); dehydro-iso-α-lapachone (**6***); 5-methoxydehydro-iso-α-lapachone (**7***); 7-hydroxydehydro-iso-α-lapachone (**8***); 5,7 or 6,8-dihydroxydehydro-iso-α-lapachone (**9***); 3-hydroxydehydro-iso-α-lapachone (**10***); 5-hydroxy-7-methoxydehydroiso-α-lapachone (**43***), 3,7-dihydroxydehydroiso-α-lapachone (**44***); 6-hydroxydehydro-iso-α-lapachone (**45***); 3-hydroxy-8-methoxydehydro-iso-α-lapachone or 3-hydroxy-5-methoxydehydro-iso-α-lapachone (**46***); 2-acetyl-5-hydroxynaphtha[2,3-b]furan-4,9-dione (**47***); 2-acetylfuronaphthoquinone (**48***); 2-acetyl-7-methoxylfuronaphthoquinone (**49**); 2-acetyl-7-methoxylfuronaphthoquinone (**50***); 2-(1′-methylethenyl)-naphtha[2,3-b]furan-4,9-dione, (**51***); 2-(1′-methylethenyl)-7-hydroxynaphtha[2,3-b]-furan-4,9-dione (**52***); 2-isopropenyl-8-hydroxynaphtho[2,3-b]furan-4,9-quinone (**53**); dehydro-α-lapachone (**54**); β-lapachone (**55**); α-lapachone (**56**); 9-hydroxy-α-lapachone (**57**); kigelinone (**58***); 2-(1-hydroxyethyl)naphtho [2,3-b]furan-4,9-dione (**59***); 2,3-dihydro-2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-dione (**60***); avicequinone D (**61***); avicequinone C (**62***); avicequinone E (**63***); tenocarpoquinone B (**64**); 7-methyljuglone (**65***); 5-hydroxy-3,6-dimethoxy-2-methylnaphtha-lene-1,4-dione(**66***); 5,8-dihydroxy-3-methoxy-2-methylnaphthalene-1,4-dione (**67***); 3-hydroxy-5,6-dimethoxy-2-methylnaphthalene-1,4-dione (**68**); diospyrin (**69***); isodiospyrin (**70***); mamegakinone (**74***); neodiospyrin (**72***); crassiflorone (**73***); diospyrone (**74***); canaliculatin (**75***); cyclocanaliculatin (**76***); pycnanthuquinone C (**77***); pentalongin (**78***); psychorubrin (**79***); (3α,3′α,4β,4′β)-3,3′-dimethoxy-*cis*-[4,4′-bis(3,4,5,10-tetrahydro-1*H*-naphtho[2,3−c]pyran)]-5,5′,10,10′-tetraone (**80***).



65: $R_1=R_2=R_3=R_4=H$; $R_5=Me$; $R_6=OH$
66: $R_1=R_4=OMe$; $R_2=Me$; $R_3=OH$; $R_5=R_6=H$
67: $R_1=OMe$; $R_2=Me$; $R_3=R_6=OH$; $R_5=R_4=H$
68: $R_1=OH$; $R_2=Me$; $R_3=R_4=OMe$; $R_5=R_6=H$



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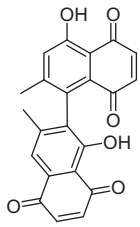

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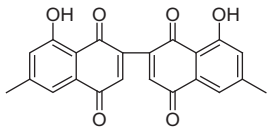

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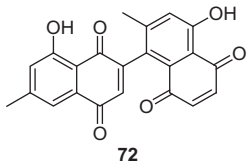

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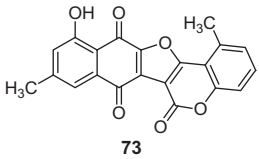

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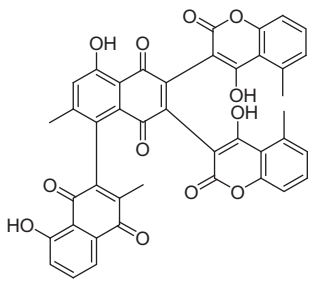

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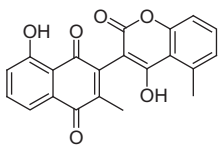

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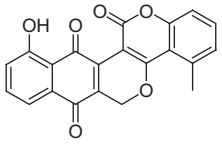

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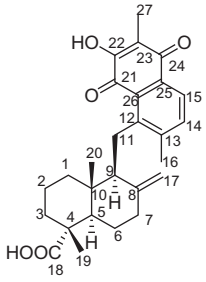

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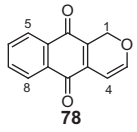

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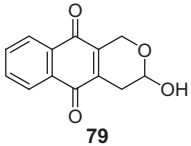

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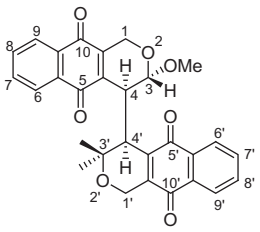

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Figure 10.9 (Continued)

Table 10.3 Benzoquinones from Some African Medicinal Plants

Compounds*	Plants(Family)	Parts
2,3-Dimethoxy-1,4-benzoquinone (**81**) 2,6-Dimethoxy-1,4-benzoquinone (**82**)	*N. laevis* (Bignoniaceae)	Stem bark [21,33]
2-Methyl-6-(-3-methyl-2-butenyl)benzo-1,4-quinone (**83**)* 3-Hydroxy-2-methyl-5-(3-methyl-2-butenyl)benzo-1,4-quinone (**84**)*	*Gunnera perpensa* (Gunneraceae)	Stem/leaves [34,35]
Rapanone (**85**) 6,6′-Biembelin (**86**)	*Myrsine africana* and *Maesa lanceolata* (Myrsinaceae)	Fruits [35−37]
7β-Methoxyabieta-8,13-diene-11,12-dione-(20,6β)-olide or rosmaquinone A (**87**)* 7α-Methoxyabieta-8,13-diene-11,12-dione-(20,6β)-olide or rosmaquinone B (**88**)*	*Rosmarinus officinalis* L. (Lamiaceae)	Aerial parts [38]
Royleanonic acid (**89**) Methylvilangin (**90**)*	*M. africana* and	
M. lanceolata (Myrsinaceae) Vilangin (**91**) Lanciaquinone (**92**)*		Fruits [37]
Methylanhydrovilangin (**93**)*	*M. africana* and *M. lanceolata* (Myrsinaceae)	Fruits [37]
2,5-Dihydroxy-3-(nonadec-14-enyl)-1,4-benzoquinone (**94**)* Maesaquinone (**95**) 2,5-Dimethoxymaesaquinone (**96**)		

*Novel derivative.

10.4 Benzophenones Identified in African Medicinal Plants

A few benzophenones were isolated from African plants (Table 10.5 and Figure 10.12), among which some were new derivatives.

10.4.1 Pharmacological Activity of Quinones Identified in African Medicinal Plants

Several quinones identified in African plants showed a wide range of biological activities. The most studied of such compounds include lapachol (**3**), plumbagin (**16**), 7-methyljuglone (**77**), and emodin (**20**).

Plumbagin (**16**) is a naphthoquinone recorded in the National Cancer Institute (NCI) database as a cytotoxic compound [21]. This compound displayed antiproliferative activity on a panel of 60 cancer cell lines recorded in the NCI database, with a mean $\log_{10}(IC_{50})$ value of −5.708 [21]. The molecular target (MT) of **16**, recorded in

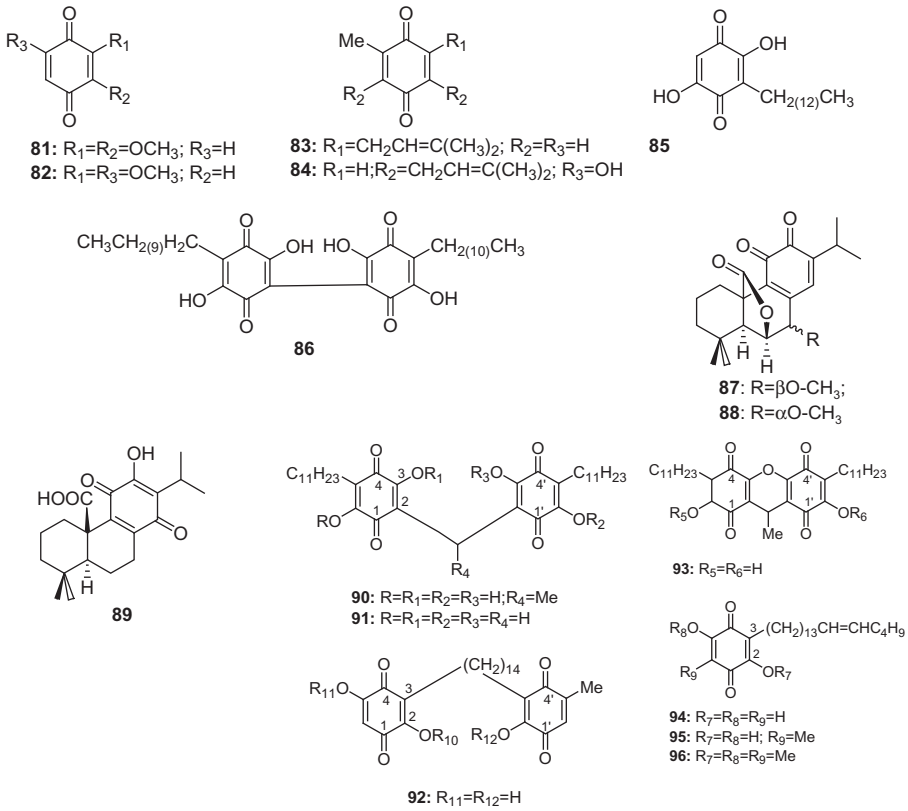


Figure 10.10 Chemical structures of benzoquinones from some African medicinal plants [(*): novel derivative]: 2,3-dimethoxy-1,4-benzoquinone (**81**); 2,6-dimethoxy-1,4-benzoquinone (**82**); 2-methyl-6-(-3-methyl-2-butenyl)benzo-1,4-quinone (**83***); 3-hydroxy-2-methyl-5-(3-methyl-2-butenyl)benzo-1,4-quinone (**84***); rapanone (**85***); 6,6′-biembelin (**86**); 7β-methoxyabieta-8,13-diene-11,12-dione-(20,6β)-olide (rosmaquinone A) (**87***); 7α-methoxyabieta-8,13-diene-11,12-dione-(20,6β)-olide (rosmaquinone B) (**88***); royleanonic acid (**89**); methylvilangin(**90***); vilangin (**91**); lanciaquinone (**92***); methylanhydrovilangin (**93***); 2,5-dihydroxy-3-(nonadec-14-enyl)-1,4-benzoquinone (**84***); maesaquinone (**95**); 2,5-dimethoxymaesaquinone (**96**).

the NCI database with the identification number MT9906, was determined as DNA (methylation of CpG sites -47.48-49 in the ARHGF12 gene) [21]. The function of the ARHGF12 gene is the regulation of RhoA GTPase by guanine nucleotide-binding alpha-12 (GNA12) and alpha-13 (GNA13); guanine nucleotide exchange factor (GEF) for RhoA GTPase; and GTPase-activating protein (GAP) for GNA12 and GNA13 [21]. However, plumbagin, identified in the Cameroonian plants *Diospyros crassiflora* and *Diospyros canaliculata*, was suggested as a promising anticancer lead drug [21].

Table 10.4 Anthraquinones from Some African Medicinal Plants

Compounds	Plants (Family)	Parts
2-Methylanthraquinone or tectoquinone (**97**) Rubiadin (**98**) Rubiadin-1-methyl ether (**99**) Nordamnacanthal (**100**) Damnacanthal (**101**) Lucidin-ω-methyl ether (**102**) Damnacanthol (**103**)	*N. laevis* (Bignoniaceae), *P. longiflora* and *P. lanceolata* (Rubiaceae)	Roots [31,39]
5,6-Dihydroxydamnacanthol (**104**)	*P. longiflora* and *P. lanceolata* (Rubiaceae)	Roots [39]
Tithoniaquinone A (**105**)*	*N. laevis* (Bignoniaceae)	Stem [40]
Aloeemodine (**106**)*	*C. nigricans* (Fabaceae)	Stem [21]
Emodin (**20**) Citreorosein (**107**) Emodic acid (**108**)	*C. nigricans* (Fabaceae)	[21,41]
Chrysophanol (**109**) Chrysophanol-8-methyl ether (**110**) Helminthosporin (**111**) Isoxanthorin (**112**) Emodin (**20**) Physcion (**113**) Asphodelin or 4,7′-bichrysophanol (**114**)* Aloesaponarin I (**115, 138**) Aloesaponarin II (**116, 139**) Laccaic acid D-methyl ester (**117**) Deoxyerythrolaccin (**118**)	*Aloe* spp. (Aloeaceae)	Roots [42,43]
Knipholone (**119**)* 4′-*O*-Demethylknipholone-4′-β-D-glucopyranoside (**120**)* 4′-*O*-Demethylknipholone (**121**)* Isoknipholone (**122**)* Knipholone-6′-methyl ether (**123**)* Gaboroquinone A (**124**)* Gaboroquinone B (**125**)*	*Kniphofia foliosa*, *Bulbine frutescens*, *Bulbine capitata* (Asphodelaceae)	Roots [44−47]
Sodium *ent*-knipholone 6′-*O*-sulfate (**126**)* Sodium 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside 6′-*O*-sulfate (**127**) 4′-*O*-Demethylknipholone 6′-*O*-sulfate (**128**) Sodium isoknipholone 6′-*O*-sulfate (**129**)	*B. frutescens* (Asphodelaceae)	Roots [45]
Rhein (**130**, **153**) Chrysophanol (**131**) Islandicin (**132**) Aloe-emodin (**133**) Aloe-emodin acetate (**134**)	*Kniphofia* spp. (Asphodelaceae), *Vismia laurentii* De Wild and *Vismia rubescens* (Guttiferae),	Roots [21,48−51] and leaves and stems [52]

(*Continued*)

Table 10.4 (Continued)

Compounds	Plants (Family)	Parts
Emodin (**20**) Physcion (**113**) 1,8-Dihydroxy-6-methoxy-3-methylanthraquinone (**135**) Chrysazin (**136**) 3-Methoxy-chrysazin (**137**)	*Xyris semijisata* (Xyridaceae)	
1,6,7-Trihydroxy-3-methoxy-8-methyl-anthraquinone (**138**) 1-Hydroxy-3,6,7-trimethoxy-8-methyl-anthraquinone (**139**) 1,3,6-Trihydroxy-8-methyl-anthraquinone (**140**) 1-Hydroxy-3,6-dimethoxy-8-methyl-anthraquinone (**141**) 1,6-Dihydroxy-3-methoxy-8-methyl-anthraquinone (**142**) 1,6-Dihydroxy-3-methoxy-8-methyl-anthraquinone-7-carboxylic acid (**143**)	*Gladiolus psittascinus* (Iridaceae)	[53]
Scutianthraquinones A (**144**)*, B (**145**)*, C (**146**)*, and D (**147**)* Aloesaponarin I (**148**)*	*Scutia myrtina* (Rhamnaceae)	Bark [54]
10-Hydroxy-10-(physcion-7′-yl)-chrysophanol anthrone (**149**)*	*Senna didymobotrya* (Fabaceae)	Pods [54]
5,10-Dihydroxy-2-methyl-9-(physcion-7′-yl)-l,4-anthraquinon (**150**)*	*S. didymobotrya* (Fabaceae)	[54]
(*P*)-8,9,1′,8′-Tetrahydroxy-3,3′-dimethyl [10,7′-bianthracene]-1,4,9′,10′-tetraone (trivial name abyquinone A)* (**151**)	*B. abyssinica* (Asphodelaceae)	Fruits [55]
(10*R*)-1,4,8,10,8′-Pentahydroxy-3,3′-dimethyl-[10,7′-bianthracene]-9,9′,10′(10*H*)-trione (trivial name abyquinone B (**152**)*	*B. abyssinica* (Asphodelaceae)	Fruits [55]
Emodin (**20**) Chrysophanol (**131**) Physcion (**113**)	*Rumex* spp. (Polygonaceae)	Roots [56]
6,7-Dimethoxyxanthopurpurin (**153**)* 6-Hydroxy-7-methoxy rubiadin (**154**)* 5-Hydroxy-6-hydroxymethyl anthragallol 1,3-dimethyl ether (**155**)* 7-Carboxy anthragallol 1,3-dimethyl ether (**156**)* Anthragallol L-methyl ether 3-*O*-D-glucopyranoside (**157**)* Anthragallol L-methyl ether 3-*O*-rutinoside (**158**)*	*Galium sinaicum* (Rubiaceae)	Roots [57]

(*Continued*)

Table 10.4 (Continued)

Compounds	Plants (Family)	Parts
Anthragallol 3-*O*-rutinoside (**159**)*		
Alizarin L-methyl ether 2-*O*-primeveroside (ruberythric acid 1-methylether) (**160**)*		
6-Hydroxy anthragallol-1,3-dimethyl ether (**161**)		
7-Hydroxy-methylanthragallol 1,3-dimethyl ether (**162**)		
7-Methylanthragallol 1,3-dimethyl ether (**163**)*	*Cassia obtusifolia* (Leguminosae), *G. sinaicum* and *R. tinctorum* (Rubiaceae)	Roots [51,58,59]
7-Methylanthragallol 2-methyl ether (**164**)*		
6-Methylanthragallol 3-methyl ether (**165**)*		
8-Hydroxyanthragallol 2,3-dimethyl ether (**166**)*		
7-Formylanthragallol 1,3-dimethyl ether (**167**)*		
Copareolatin 5,7-dimethyl ether (**168**)*		
Copareolatin 6,7-dimethyl ether (**169**)*		
6-Methoxylucidin ω-ethyl ether (**170**)*		
6-Hydroxyxanthopurpurin (**171**)*		
Quinizarin (**172**)		
2-Methylquinizarin (**173**)		
Alizarin 2-methyl ether (**174**)		
Lucidin ω-ethyl ether (**175**)		
Soranjidiol (**176**)		
Anthragallol 2-methyl ether (**177**)		
Copareolatin 6-methyl ether (**178**)		
7-Methyl-8-hydroxyanthragallol 1,3-dimethyl ether (**179**)		
7-Hydroxymethylanthragallol-1,3-dimethyl ether (**180**)		
10,2′-bi(9-Hydroxy-3-methyl-l,4-anthraquinonyl) or bisinaiquinone (**181**)*	*G. sinaicum* (Rubiaceae)	Roots [58,60]
Alizarin l-methyl ether (**182**)		
Anthragallol 1,3-dimethyl ether (**183**)		
2,6-Dihydroxy-1,3-dimethoxyanthraquinone (**184**) *		
6-(or 7) Hydroxymethylanthragallol-1,3-dimethyl ether (**185**)*		
Aloin (**186**)	*Aloe* spp. (Aloeaceae)	[61]
Laurentiquinones A (**187**)*, B (**188**)*, and C (**189**)*	*V. laurentii* (Guttiferae)	Fruits [62]
Zenkequinones A (**190**) and B (**191**)*	*Stereospermum zenkeri* (Guttiferae)	[50,63]
Sterequinone F (**192**)*		

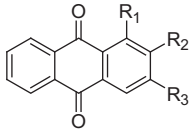
(*Continued*)

Table 10.4 (Continued)

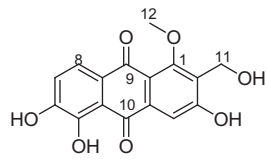
Compounds	Plants (Family)	Parts
Vismiaquinone C (**193**)*	*V. laurentii* De Wild (Guttiferae)	[64,65]
Vismiaquinone (**194**)		
3-Geranyloxy-6-methyl-1,8-dihydroxy anthraquinone (**195**)		
Madagascol (**196**)*	*Harungana madagascariensis* (Hypericaceae)	Stem bark [64−66]
Vismiaquinone B (**197**)*		
Madagascin (**198**)*		
1,8-Dihydroxy-6-methoxy-3-methylanthraquinone (**199**)		
Febrifuquinone (**200**)*	*Psorospermum febrifugum*; *Psorospermum adamauense* (Guttiferae)	Roots [67]
Laurenquinones A (**201**)* and B (**202**)*	*V. laurentii*(Guttiferae)	Stem, roots [68]
Kengaquinone (**203**)*	*H. madagascariensis* (Hypericaceae)	Stem bark [65]
Araliorhamnones A (**204**)*, B (**205**)*, and C (**206**)*	*Araliorhamnus vaginata* H. Perr (Rhamnaceae)	Bark [69]
Newbouldiaquinone (**207**)	*N. laevis* (Bignoniaceae)	Roots [70]
Newbouldiaquinone A (**208**)		

*Novel derivative.

The naphthoquinone (**3**) was also documented as a potent inhibitor of HaCaT cell growth [74]. In addition, compound **16**, along with the naphphthoquinone (**3**), diospyrin (**81**), 7-methyljuglone (**77**), and neodiospyrin (**84**), were identified as more highly active among the antimicrobial compounds isolated in African medicinal plants, with minimal inhibitory concentration values below 10 μg/mL on most of the studied microorganisms [22,75,76]. Their antibacterial and antifungal inhibitory effects were better than or close to that of gentamicin and nystatin on most of the tested microbial species, making them good candidates for antimicrobials from natural sources. McGaw et al. [26] reported antimycobacterial activities with MIC below 10 μg/mL for **77**, **81**, and **84**, all derived from South African medicinal plants, good values compared to those of the antituberculosis drugs ethambutol, isoniazid, and rifampicin. High antimycobacterial activities (MIC <10 μg/mL) against *Mycobacterium tuberculosis* and antigonorrheal (against *Neisseria gonorrhoeae*) effects have also been reported for naphthoquinones such as crassiflorone (**85**) and diospyrone (**86**), isolated from *Diospyros* species collected in Cameroon, against *M. tuberculosis* and *Mycobacterium smegmatis* [27]. The naphthoquinones (**16**), (**77**), and 2-acetylfuro-1,4-naphthoquinone (**59**), as well as the anthraquinones vismiquinone C (**193**), newbouldiaquinone (**207**), and newbouldiaquinone A (**208**) displayed antimicrobial activity against multidrug resistant (MDR) bacteria expressing active efflux pumps, including various phenotypes



97: R_1=R_3=H; R_2=Me
98: R_1=R_3=OH; R_2=Me
99: R_1=OMe; R_2=Me; R_3=OH
100: R_1=R_3=OH; R_2=CHO
101: R_1=OMe; R_2=CHO; R_3=OH
102: R_1=R_3=OH; R_2=CH_2OCH_3
103: R_1=OMe; R_2=CH_2OH; R_3=OH



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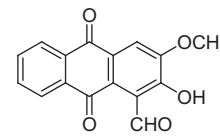

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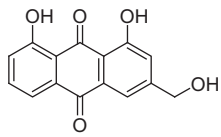

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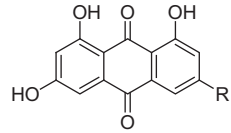
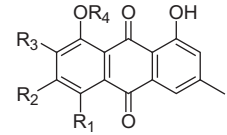
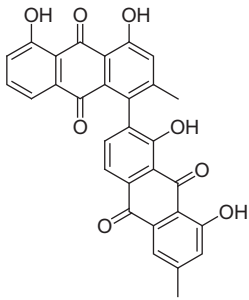


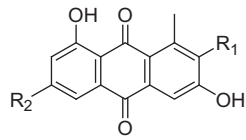
107: R=CH_2OH
108: R=COOH



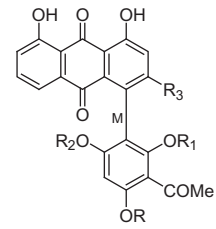
109: R_1=R_2=R_3=R_4=H
110: R_1=R_2=R_3=H; R_4=Me
111: R_1=OH; R_2=R_3=R_4=H
112: R_1=OH; R_2=H; R_3=OMe; R_4=H
113: R_1=H; R_2=OMe; R_3=R_4=H



114

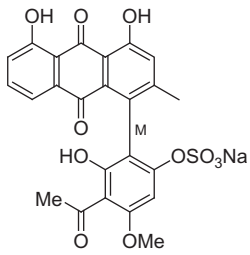


115: R_1=CO_2Me; R_2= H
116: R_1=R_2= H
117: R_1=CO_2Me; R_2=OH
118: R_1=H; R_2=OH

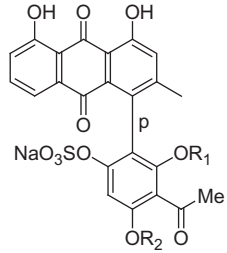


119: R=Me; R_1=H; R_2=H; R_3=Me
120: R= D-Glu; R_1=H; R_2=H; R_3=Me
121: R=H; R_1=H; R_2=H; R_3=Me
122: R=H; R_1=Me; R_2=H; R_3=Me
123: R=Me; R_1=H; R_2=Me; R_3=Me
124: R=H; R_1=Me; R_2=H; R_3=CH_2OH
125: R=Me; R_1=H; R_2=H; R_3=CH_2OH

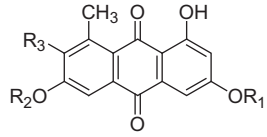
Figure 10.11 Chemical structures of anthraquinones from some African medicinal plants [(*): novel derivative]: 2-methylanthraquinone or tectoquinone (**97**); rubiadin (**98**); rubiadin-1-methyl ether (**99**); nordamnacanthal (**100**); damnacanthal (**101**); lucidin-ω-methyl ether (**102**); damnacanthol (**103**); 5,6-dihydroxydamnacanthol (**104**); tithoniaquinone A (**105***); aloeemodine (**106***); citreorosein (**107**); emodic acid (**108**); chrysophanol (**109**); chrysophanol-8-methyl ether (**110**); helminthosporin (**111**); isoxanthorin (**112**); physcion (**113**); asphodelin or 4,7′-bichrysophanol (**114***); aloesaponarin I (**115**); aloesaponarin II (**116**); laccaic acid D-methyl ester (**117**); deoxyerythrolaccin (**118**); knipholone: (**119***); 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside (**120***); 4′-*O*-demethylknipholone (**121***); isoknipholone (**122***); knipholone-6′-methyl ether (**123***); gaboroquinones A (**124***) and B (**125***); sodium *ent*-knipholone 6′-*O*-sulfate (**126***); sodium 4′-*O*-demethylknipholone-



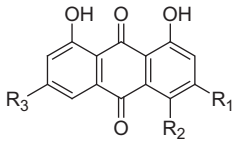
126



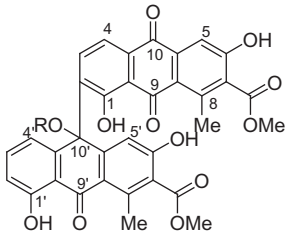
127: R_1=H; R_2= Glu
128: R_1=H; R_2=H
129: R_1=Me; R_2=H



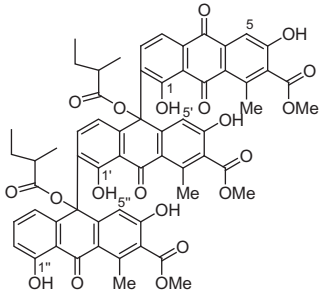
	R_1	R_2	R_3
138:	CH_3	H	OH
139:	CH_3	CH_3	OCH_3
140:	H	H	H
141:	CH_3	CH_3	H
142:	CH_3	H	H
143:	CH_3	CH_3	COOH



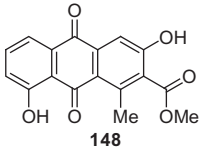
130: R_1= COOH; R_2=R_3=H
131: R_1= Me; R_2=R_3=H
132: R_1= Me; R_2=OH; R_3=H
133: R_1= CH_2OH; R_2=R_3=H
134: R_1= CH_2OAc; R_2=R_3=H
135: R_1=O Me; R_2=H; R_3=Me
136: R_1=R_2=R_3=H
137: R_1=O Me; R_2=H; R_3=H



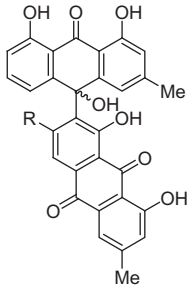
144: R=$COCH(CH_3)CH_2CH_3$
145: R=$COCH(CH_3)_2$
146: R=H



147



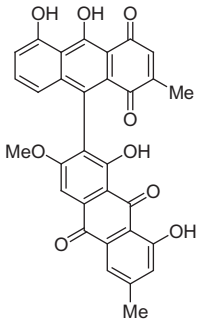
148



149: R= OMe

Figure 10.11 (Continued)

◀ 4′-β-D-glucopyranoside 6′-*O*-sulfate (**127**); 4′-*O*-demethylknipholone 6′-*O*-sulfate(**128**); sodium isoknipholone 6′-*O*-sulfate (**129**); rhein (**130**); chrysophanol (**131**); islandicin (**132**); aloe-emodin (**133**); aloe-emodin acetate (**134**); 1,8-dihydroxy-6-methoxy-3-methylanthraquinone (**135**); chrysazin (**136**); 3-methoxy-chrysazin (**137**); 1,6,7-trihydroxy-3-methoxy-8-methyl-anthraquinone (**138**); 1-hydroxy-3,6,7-trimethoxy-8-methyl-anthraquinone (**139**); 1,3,6-trihydroxy-8-methyl-anthraquinone (**140**); 1-hydroxy-3,6-dimethoxy-8-methyl-anthraquinone (**141**); 1,6-dihydroxy-3-methoxy-8-methyl-anthraquinone (**142**); 1,6-dihydroxy-3-methoxy-8-methyl-anthraquinone-7-carboxylic acid (**143**); scutianthraquinone A (**144***); scutianthraquinone B (**145***); scutianthraquinone C (**146***);



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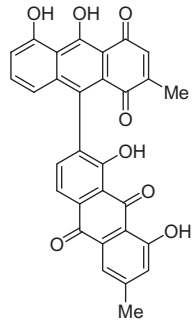

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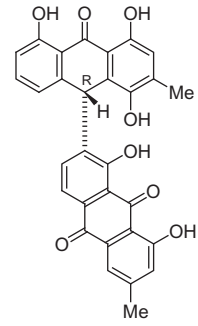

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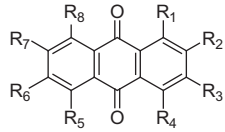
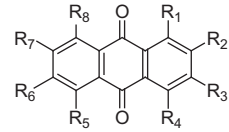
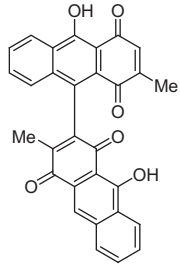


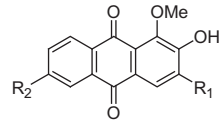


153: R_1=R_3=OH; R_6=R_7=OCH_3; others=H
154: R_1=R_3=R_6=OH; R_2=CH_3; R_7=OCH_3; others=H
155: R_1=R_3=OCH_3; R_2=R_5=OH; R_6=CH_2OH; others=H
156: R_1=R_3=OCH_3; R_2=OH; R_7=COOH; others=H
157: R_1=OCH_3; R_2=OH; R_3=O-glc, others=H
158: R_1=OCH_3; R_2=OH; R_3=O-glc(6--)1) rham, others=H
159: R_1=R_2=OH; R_3=O-glc(6---)1)rham, others=H
160: R_1=OCH_3; R_2=O-glc(6---~1)xyl, others=H
161: R_1=R_3=OCH_3; R_2=R_6=OH, others=H
162: R_1=R_3=OCH_3; R_2=OH; R_7=CH_2OH, others=H
163: R_1=R_3= OMe; R_2= OH; R_7= Me, others=H
164: R_1=R_3=OH; R_2=OMe; R_7=Me, others=H
165: R_1=R_2=OH; R_3=OMe; R_6=Me, others=H
166: R_1=R_8= OH; R_2= R_3= OMe, others=H

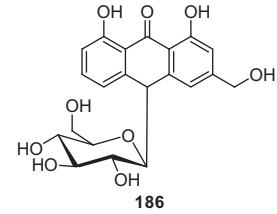
167: R_1=R_3=OMe; R_2=OH; R_7=CHO, others=H
168: R_1=R_6=OH; R_2=Me; R_5=R_7=OMe, others=H
169: R_1=R_5=OH; R_2=R_6=R_7=OMe, others=H
170: R_1=R_3=OH; R_2=CH_2-O-CH_2-Me; R_6=OMe, others=H
171: R_1=R_3=R_6=OH, others=H
172: R_1=R_4=OH, others=H
173: R_1=R_4=OH; R_2=Me, others=H
174: R_1=OH; R_2=OMe, others=H
175: R_1=R_3=OH; R_2=CH_2-O-CH_2-Me, others=H
176: R_1=R_6=OH; R_2=Me, others=H
177: R_1=R_3=OH; R_2=OMe, others=H
178: R_1=R_5=R_7=OH; R_2=Me; R_6= OMe, others=H
179: R_1=R_3=OMe; R_2=R_8=OH; R_7=Me, others=H
180: R_1=R_3=OMe; R_2=OH; R_7=CH_2OH, others=H



181



182: R_1=R_2=H
183: R_1=OMe; R_2=H
184: R_1=OMe; R_2=OH
185: R_1=OMe; R_2=OMe



186

Figure 10.11 (Continued)

◀ scutianthraquinone D (**147***); aloesaponarin I (**148***); 10-hydroxy-10-(physcion-7′-yl)-chrysophanol anthrone (**149***); 5,10-dihydroxy-2-methyl-9-(physcion-7′-yl)-l,4-anthraquinon (**150***); (*P*)-8,9,1′,8′-tetrahydroxy-3,3′-dimethyl[10,7′-bianthracene]-1,4,9′,10′-tetraone or abyquinone A (**151***); (10*R*)-1,4,8,10,8′-pentahydroxy-3,3′-dimethyl-[10,7′-bianthracene]-9,9′,10′(10*H*)-trione or abyquinone B (**152***); 6,7-dimethoxyxanthopurpurin (**153***); 6-hydroxy-7-methoxy rubiadin (**154***); 5-hydroxy-6-hydroxymethyl anthragallol 1,3-dimethyl ether (**155***); 7-carboxy anthragallol 1,3-dimethyl ether (**156***); anthragallol 1-methyl ether 3-*O*-β-D-glucopyranoside (**157***); anthragallol L-methyl ether 3-*O*-rutinoside (**158***); anthragallol 3-*O*-rutinoside (**159***); alizarin 1-methyl ether 2-*O*-primeveroside

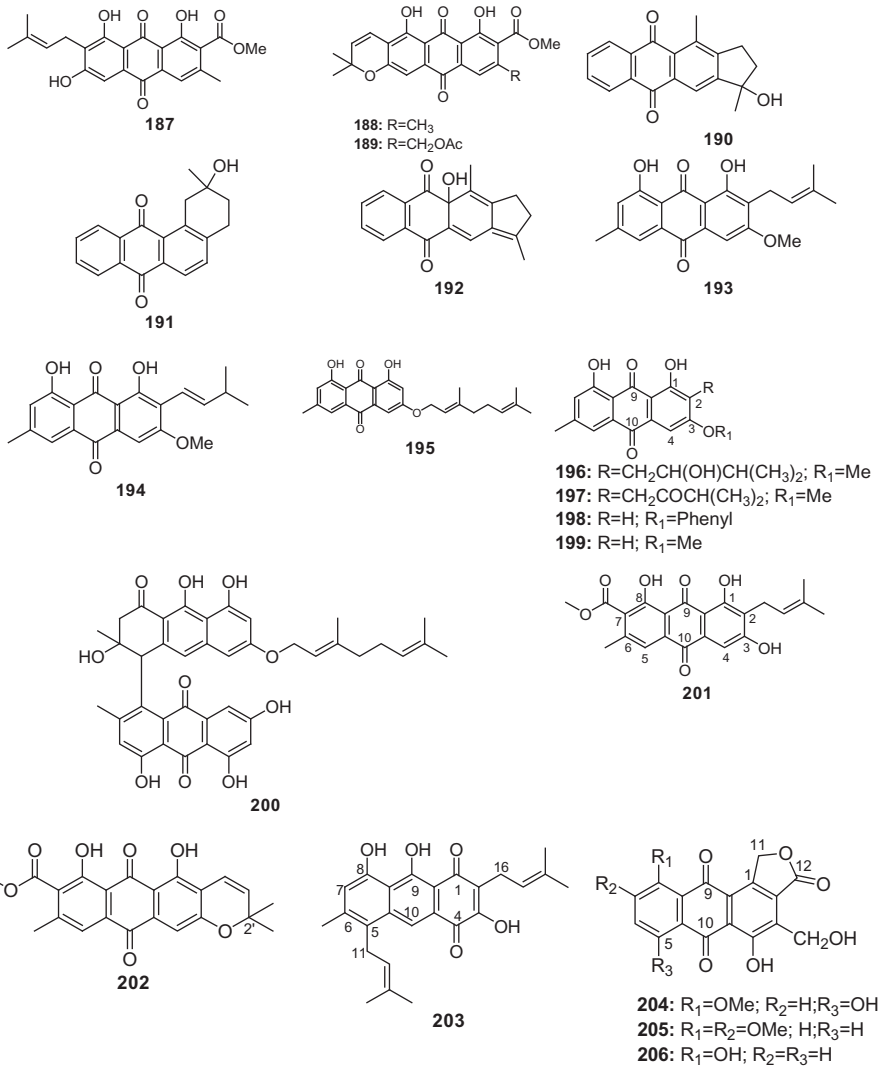
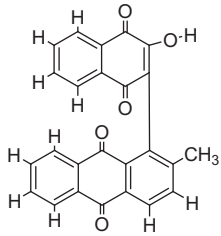


Figure 10.11 (Continued)

◀ (ruberythric acid 1-methylether) (**160***); 6-hydroxy anthragallol-1,3-dimethyl ether (**161**); 7-hydroxy-methylanthragallol 1,3-dimethyl ether (**162**); 7-methylanthragallol 1,3-dimethyl ether (**163***); 7-methylanthragallol 2-methyl ether (**164***); 6-methylanthragallol 3-methyl ether (**165***), 8-hydroxyanthragallol 2,3-dimethyl ether (**166***); 7-formylanthragallol 1,3-dimethyl ether (**167***); copareolatin 5,7-dimethyl ether (**168***); copareolatin 6,7-dimethyl ether (**169***); 6-methoxylucidin ω-ethyl ether (**170***); 6-hydroxyxanthopurpurin (**171***); quinizarin (**172**); 2-methylquinizarin (**173**); alizarin 2-methyl ether (**174**); lucidin ω-ethyl ether (**175**), soranjidiol (**176**); anthragallol 2-methyl ether (**177**); copareolatin 6-methyl ether (**178**); 7-methyl-8-hydroxyanthragallol 1,3-dimethyl ether (**179**); 7-hydroxymethylanthragallol-1,3-dimethyl ether (**180**); 10,2′-bi(9-hydroxy-3-methyl-1,4-



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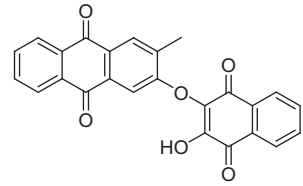


208

Figure 10.11 (Continued)

of *E. coli*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [77]. The best activities were recorded with the naphthoquinone (**16**). However, all of them were found to be the substrate of AcrAB-TolC and MexAB-OprM efflux pumps of Enterobacteriacae and *P. aeruginosa*, respectively [77]. Consequently, when compound **16** was combined with the efflux pump inhibitor phenylalanine arginine β-naphthylamide (PAβN), its activity significantly increased against *E. coli* AG100A (MIC from 2 to 0.5 μg/mL), *E. coli* ATCC 8739 (MIC from 16 to 2 μg/mL), AG100 (MIC from 32 to 1 μg/mL), AG100ATet (MIC from 8 to 0.25 μg/mL), AG102 (MIC from 16 to 0.5 μg/mL), *E. aerogenes* ATCC 13048 (MIC from 16 to 4 μg/mL), *E. aerogenes* EA294 and EA298 (MIC from 16 to 2 μg/mL), *E. aerogenes* EA27 (MIC from 32 to 4 μg/mL), *E. aerogenes* EA-CM64 (MIC from 64 to 8 μg/mL), *K. pneumoniae* ATCC 11296 (MIC from 16 to 1 μg/mL), *K. pneumoniae* KP55 and KP63 (MIC from 32 to 4 μg/mL), *P. aeruginosa* PA01 (MIC from 16 to 1 μg/mL), and *P. aeruginosa* PA124 (MIC from 32 to 05 μg/mL) [77]. In addition to its antimicrobial activity, the naphthoquinone (**59**), isolated from the Cameroonian plant *N. laevis* Seem., was also documented as a good cytotoxic compound (see Chapter 18).

7-Methyljuglone (**77**), found in the South African plant *Euclea natalensis*, is another well-studied naphthoquinone. Antifungal activity was reported against *Cryptococcus neoformans* (50% inhibition of growth concentration (GI_{50}) of 0.3 μg/mL and an MIC of 1 μg/mL), *C. albicans* (GI_{50}: 0.3 μg/mL; MIC: 20 μg/mL), *Saccharomyces cerevisiae* (GI_{50}: 0.3 μg/mL; MIC: 1 μg/mL), and *Aspergillus niger* (GI_{50}: 5 μg/mL;

◀ anthraquinonyl), named bisinaiquinone (**181***); alizarin L-methyl ether (**182**) and anthragallol 1,3-dimethyl ether (**183**); 2,6-dihydroxy-1,3-dimethoxyanthraquinone (**184***); 6-(or 7) hydroxymethylanthragallol-1,3-dimethyl ether (**185***); aloin (**186**); laurentiquinone A (**187***); laurentiquinone B (**188***); laurentiquinone C (**189***); zenkequinone A (**190**); zenkequinone B (**191***); sterequinone F (**192***); vismiaquinone C (**193***); vismiaquinone (**194**); 3-geranyloxy-6-methyl-1,8-dihydroxy anthraquinone (**195**); madagascol (**196***); vismiaquinone B (**197***); madagascin (**198***); 1,8-dihydroxy-6-methoxy-3-methylanthraquinone (**199**); febrifuquinone (**200***); laurenquinone A (**201***); laurenquinone B (**202***); kengaquinone (**203***); araliorhamnone A (**204***); araliorhamnone B (**205***); araliorhamnone C (**206***); newbouldiaquinone (**207**); newbouldiaquinone A (**208**).

Table 10.5 New Benzophenones Isolated from in African Plants

Compounds	Plants (Family)	Parts
Semsinones A (**209**)*, B (**210**)*, and C (**211**)*	*Garcinia semseii* (Guttiferae)	Stem bark [71]
30-epi-Cambogin (**212**)	*Pentadesma butyracea* (Guttiferae)	Roots [72]
Guttiferone A (**213**)	*Symphonia globulifera* Linn f (Guttiferae)	Seed shells [73]

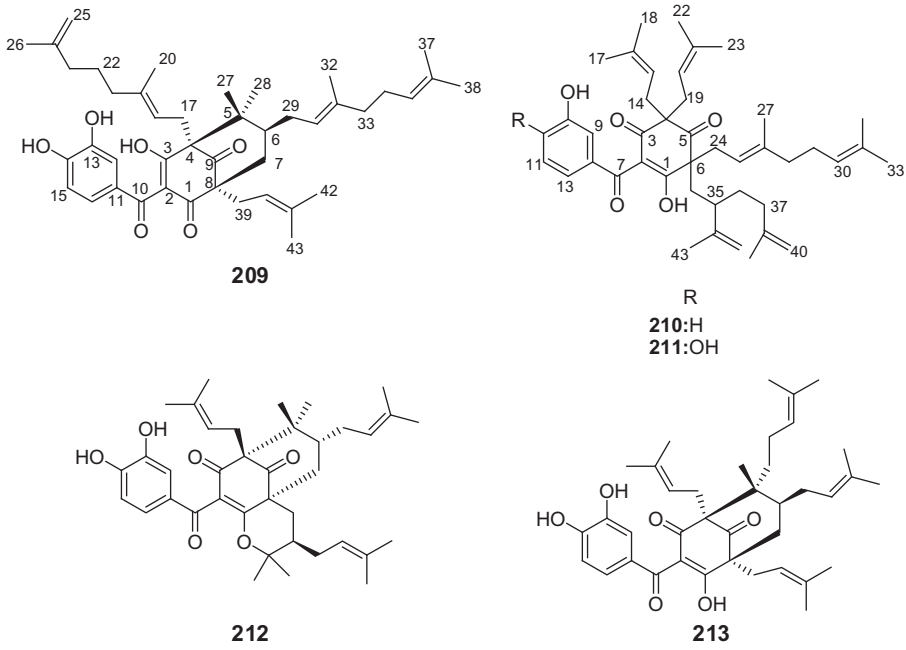


Figure 10.12 Chemical structures of benzophenones isolated from African plants [(*): novel derivative]: semsinone A (**209***); semsinone B (**210***); semsinone C (**211***); 30-epi-cambogin (**212**); guttiferone A (**213**).

MIC: 300 μg/mL) [78]. Compound **77** demonstrated inhibitory activity against the gram-positive cariogenic oral streptococci *Streptococcus mutans* (MIC: 156 μg/mL) and *Streptococcus sanguis* (MIC: 78 μg/mL), and the gram-negative anaerobic rods *Prevotella gingivalis* (MIC: 39 μg/mL) and *Prevotella intermedia* (MIC: 78 μg/mL), frequently associated with human periodontitis, known as gum disease [79]. The antibacterial activity of this compound was also noted against *Mycobacterium luteus* (GI_{50}: 20 μg/mL; MIC: 1000 μg/mL) [78]. Compound **77** showed exceptional antitubercular activity against *M. tuberculosis* H37Rv, with a MIC value of 0.5 μg/mL, combined with a very good selectivity index of 30.22 on normal vero cells [80]. This

compound was found to react as a potent subversive substrate for the NADPH-dependent enzyme mycothiol disulfide reductase of *M. tuberculosis*, which is one of several potential biological targets for its antitubercular activity [80]. The cytotoxicity of **77** was reported on several cancer cell lines including human oral epidermoid carcinoma [KB (IC_{50}: 4.1)], human lung cancer [Lu1 (IC_{50}: 13.2)], and hormone-dependent human prostate cancer (LNCaP) (IC_{50}: 3.7) [78]. Though this compound was less toxic in normal vero cells [80], its toxicity on human umbilical vein endothelial cells (HUVEC) was found to be higher (IC_{50}: 5.7), clearly indicating that possible chemotherapy involving pregnant women should be undertaken with caution.

Emodin (**20**), the most abundant and active anthraquinone in *Cassia nigricans*, is a purgative resin that was previously isolated from the Japanese knotweed (*Fallopia japonica* syn. *Polygonum cuspidatum*) [81]. Compound **20** is being studied as a potential agent that could reduce the impact of type 2 diabetes. It is a potent selective inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase type 1 [82]. In studies in obese mice, **20** limits the effect of glucocorticoids and may therefore ameliorate diabetes and insulin resistance [81]. 11β-Hydroxysteroid dehydrogenase type 1 is an nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme highly expressed in key metabolic tissues including liver, adipose tissue, and the central nervous system. In these tissues, HSD11B1 reduces cortisone to the active hormone cortisol, which activates glucocorticoid receptors. It has also been demonstrated that **20** has anticancer effects on several human cancers, including human pancreatic cancer [83–85], and its presence in extracts may also have neuroprotective properties against glutamate toxicity [78].

Aloe-emodin (1,3,8-trihydroxyanthraquinone) (**156**) is a variety of emodin also found in African plants. It is present in aloe latex, an exudate of the aloe plant. It showed a strong stimulant–laxative action [85] and was found to be carcinogenic when applied to the skin; it may also increase the carcinogenicity of some kinds of radiation [86].

10.5 Structural Elucidation of Quinones

Quinones constitute a very important group of natural products. The importance of these compounds, such as vitamins and coenzymes, and their remarkable biological activities, such as antifungal, antibacterial, herbicidal, and antitumoral, together with their association with the hydrogen pump, which serves as an inhibitor to *H. pylori*, have led to many investigations of the chemistry of these compounds. It is therefore very important to know how they can be identified by relatively simple methods.

The known structural variations of quinone compounds can be divided into many classes. In this section, an attempt is made to review chemical, color reactions, spectroscopy, and the principal degradative methods that are used in the structural elucidation of the major classes of quinones.

10.5.1 Chemical Methods

Chemical methods are avoided but may be useful in the separation of hydroxylated quinones. Hydroxybenzoquinones and 2(3)-hydroxynapthaquinones are vinylogous carboxylic acids and hence can be extracted using aqueous sodium bicarbonate. Naphthaquinones and β-hydroxylated anthraquinones in a benzenoid ring dissolve in aqueous sodium bicarbonate (some pass into bicarbonate solution), whereas the chelated α-isomers require aqueous sodium hydroxide. Similar considerations also apply to other types of quinones [36].

Derivatives can also be mentioned in this section. Methylation and acetylation are carried out to confirm the number of hydroxyl groups. Only β-hydroxyl groups are readily methylated with diazomethane or with halogeno-methane; chelated α-hydroxyl groups are normally resistant, but they succumb to methyl iodide−silver oxide−chloroform or methyl sulfate−potassium carbonate−acetone [36].

All nuclear hydroxyl groups can be esterified by reaction with acetic anhydride, but selective β-acetylation can be achieved using ketene or acetic anhydride in the presence of boroacetic, followed by hydrolysis of chelated (α) boric esters with cold water.

In addition, orthophenylene diamine has been used to confirm the structures of orthoquinones in a neat reaction with the formation of phenazines.

10.5.2 Color Reactions

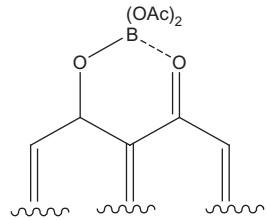
Although color reactions are much less important than formerly, they are still useful, particularly at the beginning of an investigation when the crude extract is placed on a thin layer chromatography (TLC) plate and reagents are added to yield information of value.

The most useful diagnostic tests depend on the redox properties of the quinones and the presence of hydroxyl groups. Leucomethylene blue [36] is a useful spray for the detection of benzoquinones and naphthaquinones on paper or TLC, the quinones appearing as blue spots on a white background. On reduction, the color disappears (or the product is much less highly colored), and the product is easily restored to its original color on oxidation [36]. For hydroxyquinones, the color changes are more striking in alkaline solution and reoxidation (by air) is more rapid.

Anthraquinones can be distinguished from benzoquinones and naphthaquinones as they usually give red solutions on reduction in alkaline solution (zinc or dithionite in aqueous sodium hydroxide). In a Bornträger test, a small amount of compound in 5 mL of an immiscible solvent (dichloromethane, chloroform, ether, or terachloromethane), plus an aqueous alkaline solution of 10% sodium or potassium ammonium solution, gives a rose, red, or violet coloration, indicating the presence of quinones.

Other tests for hydroxyquinones include zirconium nitrate test (a red-violet precipitate in acid solution) useful for vicinal hydroxyl groups; the Shibata's methanolic magnesium acetate reagent, originally introduced for hydroxyanthraquinones, the color obtained being indicative of the orientation of the hydroxyl groups.

Boro-acetate with boro-acetic anhydride for peri-hydroxy quinones resulting in a significant bathochromic shift in the visible region.



The Cravan or Kesting test [36] recognizes nonhydroxyl quinines, which have a free quinonoid position that is principally benzo- and naphthaquinones. In this reaction, the quinone is treated in an alcohol solution with a reagent containing a reactive methylene group (aceto-acetic ester, malonitrile, and nitromethane) and ammonia; the anion so formed then undergoes a Michael addition. The blue-green or violet-blue color that appears is that of the mesomeric anion. The mesomeric anion (**31**) may be similar to **32** given by allyl quinones in the Dam-Karrer [36] test, as summarized in Figure 10.13.

10.5.3 Spectroscopic Methods

10.5.3.1 Ultraviolet and Visible Spectrophotometry

Most, if not all, quinones are colored compounds (yellow powder, yellow needles, yellow crystalline pigments, orange, deep purple, violet, red, etc.) and absorb strongly when viewed under a UV lamp. This is due to the presence of the carbonyl-olefinic chromophores in their structures.

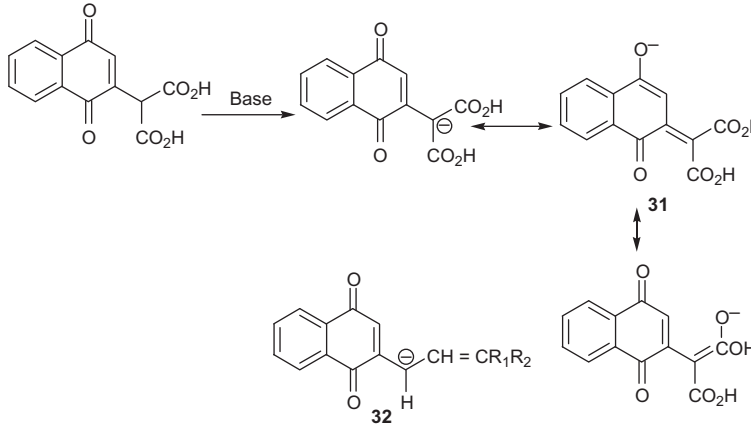


Figure 10.13 Mesomeric anions in the Dam-Karrer test [81].

10.5.3.1.1 Benzoquinones

The spectrum of *p*-benzoquinone is characterized by intense absorption near 240 nm (εmax 26,000), a medium band ~285 nm (εmax ~300), attributed to an electron transfer (ET) transitions and much weaker absorptions ($n \rightarrow \pi^*$) in the visible region [36,87].

Introduction of a substituent of the usual type into the benzoquinone nucleus produces a small bathochromic displacement of the first band in the spectrum (<10 nm), but the second band undergoes a more significant red shift in the order of Me (27 nm), MeO (69 nm), OH (81 nm) in chloroform. The visible band is little affected and is frequently obscured under the envelope of band II.

The *o*-benzoquinones are rare; hence relatively few *o*-benzoquinone spectra have been recorded [36]. They show triple absorption peaks and are easily distinguishable from the *p*-isomers by the relatively low intensity and marked bathochromic displacements. Band II is frequently shifted into the visible region, and the low-intensity ($n \rightarrow \pi^*$) absorption may extend as far as 600 nm.

10.5.3.1.2 Naphthaquinones

The spectra of naphthaquinones are inevitably more complex than those of benzoquinones since both benzenoid and quinonoid absorptions are involved, and either or both rings may be substituted. The spectra may be further complicated depending on the substituents. However, naphthaquinones show two major absorption maxima [87].

The spectrum of the parent 1,4-naphthaquinone comprises intense benzenoid and quinonoid ET absorption in the region 240−290 nm and a medium intensity benzenoid ET band at 335 nm. A broad, weak local excitation (LE) band at 425 nm (εmax ~32) is discernible in iso-octate solution but not in more polar solvents. The shoulder at 257 nm is ascribed to a quinonoid ET transition and is shifted bathochromically by + I and + M substituents in quinone rings, whereas the benzenoid absorption at 254 and 251 nm is usually scarcely affected.

10.5.3.1.3 Anthraquinones

Anthraquinones show three to four major absorption maxima: intense benzenoid absorption at ca. 250 nm and a medium absorption at 322 nm; strong quinonoid ET bands are observed at 263 and 272 nm, and a weak quinonoid absorption band at 405 nm. These areas of selective absorption are characteristic, and the pattern in the UV region is not seriously affected by substitution [36,87].

10.5.3.2 Infrared Spectrometry

Infrared spectral studies of quinones give relatively little structural information in comparison to the other spectral techniques. The carbonyl absorptions are useful diagnostic aids in the structural elucidation of quinones. The carbonyl absorption of *p*-benzoquinone occurs at 1669 cm^{-1} which is normal for an α,β di-unsubstituted ketone, and the frequency rises as the number of linear fused rings increases (1,4-naphthaquinones, 1675 cm^{-1}; 9,10-anthraquinones, 1678 cm^{-1}; naphthacene-5,12-quinones, 1682 cm^{-1}). The carbonyl frequency is lowered by hydrogen bonding,

by substitution either in the quinonoid ring or an adjacent benzenoid ring with + I or + M groups, and by separation of the carbonyl functions so that the quinonoid conjugation extends through more than one ring (extended quinones). The carbonyl frequencies are raised by − M substituents and by stearic strain [36,87].

10.5.3.3 Proton Nuclear Magnetic Resonance (^{1}H-NMR) Spectrometry

The quinonoid protons in *p*-benzoquinone resonate at 6.72 ppm and in 1,4-naphthaquinones at 6.97 ppm. The effect of substitution is analogous to that observed in comparable *cis*-vinyl compounds, and for benzoquinones the chemical shift of quinonoid protons is very similar to that found in cyclohex-2-ene-1,4-diones. On reduction to quinol, the signal shifts downfield to the aromatic region, frequently with a reduction in multiplicity, and this is a useful criterion for a quinonoid structure [36].

The signal from an alkyl substituent undergoes a corresponding shift and reduction in multiplicity. Thus, in 2-methyl-1,4-naphthaquinone, the quinonoid proton at C-3 gives rise to a quartet at 6.84 ppm (J, 1.5 Hz) coupled to a doublet from the allylic methyl protons at 2.19 ppm. It should be noted that in asymmetrical benzenoid substituted 1,4-naphthaquinones, the adjacent protons of C-2 and C-3 frequently give a singlet rather than an AB quartet, and this is also true for some monosubstituted benzoquinones [36].

The nuclear protons in simple benzoquinones give rise to multiplets which originate from long-range interactions, and the coupling constant for allylic (CH_3—C═C—H) and homo-allylic (CH_3—C═C═C—H) systems vary with the angle between the C═C double bond and the relevant C—H bond [1,87].

Chelated α-hydroxyl groups are easily recognized as their protons resonate at very low field (∼12−13 ppm), while nonchelated hydroxyl groups occur upfield. Similarly, peri-aromatic protons to carbonyl functions occur downfield from 8 ppm. For methyl and methoxyl groups, which are common substituents, additional information can be obtained from solvent shifts [1,10,36].

10.5.3.4 Mass Spectrometry

Features common to the mass spectra of all quinones are peaks corresponding to the loss of one or two molecules of carbon dioxide. Benzo- and naphthaquinones also eliminate an ethylenic (—C═C—) and/or acetylenic (O═C—C═C—) fragment from the quinine ring, and if the latter is hydroxylated, breakdown is accompanied by a characteristic hydrogen rearrangement [1,36].

10.5.4 Degradation Reactions

Degradation is often necessary when novel structures are encountered. If the basic polycyclic system is not recognizable from the ultraviolet spectrum, of the leuco-acetate or in other ways, zinc dust distillation or the less drastic zinc dust fusion can be used to obtain the parent hydrocarbon (or heterocycle).

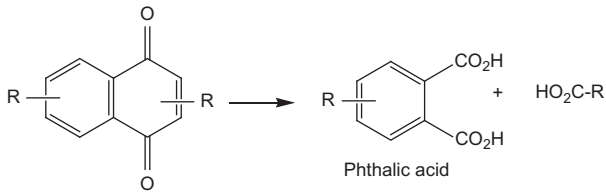


Figure 10.14 Alkaline hydrogen peroxide degradation of naphthaquinones.

Oxidative degradation is used mainly to establish the structure of a side chain attached to a quinnone ring or to obtain an identifiable fragment containing a benzenoid ring as summarized in Figure 10.14. Anthraquinones and more highly condensed compounds, where the quinone ring is protected on both sides by benzene rings, are much difficult to degrade [36].

10.5.5 Electron Spin Resonance Spectroscopy

Electron spin resonance (ESR) can be applied to the detection and identification of quinones in plant extracts without prior isolation. The compounds are converted to the corresponding semiquinone radicals, which are subsequently observed by ESR. Only the semiquinone nucleus is identified by this procedure [88].

10.6 Conclusion

In this chapter, we discussed the chemistry of quinones and benzophenones. We reviewed as much as possible the quinones reported in African plants to date and highlighted the biological activities of the promising compounds such as lapachol, plumbagin, 7-methyljugulone, diospyrin, and crassiflorone. It has been noted that the Guttiferae, Bignoniaceae, Aloeaceae, and Rubiaceae were widely reported as sources of quinones and/or benzophenones in African plants.

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11 Xanthones and Anthranoids from the Medicinal Plants of Africa

Ofentse Mazimba[a], *Frederic Nana*[b], *Victor Kuete*[c] *and Girija S. Singh*[a]

[a]Department of Chemistry, University of Botswana, Gaborone, Botswana, [b]Department of Organic Chemistry, University of Yaounde I, Cameroon, [c]Department of Biochemistry, University of Dschang, Dschang, Cameroon

11.1 Introduction

Xanthones are secondary metabolites found in a few higher plants, fungi, and lichens. The xanthone skeleton (the word "xanthon" is derived from the Greek word *xanthos*, meaning yellow) is a planar, conjugated ring system composed of carbons 1−4 (aromatic ring A) and carbons 5−8 (aromatic ring B), fused through a carbonyl group and an oxygen atom (Figure 11.1). The simplest member of the class, 9*H*-xanthen-9-one, is a symmetrical compound with a dibenzo-γ-pyrone skeleton [1]. The numbering starts from ring A, while ring B is given prime locants or consecutively numbered from ring A.

According to literature reports, around 650 xanthones are known from natural sources. These xanthones have been isolated from 62 families of higher plants, fungi, and lichens [1−5]. Xanthones from higher plants are distributed in Gentianaceae, Moraceae, Guttiferae, Polygalaceae, and Leguminosae families. The families with higher proportions are Clusiaceae or Guttiferae (55 species in 12 genera) and Gentianaceae (121 species in 21 genera) [3,6].

Xanthones have diverse pharmacological properties, mainly due to their oxygenation nature and diversity of functional groups. The biological activities discussed in some review articles on xanthones during 2000−2012 include antibacterial, antiviral, antioxidative, antiinflammatory, antiproliferative, antihypertensive, antithrombotic, *in vitro* and *in vivo* antitumor, cytotoxic, coagulant, monoamine oxidase (MAO) inhibition, gastro-protective effects, antiatherosclerotic activity, inhibition of hypotension, cardioprotection, inhibition of cholinesterase, cyclooxygenase activity, immunosuppression, and binding to transthyretin (TTR) [2−4,7−10]. The α-glucosidase inhibitory activity may lead to xanthones and their sources being used against diabetes and HIV/AIDS [11]. Xanthones have shown the potential to

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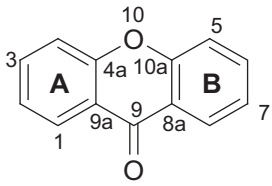


Figure 11.1 The basic skeleton of xanthone.

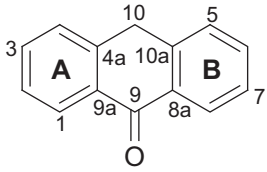


Figure 11.2 The basic skeleton of anthrone.

prevent disease development by their concerted action of protecting cells from oxidative stress damage and acting as phytoalexin to impair pathogen growth [12]. A biological activity that is of significance for tropical Africa is the antimalarial property [13,14].

The African continent has a rich treasure of plant natural resources. Several plants are in traditional use as remedies for various diseases, including life-threatening diseases such as malaria, tuberculosis, HIV/AIDS, diabetes, and hypertension. Over 90 xanthones with different functionalities are known from the plants occurring on the African continent. Some African plant sources of xanthones are *Garcinia polyantha* and *Garcinia nobilis* (Guttiferae) [15,16], *Symphonia globulifera* (Guttiferae) [17], *Securidaca longepedunculata* (Polygalaceae) [18], *Allanblackia floribunda* and *Allanblackia monticola* (Guttiferae) [19,20], *Anthocleista vogelii* (Loganiaceae) [14], *Garcinia gerrardii*, *Garcinia livingstonei*, *Hypericum roeperanum* (Guttiferae), *Polygala nyikensis* (Polygalaceae), and *Swertia calycina* (Gentianaceae) [21].

An anthrone is a planar tricyclic aromatic ketone (Figure 11.2). In the basic skeleton of an anthrone, the two aromatic rings are connected by a keto group and a methylene group (sp^3 carbon) in such a way as to form a six-membered cyclic ketone in the middle of the condensed-fused ring system (Figure 11.2). Thus, the anthrone skeleton has one keto (C=O) group reduced from the structure of anthracene-9,10-dione (anthraquinone) to form the simplest anthrone, anthracene-10(9*H*)-one.

Anthrones are widely distributed within the *Aloe* species. The common aloe anthrones, aloin A and B, aloinoside A and B, and microdontin A and B (Figure 11.3), have been found in 36 species of *Aloe* [22]. The other genera containing anthrones are *Bulbine*, *Cassia*, *Frangula*, *Hypericum*, *Harungana*, *Picramnia*, *Rhamnus*, *Rhubarb*, *Rubus*, *Senna*, and *Vismia*. From the African plants, around 30 anthrones have been isolated and characterized from the Guttiferae and aloe (Xanthorrhoeaceae) families. The ethnomedicinal uses of African plant species containing anthrone are varied. The *Harungana madagascariensis* (Guttiferae), which contain prenylated anthrones, is used as a treatment for diarrhoea and dysentery and

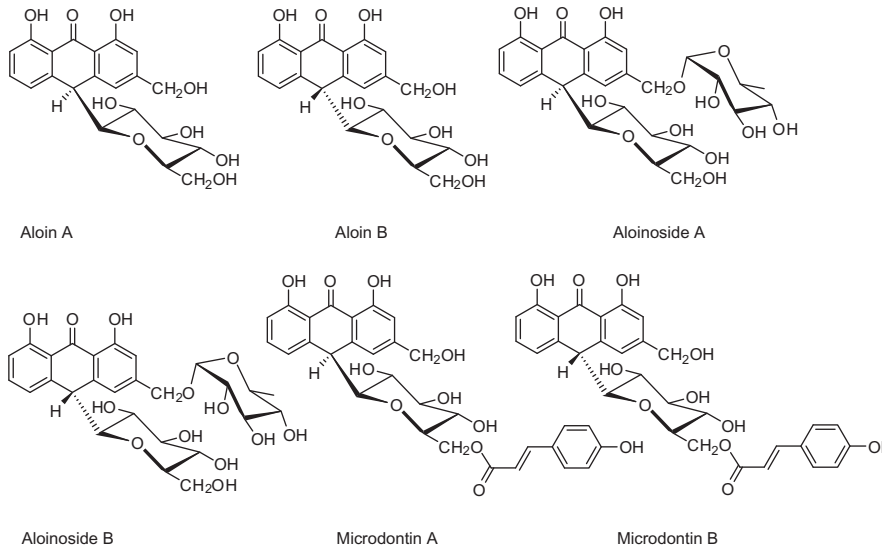


Figure 11.3 Anthrone C-glycosides from the aloe family.

is a very strong laxative [23]. *Aloe microdonta* (aloe family) is used to treat jaundice and skin diseases [24] and contains C_{10}-glucosylated anthrone derivatives. The Cape aloe, which contains anthrone C-glycosides, is used as a laxative in Africa and is considered to have antioxidant, antiinflammatory, antimicrobial, and anticancer properties [25].

The diverse pharmacological activities of anthrones include insecticidal, immunological adjuvant and wound healing, antimicrobial, antioxidant, photodynamic antitumor, antiviral, antimetastatic, and laxative activities and modulation of apoptosis [10,21,26–28]. The unsuitability of artemisinin from *Artemisia annua* and a tetrahydroanthracene from *Psorospermum febrifugum* as antimalarial drugs is due to their toxicity [21]. The ability of phenolic anthrones (e.g., anthralin) to generate free radicals is the basis for their antipsoriastic, antiinflammatory 5-lipoxygenase, and 12-lipoxygenase activity [29].

11.2 Biosynthesis and Structural Diversity

11.2.1 Xanthones

The structural diversity of xanthones lies in their mixed shikimate and acetate biogenic origin. The biosynthetic pathway defines xanthones as cyclized 2,3′-dihydroxybenzophenone derivatives. Based on the biogenic pathway, 9*H*-xanthen-9-one carbons 1–4 are assigned to the acetate-derived ring A, and carbons 5–8 to the shikimate-derived ring B. The biosynthesis of xanthones is based on the synthesis

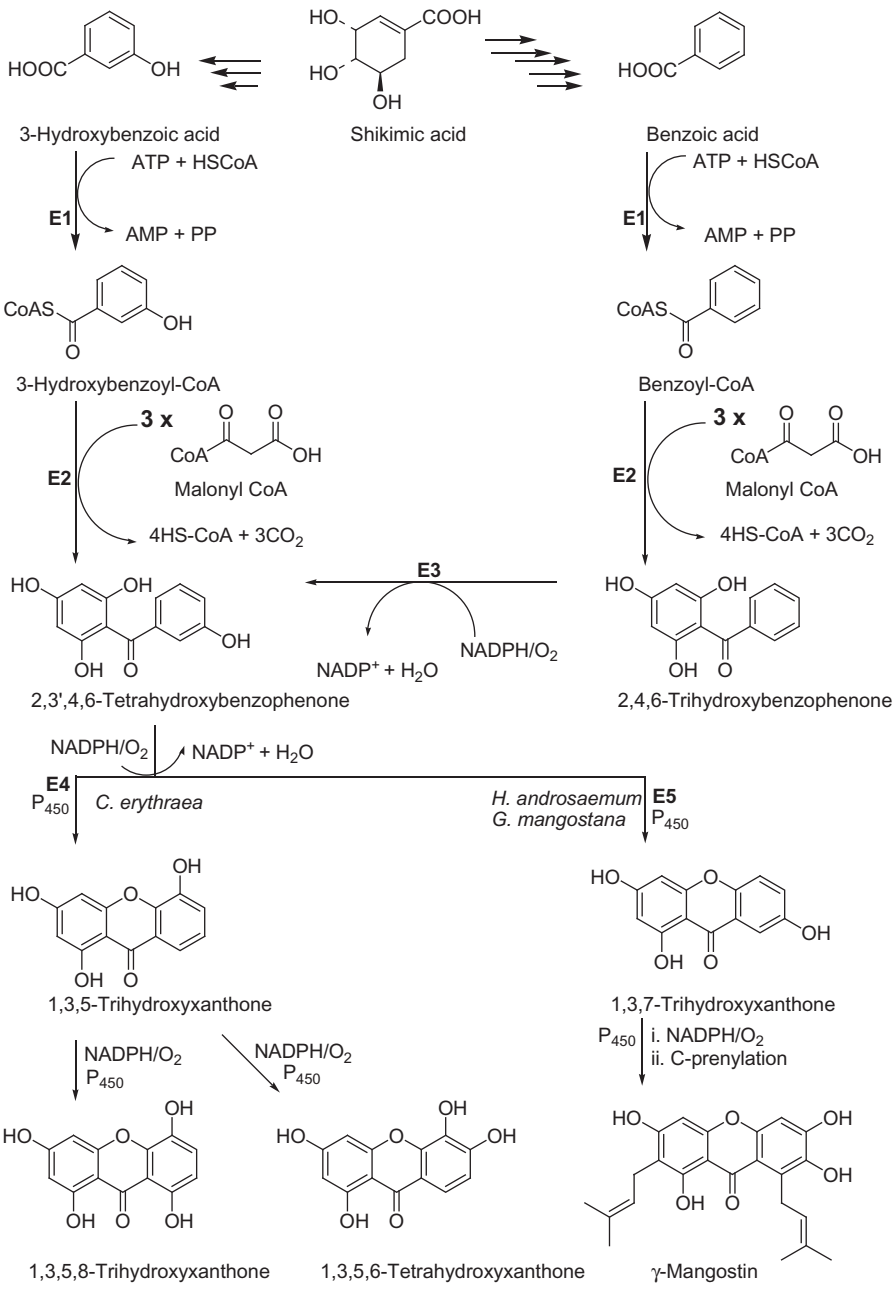


Figure 11.4 Biosynthesis of xanthones.

of 2,3′,4,6-Tetrahydroxybenzophenone [30] (Figure 11.4). The benzophenone undergoes regioselective intramolecular cyclization through one-electron oxidation steps to form the simplest xanthone. The xanthone biosynthetic pathway in higher plants has been proposed to involve the condensation of shikimate acid derivatives and malonyl-CoA as extension units [4,30]. Some xanthones are entirely derived from the acetate pathway by folding a C_{16}-polyketide in lower plants *Helminthosporium ravenielii* and *Helminthosporium turcicum* [31,32].

The use of shikimate acid derivatives as entry compounds for 2,3′,4,6-tetrahydroxy benzophenone (THPA) biosynthesis depends on the individual plants. The enzyme used is a benzophenone synthase [30], which belongs to the family of type III polyketide synthases. Type III polyketide synthases (PKSs) generate a diverse variety of secondary metabolites by varying the starter substrate, the number of condensation reactions, and cyclization reaction [33] to afford scaffolds such as chalcones, pyrones, chromones, and stilbenes [34].

In *Centaurium erythraea*, 2,3′,4,6-tetrahydroxybenzophenone is obtained from the condensation of 3-hydroxybenzoyl-CoA and three malonyl-CoA units [30,35]. The benzophenone synthase from *Hypericum androsaemum* and *Garcinia mangostana* is substrate specific on benzoyl-CoA, which is rarely used as a starter substrate by PKSs [36]. The 2,4,6-trihydroxybenzophenone intermediate is further hydroxylated by benzophenone 3′-hydroxylase and converted to 2,3′,4,6-tetrahydroxy benzophenone [37,38]. The 3-hydroxybenzoyl-CoA substrate appears to originate directly from the shikimic acid degradation (*C. erythraea*) or from 3-hydroxybenzoic acid [39,40]. In *H. androsaemum*, benzoyl-CoA is derived from cinnamoyl-CoA degradation [41]. The *m*-hydroxybenzoic acid in *Gentiana lutea* is derived from phenylalanine [10]. In *Swertia chirata*, phenylalanine, cinnamic acid, and benzoic acid were ruled out as intermediates for 3-hydroxybenzoyl-CoA, which was rather derived from an early shikimate pathway intermediate, [carboxy-^{13}C]shikimate [40].

In xanthone biosynthesis in plants, the central step is the regioselective cyclization of the 2,3′,4,6-tetrahydroxybenzophenone (THPA). The xanthone synthase from *C. erythraea* cyclizes THPA via the *ortho* position with respect to the 3′-hydroxy group to give 1,3,5-trihydroxyxanthone. A *para*-position cyclization occurs in *H. androsaemum* and *G. mangostana* to produce 1,3,7-trihydroxyxanthone [35,37]. The last step is hydroxylation to form 1,3,6,7-tetrahydroxyxanthone. The xanthone synthases are cytochrome P_{450} oxidases and require NADPH and O_2. The cyclization reaction mechanisms follow the oxidative phenol coupling reactions that are strongly favored by the presence of the *ortho*−*para*-directing 3′-hydroxyl group [10,35,42].

The structure of xanthones allows the biosynthetic buildup of an array of substances (Figure 11.5) with valuable pharmacological activities. Xanthones are classified as oxygenated xanthones, prenylated xanthones, xanthone glycosides, xanthonolignoids, bis-xanthones, and miscellaneous xanthones, which include caged xanthones [3,6,8]. The polyphenolic xanthones are further subdivided according to the degree of oxygenation into non-, mono-, di-, tri-, tetra-, penta-, and hexa-oxygenated substances [10,42,43]. The other xanthone subclasses are based on the level of oxidation of ring A, which can occur either as completely aromatic or as dihydro-, tetrahydro-, and hexahydro derivatives, either in monomeric

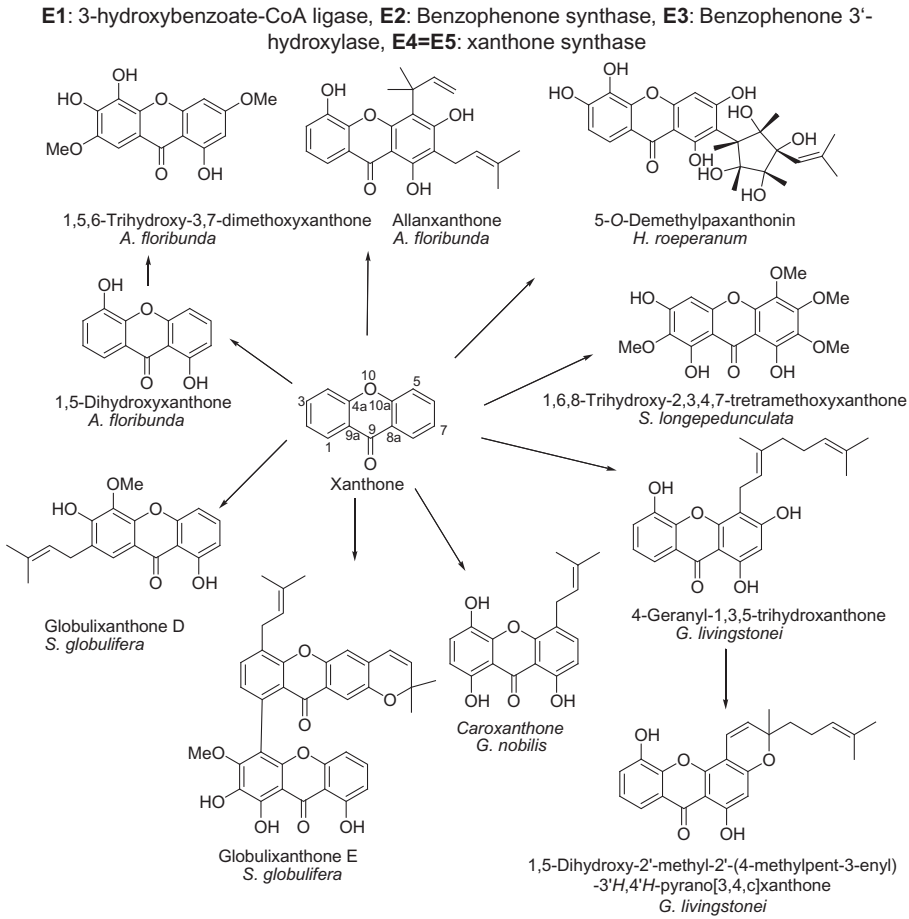


Figure 11.5 Structural diversity of xanthones from the African plants.

or dimeric form [4]. There are several xanthones which are hydroxylated xanthones with prenyl or geranyl units [10]. The Clusiaceae family mainly has prenylated xanthones, while the Gentianaceae family has oxygenated xanthones.

11.2.2 Anthrones

Anthrones are biosynthesized through the acetate pathway. The important C-16 polyketide precursor results from the condensation of one acetyl-CoA and seven malonyl-CoA units. This polyketide pathway also leads to anthraquinones, which result from anthrone metabolism. Octaketide synthase (OKS) is a novel plant-specific type III PKS that catalyzes condensations of eight molecules of malonyl-CoA. OKS uses acetyl-CoA resulting from the decarboxylation of malonyl-CoA as a starter substrate.

OKS was cloned and sequenced from *Aloe arborencens*, which is a medicinal plant rich in aromatic polyketides such as aloenin (hexaketide), aloesin (heptaketide), and aloin (octaketide-anthrone). Therefore, it has been hypothesized based on engineered plant polyketide biosynthesis studies that OKS is involved in the biosynthesis of anthrones [34]. The amino acid sequences of OKS (Mr 44 kDa proteins with 403 amino acids) have a 50−60% identity to other chalcone synthase superfamily type III PKSs of plant origin. They also have 54% identity with a heptaketide-producing aloesone synthase from rhubarb (*Rheum palmatum*) [34,44]. The physiological function of OKS in medicinal plants remains to be fully elucidated [34].

Crysophanol anthrone results from a series of aldol and enolizaton reactions and decarboxylation of the C-16 polyketide (Figure 11.6). The enzyme emodinanthrone synthase is involved in the derivation of emodinanthrone through atrochrysone carboxylic acid that undergoes decaboxylation before the aromatization of the final ring. A series of C-prenylations produces polyprenylated anthrones in *H. madagascariensis* [23]. Emodinanathrone oxygenase catalyzes the fixation of molecular oxygen into emodinanthrone to produce anthraquinone emodin. This reaction does not use NADPH/O_2, but the enzyme acts as an internal monooxygenase [45]. Radical coupling of emodinanthrone creates an emodindianthrone that undergoes further oxidative coupling to hypericin (a naphtodianthrone), found in *Hypericum perforatum* [45,46]. The ability of anthrones to generate reactive oxygen species under physiological conditions leads them to create anthraquinone and dianthrones. The anthrone derivatives are found as glycosides, oxanthrone mayoside, carboxylic acids, tetrahydroxyanthrone, and polycyclic derivatives. Polyphenolic anthrones have prenylated and methylated derivatives [23,34,46−48].

11.3 Characterization of Xanthones and Anthrones in Plants

11.3.1 Detection of Xanthones

Xanthones are commonly separated by chromatography over silica gel [49]. A rapid qualitative survey of xanthones in crude extracts can be done by liquid chromatography using UV photodiode-array detection [50,51].

The xanthoside composition of crude extract has been characterized using LC-UV diode array detection and the LC-atmospheric pressure chemical ionization-MS (APCI) methods. The presence of acylated xanthone-*O*-glucoside was determined using both positive and negative ion LC-APCI-MS methods. The structures of simple oxygenated xanthones have been established mainly using UV, IR, MS spectra, and NMR spectral data for these compounds [52−54]. Based on UV, IR, MS spectra, and NMR data [55], xanthones are commonly separated by chromatography over silica gel and also by HPLC using an appropriate solvent mixture. Reverse phase-high performance liquid chromatography (RP-HPLC) using a diode array detector (DAD) is widely applied for the analysis of these

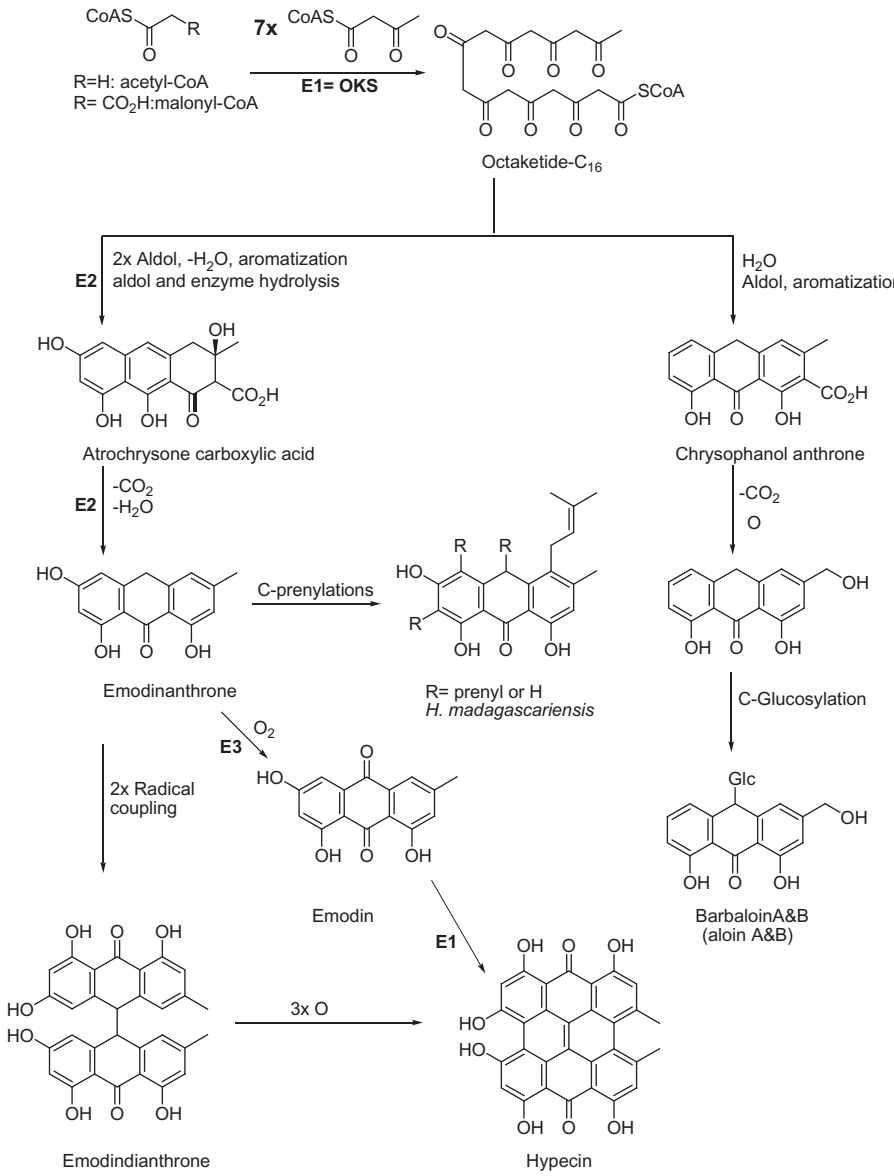


Figure 11.6 Biosynthesis of anthrones and derivatives (OKS: octaketide synthase, **E2**: emodinanthrone synthase, **E3**: emodinanthrone oxygenase).

compounds due to their high sensitivity and easy operation [56]. Xanthones can also be detected by their colors under UV light or by using a general phenolic spray [57]. Xanthones, like any other class of phenolic compounds, cannot be produced by the human body.

The UV spectrum varies in a characteristic manner, depending on the oxygenation pattern and the availability of a considerable amount of data, which makes assignment readily possible. Besides the use of $AlCl_3$ shifts for chelated hydroxyl groups, sodium acetate, sodium hydroxide, and boric acid shifts have been studied to obtain considerable information about the positions of hydroxyl groups in other locations [54,58].

The application of IR spectroscopy in xanthone chemistry is very limited in the detection of the carbonyl stretching frequency [59]. In particular, the effect of chelation observed on the infrared carbonyl frequencies of the hydroxy-xanthones may be useful in the structural elucidation of some substituted and extended xanthones [60,61]. The use of IR spectra from unchelated hydroxyl and methyl groups is very well known and does not require comment [62–64].

MS has not yet been applied extensively to the study of naturally occurring xanthones, but MS data have been extremely valuable for a preliminary examination of structures [65].

Data obtained in ^{1}H NMR spectra are extremely useful in the characterization and identification of naturally occurring xanthones [66]. These ^{1}H NMR data have been used for the structural determination of substituents and location of aromatic protons by comparison with the reference data. A closer look at the chemical shifts of the aromatic protons allows the prediction of oxygenation pattern [67]. The ^{1}H NMR for this class of compounds has been discussed in detail [68]. The ^{13}C NMR spectra of a wide variety of naturally occurring xanthones are reported in the literature and the chemical shifts assigned [69,70].

11.3.2 Detection of Anthrones

Although color reactions are much less important than formerly, they are still useful, particularly at the beginning of an investigation when the crude extract is placed on a Thin Layer chromatography (TLC) plate and reagents added to yield information of value.

Most, if not all, anthrones are colored (yellow powder, yellow needles, orange, violet, etc.) and absorb strongly when viewed under a UV lamp. This is due to the presence of the carbonyl-olefinic chromophores in their structures. The UV spectrum of anthrone is characterized by intense absorption in the region of 240–290 nm (εmax $\lambda_{26.00}$), a medium band $\lambda_{285\ nm}$ (εmax λ_{300}), characteristic of the conjugated carbonyl moiety and attributed to an electron transfer (ET) transitions, and much weaker asorptions ($n \rightarrow \pi^*$) in the visible region. Its IR spectrum reveals absorption bands for carbonyl group at 1680 cm^{-1} [60].

The most common features of the mass spectra of all anthrones are peaks corresponding to the loss of one or two molecules of carbon dioxide. Anthrone compounds eliminate an ethylenic (–C═C–) and/or acetylenic (O═C–C═C–) fragment.

The ^{13}C NMR spectra show signals of one conjugated carbonyl carbon, the aromatic carbons, and one methylene carbon [68,71].

11.4 Xanthones Isolated from African Medicinal Plants and Their Pharmacological Activities

Phytochemists in the African continent have paid considerable attention to xanthones or xanthen-9*H*-ones (dibenzo-gamma-pirone), which comprise an important class of oxygenated heterocycles from the medicinal chemistry point of view, as mentioned in the introductory section. The biological activities of xanthones are associated with their tricyclic scaffold but vary depending on the nature and/or position of the different substituents [72]. Xanthones exhibit an antidepressant action and antitubercular activity, while xanthone glycosides have a depressant action. The choleretic, diuretic, antimicrobial, antiviral, and cardiotonic action of some xanthones have also been established [73]. A summary of the compounds, their occurrence in African plants, and biological activity is given in Table 11.1. The new natural products are listed in Table 11.2.

11.4.1 Antimicrobial Activities of Xanthones Identified in African Medicinal Plants

Several antimicrobial xanthones reported in African plants have shown significant (minimal inhibitory concentration (MIC) below 10 μg/mL), moderate (10 < MIC < 100 μg/mL), and low (MIC > 100 μg/mL) activity [131,132]. Polyhydroxylated xanthones displayed activities against drug-sensitive and multidrug resistant (MDR) phenotypes. The compound 1,7-dihydroxyxanthone (**1**) (Figure 11.7) was found to be a substrate of AcrAB-TolC and MexAB-OprM efflux pumps of Enterobacteriaceae and *Pseudomonas aeruginosa*, respectively [95]. It was observed that, when compound **1** was combined with the efflux pumps inhibitor phenylalanine arginine β-naphthylamide (PAβN), its antibacterial activity significantly increased against *Escherichia coli* ATCC 8739, AG100, AG100ATet, and AG102 (MIC dropped from >256 to 32 μg/mL), *E. coli* AG100A (MIC dropped from >256 to 16 μg/mL), *Enterobacter aerogenes* ATCC 13048 (MIC dropped from >256 to 256 μg/mL), *E. aerogenes* EA294 (MIC dropped from 64 to 4 μg/mL), *E. aerogenes* EA298 (MIC dropped from 128 to 4 μg/mL), *E. aerogenes* EA27 (MIC from >256 to 256 μg/mL), *Klebsiella pneumoniae* ATCC 11296 (MIC dropped from 256 to 64 μg/mL), *K. pneumoniae* KP55 and KP63 (MIC dropped from >256 to 32 μg/mL), *P. aeruginosa* PA01 (MIC dropped from >256 to 128 μg/mL), and *P. aeruginosa* PA124 (MIC dropped from >256 to 128 μg/mL) [95]. The antifungal activity of this compound was also documented on *Epidermophyton floccosum* (MIC: 15.6 μg/mL), but it was found inactive against *Aspergillus fumigatus*, *Microsporum gypseum*, *Microsporum canis*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* [105]. The MIC of this compound on the Gram-positive bacterium *Staphylococcus aureus* was observed as 128−256 μg/mL [106]. Its isomer 1,5-dihydroxyxanthone (**2**) exhibited a similar antibacterial activity, indicating that the location of the hydroxyl group in the structure does not significantly modulate their activity [132]. Therefore, compound **2** has also

Table 11.1 Biologically Active Xanthones and Anthrones from African Medicinal Plants

Compounds	Class	Plants (Family)	Pharmacological Activities
α-Mangostin (**22**)	Xanthone	*Garcinia staudtii* Engl. (Guttiferae) [74]	Antimicrobial, cytotoxic [74]
1,4-Dihydroxy-7-methoxy-xanthone (**64**)	Xanthone	*S. longependunculata* (Fresen) (Polygalaceae)	Relaxing effect [75]
1,5,6-Trihydroxy-3,7-dimethoxyxanthone (**45**)	Xanthone	*A. floribunda* Oliver (Guttiferae)	Cytotoxic [76]
1,3,5,6-Tetrahydroxyxanthone (**40**)	Xanthone	*G. polyantha* (Guttiferae) [77]	Enzyme inhibition [77]
1,3,5-Trihydroxyxanthone (**4**)	Xanthone	*Garcinia afzelii* (Guttiferae) [78], *G. polyantha* (Guttiferae) [77], *Garcinia smeathmannii* (Guttiferae) [79]	Antimicrobial [80], enzyme inhibition [77,81]
1,3,6,7-Tetrahydroxyxanthone (**39**)	Xanthone	*G. polyantha* (Guttiferae) [77]	Antioxidant [82], enzyme inhibitor [77,83]
1,3,6-Trihydroxy-7-methoxy-2,8-diprenylxanthone (**34**)	Xanthone	*Pentadesma butyracea* Sabine (Guttiferae) [84]	Antiparasitic, cytotoxic [84]
1,3,6-Trihydroxy-8-methylxanthone (**6**)	Xanthone	*Ledebouria graminifolia* (Bak.) Jessop (Hyacinthaceae) [85]	Antimicrobial [86], cytotoxic, and enzyme inhibitor [87]
1,4,8-Trihydroxyxanthone (**3**)	Xanthone	*Vismia rubescens* Oliv. (Guttiferae) [88]	Antimicrobial [88]
1,5-Dihydroxy-3-methoxyxanthone (**8**)	Xanthone	*C. spicatum* L. (Gentianaceae) [89]	Antimicrobial [89,90], cytotoxic [81,91]
1,5-Dihydroxyxanthone (**2**)	Xanthone	*A. floribunda* (Guttiferae) [19], *Calophyllum inophyllum* (Guttiferae) [92], *G. afzelii* (Guttiferae) [93], *G. polyantha* [77], *G. polyantha* Oliv. [15], *G. smeathmannii* (Guttiferae) [79], *P. butyracea* (Guttiferae) [94]	Antimicrobial [95], antinociceptive [96], antioxidant [15], enzyme inhibitor [77]
1,6-Dihydroxy-3,5-dimethoxyxanthone (**9**)	Xanthone	*C. spicatum* L. (Gentianaceae) [89]	Antimicrobial [89], cytotoxic [97]
1,6-Dihydroxy-3-methoxy-8-methylxanthone (**7**)	Xanthone	*L. graminifolia* (Bak.) Jessop (Hyacinthaceae) [85]	Antimicrobial [98]

(*Continued*)

Table 11.1 (Continued)

Compounds	Class	Plants (Family)	Pharmacological Activities
1,6-Dihydroxy-5-methoxyxanthone (**5**)	Xanthone	*G. afzelii* (Guttiferae) [78], *G. polyantha* [77]	Enzyme inhibitor [77]
1,7-Dihydroxy-3-methylxanthone (**58**)	Xanthone	*Cassia obtusifolia* Lam. (Leguminosae) [99]	Enzyme inhibitor [100]
1,7-Dihydroxyxanthone (**1**)	Xanthone	*C. obtusifolia* Lam. (Leguminosae) [99], *G. nobilis* (Guttiferae) [101], *P. butyracea* (Guttiferae) [94], *Vismia laurentii* De Wild. (Guttiferae) [102], *V. rubescens* Oliv. (Guttiferae) [88], *P. aurantiacum* Engl. (Hypericaceae) [103], *P. molluscum* (Pers.) Hochr. (Hypericaceae) [104]	Antimicrobial [95,105,106], cytotoxic [91], enzyme inhibitor [107,108]
1,7-Dimethoxy-2-hydroxy-xanthone (**63**)	Xanthone	*G. polyantha* Oliv. (Guttiferae) [15], *G. afzelii* (Guttiferae) [78], *S. longependuncula*ta (Fresen) (Polygalaceae) [75,109]	Antioxidant [15], muscle relaxant [75]
3-Methoxy-2-hydroxyxanthone (**41**)	Xanthone	*Calophyllum flavoramulum* (Calophyllaceae) [110]	Cytotoxic [110]
4-Prenyl-2-(3,7-dimethyl-2,6-octadienyl)-1,3,5,8-tetrahydroxyxanthone (**54**)	Xanthone	*G. nobilis* (Guttiferae) [101]	Enzyme inhibitor [101]
8-Hydroxycudraxanthone G (**54**)	Xanthone	*G. nobilis* (Guttiferae) [101]	Enzyme inhibitor [101]
Caloxanthone A (**14**)	Xanthone	*C. inophyllum* (Guttiferae) [92]	Antimicrobial [111]
Decussatin (**11**)	Xanthone	*A. vogelli* Planch. (Loganiaceae) [112]	Cytotoxic [93]
Demethylcalabaxanthone (**24**)	Xanthone	*G. staudtii* Engl. (Guttiferae) [74]	Antimicrobial, cytotoxic [74]
Ferruginin B (**66**)	Anthranoid	*P. aurantiacum* Engl. (Hypericaceae) [103]	Cytotoxic [113]
Garcinone B (**25**)	Xanthone	*G. staudtii* Engl. (Guttiferae) [74]	Antimicrobial, cytotoxic [74]
Garcinone E (**35**)	Xanthone	*P. butyracea* Sabine (Guttiferae) [84]	Antiparasitic, cytotoxic [84]
Gartanin (**50**)	Xanthone	*G. nobilis* (Guttiferae) [101], *G. staudtii* Engl. (Guttiferae) [74]	Cytotoxic [114]
Globuliferin (**38**)	Xanthone	*S. globulifera* L. f. (Guttiferae) [115]	Antiplasmodial [115]

Harunganol B (**70**)	Anthranoid	*H. madagascariensis* Lam. (Hypericaceae) [23]	Antioxidant [23]
Harungin anthrone (**71**)	Anthranoid	*H. madagascariensis* Lam. (Hypericaceae) [23]	Antioxidant [23]
Kenganthranol B (**68**)	Anthranoid	*P. aurantiacum* Engl. (Hypericaceae) [103]	Enzyme inhibitor [103]
Macluraxanthone (**15**)	Xanthone	*C. inophyllum* (Guttiferae) [92]	Antimicrobial [111]
Mangiferin (**26**)	Xanthone	*Bombax malabaricum* DC (Bombacaceae) [116], *Cyclopia subternata* Vogel (Leguminosae) [117]	Analgesic [118], antioxidant [119], antiviral [86], enzyme inhibitor [120]
Rubraxanthone (**31**)	Xanthone	*A. monticola* Staner L.C. (Guttiferae) [121]	Antiparasitic [122], cytotoxic [84]
Symphonin (**37**)	Xanthone	*S. globulifera* L. f. (Guttiferae) [115]	Antiplasmodial [115]
Tovophyllin A (**30**)	Xanthone	*A. monticola* Staner L.C. (Guttiferae) [121]	Antiparasitic [122], cytotoxic [84]
Vismin (**65**)	Anthranoid	*P. aurantiacum* Engl. (Hypericaceae) [103]	Cytotoxic [113]
Vismion D (**67**)	Anthranoid	*P. aurantiacum* Engl. (Hypericaceae)	Antimicrobial, cytotoxic [123]

AChE: acetylcholinesterase

Table 11.2 New Xanthones and Anthranoids Isolated from the African Plants(−): not reported: (*): no known pharmacological activity.

Compounds	Class (Type)	Plants	Area of Plant Collection	Plant Parts	Physical Properties
3-Methoxycheffouxanthone (**78**)	Xanthone	*G. afzelii* [78] (Guttiferae)	Cameroon	Seeds	mp 123−124°C [78]
3′,4′-Deoxy-4′-chloropsoroxanthin-3′,5′-diol (**43**)	Xanthone (dihydrofurano-)	*Psorospermum molluscum* (Pers.) Hochr. (Hypericaceae) [104]	Madagascar	Wood stem	Yellow solid; $[\alpha]^{20}_{D} = -103°$ (*c* 0.08, MeOH) [104]
1,6,8-Trihydroxy-2,3,4,7-tetramethoxyxanthone (**62**)	Xanthone	*S. longepedunculata* (Polygalaceae) [18]	South Africa	Root bark	–
1,5,8-Trihydroxy-3,6,7-trimethoxyxanthone* (**81**)	Xanthone	*C. spicatum* L. (Gentianaceae) [89]	Egypt	Roots	–
1,3,6,8-Tetrahydroxy-2,5-dimethoxyxanthone (**61**)	Xanthone	*S. longepedunculata* (Polygalaceae) [18]	South Africa	Root bark	mp 152−155°C [18]
1,8-Dihydroxy-3-methoxy-6-methylxanthone* (**84**)	Xanthone	*C. obtusifolia* (Leguminosae) [99], *C. spicatum* L. (Gentianaceae) [89]	Cameroon Egypt	Leaves [99] Roots [89]	mp 152−153°C [99]
2-(3,3-Dimethylallyl)-7-methoxy-l,5,6-trihydroxy-2″,2″-dimethylpyrano(6″,5″:3,4) xanthone (**42**)	Xanthone (prenyl-)	*S. pauciflora* Baker (Guttiferae) [124]	Madagascar	Leaves	Yellow amorphous solid [124]
Allanxanthone A (**10**)	Xanthone (prenyl-)	*A. floribunda* Oliv. (Guttiferae) [19], *A. monticola* [125]	Cameroon	Stem bark, [19], fruits [125]	mp 178−180°C [19]
Allanxanthone B* (**82**)	Xanthone (isoprenyl-)	*A. monticola* Staner L.C. (Guttiferae) [121]	Cameroon	Bark	mp 158−160°C [121]
Bangangxanthone A (**59**)	Xanthone	*G. polyantha* Oliv. (Guttiferae) [15]	Cameroon	Stem bark	mp 157−158°C $[\alpha]^{29}_{D} = +25°$ (*c* 0.032, C_3H_6O) [15]

Bangangxanthone B (**60**)	Xanthone (prenyl-)	*G. polyantha* Oliv. (Guttiferae [15]	Cameroon	Stem bark	mp 199−201°C [15]
Butyraxanthone A (**32**)	Xanthone (geranyl-)	*P. butyracea* Sabine (Guttiferae) [84]	Cameroon	Stem bark	mp 131−133°C [84]
Butyraxanthone B (**33**)	Xanthone (prenyl-)	*P. butyracea* Sabine (Guttiferae) [84]	Cameroon	Stem bark	Yellow oil [84]
Butyraxanthone C* (**83**)	Xanthone (prenyl-)	*P. butyracea* Sabine (Guttiferae) [84]	Cameroon	Stem bark	Yellow oil; $[\alpha]_D^{25} = -24.4°$ (c 0.017, $CHCl_3$) [84]
Butyraxanthone D (**51**)	Xanthone (geranyl-)	*P. butyracea* Sabine (Guttiferae) [84]	Cameroon	Stem bark	Red oil [84]
Butyraxanthone E (**46**)	Xanthone	*P. butyracea* [94]	Cameroon	Roots	–
Caroxanthone* (**76**)	Xanthone (prenyl-)	*G. nobilis* (Guttiferae) [101]	Cameroon	Stem bark	–
Cheffouxanthone (**78**)	Xanthone (geranyl-)	*G. smeathmanii* Oliv. (Guttiferae) [126], *G. afzelii* [78] (Guttiferae)	Cameroon	Root bark [126], seeds [78]	mp 68−169°C [126]
Gaboxanthone (**78**)	Xanthone (prenyl-)	*S. globulifera* L. f. (Guttiferae) [115], *G. staudtii* Engl. (Guttiferae) [74]	Cameroon	Seed shells	mp 222−223°C [115]
Garceduxanthone (**49**)	Xanthone (isoprenyl-)	*Garcinia edulis* Exell. (Guttiferae) [127]	Tanzania	Root bark	mp 107.4−108.6°C [127]
Globulixanthone A (**52**)	Xanthone (isoprenoid-)	*S. globulifera* Linn. F. (Guttiferae) [128]	Cameroon	Root bark	mp 240−242°C [128]
Globulixanthone B (**17**)	Xanthone (isoprenoid-)	*S. globulifera* Linn. F. (Guttiferae) [128]	Cameroon	Root bark	Yellow oil; $[\alpha]^{25}_D = +9.5°$ (*c* 0.07, MeOH) [128]
Globulixanthone C (**16**)	Xanthone (prenyl-)	*S. globulifera* Linn. F. (Guttiferae) [129]	Cameroon	Root bark	mp 285°C [129]
Globulixanthone D (**18**)	Xanthone (prenyl-)	*S. globulifera* Linn. F. (Guttiferae) [129]	Cameroon	Root bark	mp 120°C [129]
Globulixanthone E* (**85**)	Xanthone (bis-)	*S. globulifera* Linn. F. (Guttiferae) [129]	Cameroon	Root bark	mp 228°C [129]

(*Continued*)

Table 11.2 (Continued)

Compounds	Class (Type)	Plants	Area of Plant Collection	Plant Parts	Physical Properties
Harunmadagascarin A (**69**)	Anthronoids (prenyl-)	*H. madagascariensis* Lam. (Hypericaceae) [23]	Cameroon	Stem bark	mp 149°C [23]
Harunmadagascarin B (**72**)	Anthronoids (prenyl-)	*H. madagascariensis* Lam. (Hypericaceae) [23]	Cameroon	Stem bark	mp 122.5°C [23]
Inoxanthone* (**86**)	Xanthone	*C. inophyllum* (Guttiferae) [92]	Cameroon	Root bark	mp 217°C [92]
Kenganthranol E* (**80**)	Anthranoids (prenyl-)	*P. aurantiacum* Engl. (Hypericaceae) [103]	Cameroon	Fruits	Yellow oil; $[\alpha]^{25}_{D} = +15.3°$ (*c* 0.017, $CHCl_3$) [103]
Laurentixanthone A (**12**)	Xanthone	*V. laurentii* De Wild. (Guttiferae) [102]	Cameroon	Roots	mp 156−157°C [102]
Laurentixanthone B (**13**)	Xanthone	*V. laurentii* De Wild. (Guttiferae) [102]	Cameroon	Roots	mp 112−114°C [102]
Polyanxanthone C (**77**)	Xanthone (prenyl-)	*G. polyantha* (Guttifeare) [77]	Cameroon	Wood trunk	Yellow oil [77]
Psorantin* (**79**)	Anthranoids (bis-)	*P. aurantiacum* Engl. (Guttiferae) [103]	Cameroon	Fruits	mp 200°C; $[\alpha]^{25}_{D} = 0°$ (*c* 0.023, $CHCl_3$) [103]
Psoroxanthin (**44**)	Xanthone (dihydrofurano-)	*P. molluscum* (Pers.) Hochr. (Hypericaceae) [104]	Madagascar	Roots	Yellow solid [104]
Polyanxanthone A (**56**)	Xanthone (prenyl-)	*G. polyantha* (Guttifeare) [77]	Cameroon	Wood trunk	mp 135−137°C [77]
Polyanxanthone B (**57**)	Xanthone (prenyl-)	*G. polyantha* (Guttifeare) [77]	Cameroon	Wood trunk	mp 139.9−140°C [77]
Securidacaxanthone A* (**78**)	Xanthone	*S. longepedunculata* Fres. (Polygalaceae) [109]	Cameroon	Root bark	mp 207−208°C [109]
Smeathxanthone A (**27**)	Xanthone (geranyl-)	*G. smeathmannii* (Guttiferae) [79], *G. nobilis* [101], *G. afzelii* [78]	Cameroon	Stem bark, [79], seeds [78]	mp 216−218°C [79]

Smeathxanthone B (**28**)	Xanthone (prenyl-)	*G. smeathmannii* (Guttiferae) [79], *G. afzelii* [78]	Cameroon	Stem bark, [79], seeds [78]	mp 187−189°C; $[\alpha]^{22}_{D} = +30.3°$ (*c* 0.02, MeOH) [79]
Staudtiixanthone A (**19**)	Xanthone (prenyl-)	*G. staudtii* Engl. (Guttiferae) [74]	Cameroon	Twigs	mp 201°C [74]
Staudtiixanthone B (**20**)	Xanthone (prenyl-)	*G. staudtii* Engl. (Guttiferae) [74]	Cameroon	Twigs	mp 214°C [74]
Staudtiixanthone C (**21**)	Xanthone (prenyl-)	*G. staudtii* Engl (Guttiferae) [74]	Cameroon	Twigs	mp 203°C [74]
Staudtiixanthone D (**23**)	Xanthone (prenyl-)	*G. staudtii* Engl. (Guttiferae) [74]	Cameroon	Twigs	mp 208−209°C [74]
Xanthone V_1 (**29**)	Xanthone (prenyl-)	*Vismia guineensis* [130]	Ivory Coast	Roots	mp 214−215°C [130]
Xanthone V_2 (**53**)	Xanthone (prenyl-)	*V. guineensis* [130]	Ivory Coast	Roots	mp 210−213°C [130]
Xanthone V_{1a} (**73**)	Xanthone (prenyl-)	*V. guineensis* (Guttiferae) [130]	Ivory Coast	Roots	mp 176−179°C [130]
Xanthone V_{2a} (**74**)	Xanthone (prenyl-)	*V. guineensis* [130]	Ivory Coast	Roots	mp 170−173°C [130]

(−): not reported: (*): no known pharmacological activity

been identified as a substrate of the efflux pumps in Enterobacteria and *P. aeruginosa*, and the combination with PAβN induced significant increase of the antibacterial activity against MDR bacteria [132]. The most prominent effects were obtained on *E. coli* ATCC 8739, AG100A, and AG100ATet (MIC dropped from >256 to 16 μg/mL), *E. aerogenes* EA294 (MIC dropped from 128 to 8 μg/mL), and *E. aerogenes* EA298 (MIC dropped from 256 to 8 μg/mL) [132].

The antifungal activity of **2** was also documented on *Candida albicans* and *Aspergillus terreus* (MIC_{80}: 62 μg/mL), *Aspergillus niger* (MIC_{80}: 32 μg/mL), *Aspergillus flavus* and *A. fumigatus* (MIC_{80}: 16 μg/mL) [133], and 1,4,8-trihydroxyxanthone (**3**) was observed against *Cryptococcus neoformans* (MIC: 12.5 μg/mL), *P. aeruginosa*, and *C. albicans* (MIC: 50 μg/mL) [88]. The isomer of compound **3** and 1,3,5-trihydroxyxanthone (**4**) showed an antibacterial activity against *Moraxella catarrhalis* (MIC: 16 μg/mL) but was inactive against *E. coli*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* [80]. Compound **4** also showed antimalarial activity against *Plasmodium falciparum* FcB1 (IC_{50}: 24.7 μg/mL) [134]. The xanthone 1,6-dihydroxy-5-methoxyxanthone (**5**), isolated from the *G. polyantha*, exhibited antitubercular activity against *Mycobacterium tuberculosis* [90]. 1,3,6-Trihydroxy-8-methylxanthone or norlichexanthone (**6**) displayed antimicrobial activities against *S. aureus* (IC_{50}: 20.9 μM) and *A. fumigatus* (IC_{50}: 169 μM) but was inactive against *C. albicans*, *E. coli*, and *P. aeruginosa* PA01 [98]. From the few pharmacological data available on 1,6-dihydroxy-3-methoxy-8-methylxanthone (**7**), the only pathogen found sensitive was *C. albicans* (IC_{50}: 149 μM) [98].

Though 1,5-dihydroxy-3-methoxyxanthone (**8**), isolated from the roots of the Egyptian plant *Centaurium spicatum*, was not active against *C. albicans*, *Candida krusei*, *Candida glabrata*, *E. coli*, *P. aeruginosa*, *C. neoformans*, *Mycobacterium intracellulare*, *S. aureus*, and methicillin-resistant *S. aureus* (MRSA) [89], activity was reported against *M. tuberculosis* 90-221387 (MIC: 6.3 μg/mL) [12], *A. niger* (MIC_{80}: 125 μg/mL), *A. flavus*, and *A. fumigatus* (MIC_{80}: 31 μg/mL) [133]. Also, 1,6-dihydroxy-3,5-dimethoxyxanthone (**9**) did not show any antibacterial activity but exhibited moderate antifungal activities against *C. krusei* and *C. neoformans*, with IC_{50} values of 12.82 and 17.90 μg/mL, respectively [89].

A constituent of the stem bark of the Cameroonian plant *A. floribunda*, allanxanthone A (**10**) (Figure 11.8), displayed antimicrobial activity on a range of microorganisms, including *Citrobacter freundii* and *Proteus vulgaris* (MIC: 12.84 μM), *E. aerogenes* (MIC: 102.79 μM), *Salmonella typhi* (MIC: 51.37 μM), *S. aureus* (MIC: 25.68 μM), *Bacillus megaterium* (MIC: 102.79 μM), *C. krusei*, *Bacillus thurengiensis*, and *Streptococcus faecalis* (MIC: 102.79 μM), *C. glabrata* and *K. pneumoniae* (MIC: 6.42 μM), and *Bacillus stearothermophilus* (MIC: 12.84 μM) [121]. The microbial growth inhibitory activity of decussatin (**11**) was also reported on *Candida parapsilosis* (MIC: 25 μg/mL) [135].

Laurentixanthones A (**12**) and B (**13**), isolated from *V. laurentii* exhibited good and selective antimicrobial activity [102]. Compound **12** prevented the growth of *S. faecalis* (MIC: 1.22 μg/mL), *B. megaterium* (MIC: 2.44 μg/mL), *Shigella dysenteriae* (MIC: 4.88 μg/mL), *Shigella flexneri* (MIC: 4.88 μg/mL),

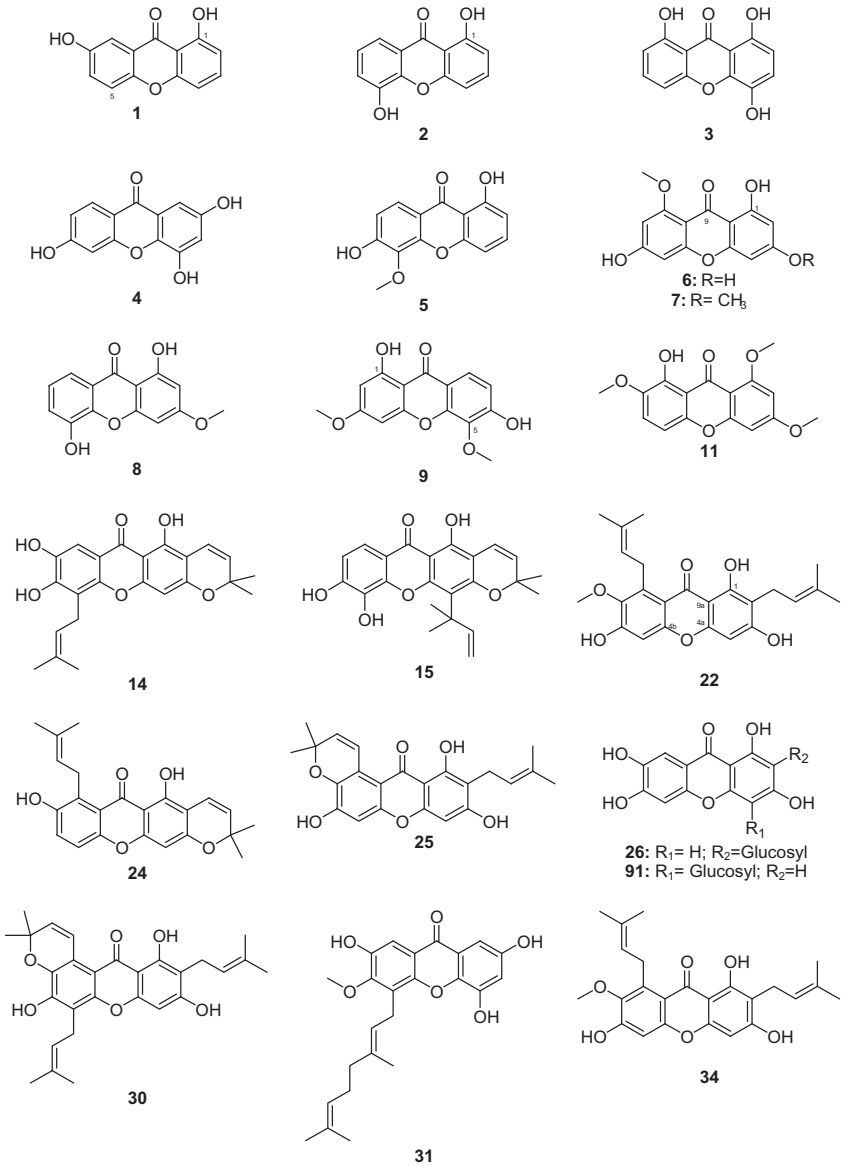


Figure 11.7 Biologically active xanthones and anthrones identified in African plants: 1,7-dihydroxyxanthone (**1**); 1,5-dihydroxyxanthone (**2**); 1,4,8-trihydroxyxanthone (**3**); 1,3,5-trihydroxyxanthone (**4**); 1,6-dihydroxy-5-methoxyxanthone (**5**); 1,3,6-trihydroxy-8-methylxanthone (**6**); 1,6-dihydroxy-3-methoxy-8-methylxanthone (**7**); 1,5-dihydroxy-3-methoxyxanthone (**8**); 1,6-dihydroxy-3,5-dimethoxyxanthone (**9**); decussatin (**11**); caloxanthone A (**14**); macluraxanthone (**15**); α-mangostin (**22**); demethylcalabaxanthone (**24**); garcinone B (**25**); mangiferin (**26**); isomangiferin (**91**); tovophyllin A (**30**); rubraxanthone (**31**); 1,3,6-trihydroxy-7-methoxy-2,8-diprenylxanthone (**34**); garcinone E

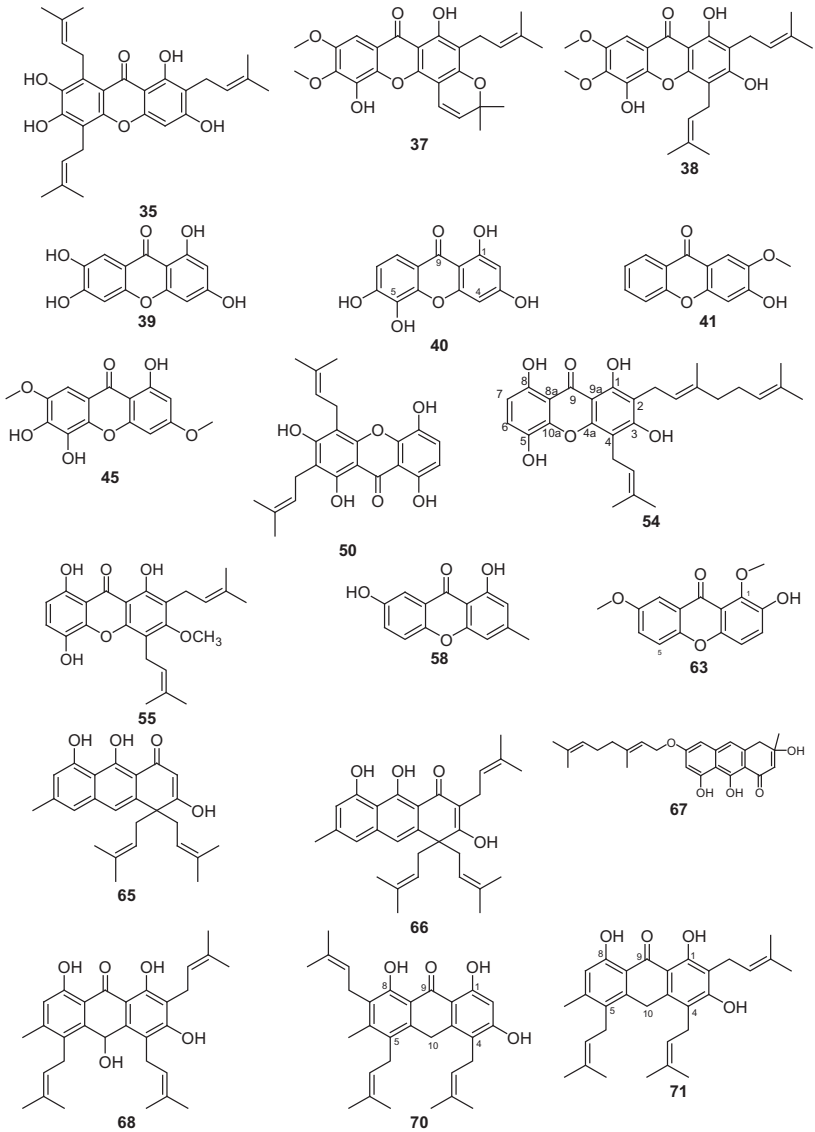


Figure 11.7 (Continued)

◀ (**35**); symphonin (**37**); globuliferin (**38**); 1,3,6,7-tetrahydroxyxanthone (**39**); 1,3,5,6-tetrahydroxyxanthone (**40**); 3-methoxy-2-hydroxyxanthone (**41**); 1,5,6-trihydroxy-3,7-dimethoxyxanthone (**45**); gartanin (**50**); 4-prenyl-2-(3,7-dimethyl-2,6-octadienyl)-1,3,5,8-tetrahydroxyxanthone (**54**); 8-hydroxycudraxanthone G (**54**); 1,7-dihydroxy-3-methylxanthone (**58**); 1,7-dimethoxy-2-hydroxy-xanthone (**63**); vismin (**65**); ferruginin B (**66**); vismion D (**67**); kenganthranol B (**68**); harunganol B (**70**); harungin anthrone (**71**).

B. stearothermophilus (MIC: 4.88 μg/mL), *Bacillus subtilis* (MIC: 4.88 μg/mL), *Enterobacter cloacae* (MIC: 39.06 μg/mL), *Proteus mirabilis* (MIC: 39.06 μg/mL), *Bacillus cereus* (MIC: 78.12 μg/mL), and fungi *C. glabrata* (MIC: 2.44 μg/mL) and *C. albicans* (MIC: 39.06 μg/mL) [102]. The inhibitory effects of **13** were recorded against *P. aeruginosa* (MIC: 4.88 μg/mL), *S. flexneri* (MIC: 19.53 μg/mL), *B. cereus* (MIC: 78.12 μg/mL), *B. subtilis* (MIC: 2.44 μg/mL), *C. albicans* (MIC: 19.53 μg/mL), and *C. glabrata* (MIC: 0.61 μg/mL) [102]. Under similar experimental conditions, the activity of **13** was better than that of the reference compound nystatin (MIC: 4.88 μg/mL) on *C. glabrata* [102]. This compound also inhibited the growth of a panel of MDR Gram-negative bacteria, and the activity significantly increased in the presence of the efflux pump inhibitor PAβN [132].

Two constituents of *C. inophyllum*, caloxanthone A (**14**) and macluraxanthone (**15**), are documented as anti-MRSA agents, with MIC values ranging from 6.25 to 25 μg/mL for both compounds [111]. Globulixanthones C (**16**), D (**17**), and E (**18**), isolated from the root bark of *S. globulifera* harvested in Cameroon, inhibited the growth of *S. aureus* (MIC: 14.05, 8.0, and 4.51 μg/mL, respectively), *B. subtilis* (MIC: 8.24, 12.5, and 3.56 μg/mL, respectively), while only **18** was active against *Vibrio anguillarum* (MIC: 5.56 μg/mL). None of the three compounds was active against *E. coli* [128].

Xanthones isolated from the twigs of *Garcinia staudtii*, staudtiixanthones A (**19**) (MIC: 16 μg/mL), B (**20**) (MIC: 32 μg/mL), D (**21**) (MIC: 64 μg/mL), and α-mangostin (**22**) (MIC: 32 μg/mL) exhibited moderate activity against MRSA, while staudtiixanthone C (**23**), demethylcalabaxanthone (**24**), and garcinone B (**25**) (MIC: 128 μg/mL) showed lower activity [74].

The glucoxanthone mangiferin (**26**) inhibited HIV-1-induced syncytium formation in the human C8166 T-cells and MT-4 T-cells, with effective concentration 50 (EC_{50}) values varying from 7.13 to 38.08 μg/mL [86].

Two new xanthones isolated from *Garcinia smeathmannii*, smeathxanthones A (**27**) and B (**28**), exhibited activity on both bacteria and fungi [79]. Compound **27** displayed activity against *E. coli*, *S. typhi*, and *S. faecalis* (MIC: 156.25 μg/mL), *K. pneumoniae*, *P. vulgaris*, *S. aureus*, *C. albicans*, and *C. krusei* (MIC: 312.5 μg/mL), while **28** was also active against *E. coli*, *K. pneumoniae*, *S. typhi*, and *S. faecalis* (MIC: 625 μg/mL), *P. vulgaris*, *S. aureus*, *C. albicans*, and *C. krusei* (MIC: 312.5 μg/mL) [79].

Antiviral activity has been documented for some xanthones identified in African plants. Compound **1** (1,7-dihydroxyxanthone) showed an anti-HIV property in cells genetically modified and infected with HIV-1 (EC_{50}) 1.00 μg/mL [136], and also inhibited HIV-1 reverse transcriptase (IC_{50}: 50.1 μg/mL) [111].

Some xanthones identified in African plants also showed antiparasitic activity. Xanthone V_1 (**29**) showed an antiprotozoal activity against *Trypanosoma cruzi* trypomastigotes [122]. The minimum concentration at which all epimastigotes terminated after 48 h was determined to be 15 μg/mL [122]. Other xanthones, tovophyllin A (**30**) and rubraxanthone (**31**), also showed antiparasitic activity against *P. falciparum* (IC_{50}: 2.8 and 3.4 μg/mL, respectively) [84]. Xanthones isolated from *P. butyracea*, butyraxanthones A (**32**) and B (**33**), 1,3,6-trihydroxy-7-methoxy-2,8-diprenylxanthone

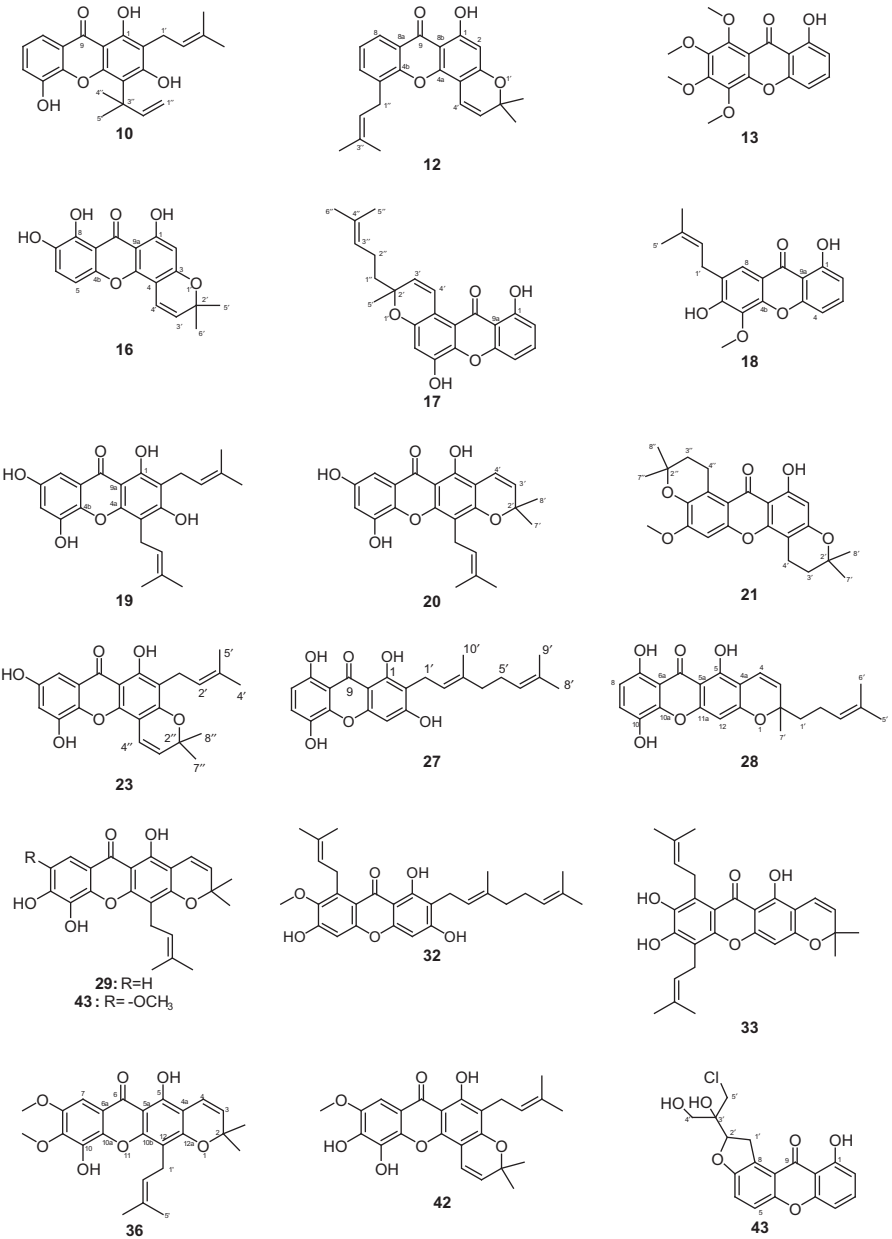
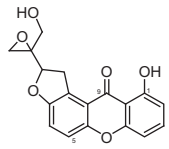
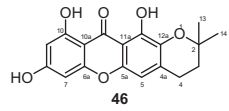
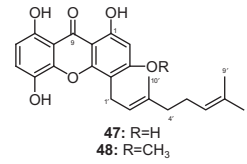
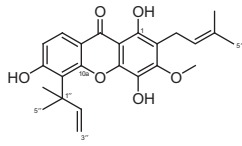


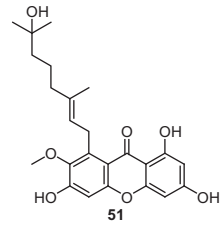
Figure 11.8 Chemical structrures of new xanthones and anthrones isolated from African medicinal plants: allanxanthone A (**10**); laurentixanthone A (**12**); laurentixanthone B (**13**); globulixanthone C (**16**); globulixanthone B (**17**); globulixanthone D (**18**); staudtiixanthone A (**19**); staudtiixanthone B (**20**); staudtiixanthone D (**21**); staudtiixanthone C (**23**); smeathxanthone A (**27**); smeathxanthone B (**28**); xanthone V_1 (**29**); xanthone V_2 (**53**); butyraxanthone A (**32**); butyraxanthone B (**33**); gaboxanthone (**36**); 2-(3,3-dimethylallyl)-7-

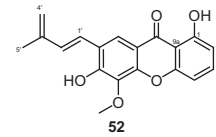


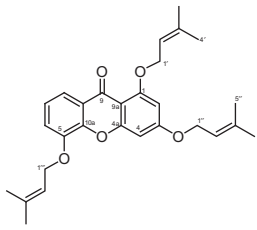


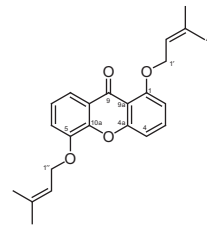


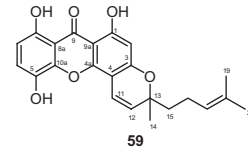


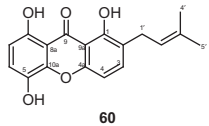


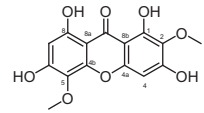


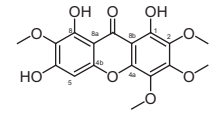


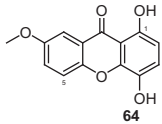


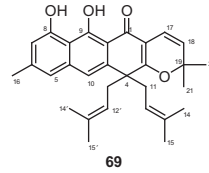












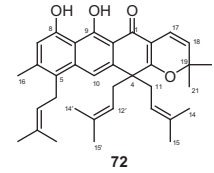


Figure 11.8 (Continued)

◀ methoxy-1,5,6-trihydroxy-2″,2″-dimethylpyrano(6″,5″:3,4) xanthone (**42**); 3′,4′-deoxy-4′-chloropsoroxanthin-3′,5′-diol (**43**); psoroxanthin (**44**); butyraxanthone E (**46**); cheffouxanthone (**47**); 3-methoxycheffouxanthone (**48**); garceduxanthone (**49**); butyraxanthone D (**51**), globulixanthone A (**52**), polyanxanthone A (**56**), polyanxanthone B (**57**); bangangxanthone A (**59**); bangangxanthone B (**60**); 1,3,6,8-tetrahydroxy-2,5-

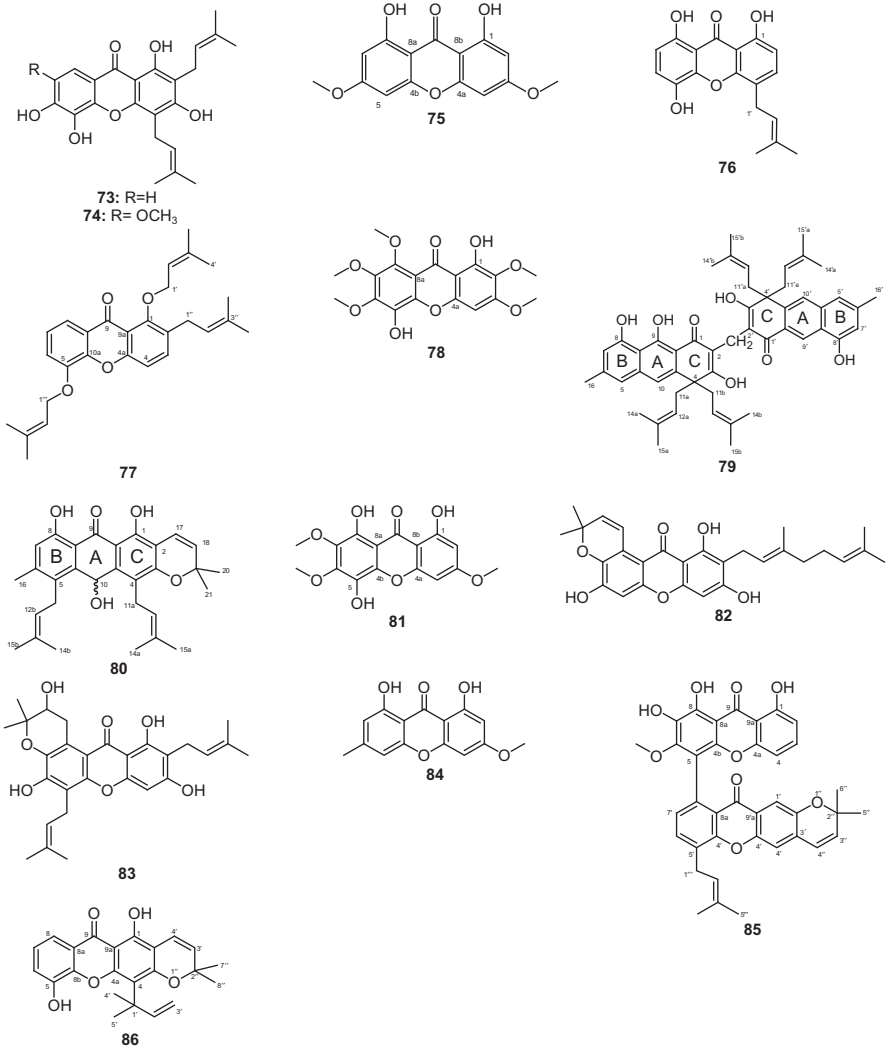


Figure 11.8 (Continued)

◀ dimethoxyxanthone (**61**); 1,6,8-trihydroxy-2,3,4,7-tetramethoxyxanthone (**62**); 1,4-dihydroxy-7-methoxy-xanthone (**64**); harunmadagascarin A (**69**); harunmadagascarin B (**72**); xanthone V_{1a} (**73**); xanthone V^{2a} (**74**); 1,8-dihydroxy-3,6-dimethoxyxanthone (**75**); caroxanthone (**76**); polyanxanthone C (**77**); securidacaxanthone A (**78**); psorantin (**79**); kenganthranol E (**80**); 1,5,8-trihydroxy-3,6,7-trimethoxyxanthone (**81**); allanxanthone B (**82**); butyraxanthone C (**83**); 1,8-dihydroxy-3-methoxy-6-methylxanthone (**84**); globulixanthone E (**85**); inoxanthone (**86**).

(**34**) and garcinone E (**35**), displayed antiparasitic activity against chloroquine-resistant *P. falciparum*, with respective IC_{50} values of 3.0, 2.7, 2.2, and 2.8 μg/mL [84]. A new compound is also isolated from *S. globulifera*, gaboxanthone (**36**), together with symphonin (**37**) and globuliferin (**38**), also exhibited antiplasmodial activities against *P. falciparum* W2 strain, with respective IC_{50} values of 3.53, 1.29, and 3.86 μM [115].

11.4.2 Cytotoxicity of Xanthones Identified in African Medicinal Plants

The potential of xanthones as anticancer agents is well known. The hit compounds involved in cancer chemotherapy include 5,6-dimethylxanthenone-4-acetic acid (DMXAA), psorospermin, mangiferin, norathyriol, mangostins, and 6-isopropoxy-9-oxoxanthene-2-carboxylic acid (AH6809), a prostanoid receptor antagonist [72]. Prenylated caged xanthones, both naturally occurring and synthetic analogs, have been identified as promising anticancer agents [137]. Gambogic acid was found to be a highly valuable lead compound for antitumor chemotherapy [137]. The cytotoxicity of several xanthones found in African plants (Figures 11.1 and 11.2; Tables 11.1 and 11.2), including mangiferin and mangostin, has been documented on a panel of cancer cell lines, and the modes of action of some of these molecules have been provided. The reported activity for some of the compounds was significantly high, with IC_{50} values below 10 μM or 4 μg/mL [138,139]. Compound **1** (1,7-dihydroxyxanthone) exhibited a selective antiproliferative activity against cancer cell lines, with its effects reported against epidermoid carcinoma of the nasopharynx KB cells (IC_{50}: 15.1 μg/mL), epidermoid carcinoma of the nasopharynx KB-C2 cells (IC_{50}: 14.5 μg/mL), resistant leukemia K-562/Adr cells (IC_{50}: 42.1 μg/mL), colon carcinoma COLO205 cells (IC_{50}: 42 μg/mL), breast carcinoma MCF-7 cells (IC_{50}: 47 μg/mL) [91], human colon carcinoma HT-29 cells (IC_{50}: 3.94 μg/mL), mouse lymphocytic leukemia P-388 cells (IC_{50}: 3.94 μg/mL) [97], renal cancer TK-10 cells (IC_{50}: 60.1 μM), and melanoma UACC-62 cells (IC_{50}: 20.2 μM) [140]. Compound **2** (1,5-dihydroxyxanthone) also significantly inhbited the proliferation of the HT-29 cells (IC_{50}: 5.01 μg/mL), mouse lymphocytic leukemia P-388 cells (IC_{50}: 4.71 μg/mL), and KB cells (IC_{50}: 3.3 μg/mL) [19]. The compound 1,3,6,7-tetrahydroxyxanthone (**39**) displayed cytotoxic effects against cancer cell lines such as KB (IC_{50}: 33.3 μg/mL), COLO205 (IC_{50}: 28.5 μg/mL), leukemia K-562/Adr (IC_{50}: 34.5 μg/mL), KB-C2 (IC_{50}: 93.5 μg/mL), leukemia K-562 (IC_{50}: 22.5 μg/mL), MCF-7 (IC_{50}: 18.6 μg/mL) [91], human CNS cancer SF-268 (IC_{50}: 53 μg/mL), and human liver cancer HepG2 (IC_{50}: 11 μg/mL) [76]. Compound **5** was highly active against HT-29 cells (IC_{50}: 0.84 μg/mL) and P-388 cells (IC_{50}: 0.27 μg/mL) [76]. Meanwhile, 1,3,5,6-tetrahydroxyxanthone (**40**) inhibited the proliferation of a panel of malignant cell lines, including KB (IC_{50}: 25.6 μg/mL), COLO205 (IC_{50}: 26.5 μg/mL), MCF-7 (IC_{50}: 18.9 μg/mL), K-562 (IC_{50}: 25.4 μg/mL), and K-562/Adr (IC_{50}: 24.7 μg/mL) [91]. Interestingly, compound **40** attenuated the increased levels of lactate dehydrogenase (LDH), tumor necrosis factor-α (TNF-α), monocyte chemo-attractant protein-1 (MCP-1), and asymmetric dimethylarginine (ADMA) induced by oxidized low-density lipoprotein (ox-LDL), and also

significantly attenuated the decreased level of nitrite/nitrate caused by ox-LDL [141]. Its cytoprotective effect was also observed on the ECV304 human umbilical vein endothelial cell line as it also significantly attenuated the increase in adhesion of monocytes caused by ox-LDL at a concentration range of 1−10 μM [141]. Compound **6** showed cytotoxic effects against mouse lymphoma L5178Y cells (IC_{50}: 1.16 μM), chronic myelogenous leukemia K562 cells (IC_{50}: 253.5 μM), ovarian cancer A2780 cells (IC_{50}: 68.2 μM), and ovarian cancer A2780CisR cells (IC_{50}: 74 μM) [141], while **8** inhibited the proliferation of a panel of malignant cell lines such as KB (IC_{50}: 28.1 μg/mL), COLO205 (IC_{50}: 44.2 μg/mL), MCF-7 (IC_{50}: 32.2 μg/mL), KB-C2 (IC_{50}: 25.9 μg/mL), K-562/Adr (IC_{50}: 15.7 μg/mL) [91], HT-29 (IC_{50}: 7.51 μg/mL), and P-388 (IC_{50}: 2.76 μg/mL) [97]. Chen et al. [97] also reported antiproliferative activity for compound **9** against HT-29 cells (IC_{50}: 7.28 μg/mL) and P-388 cells (IC_{50}: 4.74 μg/mL), while 3-methoxy-2-hydroxyxanthone (**41**) displayed cytotoxic effects against KB (IC_{50}: 20.3 μg/mL), KB-C2 (IC_{50}: 23.6 μg/mL), K-562/Adr (IC_{50}: 57.5 μg/mL), COLO205 (IC_{50}: 87.3 μg/mL), and MCF-7 cells (IC_{50}: 87.3 μg/mL) [91].

The new xanthone 2-(3,3-dimethylallyl)-7-methoxy-l,5,6-trihydroxy-2″,2″-dimethyl-pyrano(6″,5″:3,4) xanthone (**42**), isolated from the leaves of the Madagascan plant *Symphonia pauciflora*, showed good antiproliferative activity, with an IC_{50} value of 3.8 μM against the A2780 human ovarian cancer cell line [124]. Two new dihydrofurano-xanthones, 3′,4′-deoxy-4′-chloropsoroxanthin-3′,5′-diol (**43**)) and psoroxanthin (**44**), isolated from another Madagascan plant, *Psorospermum molluscum*, displayed significant cytotoxic effects against the cancer cell line A2780 (IC_{50}: 0.042 and 0.33 μM, respectively) and colon cancer HCT-116 (IC_{50}: 0.068 and 01.0 μM, respectively) [104]. In addition, compound **43** was also cytotoxic to the human breast cancer cell line SKBR3 (IC_{50}: 2.0 μM) [104].

The di-methoxylated xanthone 1,5,6-trihydroxy-3,7-dimethoxyxanthone (**45**) exhibited cytotoxic effects against cancer cell lines such as human CNS cancer SF-268 (IC_{50}: 28 μg/mL), MCF-7 (IC_{50}: 35 μg/mL), HepG2 (IC_{50}: 10 μg/mL) [76], and KB (IC_{50}: 2.5 μg/mL) [97]. The xanthones **10**[34] and **14**[92] also induced an antiproliferative effect against KB cell line, with IC_{50} values of 1.5 and 7.4 μg/mL, respectively. The cytotoxicity of compound **11** was reported against HL60 (IC_{50}: 7.58 μg/mL) and HepG2 (IC_{50}: 8.43 μg/mL) [93].

Butyraxanthone E (**46**), isolated from the roots of *P. butyracea*, did not show any cytotoxic effect on leukemia THP-1 cells or HCT116 cells, but induced a growth inhibitory effect against the S2 cells of *Drosophila* (IC_{50}: 6.27 μg/mL) [94]. Cheffouxanthone (**47**), newly isolated from the root bark of *G. smeathmannii*, and its known methoxylated derivative 3-methoxycheffouxanthone (**48**), isolated from the seeds of *G. afzelii*, exhibited significant cytotoxicity against kidney cells (IC_{50}: 4 μg/mL) [78]. A new compound isolated from the root bark of *G. edulis* harvested in Tanzania, garceduxanthone (**49**), showed high cytotoxicity against *Artemia salina* [127], while gartanin (**50**) displayed cytotoxic activity, with IC_{50} values of 1.08 μg/mL against the small-cell lung cancer NCI-H187, 15.54 μg/mL against the breast cancer BC-1, and 15.63 μg/mL against KB cells [114].

The xanthones (**32**−**35**) and butyraxanthone D (**51**) inhibited the proliferation of the breast cancer cell line MCF-7, with respective IC_{50} values of 3.5, 3.5, 3.3, 1.5, and 1.3 μg/mL [84]. The antiproliferative activity of compounds **30** and **31** has also been reported against MCF-7 cells (IC_{50}: 2.6 μg/mL for both compounds) [84].

The new xanthones **17** and globulixanthone B (**52**), isolated from the root bark of *S. globulifera*, exhibited a signigicant cytotoxic effect on KB cells, with IC_{50} values 2.15 and 1.78, respectively [129].

Compound **29** displayed significant cytotoxic effects on a panel of cancer cell lines (see Chapter 18) [142]. Xanthone V_2 (**53**) has shown activity against human gastric carcinoma SGC-7901 cells (IC_{50}: 3.4 μg/mL), hepatocellular carcinoma SMMC-7721 cells (IC_{50}: 6.2 μg/mL), and HCT-116 cells (IC_{50}: 1.3 μg/mL) [143]. The antiproliferation effects of compounds **19**−**21**, **23** were determined by measuring the inhibition of phytohemagglutinin (PHA)-induced T-cell proliferation, and they exhibited a strong suppressive effect, with IC_{50} values of 6.2, 6.4, 12.7, and 3.7 μg/mL, respectively [74].

11.4.3 Enzymatic Inhibitory Activities of Xanthones Identified in African Medicinal Plants

It has been demomstrated that the inhibitory activitiy of xanthone derivatives can be regulated by H-bond forming substituents, pi-stacking-forming aromatic rings, and softness values on the xanthone skeleton [144]. Xanthones from African plants have been documented as potent inhibitors of several enzymes. Some of them have been reported to exhibit strong inhibitory activity toward α-glucosidase (E.C.3.2.1.20), suggesting a possible role in the fight against diabetes mellitus. Compound **1** (1,7-dihydroxyxanthone), identified in several African plants, inhibited the activity of α-glucosidase from *Saccharomyces cerevisiae* (IC_{50}: 145 μM) [101]. The enzyme inhibitory activity of **1** was also reported on influenza A H1N1 neuraminidase (IC_{50}: 23.54 μg/mL), influenza A H9N2 neuraminidase (IC_{50}: 22.45 μg/mL), and the wild-type novel swine flu virus neuraminidase (IC_{50}: 11.54 μg/mL) [107]. Inhibition of α-glucosidase was also observed with compound **27** (IC_{50}: 394 μM), 4-prenyl-2-(3,7-dimethyl-2,6-octadienyl)-1,3,5,8-tetrahydroxyxanthone or 3-dimethyl-2-geranyl-4-prenylbellidifolin (**54**) (IC_{50}: 227 μM) and 8-hydroxycudraxanthone G (**55**) (IC_{50}: 76 μM) [101]. Compound **27** significantly inhibited the activity of neuraminidase (IC_{50}: 0.27 μM) [108]. Neuraminidase enzymes are glycoside hydrolase enzymes (EC 3.2.1.18) that cleave the glycosidic linkages of neuraminic acids, and their inhibitors are useful for combating influenza infection.

Inhibition of the activity of butyrylcholinesterase (EC 3.1.1.8) has also been reported for compound **2** (IC_{50}: 2.54 μM) [77]. Butyrylcholinesterase (also known as pseudocholinesterase, plasma cholinesterase, BCHE, or BuChE) is a nonspecific cholinesterase enzyme that hydrolyzes many different choline esters [145]. Cholinesterase inhibitors (or "anticholinesterase") suppress the action of the enzyme. Because of its essential function, chemicals that interfere with the action of cholinesterase are potent neurotoxins, causing excessive salivation and eye-watering in low doses, followed by

muscle spasms and ultimately death [146]. Two new xanthones isolated from *G. polyantha*, polyanxanthones A (**56**) and B (**57**), as well as compounds **4** and **5**, also showed cholinesterase inhibitory activity [77]. Compounds **4** and **5** significantly inhibited BChE, with IC_{50} values of 93.0, and 74.4 μM, respectively, while **57** showed significant inhibition against both acetylcholine esterase (AChE) (IC_{50}: 46.3 μM) and BChE (IC_{50}: 25.5 μM), compared to the standard drug galantamine (IC_{50}: 0.5 and 8.5 μM, respectively) [77]. The xanthone **56** showed 41.8% and 7.0% inhibition against AChE and BChE, respectively, at a concentration of 0.2 mM [77]. The enzymatic inhibitory activity of compound **4** has also been reported on monoamine oxidase-A (IC_{50}: 3.8 μM) and monoamine oxidase-B (IC_{50}: 73 μM) [81]. Inhibition of AchE (IC_{50}: 95 μM) and BChE (IC_{50}: 19.10 μM) was also documented for compound **10** [125].

Compound **2** also showed a reversible and time-independent inhibitory activity on the monoamines oxidase-A (IC_{50}: 0.73 μM) and oxidase-B (IC_{50}: 76 μM) [81]. L-MAO (EC 1.4.3.4) are a family of enzymes that catalyze the oxidation of monoamines [147]. Because of the vital role that MAOs play in the inactivation of neurotransmitters, MAO dysfunction (too much or too little MAO activity) is thought to be responsible for a number of psychiatric and neurological disorders [148]. For example, unusually high or low levels of MAOs in the body have been associated with depression [149], schizophrenia [150,151], substance abuse, attention deficit disorder, migraines, and irregular sexual maturation [148]. MAO inhibitors are one of the major classes of drugs prescribed for the treatment of depression, although they are often last-line treatment due to risk of the drug's interaction with diet or other drugs [148]. An excessive level of catecholamines (epinephrine, norepinephrine, and dopamine) may lead to a hypertensive crisis, whereas an excessive levels of serotonin may lead to serotonin syndrome [148]. In fact, MAO-A inhibitors act as antidepressant and antianxiety agents, whereas MAO-B inhibitors are used alone or in combination to treat Alzheimer's and Parkinson's diseases [152]. The compound 1,7-dihydroxy-3-methylxanthone (**58**) was also reported as an MAO inhibitor (IC_{50}: 20.6 μM) [100]. The inhibition of MAO activity was also documented for compound **11** on MAO-A (IC_{50}: 19 μM) and MAO-B (IC_{50}: 14.7 μM) and for **8** on MAO-A (IC_{50}: 0.04 μM) and MAO-B (IC_{50}: 33 μM) [81].

Inhibition of xanthine oxidase (XO) (EC 1.17.3.2) has been observed for compound **39** (IC_{50}: 21.73 μM) [83]. XO is a form of xanthine oxidoreductase, an enzyme that generates reactive oxygen species [153]. It catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. This enzyme plays an important role in the catabolism of purines in some species, including humans [154]. Inhibition of XO has been proposed as a mechanism for improving cardiovascular health [155].

Compound **6** is reported to inhibit the activity of a panel of protein kinases, including AKL (IC_{50}: 41.3 μM), ARK5 (IC_{50}: 33 μM), Aurora-B (IC_{50}: 3 μM), IGF-1R (IC_{50}: 33.3 μM), PIM1 (IC_{50}: 0.3 μM), PLK1 (IC_{50}: 75.7 μM), PRK1 (IC_{50}: 54.9 μM), SRC (IC_{50}: 35 μM), and VEGF-R2 (IC_{50}: 11.7 μM) [87]. A protein kinase is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). Phosphorylation usually results in a functional change of the target protein (substrate) by changing enzyme activity, cellular

location, or association with other proteins [156]. Deregulated kinase activity is a frequent cause of disease, in particular cancer, wherein kinases regulate many aspects that control cell growth, movement, and death [156]. The drugs that inhibit specific kinases are being developed to treat several diseases, and some are currently in clinical use, including Gleevec (imatinib) and Iressa (gefitinib) [156].

The antiinfective mode of action of compound **26** (mangiferin) includes the inhibition of microbial enzymes. In effect, **26** did not show any inhibitory activity on the HIV-1 reverse transcriptase and integrase but targeted the HIV-1 protease (EC_{50}: 342.8 μM) [86]. Compound **26** also inhibited the activity of neuraminidase from *Clostridium welchii* (IC_{50}: 11.2 μM) [157]. Other enzymatic inhibitory effects of **26** were reported on α-glucosidase (IC_{50}: 22.7 μg/mL) and the antioxidant enzyme XO (IC_{50}: 8.2 μM) [120]. Inhibition of HIV-1 protease (IC_{50}: 11.3 μg/mL) was also reported for compound **49** [127].

11.4.4 Antioxidant Activities of Xanthones Identified in African Medicinal Plants

Some xanthones isolated from African medicinal plants are documented as having antioxidant properties. These compounds have shown various degrees of antioxidant effects (see cutoff point in Chapter 8) in different experimental models. Two new xanthones reported in *G. polyantha*, bangangxanthones A (**59**) and B (**60**), as well as compound **2**, showed DPPH radical scavenging activities [15]. Compound **59** showed moderate activity (IC_{50}: 87.0 μM) compared to the standard 3-*t*-butyl-4-hydroxyanisole (IC_{50}: 42.0 μM) under similar experimental conditions [15]. Compound **60** was less active (IC_{50}: 482.0 μM) and **2** exhibited 39.5% inhibition at concentrations higher than 1 mM [15]. Compound **4** also exhibited a DPPH radical scavenging activity (IC_{50}: 148 mM) [82]. Compound **26** displayed various types of scavenging antioxidant activities, such as the DDPH radical (EC_{50}: 0.59 μM), ferric (3 +) 2,4,6-tris(2-pyridyl)-*s*-triazine complex (EC_{50}: 1.03 μM), and 2,2′-azobis(2-methylpropionamidine) dihydrochloride (EC_{50}: 12.85 μM) [119].

11.4.5 Other Biological Activities of Xanthones Identified in African Medicinal Plants

The xanthone (**1**) showed an antihypotensive property in ddY mice and significantly inhibited platelet activating factor (PAF)-induced hypotension by 56% at 10 mg/kg. Its isomer, compound **2**, demonstrated an antinociceptive in Swiss mice, inducing a maximal inhibition of 94% at 10 mg/kg [96]. *S. longepedunculata*'s xanthones stimulated the relaxation of corpus cavenosum smooth muscle between 0 and 60 s after the application of the compounds in a frequency-dependent manner [18]. At a concentration of 1.8×10^{-5} mg/mL, 1,3,6,8-tetrahydroxy-2,5-dimethoxyxanthone (**61**) relaxed the muscles at 97%, whereas 1,6,8-trihydroxy-2,3,4,7-tetramethoxyxanthone (**62**) relaxed them only 30.5% [18]. Under similar experimental conditions, the positive control, Viagra, relaxed the muscles 100.0% at the same concentration [18].

The compounds 1,7-dimethoxy-2-hydroxy-xanthone (**63**) and 1,4-dihydroxy-7-methoxy-xanthone (**64**), isolated from *S. longependunculata* harvested in South Africa, were tested for their activity on rabbit corpus cavernosum *in vitro* [75]. Of the two compounds, only **64** relaxed the corpus cavernosum by 63% at 1.8×10^{-5} mg/mL, the recorded activity being, however, less than that of the reference drug Sildenafil (100%) [75]. Compound **4** inhibited the arachidonic acid (AA)-induced platelet aggregation (IC_{50}: 200 μM) and also copper-catalyzed low-density lipoprotein oxidation (IC_{50}: 3.48 μM) [158]. The analgesic activity of **26** *in vivo* was reported on albino mice (IC_{50}: 12.53 mg/kg) [118].

Advanced glycation end products (AGEs) are associated with many pathogenic disorders such as Alzheimer's disease, pathogenesis of diabetes, atherosclerosis, or endothelial dysfunction leading to cardiovascular events [110]. Xanthone (**41**) was reported as a natural inhibitor of AGEs, with an IC_{50} value of 0.06 nM [110].

11.5 Pharmacological Activities of Anthrones Identified in African Medicinal Plants

Though closer to anthraquinones that are found in many African plants, few anthrones have been isolated, and the biological activities of some of them are documented. Vismin (**65**) and ferruginin B (**66**), identified in *P. aurantiacum*, prevented the proliferation of human CNS cancer SF-268 cells (IC_{50}: 5.7 and 4.0 μg/mL, respectively), lung cancer H-460 cells (IC_{50}: 7.3 and 5.0 μg/mL, respectively), and MCF-7 (IC_{50}: 5.2 and 5.0 μg/mL, respectively) [113]. Vismion D (**67**), found in *P. aurantiacum*, exhibited a microbial growth inhibitory effect against *Shigella sonnei* (MIC: 2.3 μg/mL), *S. typhi* and *S. faecalis* (MIC: $<$1.1 μg/mL), and *S. aureus* (MIC: 75 μg/mL) [159] and also produced a significant antiparasitic activity against *P. falciparum* (IC_{50}: 0.095 μg/mL) [123]. Compound **67** also induced high cytotoxic effects against KB (IC_{50}: 0.2 μg/mL), HeLa (IC_{50}: 0.6 μg/mL), and MCF-7 (IC_{50}: 0.7 μg/mL) cell lines [159]. Kenganthranol B (**68**) also significantly inhibited the activity of neuraminidase, with an IC_{50} value of 6.3 μM [103]. Other anthranoids isolated from the stem bark of *H. madagascariensis*, harunmadagascarin A (**69**), harunganol B (**70**), harungin anthrone (**71**), and harunmadagascarin B (**72**), with IC_{50} values of 60.97, 64.76, 155.39, and 92.10 μM, respectively, exhibited relatively moderate activity as free radical scavengers in the DPPH assay [23].

11.6 Some Particular Aspects of New Xanthones Isolated in African Medicinal Plants

Several new xanthones have been isolated from the African medicinal plants. Among them, xanthone V_1 (**29**), V_2 (**53**), V_{1a} (**73**), and V_{2a} (**74**) are the first prenylated xanthones isolated from the genus *Vismia*, as only simple xanthones were earlier isolated from the South American *Vismia* spp. [130]. Also, 1,8-dihydroxy-3,6-

dimethoxyxanthone (**75**), previously isolated from the fungus *Diploschistes scruposus* (Thelotremataceae) [160], was reported for the first time from a plant source in *C. spicatum* [89], harvested in Egypt.

11.7 Other Xanthones Identified in African Medicinal Plants

Some of the xanthones identified in African medicinal plants were tested in several biological systems but no activity was observed. Many others have not been submitted to any pharmacological study. Such compounds are summarized in Figure 11.9 and Table 11.3. The compounds 1-hydroxy-3,5,8-trimethoxyxanthone (**87**), 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone (**88**), and 1,8-dihydroxy-3,5-dimethoxyxanthone (**89**),

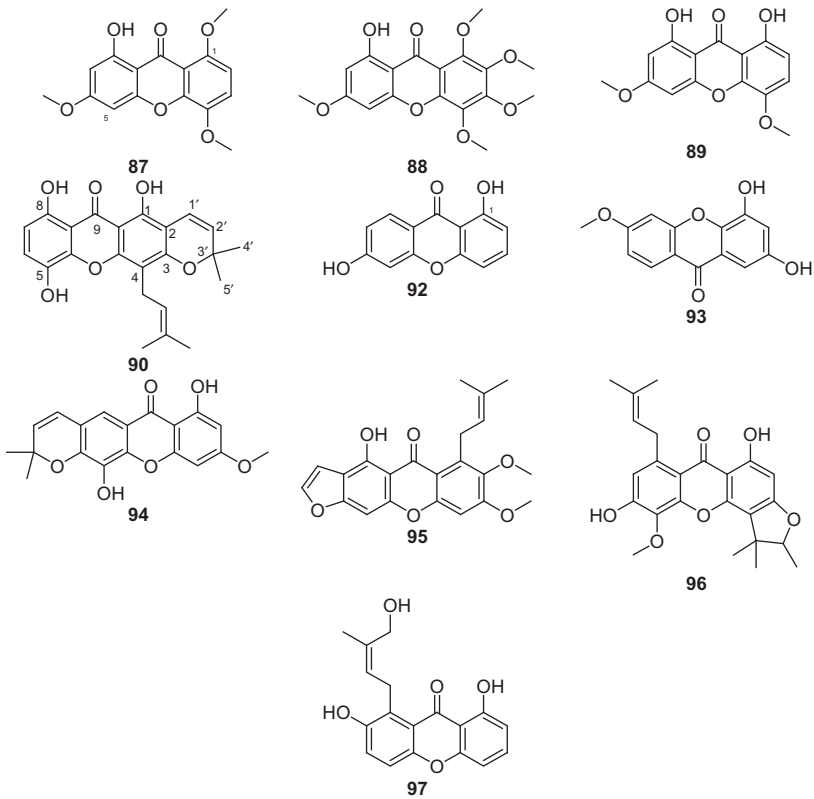


Figure 11.9 Chemical structrures of xanthones isolated from African medicinal plants without any or known pharmacological activity: 1-hydroxy-3,5,8-trimethoxyxanthone (**87**); 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone (**88**); 1,8-dihydroxy-3,5-dimethoxyxanthone (**89**); morusignin I (**90**); 1,6-dihydroxyxanthone (**92**); isogentisin (**93**); forbexanthone (**94**); garciniafuran (**95**); caloxanthone B (**96**); 8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone (**97**).

Table 11.3 Known Xanthones and Anthrones with No Known (or Devoid of) Pharmacological Activity Isolated from the African Plants

Compounds	Plants (Family)	Area of Plant Collection	Plant Parts	References
Morusignin I (**90**)	Xanthone	*G. nobilis* (Guttiferae)	Stem bark	[101]
Isomangiferin (**91**)	Xanthone (Glycoside-)	*C. subternata* Vogel (Leguminosae)	Leaves, stem bark	[117]
1,6-Dihydroxyxanthone (**92**)	Xanthone	*S. longepedunculata* Fres. (Polygalaceae)	Root bark	[109]
Isogentisin (**93**)	Xanthone	*C. obtusifolia* Lam. (Leguminosae)	Twigs	[99]
Forbexanthone (**94**)	Xanthone	*G. edulis* Exell. (Guttiferae)	Root bark	[127]
1-Hydroxy-3,5,8-trimethoxyxanthone (**87**)	Xanthone	*C. spicatum* L. (Gentianaceae)	Roots	[89]
1-Hydroxy-3,5,6,7,8-pentamethoxyxanthone (**88**)	Xanthone	*C. spicatum* L. (Gentianaceae)	Roots	[89]
1,8-Dihydroxy-3,5-dimethoxyxanthone (**89**)	Xanthone	*C. spicatum* L. (Gentianaceae)	Roots	[89]
Garciniafuran (**95**)	Xanthone	*A. monticola* Staner L.C. (Guttiferae)	Bark	[121]
Caloxanthone B (**96**)	Xanthone	*C. inophyllum* (Guttiferae)	Root bark	[92]
8-(4′-Hydroxyprenyl)-1,7-dihydroxyxanthone (**97**)	Xanthone	*P. molluscum* (Pers.) Hochr. (Hypericaceae)	Wood stem	[104]

isolated from the roots of the Egyptian plant *C. spicatum* L., were tested against *C. albicans*, *C. krusei*, *C. glabrata*, *E. coli*, *P. aeruginosa*, *C. neoformans*, *M. intracellulare*, *S. aureus*, MRSA, and *A. fumigatus* but none was found active [89]. These compounds were also screened for antimalarial and antileishmanial properties as well as for cytotoxicity against Vero cells but were found inactive.

11.8 Conclusion

This chapter presents an overview of the xanthones and a few anthranoids isolated from African plants. It can be noted that most of the xanthones discussed were isolated from the family Guttiferae, making this family the most prolific source of

xanthones among African plants. The natural sources of these compounds are confined mainly in the genus *Garcinia* in the family Guttiferae. More than 120 prenylated caged xanthones have been found in the plant genera *Garcinia*, *Cratoxylum*, and *Dascymaschalon* [137, 161]. The biological properties of most of the compounds reported in this chapter as new natural products have been studied by African scientists themselves or in collaboration with researchers across the globe. These compounds exhibit various potentially useful biological activities such as anticancer, anti-HIV-1, antibacterial, antiinflammatory, and neurotrophic activity. This is consistent with the investigation on the bioactivity of both known and new xanthones from African plants, as many xanthones reported in this chapter also display significant antiinfective, cytotoxic, and enzymatic inhibitory activity. The mode of action of compounds has been elaborated in some cases but, by and large, remain a challenging endeavor. These investigations also highlight the importance of the flora of the continent as a valuable source of bioactive compounds. This chapter thus describes advances in the search of bioactive xanthones and anthrones from the flora of Africa because the majority of new compounds isolated in the last decade have been pharmacologically studied.

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12 Lignans and Stilbenes from African Medicinal Plants

Apollinaire Tsopmo[a], *Francis M. Awah*[b] *and Victor Kuete*[c]

[a]Food Science and Nutrition, Department of Chemistry, Carleton University, Ottawa, ON, Canada, [b]Natural Product Research Unit, Department of Biochemistry, Madonna University, Elele Campus River State, Nigeria, [c]Department of Biochemistry, University of Dschang, Dschang, Cameroon

12.1 Introduction

Plants produce a vast array of natural molecules, which have evolved to confer on them selective advantage against environmental stresses while at the same time providing humans with biologically active compounds [1]. Among these, the phenylpropanoids are a large family of secondary metabolites involved in plant responses to various biotic and abiotic stresses. Many phenylpropanoids are antimicrobial compounds synthesized in response to pathogen or herbivore attack and classified as phytoalexins. However, other roles have been described for stress-induced phenylpropanoids, such as signaling of defense responses and protection against ultraviolet (UV) light damage [2].

Stilbenes are a small group of phenylpropanoids characterized by a 1,2-diphenylethylene backbone. Most plant stilbenes are derivatives of the basic unit *trans*-resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) [1], although other structures are found in particular plant families. Lignans, another group of phenylpropanoids, are dimers that often contain two phenylpropane units (C6−C3) linked by their carbon 8 (β−β′ link). Many lignans found in African medicinal plant exhibit antioxidant, antitumor, estrogenic, antimicrobial, and cholesterol lowering activities [3,4]. There are data showing that lignans and stilbenes can protect against some forms of cancer [5]. There is a demonstrated correlation between levels of excretion of lignans in human urine and the incidence of the disease [4]. Lignans display antiviral, insecticidal, and antifeedant activities. The lignans episesamin and diasesamin were reported to inhibit A5-desaturase enzymes involved in polyunsaturated fatty acid biosynthesis. Several other lignans inhibited the binding of platelet activating factor to blood platelets [6], while a number of others suppress the

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proliferation of human peripheral blood lymphocytes and may be useful as immunosuppressive agents [7].

The aim of this chapter is to provide information on different classes of lignans and stilbenes, their occurrence in African medicinal plants, and their biological activity. Although lignans have been the subject of many studies over the years, research continues concerning their natural diversity, abundance, biological properties, and biosynthesis pathways in African medicinal plants.

12.1.1 Definition, Structure, and Classes of Lignans

The lignan family is a large group of naturally abundant molecules that can be found in a plethora of higher plants. The term lignan was first defined in 1936 by Haworth as phenylpropanoid dimers consisting of two phenylpropane units (C6−C3) linked by their central C8 carbon, as represented in Figure 12.1 [8]. In 1972, Gottlieb [9] introduced the term neolignan to cover compounds composed of phenylpropane units linked in a manner other than C8−C8′. McCredie et al. [10] proposed that the definition be expended to include all natural products of low molecular weight that arise primarily from the oxidative coupling of hydroxyphenylpropene units; others proposed to name them 1,4-diarylbutane compounds [11], dimers of allyl or propenyl-phenyl monomers, or dimers of cinnamyl alcohols or cinnamic acids [12]. However, the 2000 IUPAC recommendations [13] adopted Haworth's definition of lignans [8] and Gottlieb's definition of neolignans [9]. Lignans composed of three and four phenylpropane units have been called sesquilignans and dilignans, respectively [14]. However, the terms sesquineolignans and dineolignans, respectively, are recommended by IUPAC. The term norlignan is used to indicate a lignan molecule derived from a parent compound by a loss of one carbon atom.

The most frequent phenylpropane units constitutive of lignans, often referred to as monolignol units, are *p*-coumaryl, coniferyl, and sinapyl alcohols [15]. These three phenylpropanoid molecules vary only by methoxylation on their aromatic ring. Assembly of monolignols gives rise to natural lignans and lignins, which occur in many plants (Figure 12.2) [14].

12.1.2 Occurrence of Lignans in African Medicinal Plants

In terms of evolutionary patterns, lignans are apparently absent in algae but are present in primitive early terrestrial plants like the liverworts [16]. The evolution of gymnosperms was accompanied by a massive increase in lignan structures. In addition, the transition to angiosperms was also accompanied by an increase in lignan structural types and skeletal diversity. Lignan-producing plants are distributed throughout the six subclasses of Magnoliopsida; in contrast, Liliopsida plants are rather poor lignan sources. Umezawa [14] has summarized the results of 108 families of lignan-producing plants. Many African plant species belonging to the genera

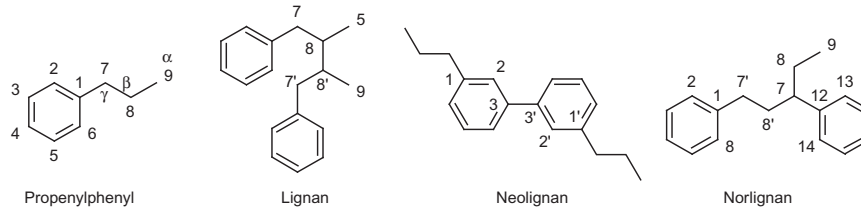

Figure 12.1 Basic skeletons of phenylpropane (C6−C3), lignans, neolignans, and norlignans.

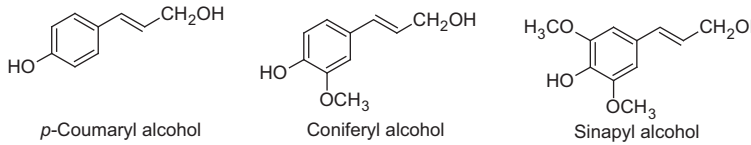

Figure 12.2 Structure of three common monolignols.

Piper (Peperaceae) and *Zanthoxylum* (Rutaceae) have been found to contain lignans [17]. Plant species belonging to the families Asteraceae, Acanthaceae, Oleaceae, Apocynaceae, Lauraceae, and Myristicaceae are also sources of lignan-type compounds.

12.1.3 Lignan Subgroups

Lignans are classified into subgroups based on the cyclization pattern and the way in which oxygen is incorporated into the skeleton. The eight subgroups recognized are furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene [18], and dibenzylbutyrolactol (Figure 12.3). Structures of compounds in each subgroup vary substantially in levels of oxidation of both the aromatic rings and propyl side chains. Some lignans belonging to the furan, dibenzylbutane, and dibenzocyclooctadiene subgroups have no oxygen at C9 (C9′), while some lignans have extra hydroxyl groups at C7 (C7′) or C8 (C8′). 3-Methoxy-4-hydroxyphenyl (guaiacyl), 3,4-dimethoxyphenyl (veratryl), 3,4-methylenedioxyphenyl (piperonyl), 3,5-dimethoxy-4-hydroxyphenyl (syringyl), and 3,4,5-trimethoxyphenyl are the most frequently occurring aromatic rings found in lignans. 4-Hydroxyphenyl and 3,4-dihydroxyphenyl lignans have also been identified [19] in a limited number of lignans.

Neolignans are C6−C3 dimers whose coupling patterns differ from 8−8′ linkage. Neolignans consist of 15 subtypes (Figure 12.4). No special names have been given, and they are designated by NL1−NL15.

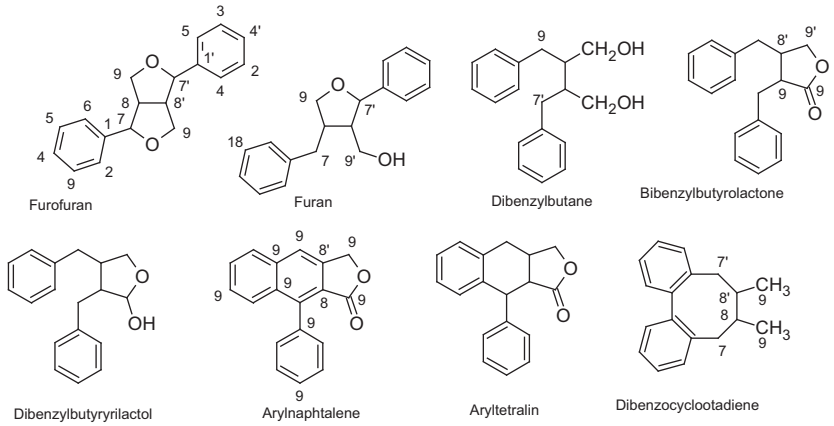

Figure 12.3 Basic skeletons of lignan subgroups.

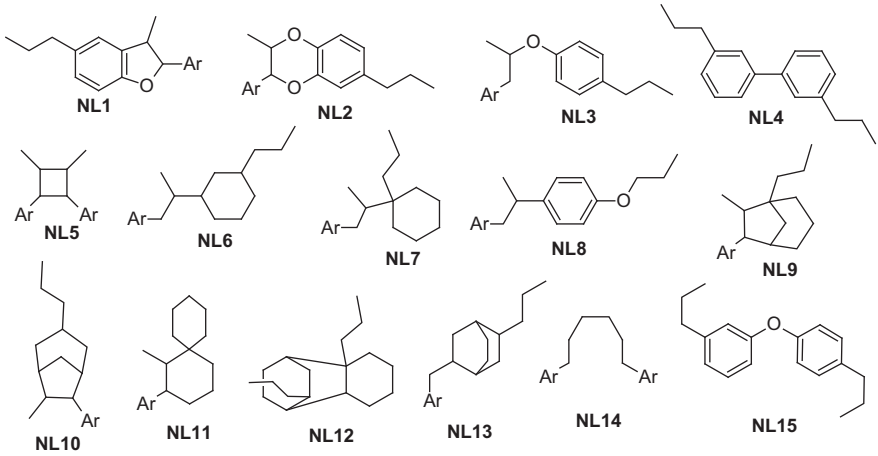

Figure 12.4 Subtypes of neolignans (NL) (Ar = aryl) [20].

12.1.4 Occurrence of Stilbenes

The essential structural skeleton of stilbenes comprises two aromatic rings joined by an ethylene bridge (1,2-diarylethenes). They were named by Gorham in 1980; however, their first isolation from plants is believed to go back to 1899 [21]. It is known that stilbenoids play the role of phytoalexins in the plants, although not all of them function as antifungals. Stilbenoids have attracted considerable attention since the finding that resveratrol, and later combretastatin A-4 (from the South African plant *Combretum caffrum*), two members of the group, possessed chemo-preventive effects against cancer cells [22,23].

They are widely distributed in liverworts and higher plants, 29 of them being found in monomeric form and as well as dimeric, trimeric, and polymeric forms (e.g., viniferins). Among monomeric stilbenes, *trans*-resveratrol has been identified as a constituent of some African plants, although it is an abundant vinefin species. Biological activities of stilbenes in plants include UV protection, signals of bacterial root nodulation, coloration, and defense against herbivory and microbial pathogens [24]. In humans, biological activities include antitumor and antioxidant [25]. Most of the studies in the literature on the physiological activity of stilbenes have focused on resveratrol and some of its glycosides (e.g., piceid or polydatin, and the viniferins) [26]. Stilbenes are synthesized by a wide range of plant species, including Dipterocarpaceae, Cyperaceae, Gnetaceae, Pinaceae, Leguminosae, Myrtaceae, Moraceae, Fagaceae, Liliaceae, and Vitaceae, where they have been found in roots, barks, rhizomes, and leaves [11].

12.1.5 Stilbene Subgroups

Stilbenes are structurally characterized by the presence of a 1,2-diphenylethylene nucleus and can be divided into two categories: monomeric and oligomeric stilbenes. Monomeric stilbenoids are further divided into four subclasses: stilbenes, bibenzyls, bisbibenzyls, and phenanthrenoids. Oligomeric stilbenes are produced by coupling between homogeneous and heterogeneous monomeric stilbenes and can themselves be classified into several groups. Sotheeswaran and Pasupathy [27] proposed a classification of oligostilbenes into two categories: Group A, containing at least one five-membered oxygen heterocycle, exemplified by lungusol A (**1**) (Figure 12.5) from the Egyptian plant *Cyperus longus* [28], and Group B containing no oxygen heterocycle [27]. This classification restricts itself to resveratrol oligomers, and so Shen et al. [29] extended it to six groups based on resveratrol (**2**), isorhapontigenin (**3**), piceatannol (**4**), oxyresveratrol (**5**), resveratrol, and oxyresveratrol (coupled heterogeneous), and finally miscellaneous oligomers.

The oligomeric construction pattern presented by Shen et al. [29] provides a convenient framework for the understanding of the structural diversity of oligomeric stilbenes. On the basis of the number of connective bonds between two

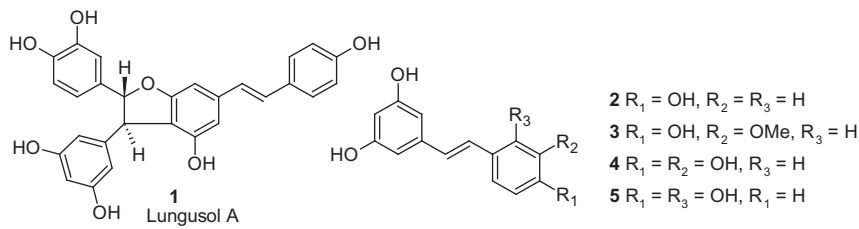

Figure 12.5 An example of stilbene dimer (lungusol A) and units comprising oligomeric stilbenes.

monomeric stilbene units, the construction patterns were divided into four major groups:

1. Two monomeric units linked by only one C—C or C—O—C bond (with two linkage points).
2. Two monomeric units linked by two C—C or C—O—C bonds (with four linkage points), commonly forming a ring. The characteristic dihydrobenzofuran moiety is commonly formed by two units with a C—C and a C—O—C linkage. An example is tingitanol, from the Egyptian plant *Iris tingitana* [30].
3. Two monomeric units linked by three C—C or C—O—C bonds (with six linkage points), leading to the formation of two rings, for example, pellidol from the Egyptian natural medicinal plant *C. longus* [28].
4. Two monomeric units linked by four C—C or C—O—C bonds (with eight linkage points). This pattern is rare.

12.2 Biosynthesis of Lignans and Stilbenes

The plant shikimate pathway is the entry to the biosynthesis of phenylpropanoids (C6—C3) and subsequent natural products including lignans and stilbenes. The phenylpropanoids have been studied extensively [31]. In general, the phenylpropyl unit (C6—C3) is obtained from L-phenylalanine or L-tyrosine, two of the shikimate-derived aromatic amino acids. The biosynthesis of monolignols (Figure 12.6) is initiated with deamination of phenylalanine by phenylalanine ammonia lyase (PAL) to form cinnamic acid, which is hydroxylated by a P450 enzyme, cinnamate 4-hydroxylase (C4H), to form *p*-coumaric acid. 4-Coumarate is then activated to the coenzyme A-thioester by 4-coumarate:CoA ligase (4CL). The formation of the coenzyme A ester facilitates the reduced-nicotinamide adenine dinucleotide phosphate (NADPH) reduction steps by introducing a better leaving group $CoAS^-$. 4-Coumarate-CoA is the precursor for many phenylpropanoid compounds, including stilbenes and lignans. To form monolignols, the aromatic ring of 4-coumarate is hydroxylated at C-3 and C-5, respectively, followed by subsequent methylation of the hydroxy groups.

12.2.1 Biosynthesis of Lignans

The initial step in the biosynthesis of lignans is the formation of monolignols (C6—C3 units) as described above (Figure 12.6). Lignan biosynthesis then starts with the coupling of two molecules of coniferyl alcohol, sinapyl alcohol, or *p*-hydroxycinnamyl alcohol. The biosynthesis of *Forsythia* lignans from coniferyl alcohol has been established [14]. Each step was found to be stereochemically controlled. A review of data of enantioselective lignan synthesis with *Forsythia* and *Arctium* enzymes indicated that different stereochemical mechanisms operated to give rise to the different enantiomers in *Forsythia* spp., *Arctium lappa*, *Wikstroemia* spp., *Phyllanthus* spp., and *Zanthoxylum* spp., and that metabolic steps to produce optically pure lignans may vary among different plant species [32]. The biosynthesis pathway taking place in African *Zanthoxylum* species may then be as shown in Figure 12.7. Monolignol monomers like coniferyl alcohol are initially oxidized by peroxidase enzymes to form phenoxy radicals; the unpaired

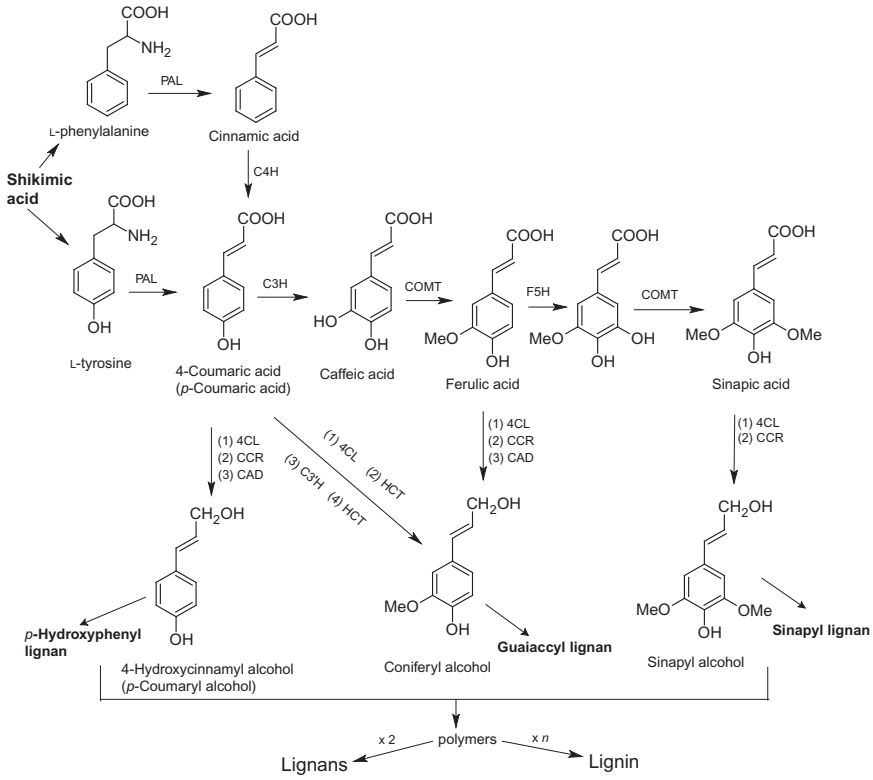

Figure 12.6 The cinnamate monolignol pathway involved in lignin biosynthesis. C4H, cinnamate 4-hydroxylase; C3H, *p*-coumarate 3-hydroxylase; 4CL, 4-hydroxycinnamate CoA ligase; HCT, hydroxycinnamoyl CoA:shikimate/quinate hydroxycinnamoyl transferase; CCR, cinnamoyl CoA reductase; CAD, cinnamyl alcohol dehydrogenase; SAD, sinapyl alcohol dehydrogenase; F5H, ferulate 5-hydroxylase; COMT, caffeic acid *O*-methyltransferase; C3′H, *p*-coumaroyl shikimate/quinate 3-hydroxylase.
Source: Adapted from Umezawa [31].

electron then delocalizes giving resonance forms. Radical pairing of resonance structures then provides a range of dimeric systems containing reactive quinone-methides, which are susceptible to nucleophilic attack. (+)-Pinoresinol is formed enantioselectively by radical coupling between C8 and C8′ of two coniferyl alcohols in the presence of oxidase and dirigent protein, followed by quinonemethide internal quenching. The formed (+)-pinoresinol is transformed to (+)-lariciresinol and then to (−)-secoisolariciresinol by pinoresinol or lariciresinol reductase (PLR) enzyme in the presence of NADPH. Secoisolariciresinol dehydrogenase (SDH) in the presence of nicotinamide adenine dinucleotide phosphate (NADP) then oxidizes secolariresinol to matairesinol. Methoxylation of matairesinol by the action of *O*-methyl transferase in the *S*-adenosyl methionine (SAM) gives

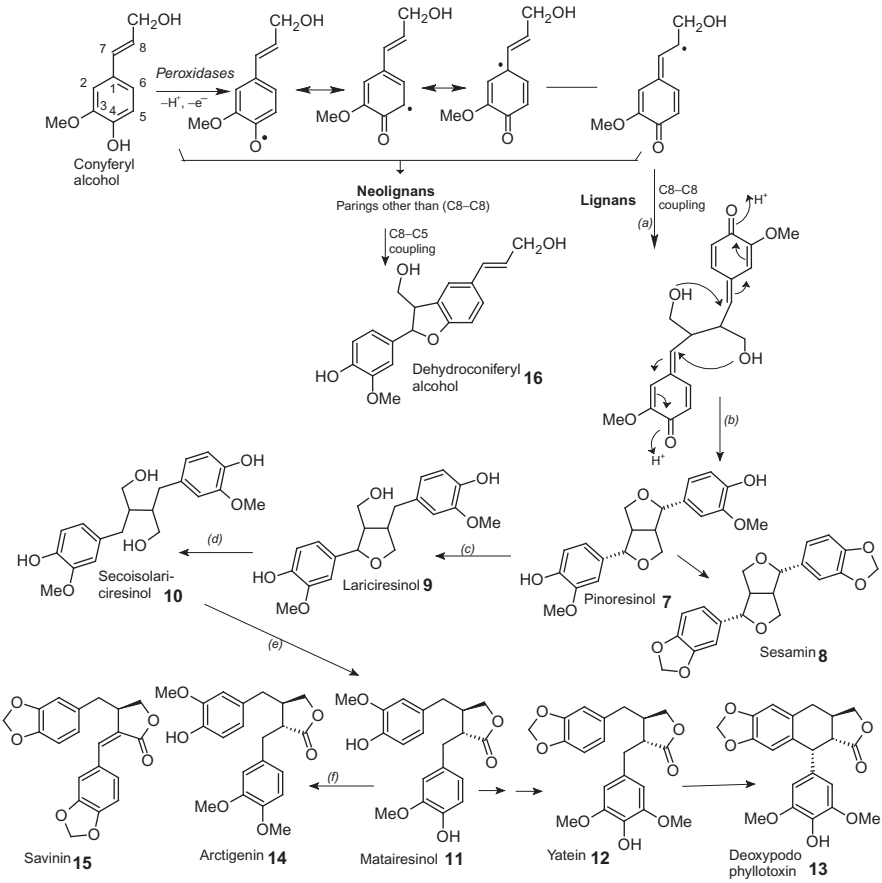

Figure 12.7 Possible biosynthetic leading to the formation of some lignans present in the genus *Zanthoxylum*: (a) dirigent protein/oxidase; (b) pinoresinol synthase; (c) and (d) pinoresinol/laricresinol reductase/NADPH; (e) secoisolariciresinol dehydrogenase; (f) *O*-methyltransferase/SAM.

artigenin, while its hydroxylation and methoxylation and methylenedioxy bridge formation produce yatein, which can cyclize to form aryltetralin lactone like deoxypodophyllotoxi. The sesamum CYP81Q protein was demonstrated to be responsible for the formation of methylenedioxy bridges, leading to furofuran and (+)-sesamin [33], a lignan also present in many African *Zanthoxylum* species. The biosynthetic route leading to the formation arylnaphthalene lignans has not fully been investigated. It is, however, believed that matairesinol is a common intermediate in all pathways. Matairesinol is therefore considered to be a key intermediate in the biosynthesis of all the diverse lignan structures. Nealignans are biosynthesized from other oxidative coupling. An example is the coupling between C5 and C8′ forms dehydrodiconiferyl alcohol.

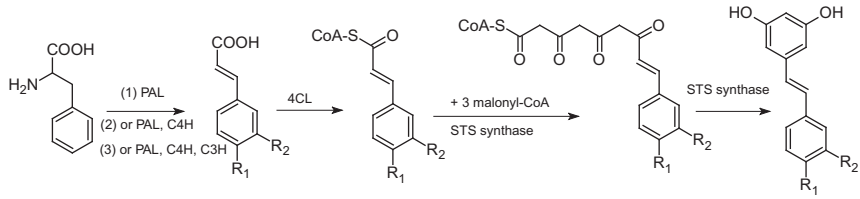

Figure 12.8 Biosynthesis of stilbenes. C4H, cinnamate 4-hydroxylase; C3H, *p*-coumarate 3-hydroxylase $R_1 = R_2 = H$, coumaric acid derivatives from action of PAL; $R_1 = OH$, $R_2 = H$, *p*-coumaric acid derivatives derived from action of PAL and C4H enzymes; $R_1 = R_2 = OH$, caffeic acid derivatives derived from action of PAL, C4H, and C3H enzymes.

12.2.2 Biosynthesis of Stilbenes

Like lignans, stilbenes are synthesized from a coenzyme A (CoA)-activated phenylpropanoid starter unit and three malonyl-CoA extender units [24]. The first step in phenylpropanoid biosynthesis is the deamination of L-phenylalanine to *trans*-cinnamic acid, catalyzed by PAL. Cinnamic acid is hydroxylated by C4H to make 4-coumaric acid, which is then activated by 4-coumaroyl:CoA ligase (4CL) to make 4-coumaroyl-CoA. A type III polyketide synthase named stilbene synthase (STS) then sequentially adds three acetate extender units, derived from malonyl-CoA, to a single activated 4-coumaroyl-CoA starter unit. Subsequent folding and cyclization of the generated tetraketide intermediate results in the production of either a chalcone or a stilbene ring structure. STS is the characteristic of stilbene-producing plants; STS enzymes may accept different cinnamic acid derivatives as substrates, and a single enzyme may be responsible for the biosynthesis of different stilbenes, depending on the starter molecule. Biosynthesis of many stilbenes has been studied in cells and leaves of peanut and grapevine, and on pine seedlings [1,34]. In these organs, stilbene biosynthesis is induced in response to a wide range of biotic and abiotic stress factors, as a result of an increased transcription of stilbene biosynthetic genes and accumulation of the corresponding enzymes [35] (Figure 12.8).

12.3 Diversity of Lignans and Stilbenes

Lignans are divided into eight groups. In each subgroup, the oxidation of both aromatic ring and propyl side chain moieties leads to broad structural varieties. Some lignans of furan, dibenzylbutane, and dibenzocyclooctadiene have no oxygen at C9 (C9′), while some lignans have extra hydroxyl groups at C7 (C7′) or C8 (C8′). 4-Hydroxyphenyl and 3,4-dihydroxyphenyl lignans have also been identified [19], though they are rare [14].

12.3.1 Glycosylation

Glycosylation is a common modification of plant secondary metabolites, and the addition of a carbohydrate moiety can alter hydrophilicity, stability, subcellular localization, and bioactivity of natural products. A significant proportion of total lignans and stilbenes can accumulate as glucosides in plant species that produce them. Some examples in African medical plants are *cis*- and *trans*-piceid (resveratrol 3-*O*-beta-glucoside), found in many species [36]. Many glucosyltransferases that produce glucose esters of hydroxybenzoic and hydroxycinnamic acids accept a wide range of structurally similar substrates [1].

12.3.2 Methoxylation

S-Adenosyl-L-methionine (SAM)-dependent *O*-methyltransferases methoxylate thousands of plant secondary metabolites. Hundreds of *O*-methylated products have been characterized among phenylpropanoids alone, ranging from mono- to polymethylated compounds belonging to the monolignols, chalcones, flavones, isoflavones, flavonols, anthocyanins, lignans, and stilbene families [37]. The most frequently encountered aromatic ring modifications in lignans are 3,4-methylenedioxyphenyl (piperonyl), 3,5-dimethoxy-4-hydroxyphenyl (syringyl), and 3,4,5-trimethoxyphenyl pinosylvin 3-*O*-methyl ether; pterostilbene and combretastatin A4 are examples of methoxylated stilbenes that exhibit promising pharmacological properties. Combretastatin A4, isolated from the South African medicinal tree *C. caffrum* (Combretaceae), is a potent inhibitor of tubulin polymerization, which inhibits tumor cell growth [38].

12.3.3 Oligomerization

Oligomeric lignans arise from oxidative coupling of more than two Ar-C_3 units. Trimers (sesquilignans), such as bonaspectins and neobonaspectins, and tetramers (dilignans) have been isolated from some African medicinal plants, such as *Bonamia spectabilis* (Convolvulaceae) and *Aptenia cordifolia* [39,40].

A large number of natural stilbenes are also present in dimeric, trimeric, and tetrameric forms. They are derived from the oxidative coupling of resveratrol or resveratrol derivatives. The diversity of stilbene oligomers and the possible mechanisms leading to their formation have been investigated [1]. The occurrence of resveratrol oligomers, termed viniferins, has been studied in transgenic plants. They are formed by oxidative coupling in the presence of peroxidases [41]. Resveratrol oligomers were demonstrated to accumulate in grapevine leaves upon fungal infection or UV irradiation [42]. *In vitro*, stilbene oligomers were obtained by enzymatic oxidation using horseradish peroxidase [43] or laccase-like stilbene oxidases from *Botrytis cinerea* [44]. On the basis of the number of connective bonds between two monomeric stilbene units, Shen et al. [29] proposed four major groups of dimeric stilbenes based on two, four, six, or eight C—C or C—O—C bond linkage points.

12.3.4 Enantiomeric Diversity of Lignans

In addition to their structural diversity, lignans vary substantially with respect to enantiomeric composition [32], because most of them contain chiral carbon atoms. Lignans can be either optically active, racemic, or optically inactive coupling products. Most naturally occurring lignans have been found to exist either exclusively as one enantiomer or as enantiomeric mixtures. Comparing the enantiomeric composition of lignans from various species in different plant families [14] has revealed that dibenzylbutyrolactone lignans are almost optically pure ($>99\%$ excess enantiomer), whereas furofuran and furan lignans are often enantiomeric mixtures with various compositions of levogyres and destrogyres. The composition of the enantiomeric mixtures is also dependent of plant species [32].

12.3.5 Trans *and* Cis *Isomers in Stilbenes*

There is no stereocenter in monomeric stilbenes, however, because the double bond does not allow free rotation, there are two spatial configurations, *trans* (*E*) or *cis* (*Z*). One aromatic ring usually carries two hydroxyl groups in the *meta*-position, whereas the other ring is generally substituted by hydroxy and methoxy groups in the *ortho*-, *meta*-, or *para* position.

12.4 Pharmacological Activity of Lignans and Stilbenes Isolated from African Medicinal Plants

12.4.1 Lignans

Lignans generally occur in the root, stem, bark, fruit, and seed parts of the plant. Several lignans like secoisolariciresinol are considered to be phytoestrogens and are converted by intestinal bacteria into enterolactone and enterodiol. These can mimic estrogen compounds in the body and may reduce the effect of estrogen by displacing it from cells, leading to the prevention of some cancers like breast cancer that are estrogen dependent [45]. Many lignans also show physiological activity like the tumor-inhibiting podophyllotoxins. This specific activity leads to interference with cell division by two different mechanisms in animals, including humans. Some are active in suppressing the central nervous system and inhibiting cyclic-AMP phosphodiesterase, whereas others act as fish poisons or germination inhibitors. There is growing interest in the lignans and neolignans for their pharmacological capabilities.

12.4.1.1 Antibacterial Lignans from African Medicinal Plants

Bacterial infections have become resistant to conventional antibiotics, hence there is a need for new antibacterial drugs. Over the last two decades, there has been interest in plant-based antimicrobials, which could have different targets in bacterial cells. Conventional antibiotics act by (1) inhibiting bacterial cell wall synthesis, (2)

inhibiting protein synthesis, (3) inhibiting DNA synthesis, (4) inhibiting RNA synthesis, (5) competitively inhibiting folic acid biosynthesis, or (6) disorganizing membranes and other mechanisms [46]. Plant-derived antimicrobial compounds might inhibit bacteria through different mechanisms than conventionally used antibiotics, and could therefore be of clinical value in the treatment of infections caused by resistant microbes. A variety of lignans with reported antimicrobial activity have been isolated from a wide variety of African medicinal plants. Four new cyclolignene derivatives, named pycnanthulignenes A (**17**) (Figure 12.9), B (**18**), C (**19**), and D (**20**), isolated from the Cameroonian plant *Pycnanthus angolensis*, also showed antibacterial capabilities [47]. The minimal inhibitory concentration (MIC) values for compound **17** varied from 28.7 μM (against *Staphylococcus aureus*) to 230.9 μM (*Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). Compound **19** also exhibited noteworthy activity against eight of the nine tested microorganisms. The lowest MIC values (63.8 μM) observed for this compound were recorded against *S. aureus*, *Escherichia coli*, and *Candida albicans* [47].

Moracin Q (**21**), R (**22**), S (**23**), T (**24**), U (**25**), C (**26**), and M (**27**) are neolignans isolated from *Morus mesozygia*, harvested in Cameroon [48]. Among these, compounds **21**, **26**, and **27** showed the best antimicrobial activity [49]. An MIC value of 5 μg/mL was obtained with compound **26** against *Shigella dysenteriae* and **24** on *E. coli*, *S. dysenteriae*, *P. aeruginosa*, *Salmonella typhi*, and *Bacillus cereus*. The MIC value (5 μg/mL) recorded with lignans **24** and **26** was equal to that of the reference antibiotic (gentamycin) on the corresponding microorganisms under similar experimental conditions [49].

Antibacterial bioassay-guided fractionation of an ethyl acetate root extract of *Terminalia sericea* led to the isolation of anolignan B (**28**) [50]. In the antibacterial test, anolignan (**28**) showed antibacterial activity against both gram-negative and gram-positive bacteria, with MIC values ranging from 3.8 μg/mL against *Bacillus subtilis* (gram-positive) to 31 μg/mL against *E. coli* (gram-negative). Glabrocoumarone A (or kanzonol U) (**29**) was evaluated for its antibacterial activity against strains of methicillin-resistant *S. aureus* (MRSA). The results showed that **29** was active against *S. aureus*, with an minimal concentration of sample that results in 50% inhibition of maximal activity (MIC_{50}) value of 12.5 μg/mL and minimum bacterial concentration (MBC_{50}) of 25 μg/mL [51].

The arylnaphthalide lignan justicidin B (**30**) was tested against different fungi species, and the MIC were ≥ 1 μg/mL for *Aspergillus fumigatus*, ≥ 4 μg/mL for *C. albicans*, ≥ 16 μg/mL for *Aspergillus flavus*, ≥ 128 μg/mL for *Blastoschizomyces capitatus*, and ≥ 128 μg/mL for *Cryptococcus neoformans* [52]. Two new 2-arylbenzofuran neolignans, zanthocapensol (**31**) and zanthocapensate (**32**), obtained from roots of *Zanthoxylum capense* from Mozambique, were tested against various bacteria species including *S. aureus*, *Enterococcus faecalis*, *P. aeruginosa*, and *E. coli*. Compound **32** showed an MIC value of 25 μg/mL against *S. aureus* and >50 μg/mL on other tested microorganisms, though no activity was observed with **31** [53]. Another new neolignan, bolusanthin IV (**33**), from *Bolusanthus speciosus*, showed activity (MIC, μg) against *E. coli* (0.50), *B. subtilis* (0.05), *S. aureus* (0.01), and *Candida mycoderma* (0.05) [54].

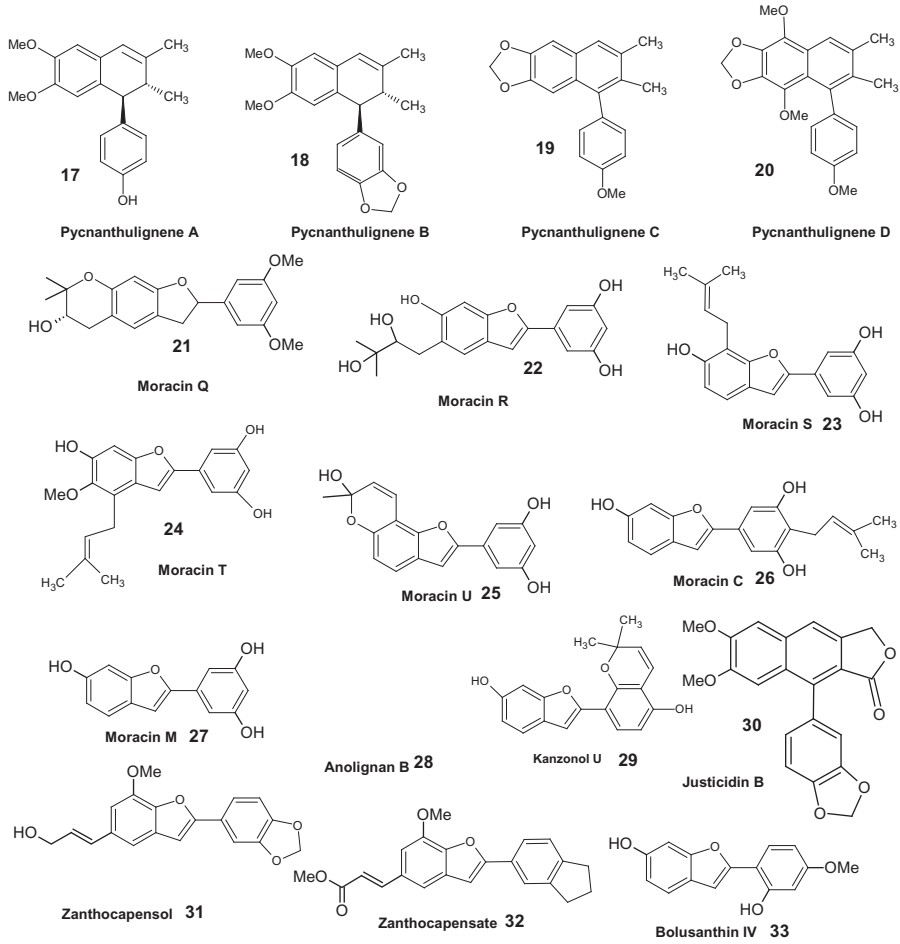

Figure 12.9 Structures of lignans with antibacterial activity.

12.4.1.2 Anti-inflammatory and Antioxidant Lignans from African Medicinal Plants

Reactive oxygen species (ROS) are also implicated in the pathogenesis of a vast variety of conditions including inflammatory diseases, cancer, etc. Recently, there has been a great increase of interest in natural antioxidant phytochemicals of plant origin, since they are viewed as promising therapeutic agents for free radical pathologies and also have been found to be useful as nutraceuticals due to their impact on the status of human health and disease prevention. Antioxidant activities are common properties of lignans because of the presence of phenolic moieties that can stabilize radicals through resonance forms. It that respect, it is not surprising

that many lignans from African medical plants have been reported to possess antioxidant properties in various systems. The metal chelating ability of some phenolic compounds is also responsible for their metal-binding capability. Free metals are known to catalyze the formation of hydroxyl radicals from hydrogen peroxide. Lignans that bind metals like iron thus prevent both hydroxyl radical and lipid peroxide generation.

Apart from the antimicrobial activity, the 2-arylbenzofuran derivatives moracin R, S, T, and U (**22**−**25**), from the trunk bark of *M. mesozygia*, also exhibited potent antioxidant activity by reacting with the stable radical DPPH (1,1-diphenyl-2,2-picrylhydrazyl) [48]. Mbaze et al. [3] identified the lignans savinin (**15**) and (+)-sesamin (**8**), from the plant *Fagara heitzii*, with suppressive effects on phagocyte oxidative burst, with concentration of sample that results in 50% inhibition of maximal activity (IC_{50}) = 5.6 μM and 2.2 μM, respectively. Compound **8** is also present in many *Zantoxylum* species and has been demonstrated to have both antioxidant and anti-inflammatory properties. Its effect has been attributed to an increased accumulation of dihomo-y-linolenic acid, a precursor of 1-series prostaglandins, and to the decreasing production of proinflammatory 2-series prostaglandins and 4-series leukotrienes by inhibiting delta-5 desaturase activity [55]. Syringaresinol (**34**) (Figure 12.10), isolated from *Drypetes molunduana* Pax [56], was recently shown to cause vasorelaxation by elevating nitric oxide (NO) production, a process that was due to the scavenging of superoxide anion radical [57]. A new lignan of the rare lactol type named carissanol (**35**) and the known carinol (**36**) were obtained from a Ghanean plant *Carissa edulis* [58]. They have been reported to scavenge DPPH free radicals, with IC_{50} values of 37.12 and 47.87 μM for **35** and **36**, respectively [59]. (+)-Lariciresinol (**9**) and (−)-secoisolariciresinol (**10**) are two other molecules present in *C. edulis* [58]. Compound **9** inhibited low density lipoprotein (LDL) oxidation isolated from human plasma, with IC_{50} values of 11.9 ± 0.5 μM [60], whereas **10** has radical scavenging properties.

Anolignan B (**28**), isolated from *T. sericea*, has shown anti-inflammatory activity using the cyclooxygenase enzyme assays (COX-1 and COX-2) and potential mutagenic effects on the Ames test. In the anti-inflammatory assays, **28** showed activity against both COX-1 (IC_{50}: 1.5 mM) and COX-2 (IC_{50}: 7.5 mM) [50]. The two known lignans denudatins A (**37**) and B (**38**), from *Magnolia soulangiana* [61], have been shown to possess anti-inflammatory properties. Compound **37** inhibited NO production by 23% in lipopolysaccharide (LPS)-activated brain microglia BV2 cells [62], whereas **38** inhibited platelet activating factor, a lipid mediator of hypersensitivity and inflammation, with an IC_{50} value of 75.6 μM [63]. In a different study, pinoresinol dimethylether or eudesmin (**39**), also present in *M. soulangiana*, inhibited the production of NO by LPS BV2, with an IC_{50} value of 30.0 μM [64]. Another lignan that inhibited NO production in LPS-activated RAW264.7 cells is olivil (**40**), found in *C. edulis*, with an IC_{50} value of 85.6 ± 1.49 μM [65]. Liriodendrin (**41**), isolated from *Strychnos spinosa* [66], has demonstrated at 5−10 mg/kg a dose-dependent anti-inflammatory activity in animal model carrageenan-induced edema [67].

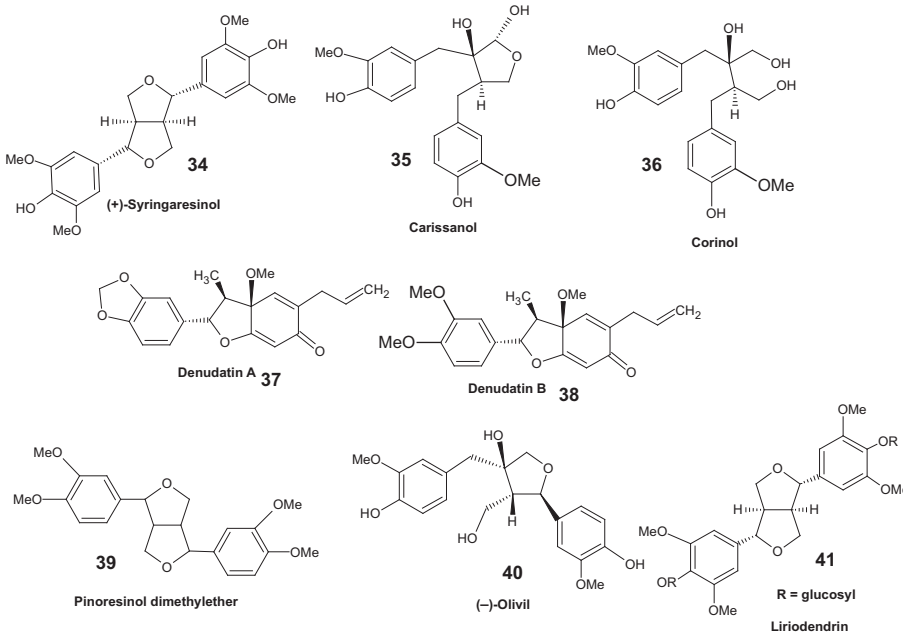

Figure 12.10 Compounds with anti-inflammatory and antioxidant properties.

12.4.1.3 Cytotoxic and Anticancer Lignans from African Medicinal Plants

Medicinal plants and natural products are important templates for chemotherapeutic agents. Several lignans have achieved continued success as pharmaceuticals and/or are showing considerable promise in cancer treatment. Studies on tumor-inhibiting properties of other classes of natural compounds show antitumor activity, and a number of them have been approved for use as anticancer drugs [65,68]. Lignans that could mediate anticancer activity via a variety of mechanisms, including induction of apoptosis, have been isolated from African medicinal plants.

Studies on aerial parts of the Egyptian plant *Bupleurum marginatum* revealed a novel aryltetralin lactone lignan identified as marginatoxin [9-(benzo[*d*][1,3] dioxol-5-yl)-6,7,8-trimethoxy-a,4,9,9-atetrahydronaphtho[2,3-c]furan-1(3*H*)-one] (**42**) (Figure 12.11) and lignan [(3,4-dimethoxybenzyl)-2-(3,4-methylenedioxybenzyl) butyrolactone] (**43**), which exhibited cytotoxic activity, with IC_{50} values of 41.3 and 52.7 mM on HeLa and HepG2 cells, respectively [69]. Anolignan B (**28**), isolated from the roots of *T. sericea* and *Anogeissus acuminate*, exhibited cytotoxic effects against fibrosarcoma cell lines [70]. In a study in Madagascar, the new lignan 4′-*O*-cinnamoyl cleomiscosin A (**44**) was isolated from *Terminalia tropophylla* H. Perrier (Combretaceae), but the compound did not show antiproliferative activity (IC_{50} values > 30 μM) [71].

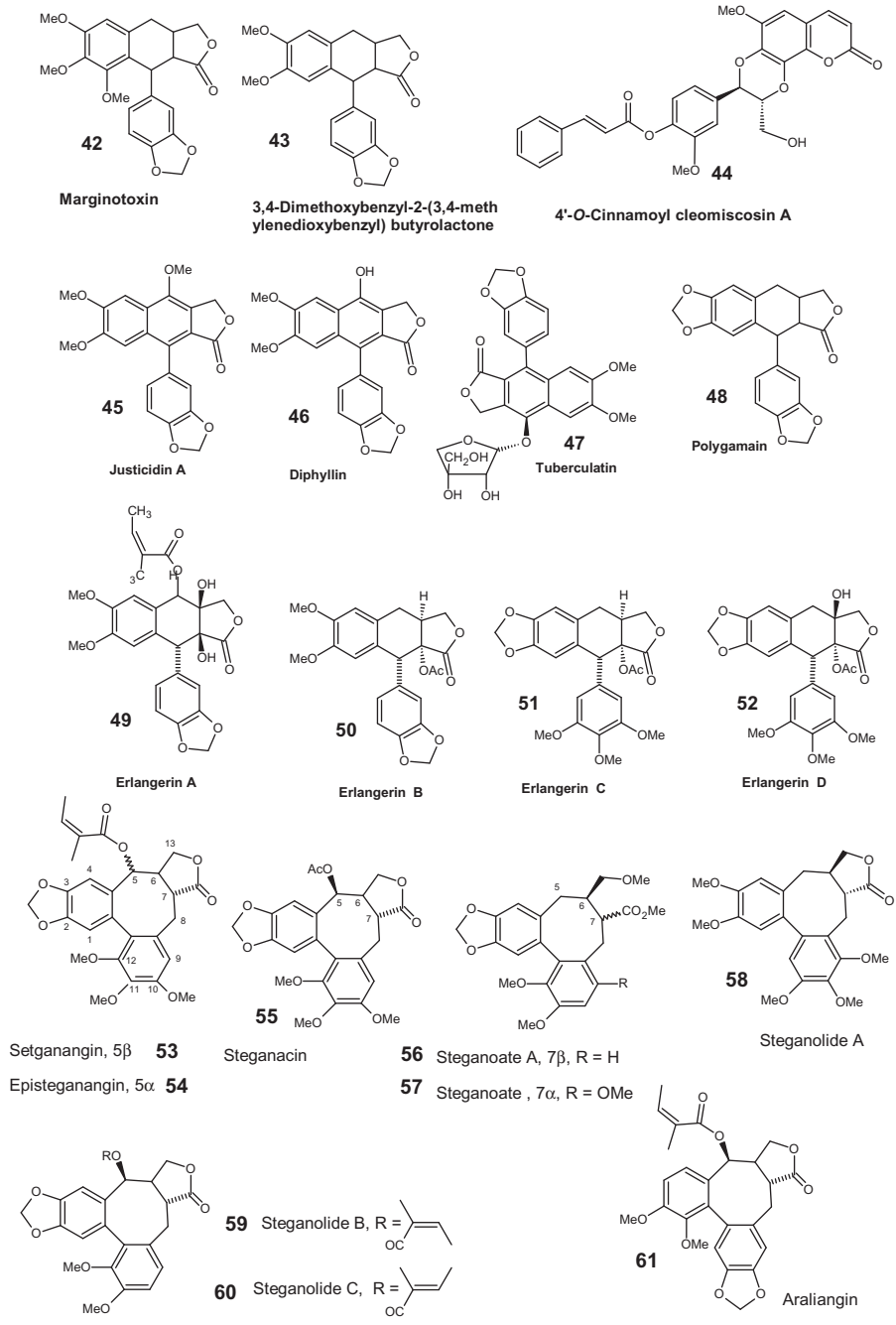

Figure 12.11 Selected cytotoxic lignans identified in African plants.

Justicidin A (**45**) and B (**30**), diphyllin (**46**), and tuberculatin (**47**), a new lignan apioside, were isolated and characterized from the Libyan plant *Haplophyllum tuberculatum* [72,73] and also from *Justicia procumbens* [74]. They were tested for cytotoxicity against a number of cancer cells *in vitro*. Compound **45** showed significant cytotoxic activity, as indicated by an Effective concentration 50 (EC_{50}) against the hepatocellular carcinoma cell lines Hep3B (0.029 μg/mL) and HepG2 (0.02 μg/mL), and breast adenocarcinoma cell lines MCF-7 (0.39 μg/mL) and MCF-7-ras (0.074 μg/mL). The effective dose 50 (ED_{50}) for **46** was 3.1 μg/mL against Hep3B, 3.9 μg/mL against HepG2, and 6.7 μg/mL against HT-29 cells. On the other hand, the novel tuberculatin (**47**) had an ED_{50} value of 0.014 μg/mL against Hep3B, 0.12 μg/mL against SiHa, 0.04 μg/mL against HepG2, 0.029 μg/mL against HT-29, 0.28 μg/mL against HCT116, 0.97 μg/mL against MCF-7, and 0.09 μg/mL against MCF-7-ras cells [74]. Compound **30** displayed cytotoxic activity against a wide range of cells, specifically KB (HeLa) cells (IC_{50}: 0.2 μg/mL), Jurkat T helper cells (IC_{50}: 3.2 μg/mL), L-6 cells (IC_{50}: 3.3 μg/mL), and PBMCs cells (IC_{50}: 4.7 μg/mL) [52]. Polygamatin (**48**), also from *H. tuberculatum*, a species collected in Libya [72,73], exhibited potent antiproliferative and microtubule-depolymerizing activities, with an IC_{50} value of 70.6 nM against human prostate cancer cell lines PC-3 cells [75].

Two new polygamatin-type lignans erlangerins A (**49**) and B (**50**), and two new podophyllotoxin-derived erlangerins C (**51**) and D (**52**) were characterized from *Commiphora erlangeriana* (Burseraceae), collected in Ethiopia [76]. The toxicity of these compounds was studied on two human (human cervical adenocarcinoma cell line HeLa and human umbilical vein cell line EAhy926) and two murine (L929 and RAW264.7) cell lines. Compounds **49** and **50** were cytotoxic to human cells. The EC_{50} for **49** and **50** were 40 and 4.0 μg/mL on HeLa cells, and 68 and 23 μg/mL on EAhy926 cells, respectively. Compounds **51** and **52** were cytotoxic on murine cells, with EC_{50} values of 5.6 and 0.97 μg/mL (**51**) (L929 and RAW 26.7) and 3.5 and 0.11 μg/mL (**52**) (L929 and RAW 26.7) [77]. A series of novel bisbenzocyclooctane lignans (**53**−**61**) have been isolated and characterized from *Steganotaenia araliacea* Hochst. (Umbelliferae), collected in various part of Africa [78−80]. These compounds have shown significant astrocyte reversal activity when tested against an astrocytoma (ASK) cancer cell line [80]. ED_{50} values for the compounds ranged from 1.7 to 78.1 μg/mL for ASK cells [80]. In addition, they demonstrated good cytotoxic activity activity on seven different human cancer cell lines.

12.4.1.4 Antimalarial Lignans from African Medicinal Plants

Malaria remains a major parasitic disease in many tropical and subtropical regions and is the cause of over a million deaths in Africa yearly. The rapid spread of drug resistance encourages the search for new active compounds, and African medicinal plants and natural products are a potential source of new antimalarial drugs, since they contain molecules with a great variety of structures and pharmacological activities. A large number of antimalarial compounds with a

wide variety of structures have been isolated from plants and may play a role in the development of new antimalarial drugs. The arylnaphthalene lignan justicidin A (**45**) has been reported to have antimalarial activity with an IC_{50} value of 1.9 μg/mL [81]. Lignans have been reported to inhibit mitochondrial electron transport, and it is hypothesized that **45** affects the parasite mitochondria by disrupting its structure and/or function, since this organelle appears to be a sensitive target for a variety of drugs and toxins [82,83]. Pycnantolol (**62**) (Figure 12.12), a new lignan from *P. angolensis* collected in São Tome, and four other liganans, (−)-dihydroguaiaretic acid (**63**), heliobuphthalmin (**64**), talaumidin (**65**), and hinokinin (**66**), were evaluated for their activity against 3D7-chloroquine-sensitive and Dd2-chlorpoquine-resistant *P. falciparum* strains [84]. In general, the activity was considered weak relative to chloroquine for both strains; however, compound **65** showed moderate activity at 20 μg/mL against the Dd2-resistant strain. IC_{50} values (μg/mL) for these compounds against 3D7 and Dd2 were 31.0 and 37.6 for **62**; 78.2 and 42.3 for dihydroguaiaretic acid (**63**); 87.4 and 35.1 (**64**); 36.2 and 20.7 (**65**); and 90.7 and 54.4 (**66**) [84].

(−)-Nortrachelogenin (**67**), present in *C. edulis* [58], showed antiplasmodial activity against the chloroquin-sensitive (D6) strains of *P. falciparum* parasite, with an IC_{50} value of 14.50 μg/mL [85]. The 2-arylbenzofuran derivative burttinol D (**68**), from the root bark of *Erythrina burtii*, was identified as the most active antiplasmodial compound, showing *in vitro* antiplasmodial activity against chloroquine-sensitive (D6, IC_{50}: 4.9 μM) and chloroquine-resistant (W2, IC_{50}: 6.3 μM) strains of *P. falciparum* [86].

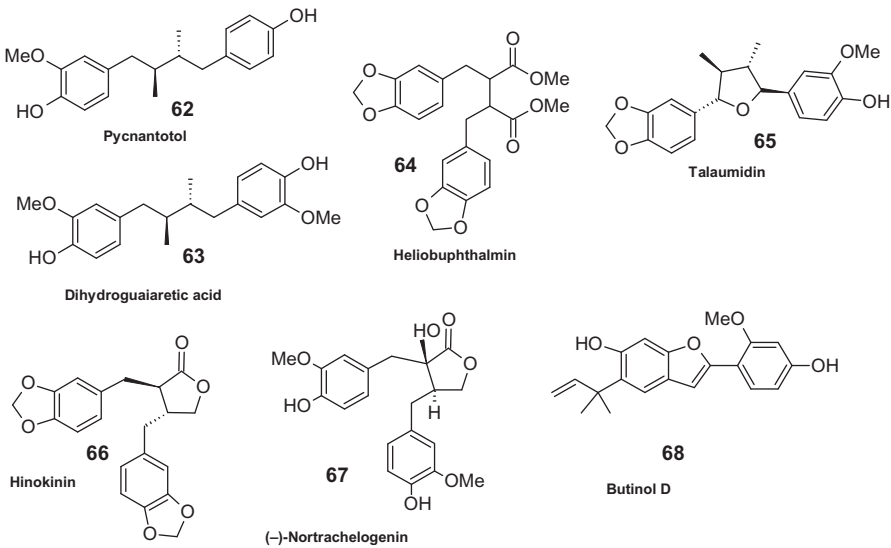

Figure 12.12 Antimalarial lignans identified in African plants.

12.4.1.5 *Other Pharmacological Activities of Lignans Identified in African Medicinal Plants*

Three new prenylated arylbenzofurans, named 2′-*O*-demethylbidwillol B (**69**) (Figure 12.13), addisofuran A (**70**), and addisofuran B (**71**), as well as three known nonprenylated derivatives, kanzonol U (**29**), glyinflanin H (**72**), and vingafuran (**73**), were obtained from the stem bark of *Erythrina addisoniae* [87]. These compounds were evaluated for their inhibitory activity on protein tyrosine phosphatase-1B (PTP1B). PTP1B has been implicated as a negative regulator of insulin action, and the overexpression of PTP1B protein has been observed in insulin-resistant states associated with obesity [87]. The new prenylated arylbenzofurans **69 − 71** inhibited PTP1B activity, with IC_{50} values of 13.6, 17.5, and 15.7 μM, respectively. Nonprenylated compounds **29**, **72**, and **73** exhibited a significantly lower PTP1B inhibitory activity [**29** (IC_{50}: 62.7 μM), **72** (IC_{50}: 64.9 μM), and **73** (IC_{50}: 74.1 μM)] [87].

The phosphodiesterase-4 (PDE4) enzymes play a vital role in regulating cyclic 3′,5′-adenosine monophosphate (cAMP) at the cellular level by hydrolyzing cAMP to 5′-AMP, which acts as a key regulator of many important biological processes. PDE4 has been identified as a promising target for the treatment of asthma. Moracin M (**27**) and C (**26**) have inhibitory affinity toward four PDE4 enzymes. Lignan **27** inhibited PDE4D2 and PDE4B2, with IC_{50} values of 2.9 and 4.5 μM, respectively. Inhibition values of **26** were 26.0 and 18.1 μM, respectively, for the same two enzymes [88].

Veraguensin (**74**) showed *in vitro* antileishmanial activity against *Leishmania donovani*, with an IC_{50} value of 18 μg/mL and IC_{90} value of 36 μg/mL. It is believed that tetrahydrofuran lignans act by inhibiting trypanothione reductase, an enzyme that protects the parasite from oxidative stress [89]. Justicidin B (**30**) exhibited strong activity against the trypomastigote form of *Trypanosoma rhodesiense*

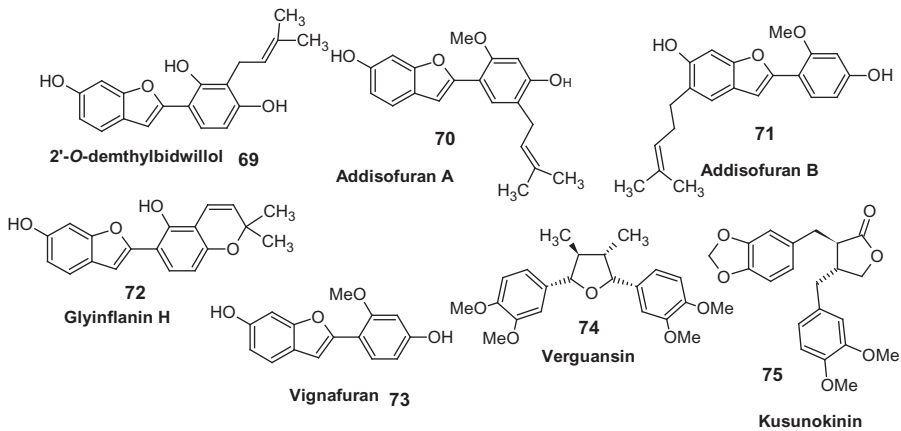

Figure 12.13 Other active lignans identified in African medicinal plants.

(IC_{50}: 0.2 μg/mL) and moderate activity against *Trypanosoma cruzi* (IC_{50}: 2.6 μg/mL) [52]. Sesamin (**8**), hinokinin (**66**), and kusunokinin (**75**) were tested against trypomastigotes and intracellular amastigotes of *T. cruzi*. In the trypomastigotes assay, the IC_{50} values (μM) were 102.8, 94.0, and 51.5 for **8**, **66**, and **75**, respectively. Compound **75** was the only active substance against intracellular amastigotes of *T. cruzi*, with a promising IC_{50} value of 17 μM. The mammalian toxicity study demonstrated that compounds **8**, **66**, and **75** presented similar toxicities on leukemia THP-1 cells, with IC_{50} values ranging from 36 to 41 μM [90] (Table 12.1).

12.4.2 Stilbenes

Stilbenes act as natural protective agents to defend plants against fungal, viral, and microbial attacks, excessive UV exposure, and disease. They have been shown to have a variety of pharmacological properties, such as anti-inflammatory activity, estrogen receptor agonist, and effects on cell signaling pathways, cell proliferation, and apoptosis [93]. Naturally occurring stilbenes overwhelmingly exist in the *E* (or *trans*) form. Resveratrol (**2**) is the only stilbene that has been extensively studied and has been shown to possess potent anticancer, anti-inflammatory, and antioxidant activities. Considerable research showing resveratrol to be an attractive candidate in combating a wide variety of cancers and diseases has fueled interest in determining the disease-fighting capabilities of other structurally similar stilbene compounds.

12.4.2.1 Antibacterial Stilbene from African Medicinal Plants

Eloff et al. [94] were the first to report that a stilbene, 2′,3′,4-trihydroxyl-3,5,4′-trimethoxybibenzyl (combretastatin B5) (**76**) (Figure 12.14), isolated from a chloroform fraction of South African *Combretum woodii* leaves, has significant antibacterial effects against *S. aureus* (MIC: 16 μg/mL) as well as some activity against the gram-negative *E. coli* and *P. aeruginosa* (MIC: 125 μg/mL). The novel geranylstilbenes schweinfurthins A (**77**) and B (**78**) were isolated from the Cameroonian *Macaranga schweinfurthii* [95,96] and later from Kenyan propolis [97]. They have been found to possess antibacterial activity against *S. aureus* with an equal inhibition zone of 19 mm at a concentration of 400 μg in the cup [97]. The new stilbene erythraddison B (**79**), with a conjugated function aldehyde, from *E. addisoniae*, was effective at inhibiting the growth of two species of influenza virus, H1N1 (IC_{50}: 8.80 μg/mL) and H9N2 (IC_{50}: 7.19 μg/mL) [98].

12.4.2.2 Anti-inflammatory and Antioxidant Stilbenes from African Medicinal Plants

Two new dimeric stilbene glucosides, tingitanol A (**80**) (Figure 12.15) and tingitanol B (**81**), together with *trans*-resveratrol 3-*O*-glucopyranoside (**82**), have been isolated from the Egyptian plant *I. tingitana* and shown to possess potent

Table 12.1 Lignans with Biological Activity from African Medicinal Plants

Compounds	Plant Species (Family)	Plant Part	Pharmacological Activities	Country of Origin
Sesamin (**8**)	*F. heitzii* (Rutaceae) [3]	Stem bark	Suppressive effect on phagocyte oxidative burst [3]	Cameroon
Savinin (**15**)	*F. heitzii* (Rutaceae) [3]	Stem bark	Suppressive effect on phagocyte oxidative burst [3]	Cameroon
Bolusanthin IV (**33**)	*B. speciosus* (Fabaceae) [54]	Root wood	Antibacterial activity [54]	Botswana
Pycnanthulignene A (**17**)	*P. angolensis* (Welw.) Ward (Myristicaceae) [47]	Roots	Antimicrobial activity [47]	Cameroon
Pycnanthulignene B (**18**)	*P. angolensis* (Welw.) Ward (Myristicaceae) [47]	Roots	Antimicrobial activity [47]	Cameroon
Pycnanthulignene C (**19**)	*P. angolensis* (Welw.) Ward (Myristicaceae) [47]	Roots	Antimicrobial activity [47]	Cameroon
Pycnanthulignene D (**20**)	*P. angolensis* (Welw.) Ward (Myristicaceae) [47]	Roots	Antimicrobial activity [47]	Cameroon
Moracin Q (**21**)	*M. mesozygia* (Moraceae) [48]	Stem/trunk bark	Antioxidant activity [48]	Cameroon
Moracin R (**22**)	*M. mesozygia* (Moraceae) [48,49]	Stem/trunk bark	Antioxidant activity [48]	Cameroon
Moracin S (**23**)	*M. mesozygia* (Moraceae) [48,49]	Stem/trunk bark	Antioxidant activity [48]	Cameroon
Moracin T (**24**)	*M. mesozygia* (Moraceae) [48,49]	Stem/trunk bark	Antioxidant activity [48]	Cameroon
Moracin U (**25**)	*M. mesozygia* (Moraceae) [48,49]	Stem/trunk bark	Antioxidant activity [48]	Cameroon
Moracin C (**26**)	*M. mesozygia* (Moraceae) [49]	Stem bark	Antibacterial activity [49]	Cameroon
Moracin M (**27**)	*M. mesozygia* (Moraceae) [49]	Stem bark	Antibacterial activity [49]	Cameroon
	Morus alba (Moraceae) [88,91]	Root bark	Phosphodiesterase inhibitory activity [88]	Egypt
Anolignan B (**28**)	*T. sericea* (Combretaceae) [50]	Roots	Antibacterial and anti-inflammatory activities [50]	South Africa
Zanthocapensol (**31**)	*Z. capense* (Rutaceae) [53]	Roots	Antibacterial activity [53]	Mozambique
Zanthocapensate (**32**)	*Z. capense* (Rutaceae) [53]	Roots	Antibacterial activity [53]	Mozambique

(*Continued*)

Table 12.1 (Continued)

Compounds	Plant Species (Family)	Plant Part	Pharmacological Activities	Country of Origin
4′-*O*-Cinnamoyl cleomiscosin A (**44**)	*T. tropophylla* H. Perrier (Combretaceae) [71]	Roots	Antiproliferative activity [71]	Madagascar
(−)-Syringaresinol (**34**)	*D. molunduana* Pax (Euphorbiaceae) [56]	Whole stem	Antioxidant activity [56,57]	Cameroon
Denudatin A (**37**)	*M. soulangiana* (Magnoliaceae) [61]	Flower buds	Anti-inflammatory activity [61]	Egypt
Denudatin B (**38**)	*M. soulangiana* (Magnoliaceae) [61]	Flower buds	Anti-inflammatory activity [61]	Egypt
9-(Benzo[*d*][1,3]dioxol-5-yl)-6,7,8-trimethoxy-a,4,9,9-atetrahydronaphtho [2,3-c]furan-1(3*H*)-one [marginatoxin (**42**)]	*B. marginatum* (Apiaceae) [69]	Aerial parts	Anticancer activity [69]	Egypt
3,4-(Dimethoxybenzyl)-2-(3,4-methylenedioxybenzyl) butyrolactone (**43**)	*B. marginatum* [69]	Aerial parts	Anticancer activity [69]	Egypt
Liriodendrin (**41**)	*Phlomis aurea* Decne (Lamiaceae) [92], *S. spinosa* [66]	Leaves	Anti-inflammatory activity [67,92]	Egypt
Carissanol (**35**)	*C. edulis* (Apocynaceae) [58]	Roots	Antioxidant activity [59]	Ghana
Carinol (**36**)	*C. edulis* (Apocynaceae) [58]	Roots	Antioxidant activity [59]	Ghana
(+)-Lariciresinol (**9**)	*C. edulis* (Apocynaceae) [58]	Roots	Free radical scavenging activity [60]	Ghana
(−)-Secoisolariciresinol (**10**)	*C. edulis* (Apocynaceae) [58]	Roots	Antioxidant activity [60]	Ghana
Justicidin B (**30**)	*H. tuberculatum* (Rutaceae) [72,73]	Aerial parts	Antifungal activity [52], anticancer activity [52], antitrypanosomal [52]	Libya, Sudan
Justicidin A (**45**)	*H. tuberculatum* [72,73]	Aerial parts	Anticancer activity [74], antimalarial activity [81]	Libya, Sudan

Diphyllin (**46**)	*H. tuberculatum* [72,73]	Aerial parts	Anticancer activity [74]	Libya
Polygamatin (**48**)	*H. tuberculatum* [72,73]	Aerial parts	Antiproliferative and microtubule-depolymerizing activities [75]	Libya
Tuberculatin (**47**)	*H. tuberculatum* [72,73]	Aerial parts	Anticancer activity [74]	Libya
Kusunokinin (**75**)	*H. tuberculatum* [73]	Aerial parts	Anticancer activity [90]	Libya
2-[2′,4′-Dihydroxy-3′-(3-methylbut-2-enyl) phenyl]-6-hydroxybenzofuran (**69**)	*E. addisoniae* (Leguminosae) [87]	Stem bark	PTP1B inhibitory activity [87]	Cameroon
2-[2′-Methoxy-4′-hydroxy-5′-(3-methylbut-2-enyl) phenyl]-6-hydroxybenzofuran (**70**)	*E. addisoniae* (Leguminosae) [87]	Stem bark	PTP1B inhibitory activity [87]	Cameroon
2-(2′-Methoxy-4′-hydroxyphenyl)-5-(3-methylbut-2-enyl)-6-hydroxybenzofuran (**71**)	*E. addisoniae* (Leguminosae) [87]	Stem bark	PTP1B inhibitory activity [87]	Cameroon

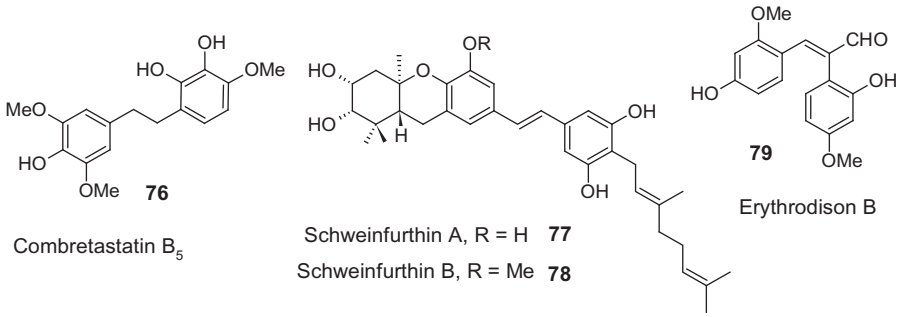

Figure 12.14 Chemical structures of antibacterial stilbenes.

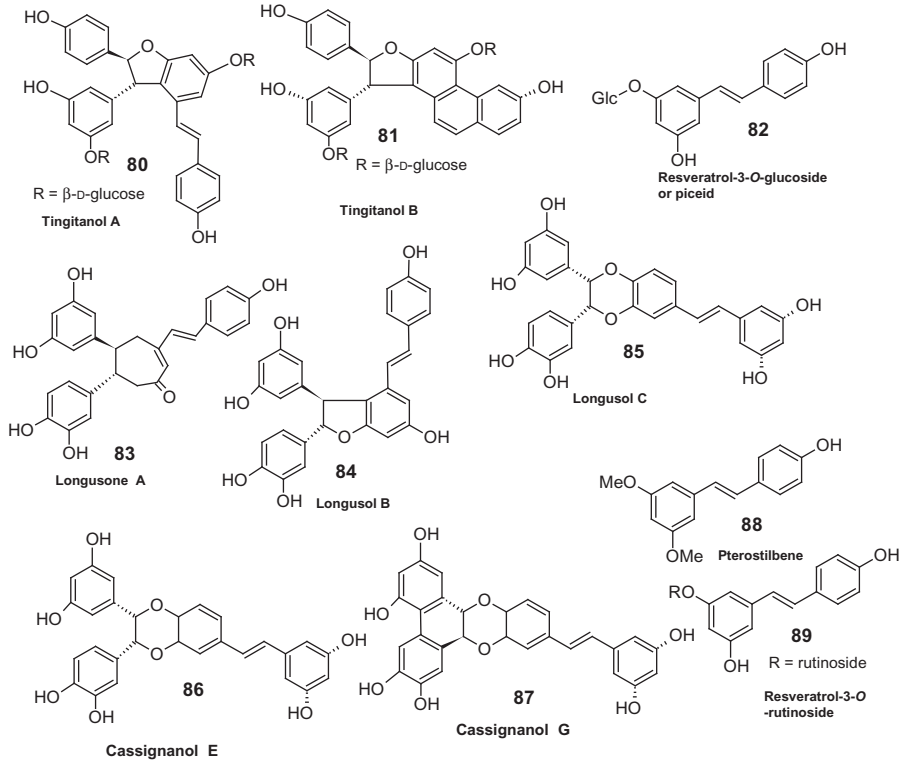

Figure 12.15 Chemical structures of antioxidant stilbenes.

antioxidant capabilities [30]. At a concentration of 2.0×10^{-4} M, the DPPH radical scavenging activity of tingitanol B (**81**) was the highest (48.5%), followed by *trans*-resveratrol glucoside or piceid (**82**) (33.1%) and tingitanol A (**80**) (22.3%) [30]. Four new stilbene dimers, longusone A (**83**) and longusols A (**1**), B (**84**), and C (**85**), with antiallergic and radical scavenging activities, have also been isolated from the Egyptian natural medicinal plant *C. longus*, together with other known compounds. Compound **84**, resveratrol (**2**), piceatannol (**4**), and cassigarols E (**86**) and G (**87**) were found to inhibit the release of β-hexosaminidase, a marker of antigen-induced degranulations, in rat basophilic leukemia cells. These constituents showed DPPH radical scavenging activity with IC_{50} values ranging from 2.8 to 29 μM [28].

Compound **4** is synthesized in response to fungal attack, UV exposure, and microbial infection [99]. This compound is a potent NO inhibitor (IC_{50}: 23 μM), and it also inhibits COX-1 (IC_{50}: 4.71 μM) and COX-2 (IC_{50}: 0.0113 μM), yielding a selectivity index of 417.08. Compound **2** also inhibits NO (IC_{50}: 68 μM) and inhibits ABAP [2,2′-azo-bis(2-amidinopropane)], derived from peroxyl radicals, with a total reactive antioxidant potential of 253 μM [100]. Compound **2** also inhibits COX-1 (IC_{50}: 0.535 μM) and COX-2 (IC_{50}: 0.996 μM), yielding a selectivity index of 0.54. It has been suggested that the oxygen groups attached to the stilbene structure are crucial for the observed activity, as evidenced by the observation that the addition of the glucoside moiety reduced pharmacological activity [101].

Pterostilbene (**88**) has been shown to elicit significant antioxidant activity *in vitro* by DPPH radicals (EC_{50}: 30 μM), inhibiting ABAP-derived peroxyl radicals, with a total reactive antioxidant potential of 237 μM [100]. Compound **88** also inhibits COX-1 (IC_{50}: 19.8 μM) and slightly inhibits COX-2 (IC_{50}: 83.9 μM) [102]. The new reveratrol-3-*O*-rutinoside (**89**), from *Elephantorrhiza goetzei* [103], showed antioxidant activity [104].

12.4.2.3 Cytotoxic Stilbenes from African Medicinal Plants

There are a number of promising antiangiogenic and antivascular agents, some of them originating from higher plants, which are undergoing clinical trials. Among them, combretastatin (**90**) (Figure 12.16) and combretastatins A and B series are the most potent. The A series possesses an ethylene bridge between the two benzyl rings, whereas the B series has an ethane bridge (dihydrostilbene). Combretastatins A-1 (**91**), A-2 (**92**), A-3 (**93**), and A-4 (**94**), as well as combretastatins B-1 (**95**), B-2 (**96**), B-3 (**97**), and B-4 (**98**) have all been isolated for the first time from the South African species of *C. caffrum*. They are well known for their outstanding antineoplastic activity [105–108].

Combretastatin of the A series are *cis*-stilbenes with potent anticancer activity [108,109]. The most potent member, combretastatin A-4 (**94**), in sodium phosphate prodrug form, has recently completed phase I clinical trials as an antiangiogenic tubulin-binding agent and in nonsmall-cell lung cancer and cervix carcinoma, and is currently being evaluated in a phase II trial concerning ovarian, thyroid, gastric, and other solid tumors [110,111]. The hydroxyl stilbenes, longistylins A and C, have

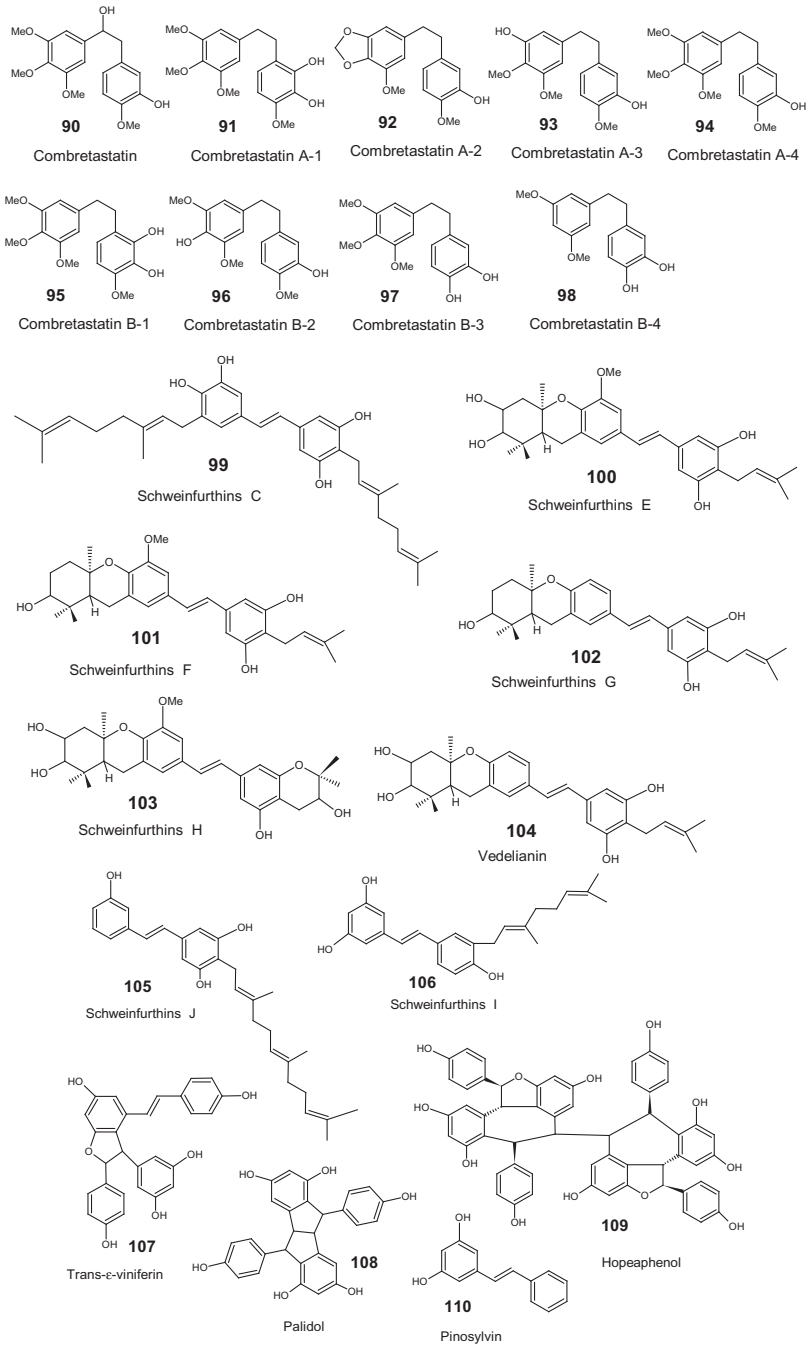

Figure 12.16 Chemical structures of cytotoxic stilbenes.

also shown anticancer activity (IC_{50}: 5.2 and 4.4 μg/mL on the MCF-7 cancer cell line) [112]. Schweinfurthins A−J are novel prenylated stilbenes, all isolated from *M. schweinfurthii* or *Macaranga alnifolia*. They have been demonstrated to be cytotoxic against several tumor cell lines. Schweinfurthins A (**77**) and B (**78**) displayed antiproliferative activities against the central nervous cells SF-295 and A549 with IC_{50} values of 43 and 47 μg/mL, respectively [95], whereas schweinfurthin C (**99**) was also cytotoxic with IC_{50} values of 2 and 2.8 μg/mL toward the same cell lines [96]. The four new prenylated schweinfurthins E−H (**100**−**103**) and the known prenylated stilbene vedelianin (**104**) have been isolated from *M. alnifolia* and are reported to have antiproliferative activity in the A2780 human ovarian cancer cell line assay [113]. Compound **104** exhibited the greatest activity among all isolates (IC_{50}: 0.13 μM), whereas schweinfurthin E (**100**) (IC_{50}: 0.26 μM) was the most potent of the new compounds. Schweinfurthins I (**105**) and J (**106**), from the leaves of *M. schweinfurthii*, had IC_{50} values of 10 and 2.8 μM, respectively, when assayed in the NCI 60 human tumor cell line screen [95,114]. Four known stilbenes, *trans*-resveratrol (**2**), *trans*-piceid (**82**), *trans*-ε-viniferin (**107**), and pallidol (**108**), as well as the new tetramer (+)-hopeaphenol (**109**), were isolated from Algerian merlot wine. Investigating the stilbenes against several tumor cell lines showed that hopeaphenol (**109**) has potent cytotoxicity on the human epidermoid carcinoma of the nasopharynx, with an IC_{50} value of 1.2 μg/mL [36]. Resveratrol (**2**) has also been extensively investigated for its role in cancer prevention.

Pinosylvin (**110**) has been shown to be a potent inhibitor of human lymphoblastoid cells, possibly due to its ability to modulate estrogen receptors. Compound **110** showed potent antiproliferation activity in both the estrogen-dependent breast cancer cell line MCF-7 and the ductal carcinoma T-47D cell line, with a reported LEC (lowest effective concentration) of 1 μM, which inhibited proliferation by 27% [115]. This compound has also been shown to be most active in HepG2 liver cancer cells and MDA-MB-231 estrogen negative breast cancer cells with an IC_{50} value of 10 μg/mL [116]. Pterostilbene (**88**) has been evaluated *in vitro* to determine its ability to induce apoptosis in leukemia cells of different sensitivity and drug resistance, and in lymphoma cell lines. In HL60 promyelocytic leukemia cells, it was found that pterostilbene (**88**) (concentration of compound needed for 50% activation relative to the reference, AC_{50}: 70 μM) was less active than resveratrol (AC_{50}: 50 μM) at inducing apoptosis. Similarly, pterostilbene (**88**) inhibited HL60 cell growth (IC_{50}: 35 μM) less potently than **2** (IC_{50}: 5 μM) [117]. However, *cis*-pterostilbene was a potent apoptosis-inducing agent with an AC_{50} equal to 5 μM compared to **2**[117]. Compound **88** was found to be an active apoptotic agent on leukemia cells that express the antiapoptotic oncogene Bcr-Abl and on cells that express the multidrug resistant (MDR) phenotype [118]. This compound also demonstrated activity in lymphoma cell lines with a mutation of the Fas gene (HUT78B1 and HUT78B3), which were surprisingly resistant to apoptosis by *trans*-resveratrol and piceatannol (**4**). Moreover, **88** was found to be nontoxic to normal hemopoietic stem cells when concentrations that elicited apoptosis in leukemia cell lines were employed. A pan-caspase inhibitor Z-VAD-fmk did not inhibit apoptosis induced by pterostilbene; therefore, it has been suggested that apoptosis is activated by pterostilbene through a caspase-independent mechanism [118].

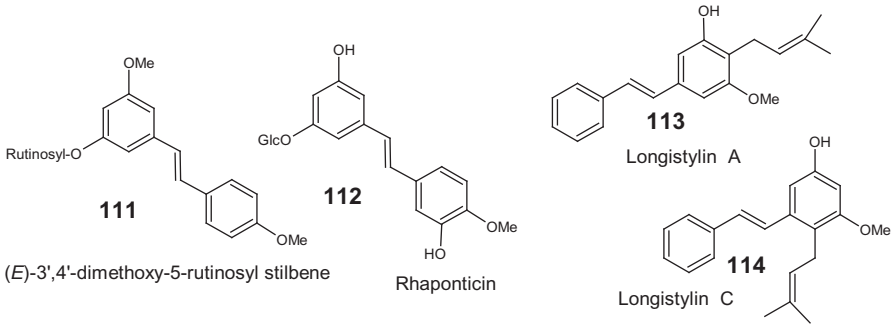

Figure 12.17 Chemical structures of antimalarial stilbenes.

12.4.2.4 Antimalarial Stilbenes from African Medicinal Plants

Traditional plants play an important role in medical systems in Africa, and plant materials remain an important resource to combat diseases like malaria. Since drugs, such as quinine and artemisinin, were isolated from plants and because of the increased resistance of malaria parasites toward existing antimalarial drugs, the investigation of new compounds from traditional plants is necessary. The stilbenes (*E*)-3,4′-dimethoxy-5-rutinosyl stilbene (**111**) (Figure 12.17), rhaponticin (**112**), and piceid (**73**) isolated from the stem bark of *Guibourtia tessmannii* displayed antiplasmodial activity (IC_{50}: 13.2 μM) [119]. Two hydroxyl stilbenes, longistylins A (**113**) and C (**114**), have been isolated from *Cajanus cajan* and also shown to possess antiplasmodial activity [120].

12.4.2.5 Other Pharmacological Activities of Stilbenes from African Medicinal Plants

Pterostilbene (**88**) has shown antidiabetic properties, lowering the blood glucose levels in streptozotocin-induced hyperglycemic rats by 42% at a dose of 20 mg/kg body weight [100]. Apart from their anticancer properties, combretastatins have also been reported to have antitubulin properties [109]. Rhapontigenin (**115**) (Figure 12.18) elicits a potent inhibitory effect on the release of histamine, which is involved in many allergic reactions [62]. Rhaponticin (**112**) and resveratrol (**2**) have the capacity to inhibit platelet aggregation *in vitro*. Compound **2** also inhibits collagen-induced aggregation at an IC_{50} value of 5 μM, and inhibits Adenosine diphosphate (ADP)-induced aggregation with an IC_{50} value of 17.75 μM. Compound **112** inhibits collagen-induced aggregation with an IC_{50} value of 124.6 μM, and inhibits ADP-induced aggregation with an IC_{50} value of 112.07 μM. Resveratrol 3-*O*-β-D-glucopyranoside or piceid (**82**), from the seeds of *Erythrophleum lasianthum*, showed an inhibitory effect on platelet aggregation induced by collagen (IC_{50}: 69 μM), adrenalin (IC_{50}: 102 μM) and, to a minor extent, by arachidonic acid (IC_{50}: 149 μM) and by ADP (IC_{50}: 218 μM). Two new stilbene glycosides, *trans*-4′,5-dihydroxy-3-methoxystilbene-5-*O*-*R*-L-rhamnopyranosyl-(1→2)-[*R*-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (**116**) and *trans*-4′,5-dihydroxy-3-methoxystilbene-5-*O*-[*R*-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (**117**), were

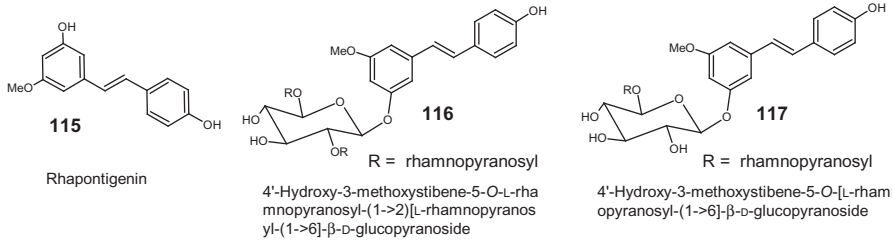

Figure 12.18 Other pharmacologically active stilbenes identified in African plants.

isolated from the stem bark of *Boswellia papyrifera* and have been shown to exhibit phosphodiesterase I inhibitory activity (IC_{50}: 178 and 129 μM) and xanthine oxidase (IC_{50}: 992 and 589 μM) [121] (Table 12.2).

12.5 New Lignans with Undefined Pharmacological Activity Isolated in African Medicinal Plants

Some lignans were isolated as new compounds from African medicinal plants [61,122,125–132]. In this section, we will discuss such compounds with no reported biological activities. Data are summarized in Table 12.3. It is important to note the particularity of some of these lignans. A sulfate lignin, pinoresinol 4-sulfate (**118**) (Figure 12.19), was isolated from the Algerian plant *Frankenia thymifolia* Desf. (Frankeniaceae) [125]. Because of the instability of the sulfate in acid media, sulfate esters of natural products are not often isolated in plants [125]. The significance of such compounds is still unclear, though they have been shown responsible for seismonastic and gravitropic movements and involved in sulfate ions sequestration [122]. When isolated for the first time in *Myrianthus arboreus*, compound myrianthiphyllin was the first natural lignan cinnamate known to occur in plants [130]. The lignan (±)2e,3e-bis-(1-oxo-dimethoxyphenyl)-3,7-dioxabicyclo-[3,3,0]-octane (**124**) isolated from the Egyptian plant *Tamarix aphylla* was also the first diaryloxy furanofuran lignan isolated from the family Tamaricaceae [131].

12.6 Stilbenes from African Medicinal Plants with Undefined Pharmacological Activity

A few novel stilbenes that have been isolated from African medicinal plants have no pharmacological activity described in the literature. They include two rutinoside glycosides (**131** and **132**) (Figure 12.20) [103]. From the underground tubers of *Schoenus nigricans*, four new stilbenes 3,5,3′,4′-tetramethoxystilbene (**133**), 3,5,4′-trimethoxy-2-prenylstilhene (**134**), 3-hydroxy-5,4′-dimethoxy-2-prenyl stilbene (**135**), and 3,4′-dihydroxy-5-methoxy-2-prenylstilbene (**136**) were isolated [132] (Table 12.4).

Table 12.2 Bioactive Stilbenes Identified in African Medicinal Plants

Compounds	Plant Species (Family)	Plant Part	Pharmacological Activities	Country of Origin
Schweinfurthin A (**77**)	*M. schweinfurthii* (Euphorbiaceae) [95]	Leaves	Antiproliferative activity [95,114]	Cameroon
Schweinfurthin B (**78**)	*M. schweinfurthii* (Euphorbiaceae) [95]	Leaves	Antiproliferative activity [95,114]	Cameroon
Schweinfurthin C (**99**)	*M. schweinfurthii* (Euphorbiaceae) [95]	Leaves	Antiproliferative activity [95]	Cameroon
Schweinfurthin E (**100**)	*M. alnifolia* (Euphorbiaceae) [113]	Fruits	Antiproliferative activity [113]	Madagascar
Schweinfurthin F (**101**)	*M. alnifolia* (Euphorbiaceae) [113]	Fruits	Antiproliferative activity [113]	Madagascar
Schweinfurthin G (**102**)	*M. alnifolia* (Euphorbiaceae) [113]	Fruits	Antiproliferative activity [113]	Madagascar
Schweinfurthin H (**103**)	*M. alnifolia* (Euphorbiaceae) [113]	Fruits	Antiproliferative activity [113]	Madagascar
Schweinfurthin I (**105**)	*M. schweinfurthii* (Euphorbiaceae) [95,114]	Leaves	Anticancer activity [95,114]	Cameroon
Schweinfurthin J (**106**)	*M. schweinfurthii* (Euphorbiaceae) [95,114]	Leaves	Anticancer activity [95,114]	Cameroon
Vedelianin (**104**)	*M. alnifolia* (Euphorbiaceae) [113]	Fruits	Antiproliferative activity [95,114]	Madagascar
Combretastatin A-1 (**91**)	*C. caffrum* Kuntze (Combretaceae) [105]	Wood	Antineoplasmic activity [105]	South Africa
Combretastatin A-2 (**92**)	*C. caffrum* Kuntze (Combretaceae) [106,108]	Wood	Antineoplasmic activity [106]	South Africa
Combretastatin A-3 (**93**)	*C. caffrum* Kuntze (Combretaceae) [106,108]	Wood	Antineoplasmic activity [106]	South Africa
Combretastatin A-4 (**94**)	*C. caffrum* Kuntze (Combretaceae) [108]	Wood	Antineoplasmic activity [106]	South Africa
Combretastatin B-1 (**95**)	*C. caffrum* Kuntze (Combretaceae) [105]	Wood	Antineoplasmic activity [105]	South Africa
Combretastatin B-2 (**96**)	*C. caffrum* Kuntze (Combretaceae) [106]	Wood	Antineoplasmic activity [106]	South Africa
Combretastatin B-3 (**97**)	*C. caffrum* Kuntze (Combretaceae) [107]	Wood	Antineoplasmic activity [107]	South Africa
Combretastatin B-4 (**98**)	*C. caffrum* Kuntze (Combretaceae) [107]	Wood	Antineoplasmic activity [107]	South Africa
Combretastatin B-5 (**76**)	*C. woodii* [94]	Leaves	Antibacterial effects [94]	South Africa
trans-ε-Viniferin (**107**)	Algerian merlot wine [36]	Fruit	Anticancer activity [36]	Algeria
Pallidol (**108**)	Algerian merlot wine [36]	Fruit	Anticancer activity [36]	Algeria
(+)-Hopeaphenol (**109**)	Algerian merlot wine [36]	Fruit	Anticancer activity [36]	Algeria
(*E*)-3,4′-Dimethoxy-5-rutinosyl stilbene (**111**)	*G. tessmannii* (Harms Leonard), Leguminosae (Caesalpiniaceae) [122]	Stem bark	Antiplasmodial activity [119]	Cameroon

Rhaponticin (**112**)	*G. tessmannii* (Harms Leonard), Leguminosae (Caesalpiniaceae) [122]	Stem bark	Antiplasmodial activity [119]	Cameroon
Piceid (**73**)	*G. tessmannii* (Harms Leonard), Leguminosae (Caesalpiniaceae) [122]	Stem bark	Antiplasmodial activity [119]	Cameroon
Rhapontigenin (**115**)	*Scilla nervosa* subsp. *rigidifolia* (Hyacinthaceae) [123]	Bulbs	Antiallergic activity [62]	Cameroon
Tingitanol A (**80**)	*I. tingitana* (Iridaceae) [30]	Bulbs	Radical scavenging activity [30]	Egypt
Tingitanol B (**81**)	*I. tingitana* (Iridaceae) [30]	Bulbs	Radical scavenging activity [30]	Egypt
trans-Piceid (*trans*-resveratrol 3-*O*-glucopyranoside) (**82**)	*I. tingitana* (Iridaceae) [30]	Bulbs	Radical scavenging activity [30]	Egypt
Longistylins A (**113**)	*C. cajan* (L) Millsp. (Fabaceae) [112]	Leaves	Antiplasmodial activity [120], anticancer activity [112]	Nigeria
Longistylins C (**114**)	*C. cajan* (L) Millsp. (Fabaceae) [112]	Leaves	Antiplasmodial activity [120], anticancer activity [112]	Nigeria
Resveratrol 3-*O*-β-D-glucopyranoside (**82**)	*E. lasianthum* (Caesalpinioidae, Leguminosae) [124]	Seeds	Antiplatelet aggregation activity [124]	South Africa
trans-4′,5-Dihydroxy-3-methoxystilbene-5-*O*-*R*-L-rhamnopyranosyl-(1→2)-[*R*-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (**116**)	*B. papyrifera* (Del.) Hochst. (Burseraceae) [121]	Stem bark	Inhibition of phosphodiesterase I [121]	Cameroon
trans-4′,5-Dihydroxy-3-methoxystilbene-5-*O*-[*R*-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (**117**)	*B. papyrifera* (Del.) Hochst. (Burseraceae) [121]	Stem bark	Inhibition of phosphodiesterase I [121]	Cameroon

(*Continued*)

Table 12.2 (Continued)

Compounds	Plant Species (Family)	Plant Part	Pharmacological Activities	Country of Origin
Longusone A (**83**)	*C. longus* [28]	Whole plant	Antiallergic and antioxidant activities [28]	Egypt
Longusol A (**1**)	*C. longus* [28]	Whole plant	Antiallergic and antioxidant activities [28]	Egypt
Longusol B (**84**)	*C. longus* [28]	Whole plant	Antiallergic and antioxidant activities [28]	Egypt
Longusol C (**85**)	*C. longus* [28]	Whole plant	Antiallergic and antioxidant activities [28]	Egypt

Table 12.3 New Lignans with Undefined Pharmacological Activity Isolated from African Plants

Compounds	Class (Type)	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
Pinoresinol 4-sulfate (**118**)	Lignan (furanofuran)	*F. thymifolia* Desf. (Frankeniaceae) [125]	Algeria	Roots	mp 147°C; $[\alpha]^{22}_{D}$ 95° (*c* 0.4, MeOH)
9,4′,9′-Trihydroxy 4,5,3′-trimethoxy aryltetralin lignan or scaphopetalone (**119**)	Lignan (aryltetralin)	*Scaphopetalum thonneri* (Sterculiaceae) [126]	Cameroon	Stem bark	Brown sticky oil
(+)-4-(3-Methylbutanoyl)-2,6-di (3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0] octane (**120**)	Lignan (furanofuran)	*Echinops giganteus* var. lelyi C.D. Adams (Compositae) [127]	Cameroon	Roots	mp 94−95°C; $[\alpha]^{22}_{D}$ +9.7° ($CHCl_3$, *c* 0.35)
(+)-4-Hydroxy-2,6-di (3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0] octane (**121**)	Lignan (furofuran)	*Echinops giganteus* var. lelyi C.D. Adams (Compositae) [127]	Cameroon	Roots	mp 171−173°C; $[\alpha]^{22}_{D}$ +29.5° ($CHCl_3$, *c* 0.45)
Myrianthiphyllin (**122**)	Lignan (cinnamate)	*M. arboreus* (Cecropiaceae) [130]	Cameroon	Trunk wood	mp 157−160°C; $[\alpha]^{18}_{D}$ −70° ($CHCl_3$)
(3*S*,3α*R*)-3α-Allyl-5-methoxy-3-methyl-2-(3′,5′-methylene dioxybenzyl)-2,3α,4,5,6-hexahydro-6-oxo-benzofwan or soulangianin I (**123**)	Neolignan (benzofuran)	*M. soulangiana* (Magnoliaceae) [61]	Egypt	Flower buds	Colorless oil; $[\alpha]^{20}_{D}$ +2.5° ($CHCl_3$, *c* 0.5)

(*Continued*)

Table 12.3 (Continued)

Compounds	Class (Type)	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
(±)2e,3e-bis-(1-Oxo-dimethoxyphenyl)-3,7-dioxabicyclo-[3,3,0]-octane (**124**)	Lignan (furanofuran)	*T. aphylla* (Tamaricaceae) [131]	Egypt	Bark	–
(−)-*trans*-9-Acetyl-4,9′-di-*O*-methyl-3′-de-*O*-methyl dehydrodiconiferyl alcohol (**125**)	Neolignan (dihydrobenzo[*b*] furan)	(Euphorbiacea) [128]	Tanzania	Stem wood	Yellowish oil, $[\alpha]^{23}_{D}$ −73.3° (*c* 0.10, $CHCl_3$)
Meso-sesamin (**126**)	Lignan	*Zanthoxylum davyi* (Rutaceae) [133]	South Africa	Stem bark	–
(7*S*,8*R*,7′*R*,8′*S*)-4′-Hydroxy-4-methoxy-7,7′-epoxylignan (**127**)	Lignan (tetrahydrofuran)	*Terminalia superba* Engl. (Combretaceae) [134]	Cameroon	Stem bark	White powder, $[\alpha]^{25}_{D}$ +35.0° (*c* 0.007, MeOH); mp 110−113°C
meso-(rel-7*S*,8*R*,7′*R*,8′*S*)-4,4′-Dimethoxy-7,7′-epoxylignan (**128**)	Lignan (tetrahydrofuran)	*T. superba* Engl. (Combretaceae) [134]	Cameroon	Stem bark	$[\alpha]^{25}_{D}$ 0° (*c* 0.010, $CHCl_3$); mp 98−100°C
Didymochlaenone A (**129**)	Lignan derivative	*Didymochlaena truncatula* (Sw.) J. Sm (Dryopteridaceae) [135]	Madagascar	Roots	Colorless oil; $[R]^{22}_{D}$ +112.5 (*c* 0.08, EtOH)
Didymochlaenone B (**130**)	Lignan derivative	*D. truncatula* (Sw.) J. Sm (Dryopteridaceae) [135]	Madagascar	Roots	Colorless oil; $[R]^{22}_{D}$ −27.5 (*c* 0.08, EtOH)

mp, melting point; (−) not reported.

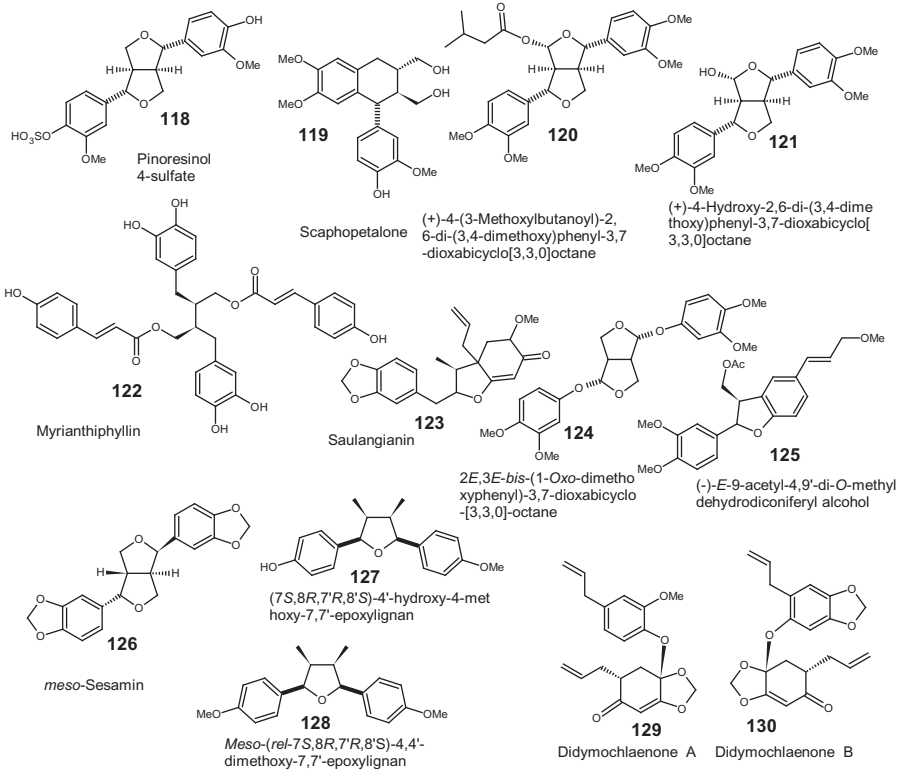

Figure 12.19 New lignans with undefined biological activities.

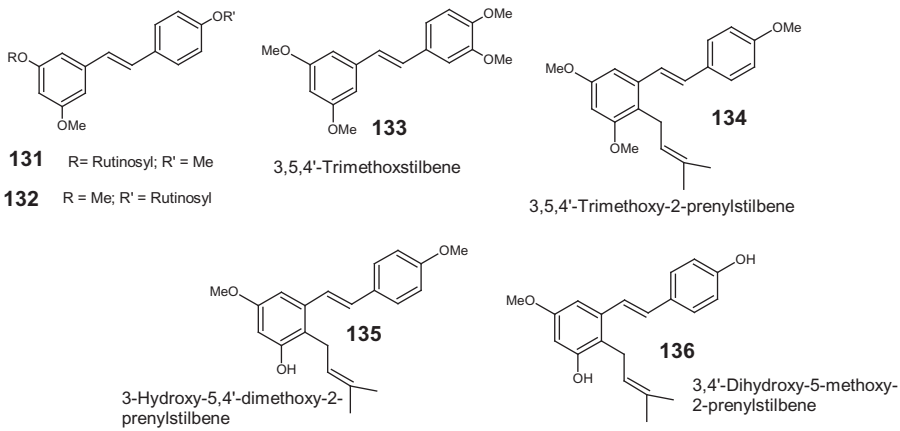

Figure 12.20 New stilbenes with no biological activity.

Table 12.4 New Stilbenes with Undefined Pharmacological Reported Activity Isolated from African Plants

Compounds	Class (Type)	Plants (Family)	Area of Plant Collection	Plant Part	Physical Properties
(*E*)-3,4′-Dimethoxy-5-rutinosyl-stilbene (**131**)	Stilbene (glycoside)	*G. tessmannii* (Cesalpiniaceae) [122]	Cameroon	Stem bark	mp 142−143°C
3,5-Dimethoxy-4′-*O*-(beta-rhamnopyranosyl-(1→6)-beta-glucopyranoside) stilbene (**132**)	Stilbene (glycoside)	*G. tessmannii* (Cesalpiniaceae) [129]	Cameroon	Stem bark	–
3,5,3′,4′-Tetramethoxystilbene (**133**)	Stilbene	*S. nigricans* (Cyperaceae) [132]	Egypt	Tubers	–
3,5,4′-Trimethoxy-2-prenylstilhene (**134**)	Stilbene (prenyl)	*S. nigricans* (Cyperaceae) [132]	Egypt	Tubers	–
3-Hydroxy-5,4′-dimethoxy-2-prenylsrilbene (**135**)	Stilbene (prenyl)	*S. nigricans* (Cyperaceae) [132]	Egypt	Tubers	–
3,4′-Dihydroxy-5-methoxy-2-prenylstilbene (**136**)	Stilbene (prenyl)	*S. nigricans* (Cyperaceae) [132]	Egypt	Tubers	–

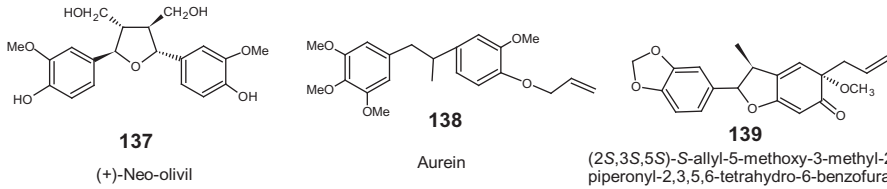

Figure 12.21 A lignan and stilbenes with no reported biological function.

12.7 Other Lignans Identified in African Medicinal Plants

Most of the lignans isolated from African medicinal plants have a biological function. Only one lignin, (+)-neo-olivil (**137**) (Figure 12.21), isolated from the roots of *Urtica dioica* (Urticaceae) [136], and two stilbenes, auren (**138**) and (2*S*,3*S*,5*S*)-*S*-allyl-5-methoxy-3-methyl-2-piperonyl-2,3,5,6-tetrahydro-6-benzofuran (**139**), both from *M. soulangiana* (Magnoliaceae) [61], have no activity reported in the literature.

Conclusion

This chapter presented the structure and biological function of about 140 lignans and stilbenes obtained from African medicinal plants. Lignans possess antioxidant, antibacterial, antimicrobial, and cytotoxic properties. Among the lignans, those from *S. araliacea* have unique chemical structures and possess potent antitumor properties. A series of unusual *cis*-stilbenes, combretastatins from *Combretum* species, and a series of prenylated stilbenes from *M. schweinfurthii* and *M. alnifolia* also possess promising antiproliferative properties.

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13 Tannins and Related Compounds from Medicinal Plants of Africa

Abdelaaty A. Shahat[a,b] *and Mohamed S. Marzouk*[c,d]

[a]Medicinal, Aromatic and Poisonous Plants Research Centre, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [b]Department of Phytochemistry, Center of Excellence for Advanced Sciences, National Research Center, Dokki, Cairo, Egypt, [c]Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [d]Chemistry of Natural products Group, Center of Excellence for Advanced Sciences, National Research Center, Dokki, Cairo, Egypt

13.1 Introduction

Plants produce hundreds of different types of polyphenols, and because the compounds are found in plants used as foods and beverages, humans can consume as much as 1 g/day of tannins. The biochemical consequences of phenolic consumption are not well understood, although both positive (antioxidants) and negative (antinutrient) activities have been ascribed to various tannins [1].

Confronted with the task of presenting an overview of the current state of our knowledge and recent collective literature on the very interesting topic of this chapter, it is difficult to know quite where to start. This is due to the fact that the vegetable tannins (VTs) constitute one of the most widely distributed groups of all polyphenols in the plant kingdom [2], exhibiting a remarkably high structural diversity and wide range of physiological, biochemical, and pharmacological properties (antioxidant, antitumor, antiviral, antimicrobial, enzyme inhibition, radical scavenging, chemical defense, etc.) [3]. To draw a clear picture about this topic, it is also necessary to discuss at least briefly some related subtopics, e.g., definition, occurrence, structural diversity (classification), and the complex reactions of tannins, on which all their biochemical and pharmacological activities are dependent.

13.1.1 Definition

The word "tannin" is very old and reflects a traditional technology. "Tanning" (waterproofing and preserving) was the word used in the scientific literature to describe the process of transforming raw animal hides or skins into durable, nonputrescible leathers by using plant extracts [4] from different plant parts (bark, wood, fruits, leaves, fruit

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pods, roots, and plant galls) of different plant species (wattle (*Acacia* sp.), oak (*Quercus* sp.), birch (*Betula* sp.), eucalyptus (*Eucalyptus* sp.), willow (*Salix caprea*), pine (*Pinus* sp.), and quebracho (*Scinopsis balansae*)). Beyond that old definition, by the 1950s, the topic had become one of the dark, impenetrable areas of organic chemistry. Its renaissance coincided with the advent of new methods of analysis and separation, starting in the 1960s [5]. As pointed out by Haslam in 1996 [3], the most acceptable definition of VTs is still that of Bate-Smith and Swain, formulated in 1962. They adopted the earlier ideas of White (1957) and labeled these higher plant metabolites as water-soluble phenolic compounds having molecular weight (MW) between 500 and 3000 Da; in addition to the usual phenolic reactions, they have special characteristics such as the ability to precipitate alkaloids, gelatin, and other proteins. This agreed with the definition given by Mole and Waterman 1987 [6].

In Internet reports, several definitions are given for tannins, e.g.:

- Uncrystallizable colloidal substances have pronounced astringent properties and ability to precipitate gelatin from solution, forming insoluble compounds with gelatin-yielding tissues, the property on which manufacture of leather is dependent [7].
- Polyphenolic molecules of varying structures, defined primarily by its tendency to produce the sensation of astringency in the mouth [8].

In 1996 [3], Haslam gave a broad definition of VTs as "plant polyphenols," secondary metabolites widely distributed in various sectors of the higher plant kingdom and distinguished by the following features:

- They are highly water soluble, particularly those in natural plant extracts, due to the polyphenol−polyphenol interactions (except for some macromolecules of proanthocyanidins, PAs).
- They are characterized by a MW range of 500-4000, or up to 27,000 Da in PAs.
- In terms of structural and polyphenolic character, they possess some 12−16 phenolic groups and 5−7 aromatic rings per 1000 relative molecular mass.
- In addition to their intrinsic reactions, they are characterized by their high capability to precipitate some alkaloids, gelatin, and other proteins. Indeed these complexation reactions are of scientific interest as the basis of their biological effects and uses in the manufacture of leather, foodstuffs and beverages, herbal medicines, and in chemical defense and pigmentation in plants.
- Structurally, they can be classified into two main classes, galloyl and hexahydroxydiphenoyl (HHDP) esters and their derivatives (hydrolyzable tannins, HTs), and condensed tannins (PAs).

Generally, VTs, now often called "plant polyphenols" [9] in an attempt to describe their heterogeneous chemical structures and manifold reactions more adequately [10,11], have exerted a strong impact in human life for millennia. As common components of foods and beverages of plant origin, they influence their test by providing a more or less appreciated astringency (which must not necessarily be negative if one considers the recently discussed "French paradox" [12], i.e., reduced incidence of coronary artery disease supposed to be caused by ingestion of red wine tannins). They were later recognized as valuable chemicals for technical process (e.g., in tanneries to convert raw hides to durable leather, or for the production of dyes and inks), and as versatile medicinal agents that have been widely used in traditional folk

medicine to cure a variety of physical disorders [3,10], exhibiting a wide range of pharmacological effects [13]. It is thus not surprising that chemists started studies on the occurrence and structure of tannins more than a century ago. These efforts were, however, rewarded by significant progress only during the past decades when the problems that arose from the complexity of these substances and their facile isolation and an equivocal characterization had been solved by the introduction of modern separation and analytical techniques such as droplet counter-current chromatography (DCCC), centrifugal partition chromatography (CPC), high performance liquid chromatography (HPLC), liquid chromatography/mass Spectrometry (LC/MS), liquid chromatography/mass spectrometry-nuclear magnetic resonance (LC/MS-NMR) and two dimensional nuclear magnetic resonance (2D NMR).

13.1.2 Occurrence

VTs constitute one of the most ubiquitous groups of all plant polyphenols, being commonly found in a large array woody and some herbaceous higher plant species [2]. In contrast to the HTs, which occur only in some orders of dicotyledons, PAs are extremely widespread, having also been found in numerous species of monocotyledons and gymnosperms; they do not occur in fungi or animals [14]. VTs can occur in bark, wood, fruits, fruit pods, leaves, roots, stems, seeds, and plant galls [7].

Plant galls: The most familiar examples are those caused by insect attack. Some plant galls have an abnormally high content (≥70% of dry weight), e.g., oak (*Quercus* sp.), Chinese sumac (*Rhus semialata*), tamarisk (*Tamarix articulata*), pistacia (*Pistacia* sp.), and aleppo (*Quercus infectoria*).

Plant species used, for example, for tanning purposes include wattle (*Acacia* sp.), oak (Quercus sp.), eucalyptus (*Eucalyptus* sp.), birch (*Betula* sp.), willow (*Salix cabrea*), pine (*Pinus* sp.), quebracho (*Scinopsis balansae*), and *Terminalia* sp. [4].

Medicinal plants-containing polyphenols: (a) Bearberry (*Arctostaphylos uva-ursi*, rich in galloyl esters, especially arbutin); infusion of astringent dried leaves is used as a diuretic, and in kidney and urinary tract disorders. (b) Agrimony (*Agrimonia* sp., rich in ellagitannins (ETs)); infusion of roots and dried aerial parts is used as an astringent on the digestive system, a diuretic, and haemostatic agent. (c) Three paeony (*Paeonia lactiflora*, rich in octagalloyl-glucose); outer skin of the root used to cure disorders of the bloodstream, including high blood pressure [3].

Foods-containing polyphenols [15,16]: Common beverages (coffee bean, 90,000 ppm); spices (allspice, cinnamon); nuts (black walnut, 147,000 ppm); fruits (kiwi, 9000 ppm); and berries (raspberry, 6200 ppm). Some other examples are given in Table 13.1.

13.1.3 Classification

Because they are extremely complex substances, VTs are difficult to classify; however, they have recently been considered to consist of two major types of polyphenolic systems: HTs (pyrogallol class) and condensed tannins (CTs, catechol class), which were also called PAs [4,17,18]. With the rapid development of spectroscopic tools and

Table 13.1 Tannin-Containing Plants of Economic Importance for Food

Family	Latin Name	Vernacular Name
Anacardiaceae	*Anacardium occidentale*	Cashew nut
	Pistacio vera	Pistachio
	Mangifera indica	Mango
Betulaceae	*Corylus avellana*	Hazelnut
Ebenaceae	*Diospyros kaki*	Persimmon
Fabaceae	*Castanea sativa*	Chestnut
Juglandaceae	*Juglans regia*	Walnut
Myrtaceae	*Psidium guajava*	Guava
	Eugenia caryophyllata	Cloves
	Pimenta officinalis	Pimento
Punicaceae	*Punica granatum*	Pomegranate
Rosaceae	*Prunus domestica*	Plum
	Prunus armeniaca	Apricot
	Prunus pesica	Peach
	Prunus avium	Bird cherry
	Fragaria spp.	Strawberry
	Rubus idaeus	Raspberry
	Rubus fruticosus	Blackberry
	Crataegus spp.	Hawthorn
Saxifragaceae	*Ribes nigrum*	Blackcurrant
	Ribes rubrum	Redcurrant
	Ribes grossularia	Gooseberry
Theaceae	*Camelia sinensis*	Tea
Vitaceae	*Vitis vinifera*	Grape
	Vitis rotundifolia	Muscadine grape

high structural diversity in a huge number of new isolated plant polyphenols and related compounds, some authors define two additional types as conjugate tannins with other natural product classes, e.g., terpenes, alkaloids, iridoids, and caffee- or labia-tannins (Figure 13.1) [19–22].

13.1.3.1 Hydrolyzable Tannins

HTs are considered by Okuda et al. [17,23] to be complex monomeric or oligomeric polyester molecules of phenolic acid (gallic or one of its congeners; Figure 13.2) [10,24–26] and D-glucose or a related sugar or polyol (fructose, sucrose, sedoheptulose, *proto*- and *scyllo*-quercitols, or their conjugation with some simple phenols in the form of ester or glycoside function; Figure 13.3) [27–35]. HTs can be readily hydrolyzed to phenolic acid and its corresponding polyol by acidic, alkali, or enzymatic (tannase or β-glucosidase) hydrolysis. Polygalloyl esters are called gallotannins (GTs), which give gallic acid (GA) on hydrolysis (Figure 13.4), whereas ETs give hexahydroxydiphenic acid (which spontaneously dehydrates to ellagic acid (EA); Figure 13.5). Monomeric and oligomeric HTs contain one or more polyhydroxyphenoyl groups such as HHDP

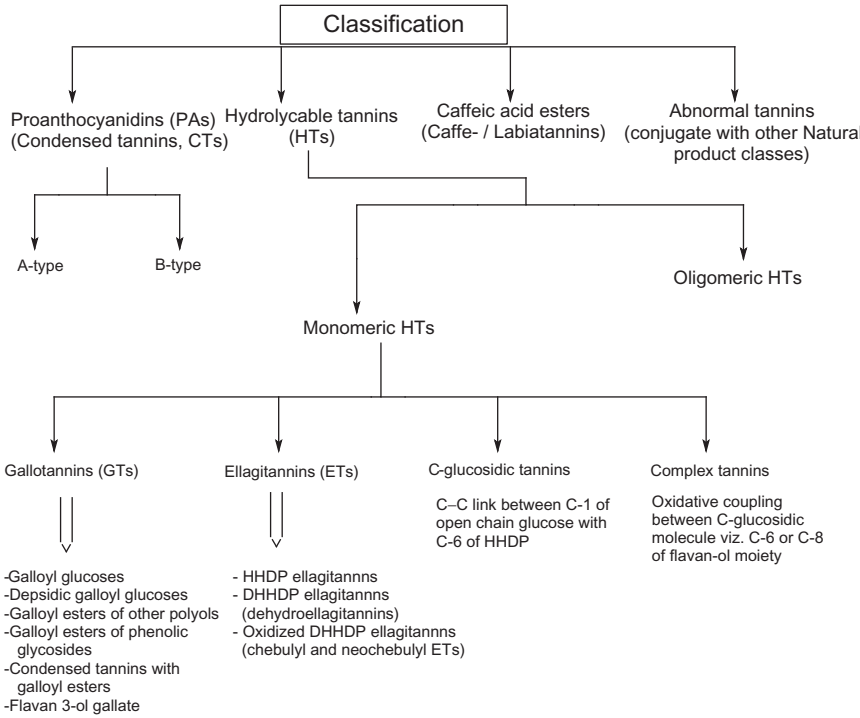


Figure 13.1 General classification of tannins and related polyphenols.

or its oxidized forms (dehydrohexahydroxydiphenoyl, DHHDP, chebuloyl, or neochebuloyl; Figure 13.6), *m*- or *p*-dehydrodigalloyl and valoneoyl (VL), tergalloyl (TG), macaranoyl, or flavogallonoyl as tris-galloyl and/or gallagyl as tetrakis-galloyl group (Figure 13.2), and so on. The D-glucose moiety, in all tannin molecules, is present in the conformation of $^{4}C_{1}$- or $^{1}C_{4}$-pyranose (chair) and $B_{1,4}$ (boat), except for C-glucosidic and complex HTs, which contain open chain D-glucose (Figures 13.3 and 13.5). Also, in the molecules of the last two HT subclasses, there is a C−C linkage between C-1 (glucose) and C-6 (often of HHDP) in the first subclass and C-6 or C-8 (flavan 3-ol) in the second (Figures 13.3 and 13.7). Under HTs, there is also an additional subclass, called caffee- or labiatannins, which are caffeic acid esters isolated from coffee beans and some species of Labiateae or Boraginaceae, respectively (Figure 13.1) [17].

13.1.3.2 Proanthocyanidins

PAs are more widely distributed than HTs. PAs are named in a way similar to polysaccharides, where C-4 of the flavan monomer unit is equivalent (in the nomenclatural sense) to C-1 of a monosaccharide in an oligo- or polysaccharide

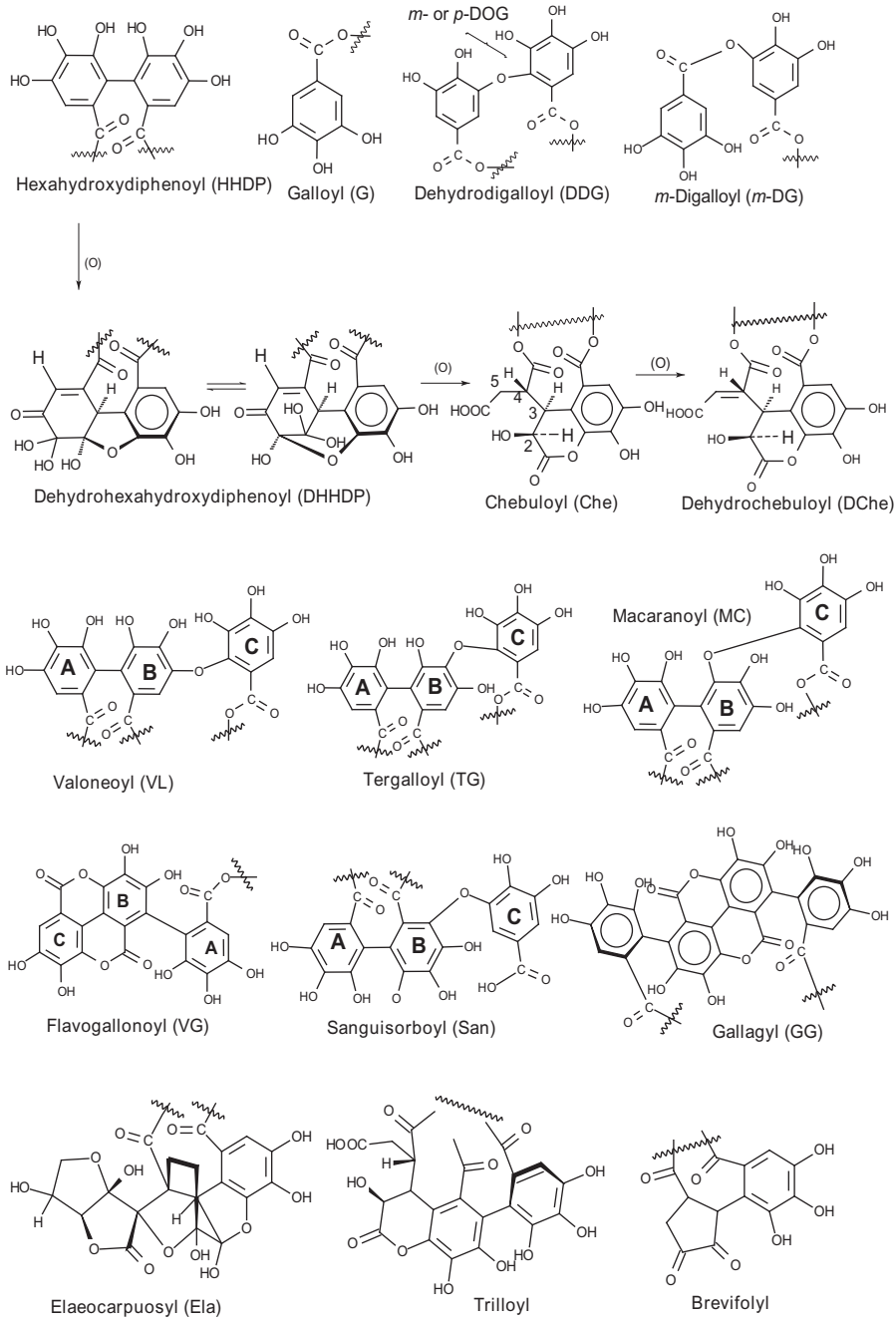


Figure 13.2 Galloyl and its congener esters in the structure of HTs and related polyphenols.

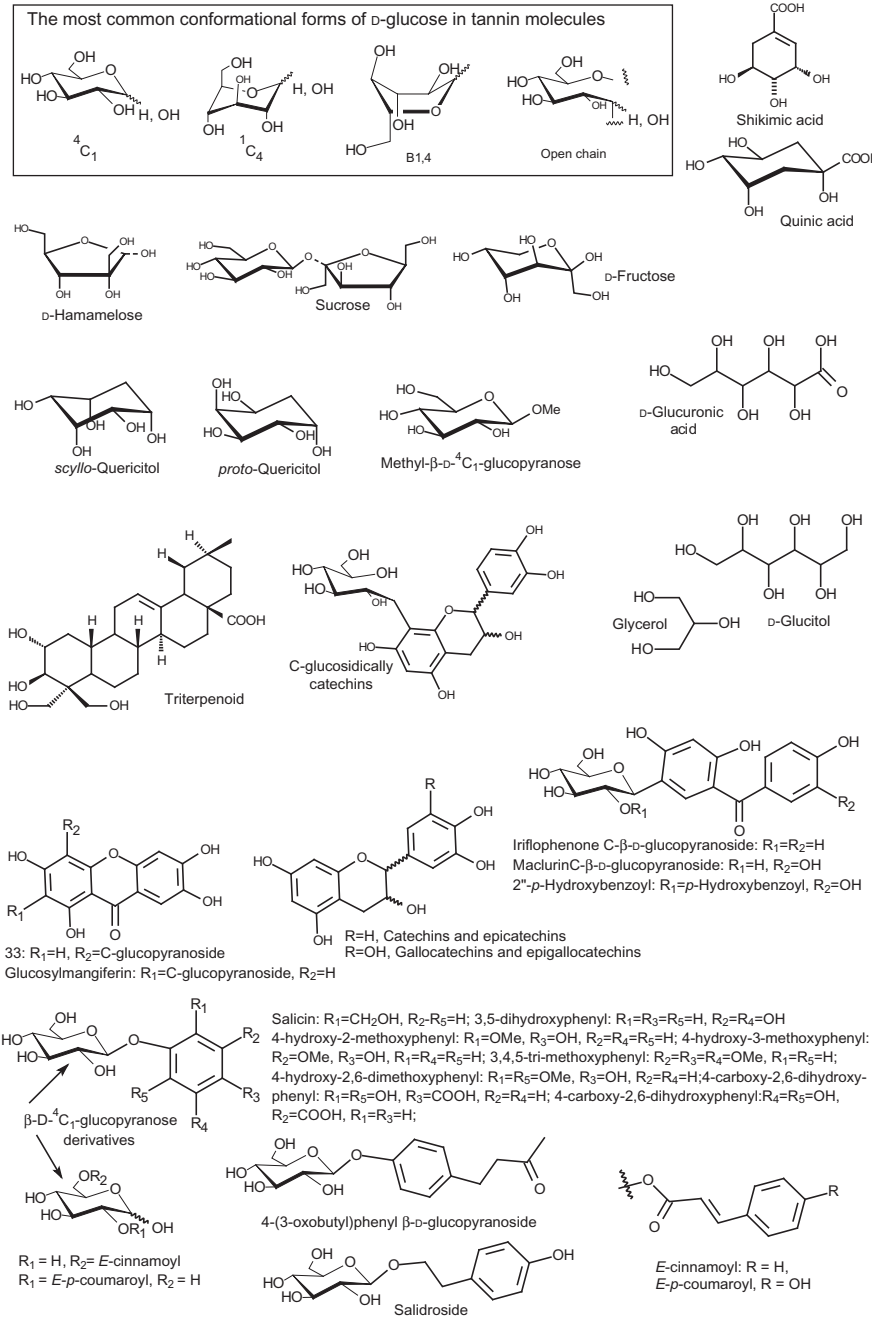
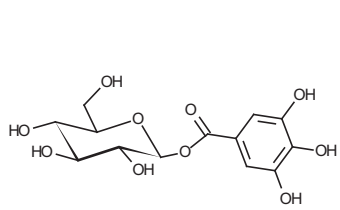
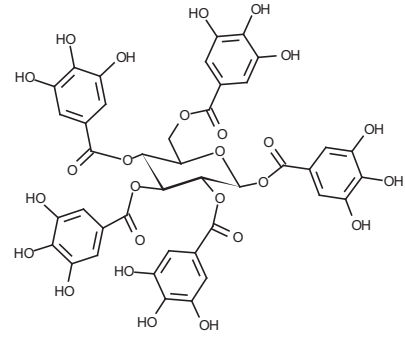


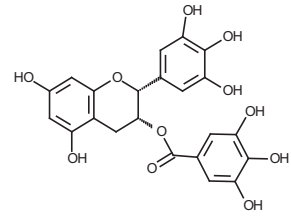
Figure 13.3 Polyols and their conjugates with simple phenols in the structure of tannins and related polyphenols.



β-Glucogallin (**1**)
1-*O*-galloyl-β-D-glucopyranose

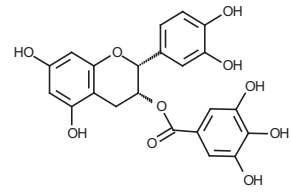


1,2,3,4,6-Penta-*O*-galloyl-β-D-glucopyranose (**2**)

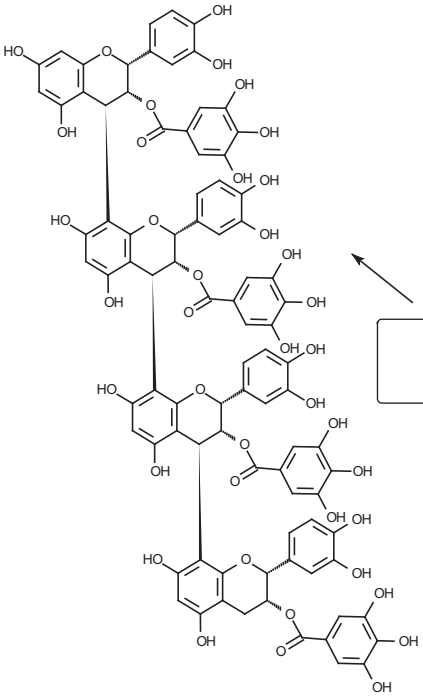


(–)-Epigallocatechin gallate (**3**)
EGCG

Tea tanning
camellia sinensis



(–)-Epicatechin gallate (**4**)
ECG



3-*O*-Galloylepicatechin-
(4β→8)-3-*O*-galloylepicatechin-
(4β→8)-3-*O*-galloylepicatechin-
(4β→8)-3-*O*-galloylepicatechin (**5**)

Figure 13.4 Examples of GTs.

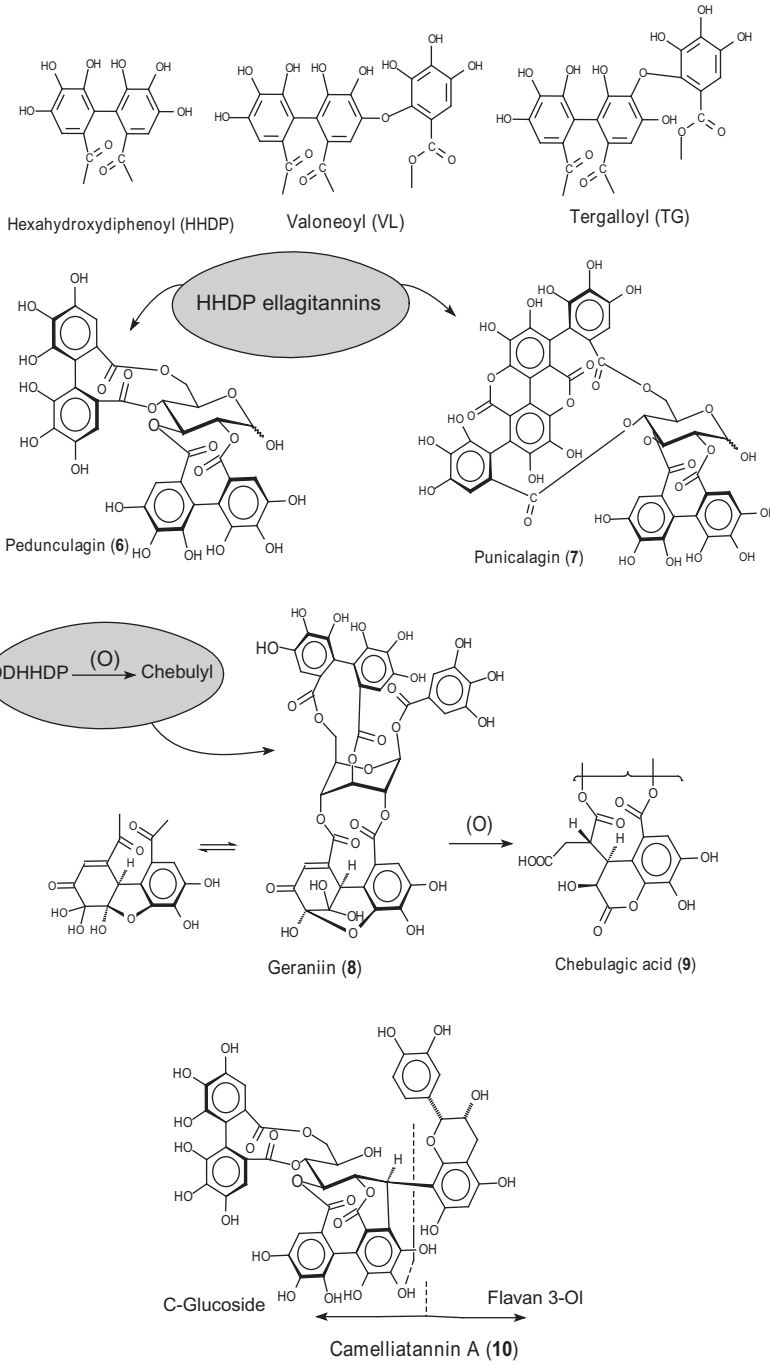
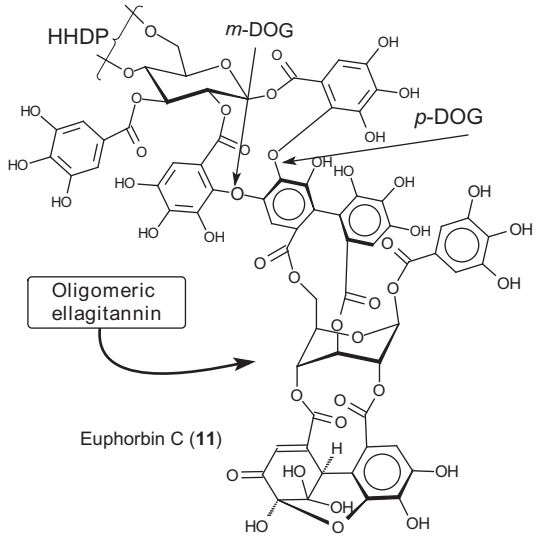
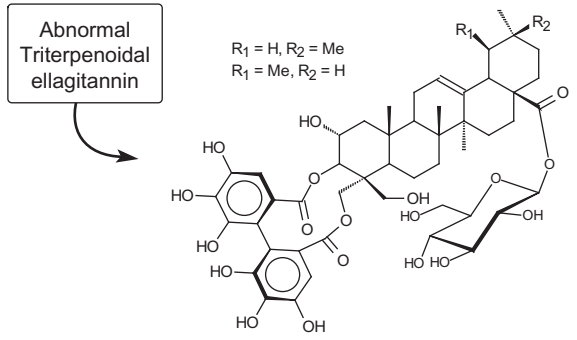


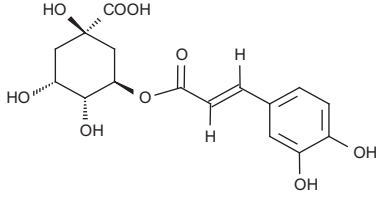
Figure 13.5 Examples of ETs.



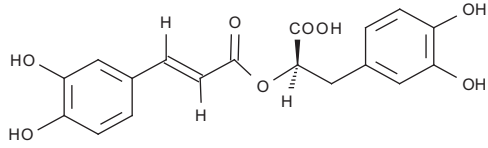
Euphorbin C (**11**)



Castanopsinin A (**12**)



Chlorogenic acid (**13**)



Rosmarinic acid (**14**)

Figure 13.6 Examples of oligomeric and abnormal HTs.

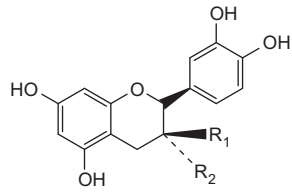


Figure 13.7 2*S*-Configuration of monomeric procyanidin.

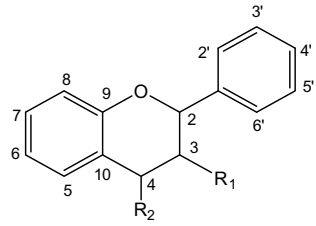
chain. The system assumes that the flavonoid skeleton is drawn and numbered in the usual way, as illustrated for epicatechin (**16**) (Figure 13.8) [10]. The interflavonoid linkage is indicated in the same way as polysaccharides, the bond and its direction being contained in parentheses (4→). The stereochemistry of the C2−C3 linkage may be either *trans* (2*R*,3*S*) or *cis* (2*R*, 3*R*), as in (+)-catechin and (−)-epicatechin. The configuration of the interflavonoid bond at C-4 is indicated by α or β nomenclature (IUPAC, 1979) within the above parentheses.

The flavonoid monomer units are defined in terms of the trivial names of monomeric flavan-3-ols; the names catechin (**15**), epicatechin (**16**), gallocatechin (**17**), epigallocatechin (**18**), afzelechin (**19**), epiafzelechin (**20**), etc. are thus reserved for units with the most commonly encountered 2*R*-absolute configuration, whereas those with 2*S*-configuration are distinguished by the enantio (*ent*-) prefix. Typical examples are compounds **21** and **22** (Figure 13.7), called *ent*-catechin and *ent*-epicatechin, respectively, the dimer structure called epicatechin-(C4→C8)-catechin (B1) (**35**), and the dimer (**23**) named *ent*-epicatechin-(C4→C8)-epicatechin and *ent*-B2, *ent*-epicatechin-(C4→C8)-*ent*-epicatechin (**24**). All flavan-3-ol with 2*R*,3*S* are listed in Table 13.2, and those with a 2*R*,3*R* configuration are prefixed with "epi," e.g., epicatechin (**16**) or epigallocatechin (**18**) [36].

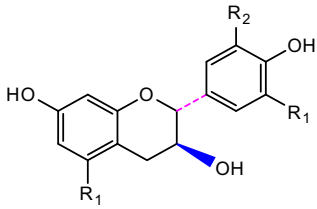
Correspondingly, procyanidins designate oligomers and polymers with the 3′,4′-dihydroxyl pattern [(+)-catechin and/or (−)-epicatechin units] extension units, while propelargonidins or prodelphinidins designate oligomers and polymers with extension units of the 4′-hydroxyl pattern [(+)-afzelechin and/or (−)-epiafzelechin units] or 3′,4′,5′-trihydroxyl pattern [(+)-gallocatechin and/or (−)-epigallocatechin], respectively (Figure 13.8).

PAs are classified according to their hydroxylation pattern into several subgroups including procyanidins (3,5,7,3′,4′-OH), as in Table 13.2 [24,36,37].

The procyanidins are broadly distributed in the leaves, fruits, bark, and less commonly in the wood of a wide spectrum of plants. About 50 procyanidins, ranging from dimers to pentamers, have now been isolated and their structures defined. The 2*R*,3*R*-(2,3-*cis*)-procyanidins linked by (4β→8)- and/or (4β→6)-interflavonoid bonds occur most frequently. Many plants contains mixtures of 2*R*,3*R*-(2,3-*cis*) and 2*R*,3*S*-(2,3-*trans*) procyanidins, but the compounds of the former stereochemistry normally predominate [38,39]. The plants that contain predominantly 2*R*,3*S*-(2,3-*trans*)



Flavan-3-ol (monomeric units in proanthocyanidins)

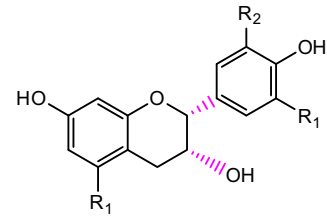


(A) 2*R*, 3*S* Flavan-3-ol

R_1=OH, R_2= H (+)-Catechin (**15**)

R_1=OH, R_2= OH (+)-Gallocatechin (**17**)

R_1=R_2=H (+) –Afzelichin (**19**)

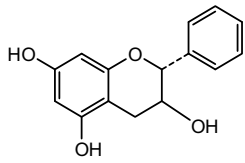


(B) 2*R*, 3*R* Flavan-3-ol

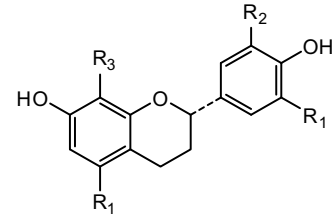
R_1=OH, R_2= H (–)-Epicatechin (**16**)

R_1=OH, R_2= OH (–)-Epigallocatechin (**18**)

R_1=R_2=H (–)-Epiafzelichin (**20**)



Distenin (**25**)

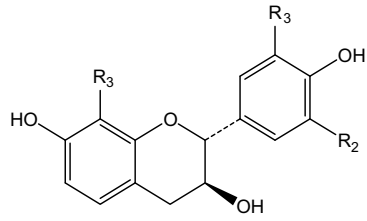


R_1=R_2=R_3=H Cassiaflavan (**26**)

R_1=OH, R_2=R_3=H Apigeniflavan (**27**)

R_1= R_3= OH, R_2=H Luteoliflavan (**28**)

R_1= R_2=R_3= OH Tricetiflavan (**29**)



R_1=R_2=R_3=H Guibourtinidol (**30**) R_1=OH, R_2=R_3=H Fisetinidol (**31**)

R_1= R_2=OH, R_3=H Robinetinidol (**32**) R_1= R_2=H, R_3=HO Oritin (**33**)

R_1= R_3=HO, R_2=H Mesquitol (**34**)

Figure 13.8 The most frequent structure units of CTs.

Table 13.2 PA Nomenclature: PA Type and Names of (*2R*,*3S*) Monomer Units

PA Class	Monomer Units	Hydroxylation Patterns
Procyanidin	Catechin (**15**)	3,3′,4′,5,7
	Epicatechin (**16**)	3,3′,4′,5,7
Prodelphinidin	Gallocatechin (**17**)	3,3′,4′,5′,5,7
	Epigallocatechin (**18**)	3,3′,4′,5′,5,7
Propelargonidin	Afzelechin (**19**)	3,4′,5,7
	Epiafzelechin (**20**)	3,4′,5,7
Prodistenidin	Distenin (**25**)	3,5,7
Procassinidin	Cassiaflavan (**26**)	4′,7
Proapigeninidin	Apigeniflavan (**27**)	4′,5,7
Proluteolinidin	Luteoliflavan (**28**)	3′,4′,5,7
Protricetinidin	Tricetiflavan (**29**)	3′,4′,5′,5,7
Proguibourtinidin	Guibourtinidol (**30**)	3,4′,7
Profisetinidin	Fisetinidol (**31**)	3,3′,4′,7
Prorobinetinidin	Robinetinidol (**32**)	3,3′,4′,5′,7
Proteracacinidin	Oritin (**33**)	3,4′,7,8
Promelacacinidin	Mesquitol (**34**)	3,3′,4′,7,8

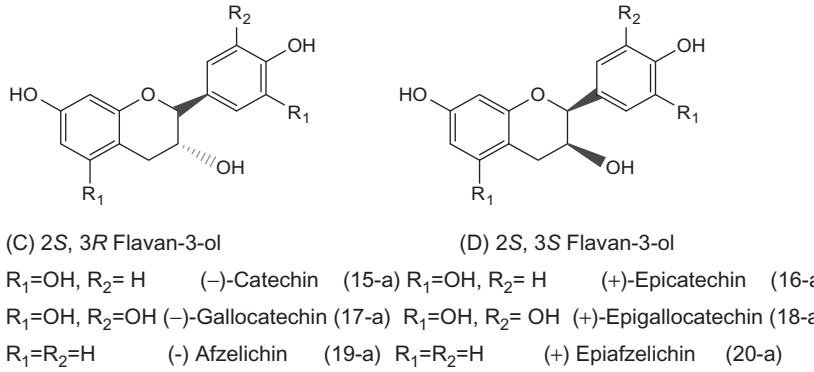


Figure 13.9 Structures of the 2*R*-type flavan-3-ols A, B and the 2*S*-type *ent*-flavan-3-ols C, D [41].

compounds are, so far, restricted to a few plant genera, including fruits of *Ribes* species or the catechins of *Salix* species. All 2,3-*cis* procyanidins have [4β]-interflavonoid bonds (i.e., 3,4-*trans* configuration). Most natural 2,3-*trans* procyanidins isolated to date have [4α]-interflavonoid bonds (i.e., also 3,4-*trans* but in the opposite configuration) (Figure 13.9).

The simplest procyanidins are dimeric, and the most common of these are the four procyanidins B1−B4, characterized by the 4β→8 linked dimers. These are

always accompanied by even lower concentrations of the corresponding 4→6 (B5−B8) linked isomers:

Epicatechin-(4β→8)-catechin	Procyanidin B1	**35**
Epicatechin-(4β→8)-epicatechin	Procyanidin B2	**36**
Catechin-(4β→8)-catechin	Procyanidin B3	**37**
Catechin-(4β→8)-epicatechin	Procyanidin B4	**38**
Epicatechin-(4β→6)-epicatechin	Procyanidin B5	**39**
Catechin-(4β→6)-catechin	Procyanidin B6	**40**
Epicatechin-(4β→6)-catechin	Procyanidin B7	**41**
Catechin-(4β→6)-epicatechin	Procyanidin B8	**42**

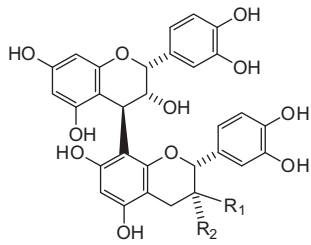
Many diastereoisomeric procyanidins have been isolated from the pith of the palm *Metroxylon saugus* [24]; compounds included the first reported natural occurrence of *ent*-epicatechin-(4β→8)-catechin (**41**) (Figure 13.10) and *ent*-epicatechin-(4β→8)-epicatechin (**23**) (Figure 13.11).

A number of trimeric, tetrameric, and pentameric compounds are now known; epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (procyanidin C1) (**45**) (Figure 13.12), catechin-(4β→8)-catechin-(4β→8)-catechin (procyanidin C2) (**46**), and also a number of trimers have been isolated consisting of procyanidin units with different structures. For example, epicatechin-(4β→8)-catechin-(4β→8)-epicatechin and epicatechin-(4*β*→8)-catechin-(4*β*→8)-catechin were isolated from yam tubers [41], and catechin-(4β→8)-gallocatechin-(4β→8)-catechin and gallocatechin-(4β→8)-catechin-(4β→8)-catechin were isolated from barley.

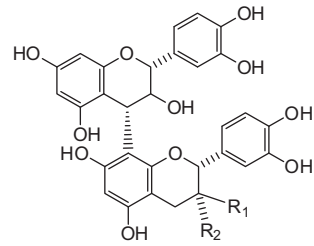
The trimeric procyanidin obtained from *Pinus laeda* [38] has both (4β→8) and (4β→8) bonds within the same molecule [42]. Two trimeric procyanidins have been isolated that contained both (4β→8) and (2β→O→7; 4β→8) interflavonoid bonds and their structures were partially identified. A comparatively large group of doubly linked type A-PAs (i.e., 4β→8) and the second between C-2 of the "upper" unit and O-7 of the lower unit of a dimer. Until recently, these compounds were represented only by epicatechin-(2β→O→7; 4β→8)-epicatechin (proanthocyanidin A-2) (**47**), from *Aesculus hippocastanum*, and proanthocyanidin A-1 (**48**), assigned as epicatechin-(2β→O→7; 4β→8)-catechin on the basis that its spectroscopic properties match those of A-2 closely, and it produces a low yield of catechin on acid hydrolysis. A novel A-type dimer was isolated from cacao beans [43]. It was epicatechin-(2β→5; 4β→6)-epicatechin, the first example of a dimer with a 5-ether linkage. By now the three possible modes of double β-linkage are known, i.e., 2β→O→7; 4β→8, 2β→O→7; 4β→6, and 2β→5; 4β→6 (e.g.: procyanidin B2 and proanthocyanidins A1, A2 and C1), (Figure 13.12).

13.1.4 Pharmacological Activity

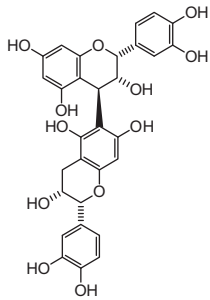
Many medicinal plants containing VTs as their active principles used for a range of ailments and disorders. *In vitro* assays have revealed a variety of significant



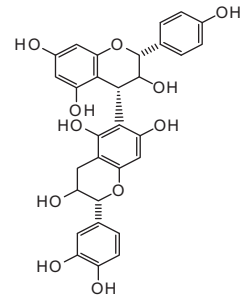
R_1=OH, R_2=H
Epicatechin-(4β→8)-catechin (B1) (**35**)
R_1=H, R_2=OH
Epicatechin-(4β→8)-epicatechin (B2) (**36**)



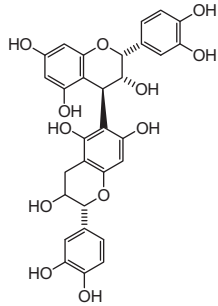
R_1=OH, R_2=H
Catechin-(4β→8)-catechin (B3) (**37**)
R_1=H, R_2=OH
Catechin-(4β→8)-epicatechin (B4) (**38**)



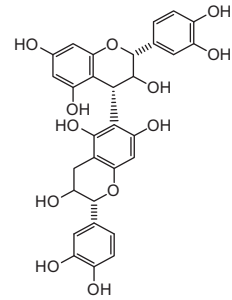
Epicatechin-(4β→6)-epicatechin (B5) (**39**)



Catechin-(4β→6) Catechin (B6) (**40**)



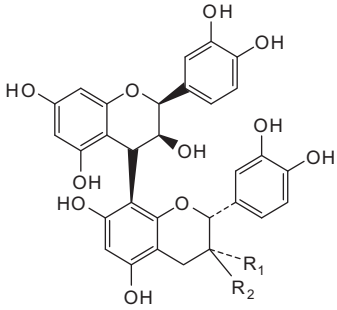
Epicatechin-(4β→6)-catechin (B7) (**41**)



Catechin-(4β→6)-epicatechin (B8) (**42**)

Figure 13.10 Procyanidin dimer, B type.

biological activities of polyphenolic plant extracts [3]. Although differences in pharmacological activity are observed between individual polyphenols or between different subclasses of VTs, most of this variability can be approached as some selectivity rather than specificity toward a specific target system. Their anticipated interaction with biological system originates primarily from their characteristic ability to form complexes, both with metal ions and with macromolecules such as proteins and polysaccharides, and from their antioxidative and radical scavenging

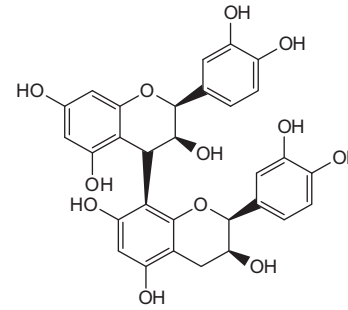


R_2 = OH

Ent-epicatechin-(4β→8)-catechin (**43**)

R_1 = OH

Ent-epicatechin-(4β→8)-epicatechin (**23**)



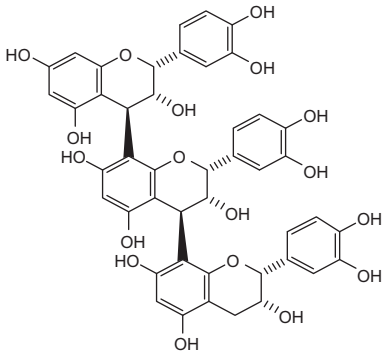
Ent-Epicatechin-(4β→8)-*ent*-epicatechin (*ent*-B2) (**24**)

Figure 13.11 *Ent*-procyanidin dimer.

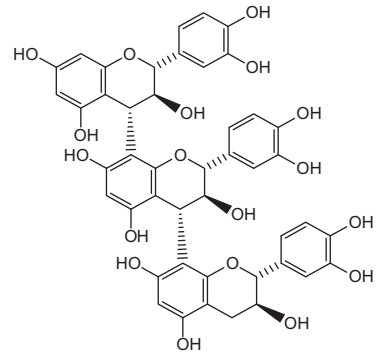
properties. All those interactions at the bases of their physiological and pharmacological effects are in principle directly derived from the physical and chemical properties of the polyphenolic skeleton. However, in a recent publication on the inhibition of radioligand binding to a panel of 16 receptors by tannins, it was concluded that tannins did show specific activities at the receptor level, which could not be explained solely in terms of protein binding. The most susceptible receptors to phenolic binding were β-adrenergic, 5-HT1, and opiate receptors, while some of the compounds tested showed selectivity for single or for two receptors. These results suggest that although VTs have intrinsically the same chemical modes for interference with biological systems, the effective manifestation of a physiological effect is strongly dependent on the chemical and electronical surroundings and conformation of polyphenol and target [44].

13.1.4.1 Antioxidant Activity

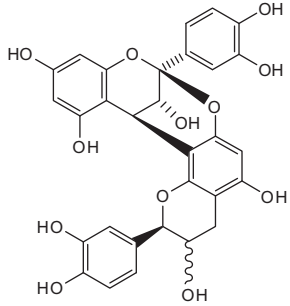
Recently, much attention has been focused on oxidative stress caused by free radical reactions to produce deleterious modification in membranes, proteins, enzymes, and DNA. Age-related diseases such as cancer, atherosclerosis, and diabetes are supposed to be correlated with oxidative stress; however, the detailed mechanisms are still unclear. From the hypothesis that endogenous antioxidants in plants must play an important role in antioxidative defense systems, an intensive search for novel types of antioxidants has been carried out on numerous plant materials, including those used as food, and a number of lipid- and water-soluble dietary antioxidative polyphenols have been isolated and identified [45]. Since polyphenols are composed of huge conjugated π-electron aromatic rings with large numbers of



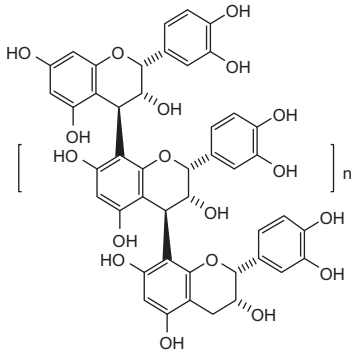
Procyanidin C1 (**45**)
Epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin



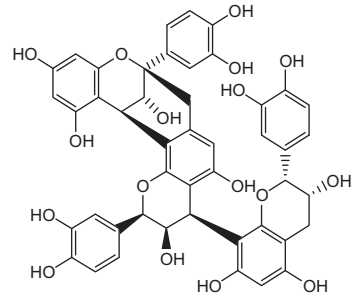
Procyanidin C2 (**46**)
Catechin-(4β→8)-catechin-(4β→8)-catechin



Proanthocyanidin (A_2) (**47**)
Proanthocyanidin (A_1) (**48**)



N=3 Procyanidin hexamer (**49**) Epicatechin (4β→8, 2β→O→7) -Epicatechin-(4β→8) Epicatechin
N=2 Procyanidin tetramer (Cinnamatannin A2) (**50**)



(Proanthocyanidin D1) (**51**)

Figure 13.12 Representative structures and examples of PAs.

hydroxyl groups bearing lone pairs of electrons, their chemical and biochemical activities are broad ranged. Depending on the neighboring substituents of the phenolic hydroxyl group that may reinforce conjugation, their antioxidative properties are outstanding. This is of special importance not only for the plants themselves but also for humans and animals. Thus, they act as vitamins and/or protectants against "oxidative stress," since oxygen is toxic principally due to its chemical properties.

In cellular prooxidant states, the intracellular concentration of activated forms of oxygen (reactive oxygen species, ROS) is increased, presumably because cells either overproduce these reactive substances or are deficient in their ability to destroy them. Reactivity of oxygen can be enhanced in a number of ways [46–48].

13.1.4.1.1 Antioxidant Activity of HTs

The antioxidant activity of tannins in foods and beverages was first demonstrated when their influence in suppressing the oxidation of ascorbic acid came to light. Later [49], the effect of tannins on Cu (II)-catalyzed auto-oxidation of ascorbic acid was studied by kinetic and electron spin resonance (ESR) measurements. In these studies, geraniin (**8**), isolated from *Geranium thunbergii*, showed marked inhibitory effects, attributable to its radical scavenging activity (stable ESR) rather than to Cu (II)-blocking, while the inhibitory effect of lower MW polyphenols as GA was low (unstable ESR), where low potent compounds give unstable or no ESR signals [50].

Tannins exhibit remarkable inhibitory effects on lipid peroxidation (LP) induced by adenine 5′-diphosphate (ADP) and ascorbic acid in rat liver mitochondria, and on that induced by ADP and NADPH in rat liver microsomes. Almost complete inhibition of LP was exhibited in these two systems by some ETs, such as pedunculagin (**6**) and isoterchebin. In both systems, the inhibitory effects of most HTs were stronger than those of CTs. The dicaffeoyl-quinic acids isolated from genus *Artemisia* exhibited inhibitory effects through these systems [51] as well.

The radical scavenging ability of tannins was also manifested by their ability to scavenge the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. The effect of licorice phenolics [52], and those of a number of polyphenols of various structures and origins, were generally stronger than those of α-tocopherol and ascorbic acid [53]. It was demonstrated, by an experiment employing alkyl gallate as the scavengers, that a stable free radical was generated from these polyphenols upon scavenging the DPPH radical. In this experiment, formation of the gallate radical was proved by ESR measurement and by isolation in a high yield of dialkyl 3,4,5,3′,4′,5′-hexahydroxydiphenoyl (HHDP) produced by the mutual coupling of the transient C-centered galloyl radicals [54]. Two ETs, pedunculagin (**6**) and 2,3-(*S*)-hexahydroxydiphenoyl-D-glucose, isolated from *Rubus coreanus* [55], showed much higher potency as antioxidants using DPPH and LP generation systems mediated by addition of H_2O_2 to relatively homogenate thiobarbituric acid reactive substances assay (TBARS). The antioxidant activity of pomegranate juice, high percentage of punicalagin (**7**) and pedunculagin, was found to be three times higher than that of green tea [56] using the ABTS, DPPH, DMPD, and FRAP methods. Tannins isolated from *Terminalia catappa*, especially punicalagin and

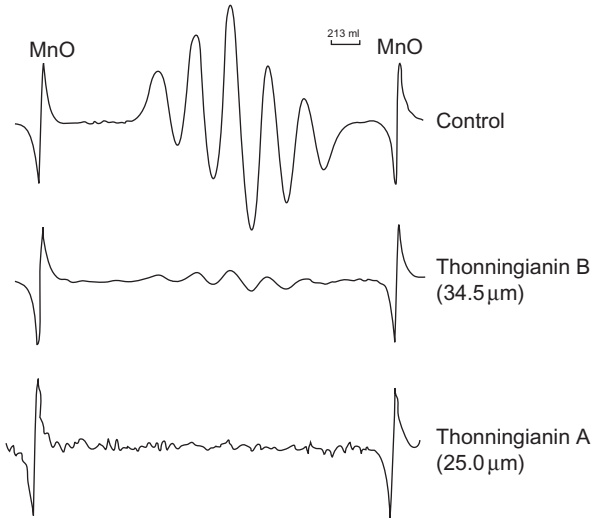


Figure 13.13 Effect of thonningianins A and B on the ESR signals of DPPH (100 μM, E*t*OH), where the spectra were recorded 40 s after mixing.

punicalin, exhibited potent antioxidant activity; their LP activity was quantified by measuring TBARS [57–59]. Crude tannins of *Canola* and rapeseed hull extract exhibited significant antioxidant activity, evaluated by β-carotene-linoleate, DPPH radical, and reducing power assay [60]. The two ETs thonningianins A and B, isolated from *Thonningia sanguinea*, as well as ellagic acid 3,4-methylene-dioxy-3′-*O*-methyl-4′-*O*-glucoside and ellagic acid 3,3′-di-*O*-methyl ether, isolated from *Pteleopsis hylodendron*, exert a strong free radical scavenging activity against DPPH, as shown by ESR analysis (Figure 13.13) [61,62].

In an investigation of the protective effects exerted by tannins against oxidative damage induced in mouse ocular lenses by incubation with xanthine-xanthine oxidase ADP and Fe^{+3} (X-XOD system), geraniin and pentagalloyl glucose markedly decreased LP concentration in the lens [63]. Also, it was found that tannic acid (TA) is more efficient than its main component, GA, when studied by its effect on OH radical and singlet oxygen mediated cleavage of plasmid DNA and ESR [64]. The natural food additive "eucalyptus leaf extract" showed strong antioxidative activity by several assays, mostly attributed to the GA and EA present in the extract [65]. In addition, it was found that black currants have much higher antioxidant activity than highbush blueberries and boysenberries due to higher content of polyphenols [66]. The leaves of *Fragaria vesca* showed significant antioxidant activity on DPPH and photoperoxidation of linoleic acid due to its ETs and EA [67].

13.1.4.1.2 Antioxidant Activity of PAs

Procyanidins B_1 and B_3 were demonstrated to have stronger antioxidant activity for linoleic acid in aqueous systems than ascorbic acid or α-tocopherol [68]. It was seen that the dimeric procyanidins could trap eight peroxy radicals from a study of

their radical scavenging properties toward radicals induced from methyl linoleate. The higher the degree of polymerization, the more radicals are scavenged per molecule [69]. The radical scavenging action of galloylated CTs for DPPH, $OH^{\cdot}$, and $OOH^{\cdot}$ radicals and for superoxide anions was dose-dependent and proportional to the degree of polymerization and number of galloyl groups in the oligomer [70]. A study of various procyanidins, galloylation, preferably at the 3′-position, increases the scavenging ability of both O_2^{-} and OH^{-}. O_2^{-}-scavenging was more prominent for (4→8)-coupled dimers than for (4→6)-linked procyanidins; differences were not seen for OH^{-} scavenging activity [71]. In *in vivo* studies, it was shown that PAs from grape (*Vitis vinifera*) seeds act as better free radical scavengers and inhibitors of oxidative tissue damage than vitamin C, vitamin E succinate, vitamin C and vitamin E succinate combined, and β-carotene. Moreover, *in vitro* experimental results have demonstrated that PAs have specificity for the OH radical in addition to having the ability to noncompetitively inhibit the activity of xanthine oxidase (XOD), a major generator of free radicals [21]. Six PAs isolated from *Vaccinium vitis-idaea* L. exhibit anti-LP and anti-SO formation, and SO scavenger activities, which are useful for the treatment of oxidative damage to tissues caused by the generation of ROS [72]. The scavenging activity of tea catechins [(−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin (EGC), and (−)-epicatechin] and their corresponding epimers [(−)-gallocatechin gallate (GCG), (−)-gallocatechin (GC), and (+)-catechin] on the free radicals generated from 2,2′-azo-bis-(2-amidinopropane)-hydrochloride (AAPH) and DPPH, as evaluated by ESR measurement. This result showed that the scavenging effects of galloylated catechins (ECGG and GCG) are stronger than nongalloylated catechins and those of EGC and GC were stronger than EC and C. Thus, it was suggested that the presence of the galloyl group at the 3′-position plays the most important role in their free radical scavenging; the hydroxyl group at the 5′-position in the B-ring also contributes to their scavenging activities [73–76]. The A-type of PAs, EGC-(2β→7, 4β→8)-EC, and EC isolated from *Dioclea lasiophylla* exhibit considerable antioxidant activity compared to propyl gallate and α-tocopherol [77]. A study of the free radical scavenging activity of *Uncaria tomentosa* decoction by DPPH suggested that the activity was mainly correlated with the presence of PAs [78]. The antioxidant activity of the epicatechin hexamer, isolated from the methanol extract of *Bursera lancifolia*, showed that it would be an effective antioxidant [79]. Also, the PA oligomers and catechins of mocon (*Visnea mocanera*) exhibit potent antioxidant activity [80].

13.1.4.2 Antitumor Activity

Much information about the inhibitory activity of tannins on tumor incidence and propagation has been gathered in the last decade, although there have been some suggestions that the crude extract of some tannin-containing plants induced cancer [81] and that tumors were induced by extraordinarily high doses of low MW polyphenols [82].

13.1.4.2.1 Inhibition of Mutagenicity of Carcinogens

Significant inhibition of the mutagenicity of 7β,8α-dihydroxy-9α, 10α-epoxy-7,8,9,10-tetrahydrobenzo-[*a*]pyrene-(B-[*a*]-*p*-diol-epoxide) by EA was attributed to formation of its collision complex with the carcinogen [83].

Because EA in plant extracts is produced mostly by hydrolysis of the ETs originally present in the plants, the antimutagenic activity of extracts of *Geranium* species [84] against some carcinogens such as B-[*a*]-*p*-diol-epoxide, a direct-acting mutagen, was studied and the correlation between the inhibitory activity and hydrolysis of geraniin was investigated. It was found that the inhibitory effect depends on the extent of hydrolysis and type of carcinogen [85]. TA and some other phenolics inhibited the mutagenicity of bay-region-diol epoxides of polycyclic aromatic hydrocarbons [86,87]. The HTs from *Terminalia chebula* exhibit partially antimutagenic activity against direct-acting mutagens 4-nitro-*O*-phenylenediamine (NPD) but show no effect against 4-nitro-quinoline-*N*-oxide (4NQNO) [88]. In addition, tannin fractions from *Terminalia arjuna* have an inhibitory effect against the mutagenicity of 2-aminofluorene [89]. Tea extract and its major components, i.e., ECG and EGCG, exhibit antimutagenic activity against various mutagens, and its mechanism of action may be due to the extracellular and intracellular mechanisms [90].

13.1.4.2.2 Inhibition of Tumor Promotion

Considerable effort has been made in recent years to find agents inhibiting tumor promotion. The main polyphenol of green tea tannins, i.e., (−)-EGCG, can significantly inhibit tumor promotion on mouse skin by teleocidin [91,92] and okadoic acid [93,94] after initiation with 7,12-dimethylbenz[*a*]anthracene (DMBA). EGCG produced significantly inhibitory effects on tumor promotion in the gastrointestinal tract, with duodenal carcinogenesis induced by *N*-ethyl-*N*′-nitro-*N*-nitro-soguanidine in mice [44,95]. Similar effects of EGCG have also been observed in several different systems of tumor promotion [93,96], e.g., breast, colon, and lung carcinomas. Pentagalloylglucose inhibited tumor promotion as potently as EGCG [92,93]. Tetra- and penta-galloylglucoses have suppressing effects on tumor promotion induced by 12-*O*-tetradecanoyl-pharbol-13-acetate JB6 mouse epidermal cells. The number of hydroxyl groups in the molecule is closely related to this activity [97].

Many other studies concerning the inhibition of tumor promotion by tea polyphenols or tea extracts have been carried out [96,98,99], including effects of oral administration against skin tumor [99]. Tara pods and oak TA have inhibitory effects on the tumor promotion induced by ultraviolet β-radiation in mouse skin *in vivo* [100,101], and thus could be useful as photoprotectants.

13.1.4.2.3 Host-Mediated Antitumor Activity

Inhibition of tumor growth by administration of some oligomeric hydrolyzable tannins (OHTs), either before or after ip inoculation of tumor cells, is one of the most conspicuous antitumor effects of OHTs [102,103]. The dimers oenothein B and woodfordins A, B, and C, the trimers oenothein A and woodfordin D [104,105], and the tetramer woodfordin F exhibit host-mediated activity, attributable to enhancement of the immune response of the host animal, as shown by stimulation

of interleukin-I production from human peripheral macrophages [106]. 1-*O*-Galloylcastalagin and casuarinin, two HTs isolated from *Eugenia jambos*, and cuphin D_1, isolated from *Cuphea hyssopifolia*, significantly inhibited the human promyelocytic leukemia cell line HL-60 [107,108]. The HTs, isolated from methanolic extract of three *Cytinus* species, were examined against four human solid tumor cell lines, as well as against the established murine leukemia cell line (L1210). These compounds are effective, with LD_{50} values ranging from 5.8 to 55 μg/mL; the most sensitive cell lines were A549 and L1210. However, they are inactive against normal human skin fibroblasts under conditions identical to those of the tests on the carcinoma cell lines [109]. The cytotoxic activity of dimeric tannins was generally higher than that of monomeric ones. Oligomeric macrocyclic ETs exhibited the greatest cytotoxic activity, one order higher than those of GA and EGCG, the major components of green tea [110]. GA and chebulagic acid, isolated from *T. chebula* fruits, can block the cytotoxic T lymphocyte (CTL)-mediated cytotoxicity. They inhibited the killing activity of $CD8^+$ CTL colon at LC_{50} values of 30 and 50 μg/mL, respectively [111].

13.1.4.3 Antiviral Activity

Recently, much progress has been made in the study of the human immunodeficiency virus [HIV-1 (HTLV-III/LAV)], the causative agent of acquired immunodeficiency syndrome (AIDS), including the elucidation of the genomic structure of HIV as well as the mechanism of HIV infection [112]. The activities of HTs were dependent on the number of galloyl or HHDP groups, while in case of PAs the extent of oligomerization, the difference in the interflavan linkage type, and the stereochemistry of the 3-ol function strongly influence the inhibitory capacity [113,114].

1,3,4-Tri-*O*-galloylquinic acid, isolated from *T. catappa* leaves, inhibited HIV replication in infected H9 lymphocytes with little toxicity. Two tannins, punicalin and punicacortein, inhibited purified HIV-transcryptase; chebulagic acid and punicalin did not inactivate the virus directly. However, 1,3,4-tri-*O*-galloylquinic and 3,5-di-*O*-galloyl-shikimic acids were more effective inhibitors under those conditions. All tannins appeared to inhibit virus cell interactions. Thus, in spite of their anti-RT activity, the mechanism by which tannins inhibit HIV may not be associated with enzymes [112]. Also, two new HTs, shephagenins A and B, isolated from *Shepherdia argentea*, showed remarkable inhibitory activity against HIV-1 reverse transcriptase. The inhibitory effect of the leaf extract on HIV-1 was found to be due to its tannin content, and their activity was stronger than that of (−)-EGCG as a positive control [115]. Putranjivain A, 1,6-di-*O*-galloyl-β-D-glucose, and digallic acid, isolated from *Phyllanthus emblica*, have shown a potent effect against HIV-1, and their mode of action was noncompetitive with respect to the substrate but competitive with respect to a template-primer [116]. EGCG had a destructive effect on the viral particles, and post-adsorption entry and RT in acutely infected monocytoid cells were significantly inhibited at concentrations

of EGCG greater than 1 M; protease kinetics were suppressed at a concentration higher than 10 M in the cell-free study. Viral production by THP-1 cells chronically infected with HIV-1 was also inhibited in a dose-dependent manner, and the inhibitory effect was enhanced by liposome modification of EGCG. As expected, increased viral mRNA production was observed in lipopolysaccharide (LPS)-activated chronically HIV-1-infected cells. This production was significantly inhibited by EGCG treatment of THP-1 cells. In contrast, production of HIV-1 viral mRNA in unstimulated or LPS-stimulated T-lymphoid cells (H9) was not inhibited by EGCG. Anti-HIV viral activity of EGCG may thus result from an interaction with several steps in the HIV-1 life cycle [117]. EGC-(4β-8, 2β-*O*-7)-EC, isolated from the wood of *Xanthoceras sorbifolia*, was found to be inhibitory against HIV-1 protease [118]. Three ellagitannins, corilagin, repandusinic acid, and geranin, which contain a HHDP unit linked to the O-3 and O-6 positions of the sugar, were found to strongly inhibit HIV-1 protease; the result indicated that the presence of HHDP is important for the inhibition effect [119]. It was found that the galloyl moiety in GA and three GTs isolated from *T. chebula* play a major role in inhibition against the 3′-processing of HIV-1 integrase [120]. Seven ETs isolated from *Phyllanthus myrtifolius* and *Phyllanthus urinaria* have been found to be active against Epstein−Barr virus DNA polymerase (EBV-DP) [121]. Eugeniflorins D1 and D2, isolated from the *Eugenia uniflora*, have shown an inhibiting effect on the EBV by the inhibition of EBV-DNA-polymerase enzyme [122].

HTs and galloylated CTs showed antiviral activity against the *Herpes simplex* virus (HSV-1, HSV-2); their effects were due to inhibition of virus adsorption [123]. Geponin and gallic aldehyde, isolated from *Geum japonicum*, show potent antiviral activity against HSV-1 [124]. Alkaline auto-oxidized catechinic acid (AOCA) is effective against HSV-1 and HIV-1 viruses; this compound was seen to inhibit the viruses even after viral penetration. Catechin and condensed catechinic tannins, which produce AOCA via rearrangement to catechinic acid and subsequent auto-oxidation, exhibited inhibitory effects against HSV-1 and HIV-1 viruses [125]. Potent anti-HIV activity was found for the dimeric HTs oenothein B, coriariin A, and agrimoniin [126]. Significant anti-HIV activities were observed for gemin D (monomer), camelliin B, and nobotannin B (dimers), as well as trapanin B (tetramer) [127].

Procyanidin and prodelphinidin-type B-ring moieties, were isolated from the latex of *Croton lechleri*, exhibit antiviral activity against the respiratory syncytial virus (RSV), influenza A virus (FLU-A), and parainfluenza virus (PIV) comparable to that of ribavirin [128].

13.1.4.4 Antibacterial Activity

Tannins and related compounds have long been recognized to exhibit quite potent antibiotic activity. In a recent authoritative review, tannin toxicity for fungi, bacteria, and yeasts is summarized and some reasonable mechanisms are presented to explain tannins antimicrobial activity [129]. The polyphenols of oolong tea strongly

inhibited glucotransferase (GTF-types) of *Streptococcus mutans* as a primary cariogenic bacterium. Oolong tea is semifermented, which results in polymerization accompanied by conformational changes, which in turn led to such a critically important effect. Green tea polyphenols showed inhibitory effect on the growth and cellular adherence of the oral bacterium *Porphyromonas gingivalis*, responsible for the majority of adult periodontitis cases [130]. Three PA trimers from the A-type, EC-(4β→6)-EC-(4β→8, 2β→*O*-7)-epicatechin, EC-(4β→8, 2β→*O*-7)-EC-(4β→8)-EC, and EC-(4β→8)-EC-(4β→8, 2β→*O*-7)-EC, isolated from ripe fruits of *Vaccinium macrocarpon*, prevented adherence of P-fimbriated *Escherichia coli* isolated from the urinary tract to cellular surfaces containing α-cell (1→4)-β-gol receptor sequences similar to those on uroepithelial cells [131,132]. CTs also showed inhibitory effects on the growth of several species of rumen bacteria, including *Streptococcus bovis*, *Eubacterium* spp., and *Prevotella bryantii*, as well as bacteria in the gastrointestinal tract [133,134]. ETs exhibit a dose-dependent inhibition on *Helicobacter pylori* isolated from peptic ulcer patients, as well as a wide range of pathogenic organisms including *Vibrio cholerae*, *Shigella dysenteriae*, and *Campylobacter* spp. [135]. Simple galloyl esters, HTs and PAs, were generally found to possess only weak to moderate antibacterial effects but fairly high anticryptococcol activity against two Gram-positive and Gram-negative bacteria, and two types of yeast [136]. The HTs isoterchebulin, 4,6-*O*-(*S*)-isoterchebulyl-D-glucose, punicalin, terflavan A and B, 2-*O*-galloylpunicalin, and punicacortein C, isolated from *Terminalia macropetra*, exhibit antimicrobial activity against *Bacillus subtilis* [137]. Four ETs isolated from *P. hylodendron* were found to have significant antibacterial activity against different pathogenic bacteria [62]. While a series of HTs had no activity against filamentous fungi, they displayed significant potencies against all opportunistic yeasts tested except for *Candida albicans* [138]. Geranins A and B exhibit potent antiprotozoal activity against *Giardia lamblia*, the most sensitive protozoan [139].

13.1.4.5 Antileishmanial Activity

In *in vitro* study of their activity against *Leishmania donovani* amastigotes and promastigotes, most of a series from 27 HTs [140], 17 PAs [141], and structurally related compounds inhibited the intracellular survival of *L. donovani* amastigotes (EC_{50} <0.4−12.5 μg/mL and 0.8−10.6 nM, respectively) when compared with the antileishmanial drug pentostam, but all were inactive against the extracellular form. All of a series of 28 polyphenols, except GA, its methyl ester, shikimic acid, and catechin, significantly inhibited intracellular survival of *L. donovani* amastigotes when compared with the clinically used agent sodium stibogluconate, but they are inactive against the extracellular form [142].

13.1.4.6 Anthelmintic Activity

Penta- and tetra-galloylglucoses and 6-*O*-(*m*-galloyl)-galloyl 1,2,3,4-tetra-*O*-galloyl-β-D-glucose, isolated from fresh *Paeonia suffruticosa* leaves, and CTs from its

bark had high nematicidal activities toward egg-bearing adults of *Caenorhabditis elegans* [143]. Also, isoterchebulin isolated from *T. macroptera* had the same effect [137]. Generally, CTs appeared to have direct anthelmintic properties on gastrointestinal nematodes, reducing larva migration [144].

13.1.4.7 Enzyme-Inhibitory Activity

Sometimes the activities of tannins are inverted when the concentration or combination of tannins and substrate is varied. Tannins usually inhibit the activity of enzymes at relatively high concentration. However, at low concentration they often stimulate enzymatic activity. The correlation between inhibition and stimulation varies depending on the enzyme and the structure and concentration of the tannins. ETs and complex tannins were found to be more effective inhibitors of protein kinase C than GTs and CTs [26]. The selectivity was shown by the lack of inhibition versus c-AMP-dependent protein kinase, while the phorbol displacement assay pointed to interaction with the regulatory site of the enzyme. Several tannins inhibited adrenaline- and ACTH-induced lipolysis and insulin-induced lipogenesis from glucose in fat cells of rats [145,146]. However, ACTH-induced lipolysis was strongly promoted by chebulinic acid and tellimagrandin I at concentrations between 5 and 100 μg/mL, although adrenaline-induced lipolysis was inhibited regardless of the concentration [147]. Both HTs and CTs have inhibitory effects on XOD, which depend on the number of phenolic groups, the location of acyl groups in the first, and the galloylation and degree of polymerization in the second type [53]. Absence of correlation between the inhibitory effect and the binding activity to hemoglobin for several tannins proved that the inhibition was not due to nonspecific binding to proteins. Since XOD is used in a test system to evaluate the superoxide-anion radical scavenging ability of polyphenols, their O_2 scavenging and the XOD-inhibiting properties were compared. It was concluded that the order of strength of inhibition of XOD among the tannins was considerably different from that of the inhibitory effects on O_2 generation from the hypoxanthine-XOD system. Therefore, inhibition of O_2 generation is caused by the radical scavenging effect, rather than by the XOD-inhibition, which was confirmed in a recent publication for (−)-EGC [148]. (2*S*)-3′,4′,7-Trihydroxyflavan-(4α→8)−catechin is a flavan dimer isolated from *Cassia nomame*; it showed a potent lipase-inhibitory effect, while (+)-catechin and (−)-EC showed negligible inhibitory effects on lipase [148]. ETs, casuarictin, and eugeniin, isolated from *Syzygium aromaticum* (clove), showed maltase-inhibiting activity toward the human intestinal epithelial cell line [149]. Results indicated that an increasing number of galloyl units in the molecule might lead to an increase in the inhibitory activity. Eugeniin also inhibited maltase activity toward the human intestinal epithelial cell line Caco-2. Pentagalloylglucose, sanguiin H-11, and oolonghomobisflavan A were found to be potent inhibitors of NADH dehydrogenases [150]. TA, theaflavins (tea extract), and grape seed PA extract have an inhibitory effect on the mitochondrial proton F0FI-ATPase/ATP synthase during oxidative phosphorylation [151]. Pedunculagin (LC_{50} = 20 μM) and eugenin (LC_{50} = 1.6 μM) both contain (*S*)-HHDP ester groups,

and EA ($LC_{50} = 2\ \mu M$) showed remarkable inhibition against squalene epoxidase, a rate-limiting enzyme cholesterol biosynthesis [152].

13.1.4.8 Vascular and Cardiac Activities

It was found that TA affected calcium availability for the contraction of smooth and cardiac muscle. Indeed, by complexating Ca^{2+}, TA shows a hypotensive effect [44]. Two trimeric procyanidins were investigated for their ability to inhibit platelet aggregation in human and rat plasma; this could be explained by the inhibition of platelet thromboxone biosynthesis from arachidonic by cyclooxygenase, observed for the same products [44]. Also, catechin can protect platelets from peroxidative stress and aggregation. The high MW procyanidin fraction from *V. vinifera* (grape) exhibits a protective effect in myocardial ischemia and reperfusion injury [153]. This effect is probably the consequence of the radical scavenging properties of the procyanidin fraction, and of their chelating effect on Fe^{2+} and Cu^{2+}, the catalysts of the free radical cascade in vascular and cardiac tissue. The major green tea catechins, especially (−)-EGCG, were found to have antithrombotic activity and the mode of action may due to the antiplatelet activity, rather than to anticoagulating activity [154].

13.1.4.9 Hepatoprotective Activity

Punicalagin and punicalin, isolated from leaves of *T. catappa* [58,155], and flavogallonic acid, methyl flavogallonate, and 2,3-(*S*)-hexahydroxydiphenoyl-glucose, from leaves of *Terminalia myriocarpa*, have antihepatotoxic effects on carbon tetrachloride (CCl_4)-induced toxicity in the rat liver. Their antihepatotoxic activity on acetominophen-induced toxicity in the rat liver was also evaluated; the data show that both compounds showed antihepatotoxic activity but treatment with larger doses enhanced liver damage.

13.1.4.10 Antidiarrheal Activity

The antidiarrheal activity of a *Sclerocarya birrea* PA against diarrhea experimentally induced in mice by $MgSO_4$, castor oil, and arachidonic acid was reported [156]. For prostaglandin E2 (PGE_2)-induced diarrhea, the PAs were active only at higher doses. It was postulated that the antidiarrheal activity of PAs is related to inhibition of intestinal motility and that their action is concentrated at the level of the effector cells.

13.1.4.11 Antiulcer Activity

Several plant extracts containing tannins are reported as antiulcer agents. A crude extract of *Lindera umbellata* exhibited antipeptic and antiulcerogenic activities, and these activities were considered ascribable to the presence of tannins. Antipeptic and antiulcerogenic activities of nine PAs (monomers−tetramers) have been studied [157]. Monomers and dimers clearly suppressed the peptic activity of gastric juice *in vivo* but did not inhibit it *in vitro*. Their effect *in vivo* may not correlate to the direct inhibition

of pepsin but may be related to the influence of the secretion mechanism of pepsin. Trimers displayed higher inhibition of peptic activity than tetramers. Catechins, gallocatechins, and their gallic esters inhibited gastric H^+ and K^+-ATPase, leading to a reduction of gastric acid secretion. The inhibitory activity was proportional to the number of hydroxyl groups in the tested compounds [158].

13.1.4.12 Antiallergic Activity

Extracts from some kinds of teas (green, oolong, and black) are known to exhibit antiallergic effects in rats, mice, and guinea pigs. The inhibitory effects of tea catechins on the oxazolone-induced type IV allergy in male ICR mice were investigated. Results indicated that (−)-epigallocatechin-3-*O*-(3-*O*-methyl)-gallate (EGCG3″Me), (−)-epigallocatechin-3-*O*-(4-*O*-methyl)-gallate (EGCG4″Me), (−)-epicatechin-3-*O*-gallate (ECG), and (−)-epigallocatechin gallate (EGCG) inhibited the mouse type IV allergy by oral administration at 1 h before the sensitization and 1 h before the challenge with oxazolone. Therefore, daily intake of tea drinks could have potential to prevent type IV allergy [159]. EGCG3″Me and EGCG4″Me also inhibited type I allergy more effectively compared with EGCG [160].

13.1.4.13 Anti-Inflammatory Activity

Prodelphinidins, isolated from *Ribes nigrum*, showed important anti-inflammatory activity in the carrageenan rat paw edema [161]. Four CTs, (−)-EC, (−)-EGC, procyanidin B-2, and trimeric PAs (cinnamtannin B1), isolated from *Lindera aggregata* root, have a curing power against the wind−cold−dampness arthralgia syndrome.

13.2 Biosynthesis and Structural Diversity

13.2.1 Biosynthesis of HTs

Because of the great importance of plant polyphenols in human and animal life, and because information about the biosynthesis of complicated HTs is limited, many literature surveys and searches have been directed to establishing understandable and reasonable biosynthetic routes during last few years [162,163]. In general, it is known that the total biosynthesis of tannins begins when a gallic acid (GA I) molecule forms a complex with a glucose molecule, forming 1-*O*-β-D-galloylglucopyranose (β-glucogallin II; Figure 13.14) [164]. Later, four consecutive galloylation reactions are carried out to form 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (pentagalloyl glucose, PGG). More complex monomers or oligomers of GTs and ETs derive from the same predecessor, PGG, where complex metabolites from GTs can be formed through addition of 10 or more galloyl units [165]. On the other hand, ETs come from the result of the molecular oxidations between adjacent galloyls by action of the polyphenoloxidase enzyme, forming the 3,4,5,3′,4′,5′-hexahydroxydiphenoyl moiety, a typical unit of all ET-type C-glucosidic and/or complex momomers or oligomers [166].

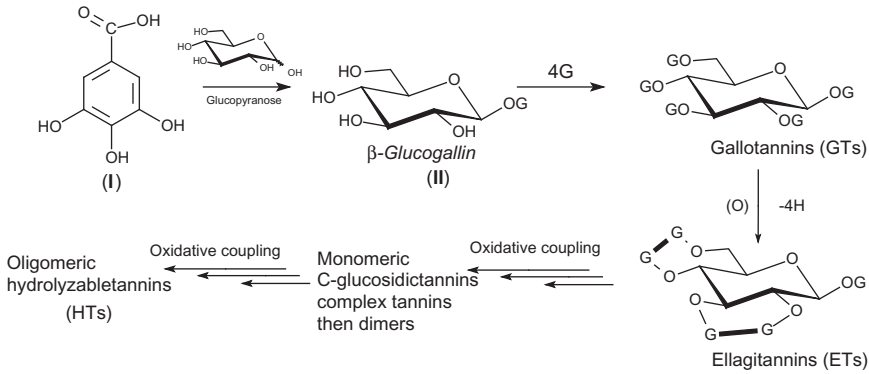


Figure 13.14 Schematic diagram for general and complete biosynthesis of HTs.

13.2.1.1 Origin of Gallic Acid [167,168]

The exact mechanism has long been a matter of dispute, and in 1996 it was proven that the 30-year-old proposal of Zenk of a cinnamoyl-CoA-dependent β-oxidation sequence is indeed realized in higher plants. Some essentials of the conflicting proposals regarding biosynthesis of (**I**), which usually were the result of feeding experiments with putative precursors, are depicted in Figure 13.15. A rather conventional pathway (route a), assuming CoA-dependent β-oxidation of 2,3,4-trihydroxycinnamic acid (**VII**) to yield **I** was formulated by Zenk; the major objection to his proposal was the fact that this precursor, thought to be produced by hydroxylation of caffeic acid (**VI**), has never been identified as a natural product and was thus occasionally regarded as the "missing cinnamic acid." Route b avoided this problem by putting the side-chain degradation one step forward, resulting in the putative sequence: caffeic acid (**VI**)→protocatechuic acid (**VIII**)→(**I**). A quite different pathway (c) was proposed after tracer experiments with the fungus *Phycomyces* and various higher plants, postulating a direct aromatization of shikimic acid (**IV**) or a biogenetically closely related compound, most likely 3-dehydroshikimic acid (**III**).

After further investigation, it appears most plausible to regard the direct aromatization of **III** at least as a significant, if not the predominant, route to **I**. Strong evidence has been obtained by feeding [^{13}C] glucose to cultures of the *Phycomyces blakesleeanus* fungus and *Rhus typhina* leaves, followed by determination of isotope distributions of isolated **I** and aromatic amino acids and interpretation of the resulting isotopomer patterns [169]. The data showed that **I** was derived in both species from an early intermediate of the shikimate pathway, most probably **III**. Notably, the carboxyl group of **I** was found to originate from a C6−C1 intermediate of the shikimate pathway and not from the side chain of phenylalanine or hydroxylated cinnamic acids (a C6−C3 metabolite), thus ruling out routes a and b as major pathways. It was concluded that dehydrogenation of **III** in both the fungus and the plant was the predominant pathway to **I**. However, the available data could not exclude

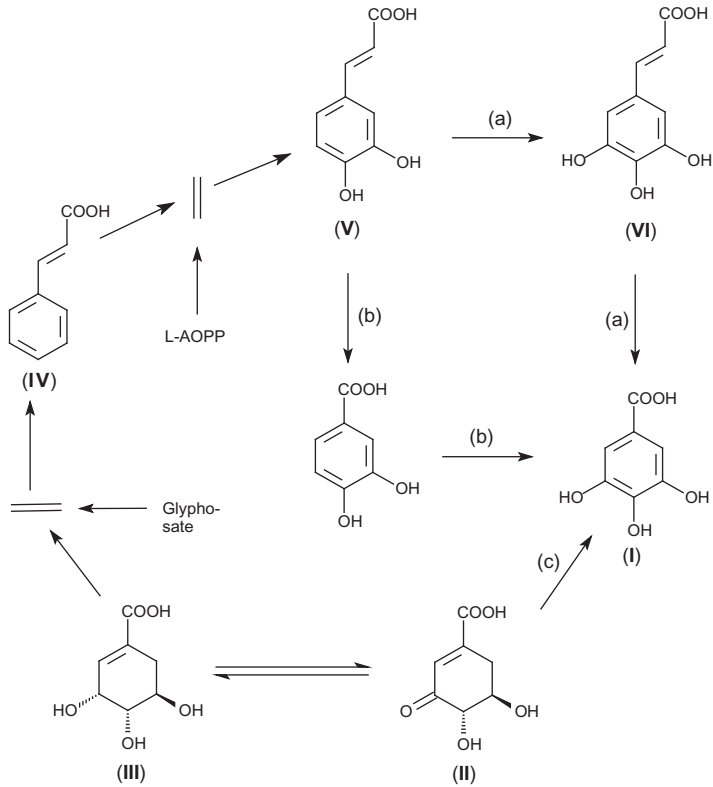


Figure 13.15 Proposed biosynthetic routes of gallic acid (I).

an alternative route to **I** by dehydration of **III** to **VIII** and subsequent introduction of a third phenolic OH-group by a monooxygenase.

13.2.1.2 Biosynthesis of β-Glucogallin

The naturally occurring **II** was first isolated from Chinese rhubarb (*Rheum officinale*) in 1903 and is regarded as the primary metabolite in the biosynthesis of HTs [167]. After many investigations [167,170,171], it was became conceivable that galloyl-CoA (**XII**) might represent the energy-rich metabolite required for the biosynthesis of β-glucogallin (**II**). To test this hypothesis, this then unknown thioester was synthesized chemically [172]. As summarized in Figure 13.16, **I** was converted to 4-O-β-D-glucosidogallic acid (**IX**) to block the reactive phenolic hydroxy groups, followed by transformation to *N*-succinimidyl-4-*O*-β-D-glucosidogallate (**X**) in the

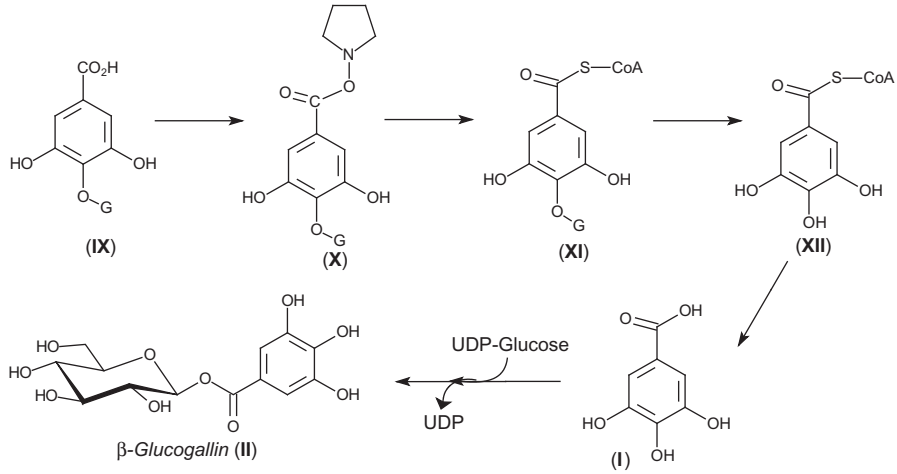


Figure 13.16 Main biosynthesis route of the first isolated GT β-glucogallin (βG II).

presence of DCC. Subsequent transacylation of **X** with CoA yielded 4-*O*-β-D-glucosidogalloyl-CoA (**XI**), from which galloyl-CoA (**XII**) was liberated by treatment with the enzyme β-glucosidase. In enzymatic studies with cell-free extracts from higher plants, however, no evidence has been found to date that galloyl-CoA (**XII**) is involved in the biosynthesis of β-glucogallin (**II**) or its higher galloylated derivatives. Instead, the second of the above alternatives was found to be realized in nature, i.e., the (reversible) reaction of free gallic acid (**I**) with UDP-glucose to yield **II** and UDP. The enzyme catalyzing this reaction was detected in leaves of *Quercus robur* [173] and partially purified from cell-free extracts of *Q. rubra* [174]. UDP-glucose was found to act as the exclusive sugar donor, while numerous benzoic and, at significantly lower rates, cinnamic acid molecules could serve as acceptors. According to the best substrate, vanillic acid, the systematic name UDP-glucose, vanillate 1-*O*-glucosyltransferase was proposed; however, it was concluded that the physiological role of the enzyme is the formation of β-glucogallin.

In light of the available evidence, the existence of this glucosyltransferase is not surprising; numerous enzymes have meanwhile been identified from various plant sources that all catalyze the formation of phenolic 1-*O*-acylglucoses [170,171], and it appears that UDP-glucose must be regarded as the general activated donor required for the esterification of glucose with phenolic acids.

*13.2.1.3 Biosynthesis of Simple Galloylglucoses—the Pathway to PGG (**XVI**) [163]*

As was explained in the previous section, the first specific metabolite in the route to HTs is β-glucogallin (**II**), which was catalyzed by enzyme extracts from oak leaves with UDP-glucose serving as activated substrate [174]. This enzyme

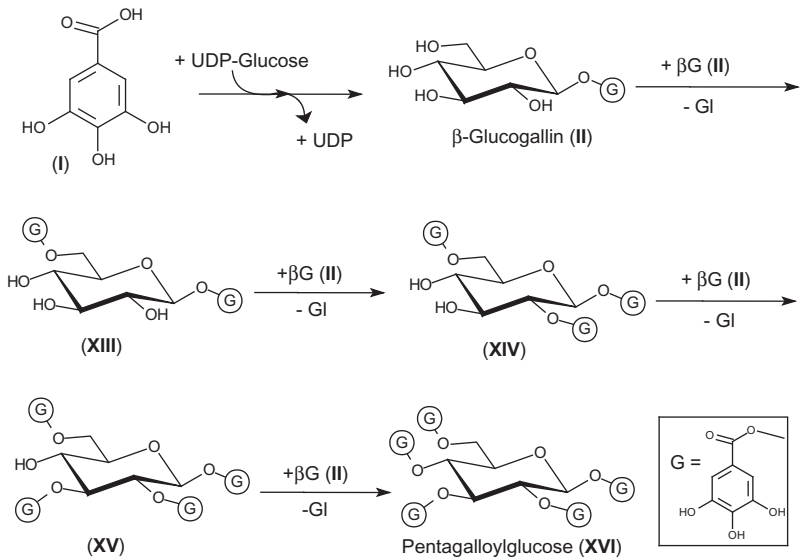


Figure 13.17 Stepwise enzyme reactions catalyzing the pathway from gallic acid (**I**) to 1,2,3,4,6-PGG (**XVI**).

preparation was also found to catalyze the transformation of *in situ* formed **II** to di- and trigalloylglucoses (**XIII**, **XIV**) without any further cofactors, indicating that **II** exerted a dual role, functioning not only as acyl acceptor but also as efficient acyl donor, i.e., it acts as an energy-rich-activated compound [175]. Further studies with enzymes isolated from oak or sumac revealed that this reaction mechanism applied to the entire route from **II** to PGG (**XVI**). As depicted in Figure 13.17, esterification of glucose-OH was not randomly distributed in these conversions but displayed an unexpected extreme specificity; thus, constituting the metabolic sequence: **II**→1,6-di- (**XIII**)→1,2,6-tri- (**XIV**)→1,2,3,6-tetra- (**XV**)→1,2,3,4,6-penta-galloylglucoses (**XVI**) [163,176]. Interestingly, this was explained as a combination of reactivity differences arising from variations in chemical nature (primary versus secondary hydroxyls), neighbor-activation effects, and steric hindrance [177].

13.2.1.4 Biosynthesis of Depsidic GTs: The Pathway from PGG to Complex GTs

This pathway is marked by the addition of further galloyl residues to **XVI** to yield their characteristic meta depside groups as continuation steps; it must be emphasized, however, that GA now combines with phenolic hydroxyls whose chemical properties are significantly different from those of the aliphatic-OH of glucose. It was thus interesting to discover that cell-free extracts from sumac (*R. typhina*) leaves catalyzed the acylation of pentagalloylglucose exactly according to the same

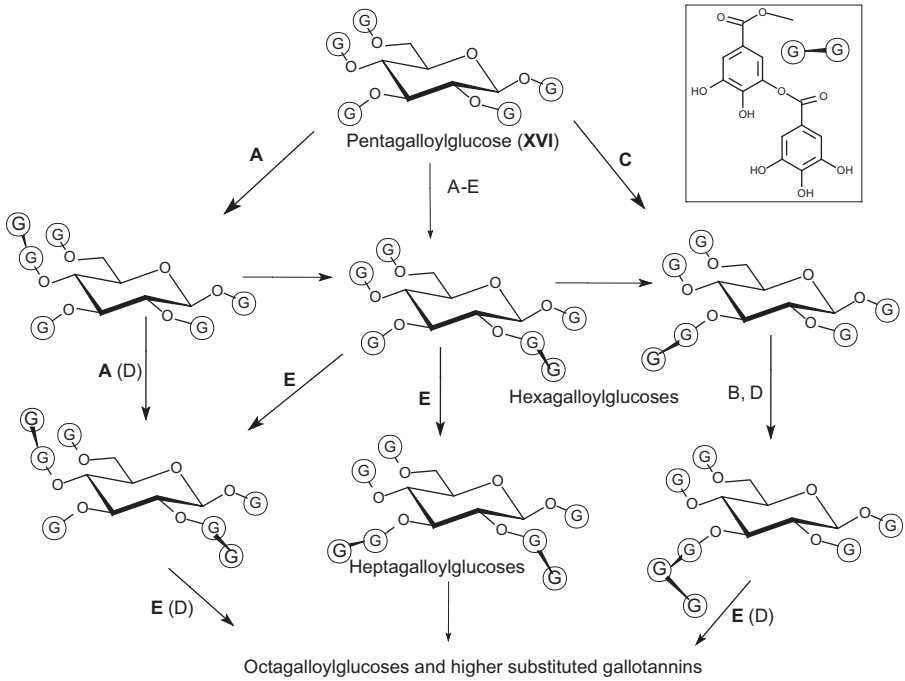


Figure 13.18 Metabolic routes to GTs in staghorn sumac (*R. typhina*).

reaction mechanism as described above, i.e., by utilizing **II** as a specific galloyl donor. In these studies, sequential galloylation of **XVI** to hexa-, hepta-, and octagalloylglucoses was observed (Figure 13.18) [178]. Additional evidence for products up to decagalloyl arose from degradation studies, treatment with fungal tannase, methanolysis of normal- and reversed-phase HPLC, and semi-preparative RPHPLC for quantitation [163]. Their structures were unequivocally identified by ^{1}H and ^{13}C NMR spectrometry. Interestingly, the substitution pattern and the relative amounts of these *in vitro* reaction products from *R. typhina* closely resembled those of *in vivo* formed GTs in the related species *R. semialata*. It appears to be a particular feature of Chinese GT from sumac that the C-1 and C-6 positions generally remain free of depside residues, in contrast to the GTs from *Q. infectoria* (Turkish GT), or *P. lactiflora*, where depside substituents are also found at C-6 of the glucose core [163]. It is evident from the above data that a multitude of different GTs is formed by one common, general reaction mode. The question arose whether these transformations were catalyzed by only one (or eventually a few) unspecific enzymes or if specific enzymes were involved in the individual biosynthetic steps. Investigations regarding this problem led to the isolation of three β-glucogallin-dependent galloyltransferases from crude leaf extracts of sumac (A, B, and C, according to their elution pattern upon gel filtration), that preferentially

acylated **XVI** and hexagalloylglucoses [163,179]. These enzymes had been detected in screening experiments with **XVI** as standard acceptor substrate. However, substantial hints of the existence of additional enzymes were obtained in these investigations, pointing to the specific acylation of higher substituted GT substrates. Screening experiments based on this observation with a hexagalloylglucose substrate (2-*O*-digalloyl-1,3,4,6-tetragalloyl-β-D-glucose) led to the detection of two further galloyltransferases (named D and E), which displayed pronounced affinity toward hexa- and heptagalloylglucoses as substrates [180]. All five enzymes could be highly purified from sumac leaves.

The scheme in Figure 13.18 shows the metabolic routes to GTs in staghorn sumac (*R. typhina*). The main reactions are marked by bold arrows, the minor reactions by thin arrows. The enzymes are galloyltransferases A [181], B [179], C [182], D, and E [180]. Major enzyme activities are symbolized by bold letters, minor activities by plain letters in parentheses.

13.2.1.5 Biosynthesis of Ellagitannins [163]

In contrast to the rather limited distribution of GTs in nature, ellagitannins are typical constituents of many plant families; they display enormous structural variability due to the manifold possible sites for the linkage of HHDP residues with the glucose moiety, and particularly by their strong tendency to form dimeric and oligomeric derivatives. As early as the 1930s it was postulated that the HHDP residues of ellagitannins originated from the dehydrogenation of GA esters. Twenty years later, PGG (**XVI**) was explicitly proposed as the immediate precursor of ETs that should be produced by oxidative biaryl coupling of neighboring galloyl groups, a view that was corroborated and refined later by Haslam [10]. Many attempts to unravel the mechanism of ET biosynthesis have been carried out in the past either by experiments with chemical oxidants (e.g., O_2, Fe^{3+}) or by studies with the enzymes laccase and peroxidase, using GA, methyl gallate, **II**, or PGG (**XVI**) as substrates. Only free EA, however, was detected in these experiments, while the formation of true ellagitannins, characterized by glucose-bound HHDP residues, was never observed [163]. [U-^{14}C]pentagalloylglucose was produced by photoassimilation of $^{14}CO_2$ in leaves of sumac [183]. This compound was used as the standard substrate in an extended screening program for enzymes that formed reaction products liberating [^{14}C]-EA upon hydrolysis, thus providing a general probe for the *in vitro* synthesis of ellagitannins of widely differing structures. By this strategy, a novel soluble enzyme in leaves of *Tellima grandiflora* (fringe cups, Saxifragaceae), a weed that is known as a rich source of ETs. A partially purified enzyme preparation was found to catalyze the conversion of [U-^{14}C]pentagalloylglucose to several radioactively labeled products, while no evidence for the formation of EA was obtained, but the most prominent product was co-eluted with authentic tellimagrandin II (Figure 13.19). This compound was proposed traditionally to be the primary metabolite in the biosynthesis of $^4C_1$-PGG derived ETs [179]. Scaled-up enzyme assay mixtures with enzyme that had been purified to apparent homogeneity revealed the formation of a single reaction product that was

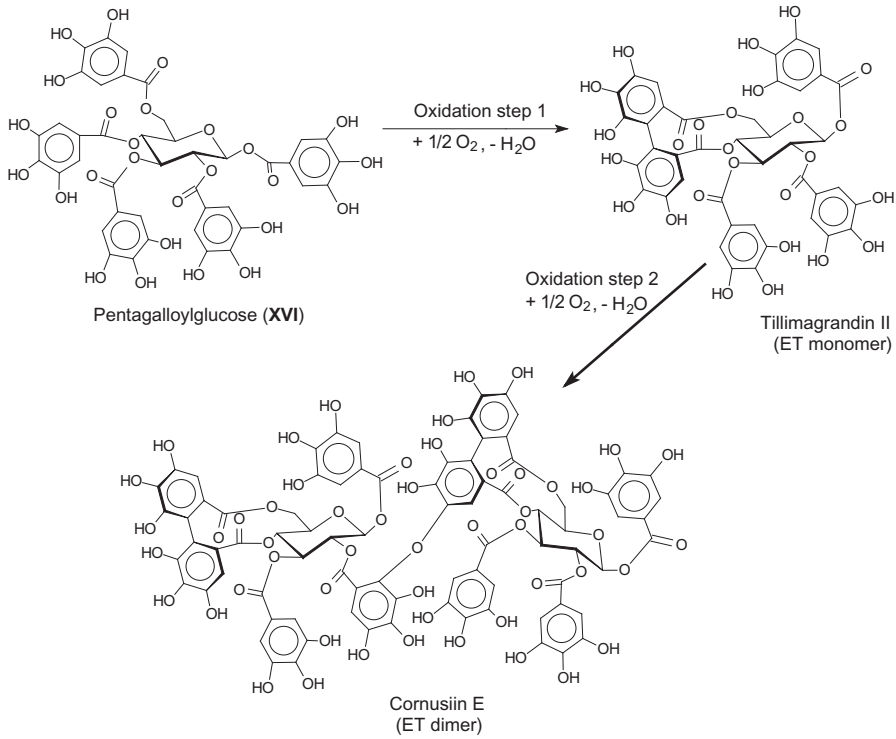


Figure 13.19 Pathway from PGG to the dimeric ET, cornusiin E in *T. grandiflora* (fringe cups).

unequivocally proven to be tellimagrandin II by chemical degradation, negative FAB-MS, and ^{1}H and ^{13}C NMR spectrometry [163]. Circular dichroism (CD) spectroscopy demonstrated that the HHDP residue of the enzyme reaction product had (*S*)-stereoconfiguration, which correlated well with published data for the naturally occurring compound [163,184] and for synthetically obtained material [185]. Analysis of side products encountered in the above studies, obtained with crude enzyme preparations from *T. grandiflora* leaves, revealed the existence of a higher MW compound that was later identified as cornusiin E (Figure 13.19), i.e., a dimeric ellagitannin that must have resulted from the oxidative condensation of two molecules of tellimagrandin II. Analysis of this phenomenon in a time course experiment with [U-^{14}C]PGG corroborated the postulated intermediacy of tellimagrandin II. As depicted in Figure 13.19, the PGG substrate was rapidly oxidized to monomeric tellimagrandin II, which could not accumulate because it was almost simultaneously transformed to dimeric cornusiin E. After about 3 min, net synthesis was observed only for this end product, at the expense of intermediate tellimagrandin II [186]. The structure of the dimer was proven by MALDI-TOF analysis and ^{1}H and ^{13}C NMR spectrometry.

13.2.2 Biosynthetic Pathway of Procyanidins [40]

The first step of the pathway is the condensation and subsequent intramolecular cyclization of three malonyl-CoA molecules with one 4-coumaroyl-CoA molecule to produce a naringenin chalcone. The second step of the pathway is the isomerization of the naringenin chalcone to the naringenin, which can occur spontaneously, without enzymatic activity. However, chalcone isomerase (CHI) stereospecifically directs and greatly accelerates the intramolecular cyclization of chalcones to form the flavonones in the cytoplasm of plant cells.

Flavonoid 3′-hydroxylase (F3′H) or flavonoid 3′,5′-hydroxylase (F3′5′H) can catalyze the conversion of naringenin into eriodictyol or pentahydroxyflavonone, respectively. However, dihydrokaempferol can also be the potential substrate of F3′H or F3′5′H, which can convert it to dihydroquercetin or dihydromyricetin, respectively. Thus, both flavonones and dihydroflavonols can be hydroxylated by F3′H and F3′5′H. In one pathway branch, leucoanthocyanidin molecules are oxidized by the catalysis of anthocyanidin synthase (ANS) to form colored anthocyanidins (pelargonidin, cyanidin, and delphinidin, respectively). These unstable anthocyanidins could be further converted into colorless (2*R*,3*R*)-flavan-3-ols [(−)-epiafzelechin (**20**), (−)-epicatechin (**6**), and (−)-epigallocatechin (**18**), respectively] by the action of anthocyanidin reductase.

In another pathway branch, leucoanthocyanidins can be converted into (2*R*,3*S*)-flavan-3-ols [(+)-afzelechin, (+)-catechin, and (+)-gallocatechin, respectively] by leucoanthocyanidin reductase (Figure 13.20).

13.3 Pharmacological Activity of Tannins and Their Monomers Isolated from African Medicinal Plants

13.3.1 Pharmacological Activity of HTs Isolated from African Medicinal Plants

Many medicinal plants used for a range of ailments and disorders contain VTs as their active principles. *In vitro* assays revealed a variety of significant biological activities of polyphenolic plant extracts. Generally, it was of particular importance to notice that antioxidant, antitumor, cytotoxicity, antibacterial, and antiviral activities are the most frequently considered in large numbers of research programs, whether for polyphenolic-containing extracts, fractions, or even pure polyphenols from African medicinal plants. Depending on the structural features of polyphenols, particularly a huge π-conjugated electronic system of unshared *O*-electrons (through large numbers of OH), attached normally to the main conjugated polyaromatic structures to create very strong and intrinsically highly energetic antioxidative systems. This structural property of plant polyphenols has attracted the attention of several natural products research teams all over the world to direct special effort to studying the biological effects of polyphenols that interfere with and directly disrupt vital reactions in biosystems through physical bonding of their OH-groups. Depending on the relative polarity of tannins among

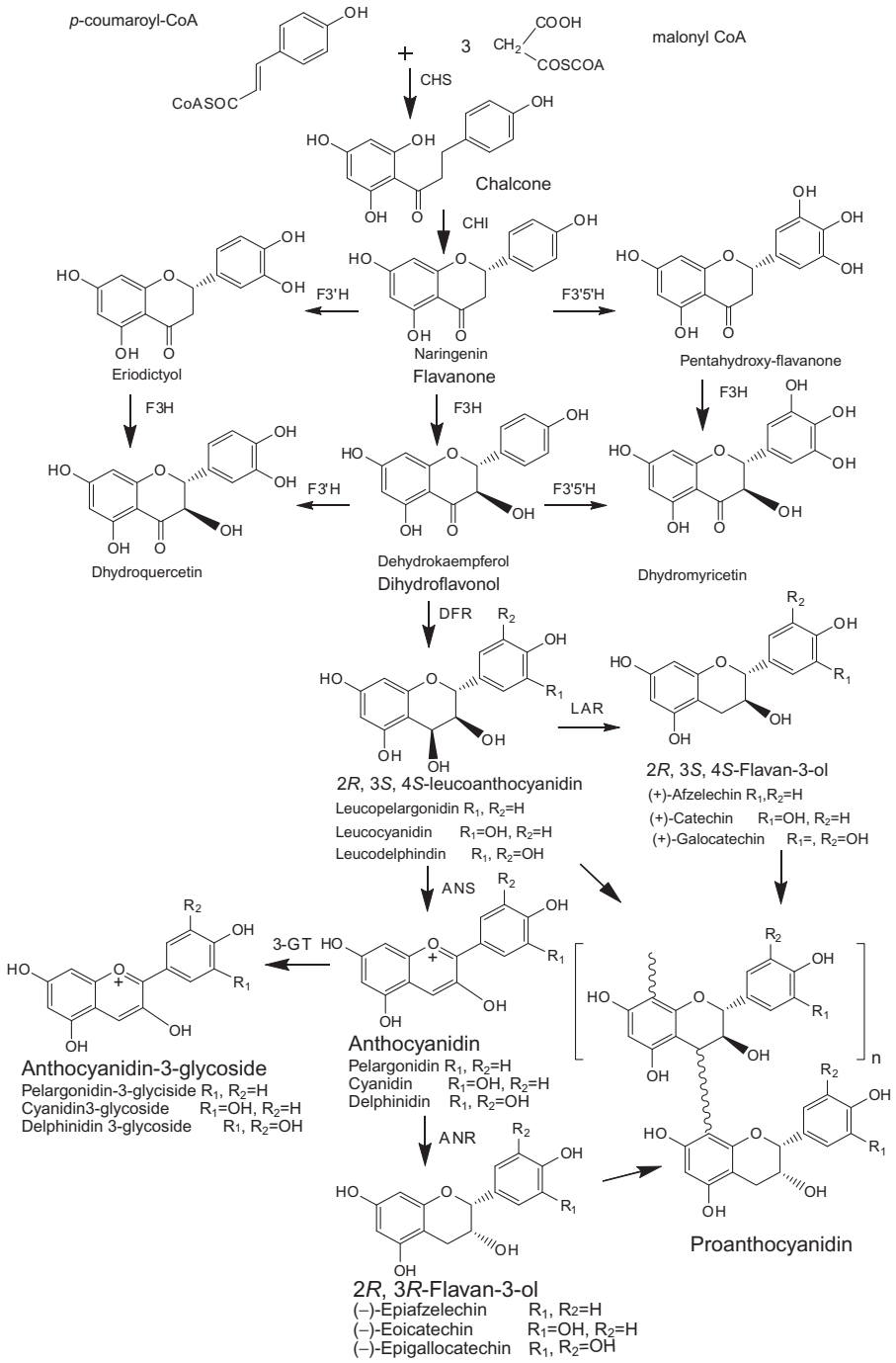


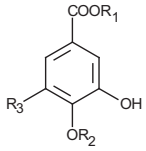
Figure 13.20 The general pathway leading to the biosynthesis of PAs.

different natural product classes, most biological studies were focused on the aqueous extracts of polyphenol-rich plants. Some novel and known bioactive HTs and related phenolic compounds were displayed with promising pharmacological values; plant sources are shown in Table 13.3 and their structures are compiled in Figure 13.21 (**2**, **7**, **52**−**74**). Flavogallonic acid (**52**), new methyl-(*S*)-flavogallonate (**53**), punicalagin (**7**), and nilocetin (**54**), isolated from *T. myriocarpa* leaves, showed significant antioxidant, hypoglycemic, and hepatoprotection effects (hepatoprotection potency: (**53**) > (**7**) > (**54**); **52** has no significant effect [187]). From *Callistemon lanceolatus*, HTs **2**, **56**, and **57**, and new *n*-butylgallate 4-*O*-(2′,6′-di-*O*-galloyl)-β-D-glucopyranoside (**55**) demonstrated significant antioxidant and hepatoprotective activity, where **55** gave higher activities [188]. Grandinin (**58**), isolated from *M. quinquenervia*, was found to be a significant antioxidant and hypoglycemic C-glucosidic tannin: acute toxicity: LD_{50} of 316 mg/kg; EC_{50} of 4.3 μ/mL. [189] Also, a promising group of labiatannins were identified from leaves and flowers of *T. stans* and exhibited strong antiproliferative activity [IC_{50} μM: **61** (40.1) > **60** (63.1) > **59** (98.4)-HEP-G2; **61** (−) > **11** (23.9) > **59** (113)- MCF-7] and antioxidant effects [SC_{50} μg/ml: **59** (0.27) > **60** (0.37) > **61** (18.42)-DPPH; **61** (1.1) > **60** (2.2) > **59** (2.4)-oxygen radical absorbance capacity (ORAC) versus 6.8 μM (ascorbic acid)] [190]. In another antiproliferative and antioxidant study on *P. dioica* leaves, 18 polyphenols were isolated for the first time, including a novel C-glycosidic ellagitannin (**65**) [191]. The study proved that seven of them showed strong antioxidant activity [SC_{50}: **2** (0.11 ± 0.04) > **64** (0.12 ± 0.08) > **54** (0.25 ± 0.03) > **66** (0.32 ± 0.06) > **65** (1.20 ± 0.03) > **63** (1.33 ± 1.60) > **58** (1.94 ± 0.13)-DPPH]. Compound **54** was found to be the strongest NO inhibitor, **65** was the most active inducer of macrophage proliferation, and **2** was the most cytotoxic compound against solid tumor cancer cells and the most potent scavenger for DPPH radicals. Among 13 phenolic metabolites isolated from *E. cotinifolia*, two new ETs (**67**, **68**) have shown, by NMR, a new structural configuration feature as β-$B_{1,4}$-pyranose for glucose core depending on J_{12} value (> 7 Hz). They were found to be the strongest antioxidant (SC_{50} = 7.4 and 8.4 μg/mL) versus ascorbic acid (SC_{50} = 6.8 μg/mL). Against the HEP-G tumor cell line, **67** showed moderate and **68** strong inhibition [IC_{50} μg/mL: **67** (71.36), **68** (32.84)], while in the case of HCT-116 colon cell line, **67** (55.6) was stronger than **68** (68.1) [192]. In addition, an abnormal GT, eugenol 5-*O*-β-(6-*O*-galloylglucopyranoside), ericifolin (**69**), and a new one, 2-*O*-*p*-hydroxybenzoyl-6-*O*-galloyl-(α/β)-$^4C_1$-glucopyranose (**70**) were isolated from *M. ericifolia*, and their antibacterial activity was evaluated together with 3-methoxyellagic acid 4-*O*-α-rhamno-pyranoside (**71**) [193]. Another abnormal GT (called red GT, (**72**)), identified from *P. africanum* as a partially oxidized poly-protocatechuoyl ester of isobutanoylglucose ester. It showed high anti-HIV-1 RT RDDP activity [IC_{50} of 6.0 versus 0.048 μM for AZT-TP (positive control)] and anti-RNase H [IC_{50} of 5.0 0.5 μM for ODN-93 (positive control)] [194]. From *R. vermiculata*, two new GTs were identified and proved to be DHDG-type esters, i.e., 2-*O*-dehydrodigallic acid monocarboxyloyl-3-*O*-galloyl-(α/β)-glucose (**73**) and vermiculatin (**74**) [195]. They showed strong antioxidant activity and significant cytotoxicity against the prostate PC-3 cell line [IC_{50} = 1.5 ± 0.33 (**73**), 0.54 ± 0.09 μM (**74**)].

Table 13.3 Bioactive Tannins or Tannin Monomers from African Medicinal Plants

Compounds	Type	Plant Source	Activities
Flavogallonic acid (**52**), methyl-(*S*)-flavogallonate (**53**), punicalagin (**7**), nilocetin (**54**)	ETs	*T. myriocarpa* Heurck (Combretaceae)	Hepatoprotection (potency: **53** > **7** > **54**; **52** has nonsignificant effect) [187]
n-Butylgallate 4-*O*-(2′,6′-di-*O*-galloyl)-β-D-glucopyranoside (**55**), 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (**2**), gemin D (**56**), pterocaryanin (**57**)	HTs	*Callistemon lanceolatus* DC. (Myrtaceae)	Antioxidant and hepatoprotection [188]. All are significant antioxidant and hepatoprotective; **55** gave superior activity
Grandinin (**58**)	ET	*Melaleuca quinquenervia* (Clav.) S.T. Blake (Myrtaceae)	Acute toxicity: LD_{50} of 316 mg/kg; antioxidant: $EC_{50} = 4.3 \pm 0.3$ μ/mL; hypoglycemic: significant effect [189]
4-*O*-*E*-Caffeoyl-α-L-rhamnopyranosyl-(1′→3)-α/β-D-glucopyranose (**59**), *E*/*Z*-acteoside (**60**), isoacetoside (**61**)	Caffetannins	*Tecoma stans* (L.) Juss. (Bignoniaceae)	Antiproliferative (IC_{50} μM): **61** (40.1) > **60** (63.1) > **59** (98.4)-HEP-G2; **61** (−) > **11** (23.9) > **59** (113)-MCF-7; antioxidant (SC_{50}): **59** (0.27) > **60** (0.37) > **61** (18.42)-DPPH; **61** (1.1) > **60** (2.2) > **59** (2.4)-ORAC versus 6.8 μM (ascorbic acid) [190]
54, **58**, 1-*O*-Galloyl-4,6-(*S*)-hexahydroxydi-phenoyl-(α/β)-D-glucopyranose (**62**), 4,6-(*S*)-hexahydroxydi-phenoyl-(α/β)-D-glucopyranose (**63**), 3,4,6-valoneoyl-(α/β)-D-glucopyranose (**64**), pedunculagin (**2**), vascalaginone (**65**), castalagin (**66**)	ETs	*Pimenta dioica* (Merr.) L. (Myrtaceae)	Antioxidant (SC_{50}): **2** (0.11) > **64** (0.12) > **54** (0.25) > **66** (0.32) > **65** (1.20) > **63** (1.33) > **58** (1.94)-DPPH; **54**: strongest NO-inhibitor; **65**: most active inducer of macrophage proliferation; **2** was the most cytotoxic compound against solid tumor cancer cells, the most potent scavenger for DPPH radical [191]

1-*O*-Galloyl-3,6-hexahydroxydiphenoyl-D-$B_{1,4}$-glucopyranose (**67**), 1-*O*-galloyl-3,6-valoneoyl-D-$B_{1,4}$-glucopyranose (**68**)	HTs	*Euphorbia cotinifolia* L. (Euphorbiaceae)	[192]
Eugenol 5-*O*-β-(6-*O*-galloylglucopyranoside), ericifolin (**69**), 2-*O*-*p*-hydroxybenzoyl-6-*O*-galloyl-(α/β)-4C1-glucopyranose (**70**), 3-methoxyellagic acid 4-*O*-α-rhamnopyranoside (**71**)	HTs	*Melaleuca ericifolia* Sm. (Myrtaceae)	Antibacterial [193]
Red GT (**72**)	GTs	*Peltophorum africanum* Sond. (Fabaceae) roots and stem bark	HIV-1 RT RDDP activity: IC_{50} of 6.0 versus 0.048 μM for AZT-TP (positive control); RNase H activity with an IC_{50} of 5.0 μM compared to 0.5 μM for ODN-93 (positive control) [194]
2-*O*-Dehydrodigallic acid monocarboxyloyl-3-*O*-galloyl-(α/β)-glucose (**73**), vermiculatin (**74**)	HTs	*Reaumuria vermiculata* L. (Tamaricaceae), aerial parts	Antioxidant: high activity; cytotoxicity: IC_{50} values of 1.5 (**73**), 0.54 μM (**74**) against prostate PC-3 cell line [195]



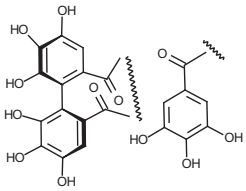
143: R_1= R_2= H, R_3= OH

144: R_1= H, R_2= Me, R_3= OH

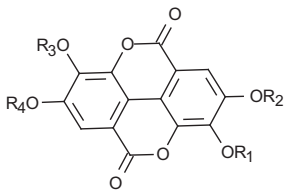
146: R_1= R_2= R_3= H

148: R_1= Me, R_2= H, R_3= OH

149: R_1= Me, R_2= Me, R_3= OH



(***S***)-HHDP G = Galloyl



71: R_1= Me, R_2= Rha, R_3= R_4= H

112: R_1= Me, R_2= R_4= SO_3Na, R_3= H

92: R_1= R_3= Me, R_2= Glu, R_4= OH

100: R_1-R_2= -CH_2-, R_3= Me, R_4= H

145: R_1= R_2= R_3= R_4= H

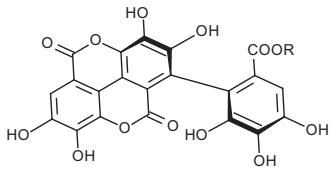
164: R_1= Me, R_2= R_3= R_4= H

165: R_1= R_2= R_3= Me, R_4= H

175: R_1= R_3= R_4= H, R_2= Me

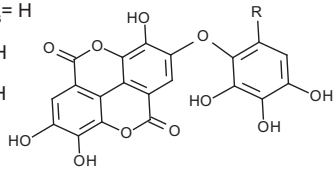
176: R_1= R_3= Me, R_2= R_4= H

186: R_1= Me, R_2= SO_3Na, R_3= R_4= H



52: R= H

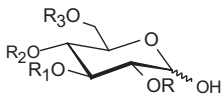
53: R = Me



90: R= H

88: R = $CONH_2$

147: R = COOH



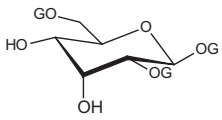
54: R= R_1= G, R_2= R_3= H

56: R= G, R_1= H, R_2-R_3= *S*-HHDP

70: R= *p*-hydroxybenzoyl, R_3= G, R_1= R_2= H

150: R= R_1= R_2= H, R_3= G

185: R_1= R_2= H, R= R_3= G



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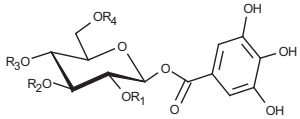


57: R_1-R_2= HHDP, R_3= R_4= G

93: R_1= R_4= H, R_2= R_3= G

94: R_1= R_4= H, R_2= R_3= G

151: R_1= R_2= R_3= H, R_4= G

152: R_1= R_4= G, R_2= R_3= H

159: R_3= R_4= G, R_1= R_2= H

162: R_1= R_2= R_3= G, R_4= H

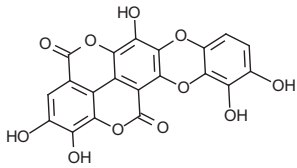
163: R_1= R_2= R_4= G, R_3= H

171: R_1= R_3= R_4= G, R_2= H

174: R_1= R_3= H, R_2= R_4= G,

G= galloyl,

***S*-HHDP**= hexahydroxydiphenoyl



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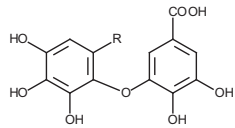
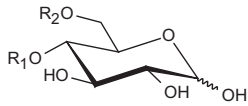
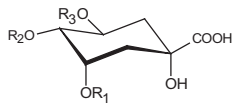


87: R= H, **187:** R = COOH



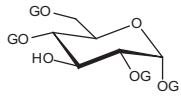
63: R_1-R_2= *S*-HHDP

Figure 13.21 Structures of HTs and related compounds isolated from African medicinal plants.



153: R= H, R_2= R_3= G

154: R_1= R_2= R_3= G



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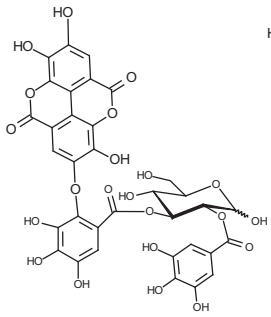

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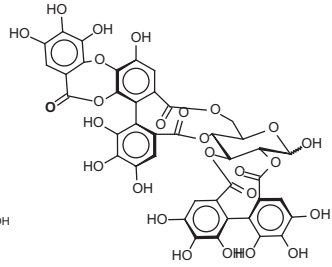

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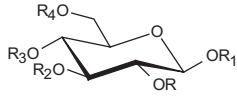


62: R_1= G, R= R_2= H,

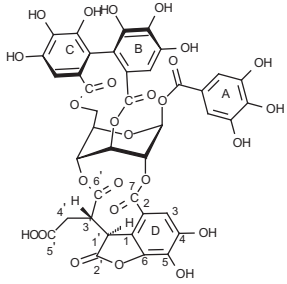
R_3-R_4= *S*-HHDP

180: R_1= R_2= G, R= H,

R_3-R_4= *S*-HHDP

181: R_1= R_2= H, R= G,

R_3-R_4= *S*-HHDP



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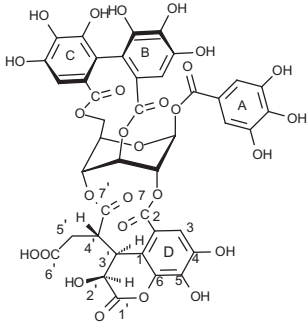

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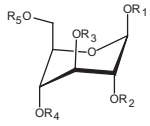


95: R_1= R_4= G, R_2= H,

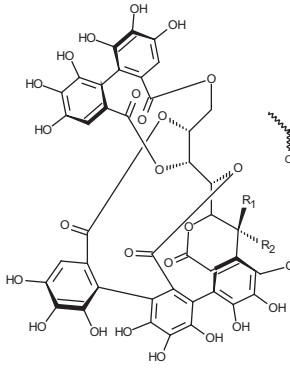
R_3-R_5= *R*-HHDP

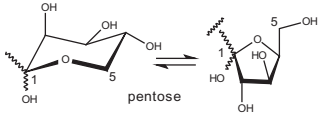
157: R_1= G, R_2= R_4= H,

R_3-R_5= *S*-HHDP

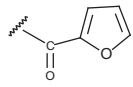
161: R_1= R_2= R_4= G,

R_3-R_5= *S*-HHDP



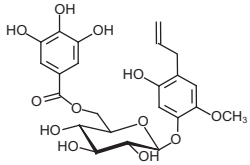


pentose



65: R_1=H, R_2=

66:R_1=OH, R_2=H; **169**: R_1=H,R_2=OH
104:R_1=pentose, R_2=OH
58:R_1=H, R_2=pentose



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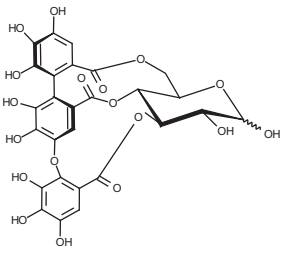

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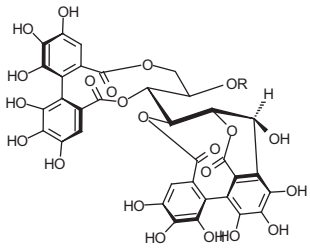
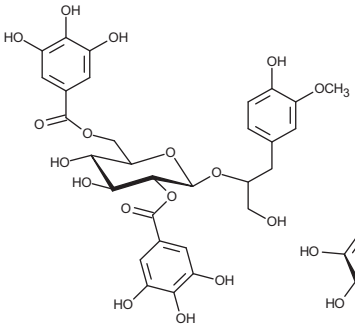


167: R= H, **168**: R= G

Figure 13.21 (Continued)



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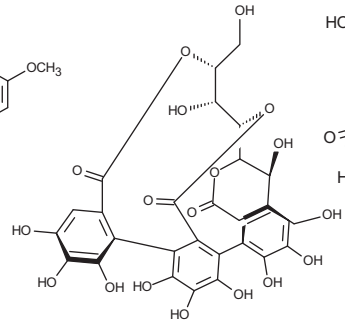

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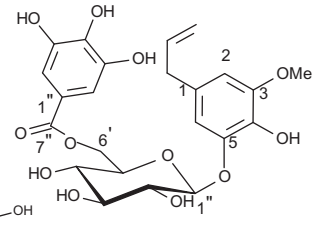

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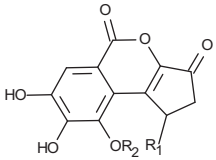
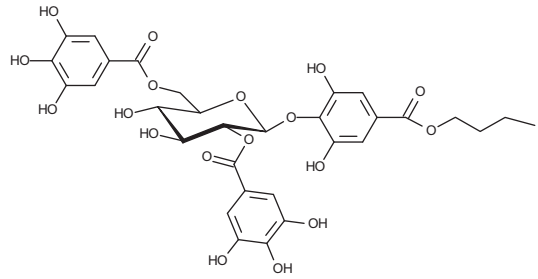


96: R_1= COOH, R_2= SO_3K

155: R_1= R_2= H

156: R_1= COOH, R_2= H



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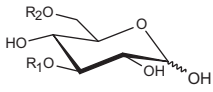
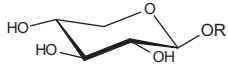
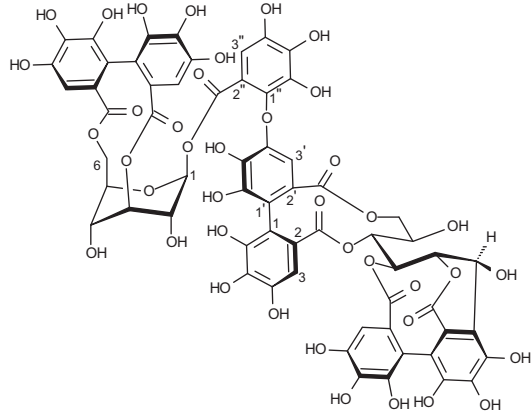


97: R_1= R_2= *E*-caffeoyl



98: R_1= R_2= *E*-caffeoyl



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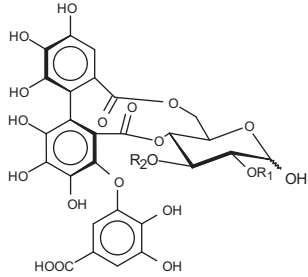
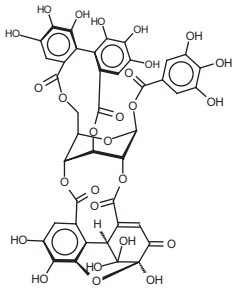


99: R_1-R_2= *S*-HHDP

Figure 13.21 (Continued)



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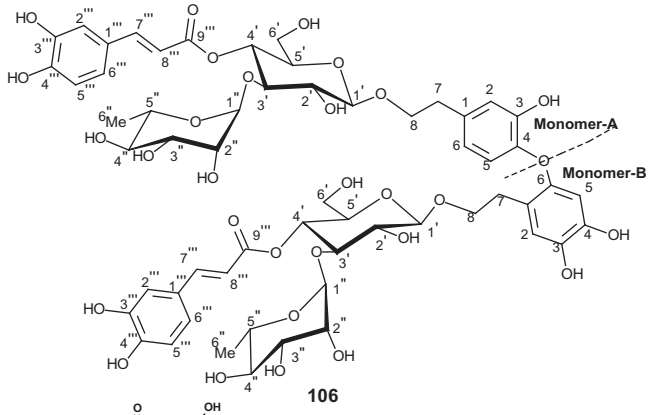

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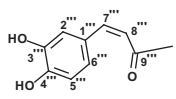
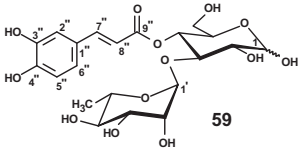


Z-caffeoyl



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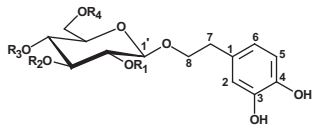
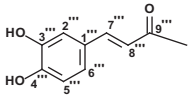
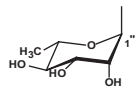


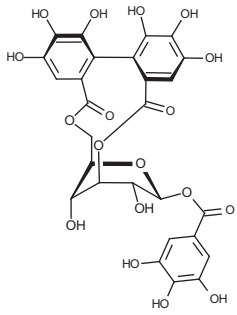
60: R_1= R_4= H, R_2= α-L-Rha, R_3= *E*/*Z*-caffeoyl; **61**: R_1= R_3= H, R_2= α-L-Rha,R_4= *E*-caffeoyl; **101**: R_1= α-L-Rha, R_2= R_4= H, R_3= *E*-caffeoyl



E-caffeoyl



α-L-rhamnopyranosyl



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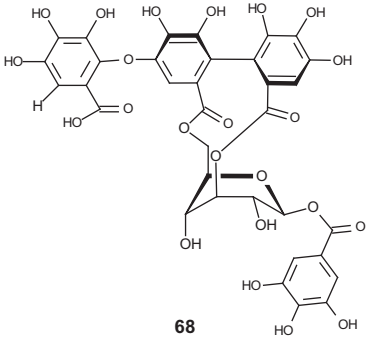

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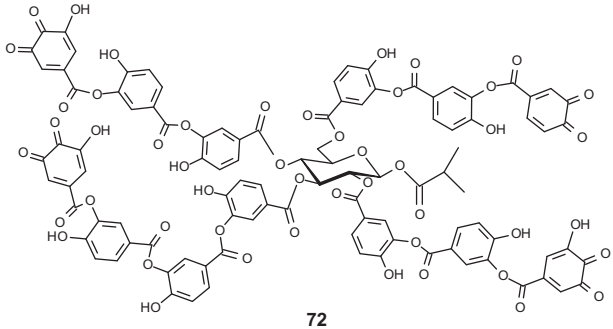
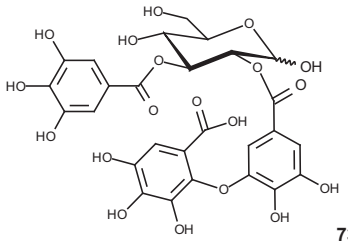


72

Figure 13.21 (Continued)



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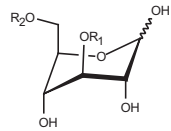
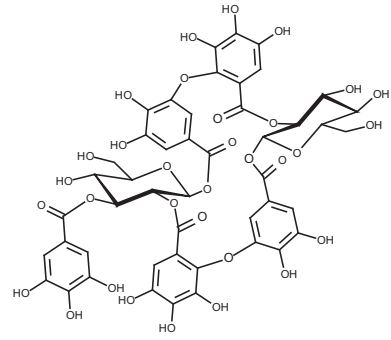


158: R_1-R_2= *R*-HHDP



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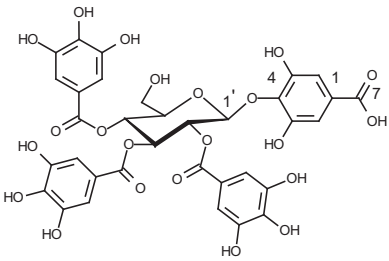

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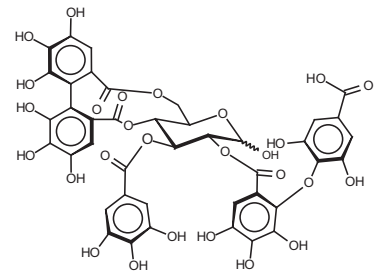

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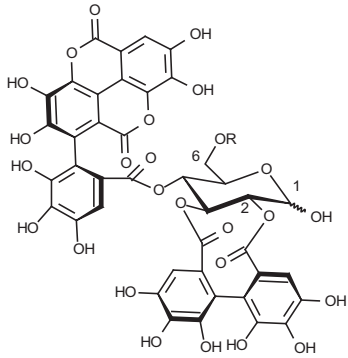
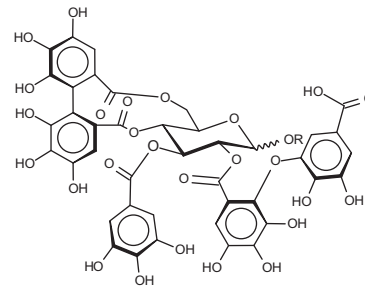


182: R= G, 183: R= H



178: R= G; **179**: R= H

Figure 13.21 (Continued)

13.3.2 Pharmacological Activity of CTs from African Medicinal Plants

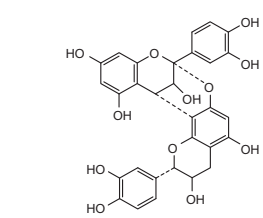
The antiviral and antioxidant activity of a series of PAs obtained from *C. sinaica* were evaluated. The oligomeric PAs exhibited significant inhibitory activity against *Herpes simplex* virus type 1 (HSV-1), while procyanidin C-1 had the highest antioxidant activity in both the microsomal LP and the hydroxyl radical scavenging assay (IC_{50} of 0.8 μM and 57%, respectively). The same study demonstrated that at a maximal nontoxic dose of 100 μg/mL, procyanidin C1 and a tetrameric PA, called cinnamtannin A2, exhibited a complete HSV-1 titer reduction, which was ascribed to extracellular antiviral activity [196].

The antioxidant activity of the compounds isolated from *I. coccinea*, epicatechin (**16**), A2 (**47**), cinnamtannin B-1 (**85**) (Figure 13.22), and ixoratannin A-2 (**86**), were evaluated using the DPPH, inhibition of lipid peroxidase, and nitric oxide radical scavenging assays. IC_{50} was calculated to compare their antioxidant potencies. Epicatechin (**16**), proanthocyanidin A2 (**47**), ixoratannin A-2 (**86**), and cinnamtannin B-1 (**85**) showed similar antioxidant activity trends in the three assay systems. Cinnamtannin B-1 (**85**) (IC_{50} of 6.14, 159.74, and 10.28 μM) and ixoratannin A-2 (**86**) (IC_{50} of 6.37, 179.48, and 11.50 μM) were the most active compounds in all three test systems. Their activity was remarkably higher than that of the controls; however, cinnamtannin B-1 (**85**) was marginally more active than ixoratannin A-2 (**86**) in all three test systems [197]. Different tannin compounds with different biological assays are summarized in Table 13.4.

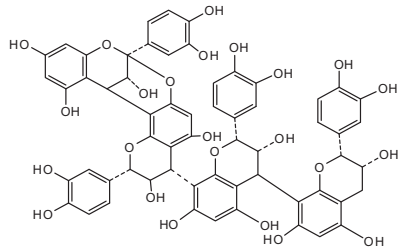
13.4 New Tannins Isolated in African Medicinal Plants

13.4.1 New HTs Isolated in African Medicinal Plants

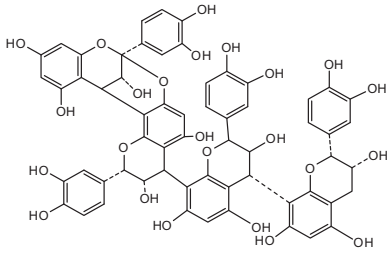
A representative group of new HTs and their related derivatives isolated from African medicinal plants is complied in Table 13.5 and Figure 13.22. The structural elucidation of such complex phenols started with chromatographic behavior for identification or the main type and basic skeleton and functional groups (Rf-values, response with specific spray reagents, and UV light). UV-spectroscopy also plays a helpful role for general subclass determination. In contrast, MS and NMR techniques play, with X-rays, the essential role for confirmation of 3D structures, especially if the compound is quite pure and crystallizable. However, such complex, highly polar, and high MW tannins are mostly not likely to crystallize easily and X-ray becomes impossible. Accordingly, HR-MS and 2D NMR analyses become necessary in most cases, particularly to differentiate or establish stereochemical features of similar isomers or analogs. Of course, HR-MS must be carried out with soft ionization techniques (e.g., ESI) because of the very high thermal sensitivity of complex polyphenols, which leads to 0% abundance of molecular ion and loss of accurate MW information. The negative mode of ionization in the case of polyphenols is very important, because they are considered pseudo-acids and form quite stable phenoxy ions under negative potential conditions. In our compounds,



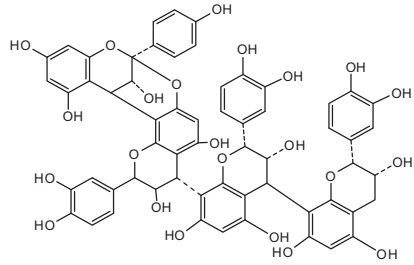
Pavetannin A (**113**)



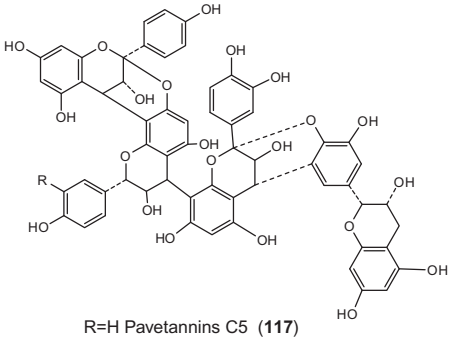
Pavetannins C2 (**114**)



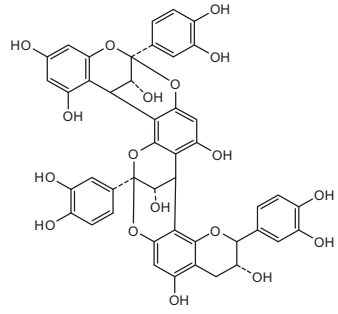
Pavetannins C3 (**115**)



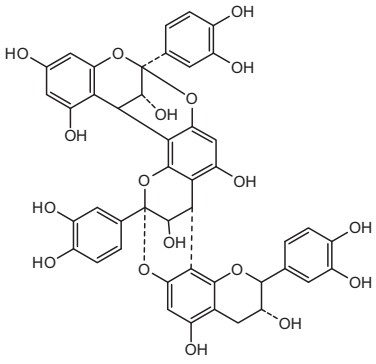
Pavetannins C4 (**116**)



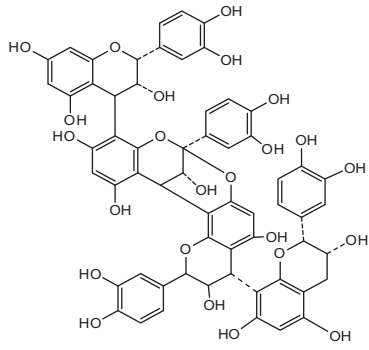
R=H Pavetannins C5 (**117**)
R=OH Pavetannins C6 (**118**)



Pavetannin B7 (**119**)

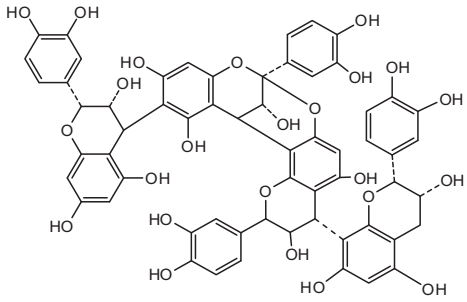


Pavetannin B8 (**120**)

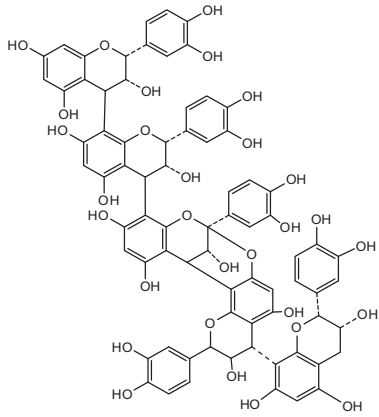


Cinnamtannin B2 (**121**)

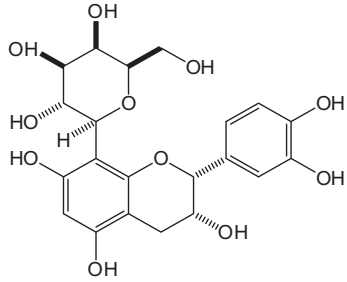
Figure 13.22 New tannins isolated in African medicinal plants.



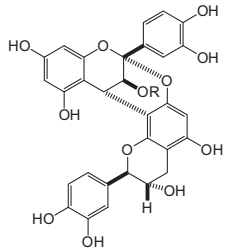
Pavetannin C1 (**122**)



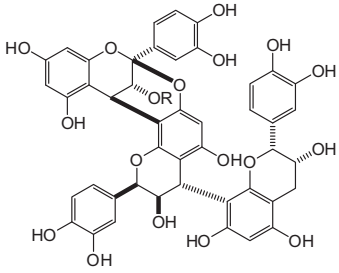
Pavetannin D1 (**123**)



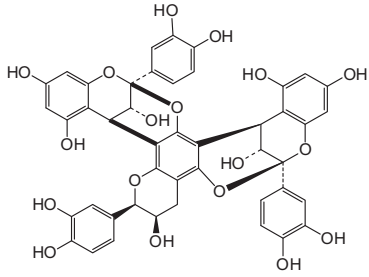
(–)-Epicatechin8-C -β-D-galactoside (**124**)



R=Arb
3*T*-*O*-Arabinopyranosyl-*ent*-epicatechin-(2α→7, 4α→8)-catechin (**125**)

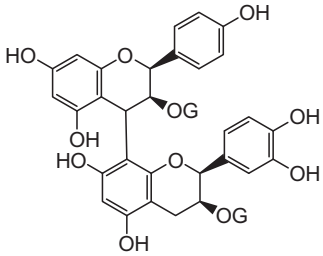


R=Arb
3*T*-*O*-α-L-Arabinopyranosylcinnamtannin B_1 (**126**)
R= Gla
3*T*-*O*-β-D-Galactopyranosylcinnamtannin B_1 (**127**) [**211**]

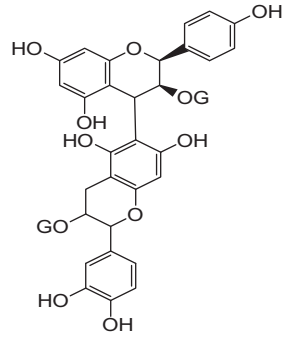


Epicatechin-(2β→*O*→7,4β→8)–epicatechin-(5→*O*→β→2β,6→4β)–epicatechin (Ixoratannin A-2) (3) (**86**) [**213**]

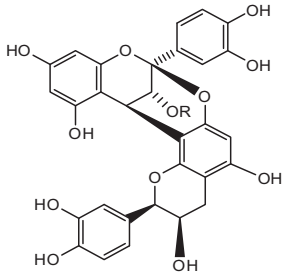
Figure 13.22 (Continued)



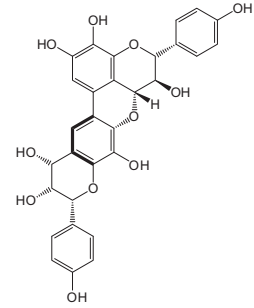
3-*O*-galloyl-epiafzelechin-(4β→8)-epicatechin-3-*O*-gallate (**129**)



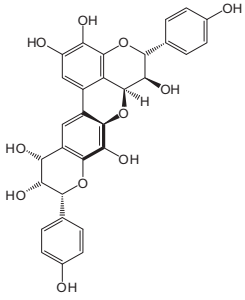
3-*O*-galloyl-epiafzelechin-(4β→6)-epicatechin-3-*O*-gallate (**130**) [**228**]



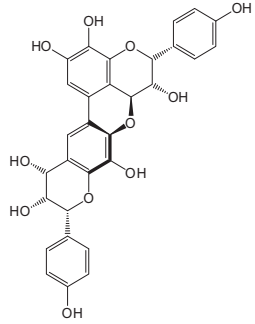
R=β-D-galactopyranos: 3*T*-*O*-β-D-galactopyranosyl-*ent*-epicatechin (2α→7,4α→8)-epicatechin (**131**);
R=β-L-arbinopyranos: 3*T*-*O*-L-arabinopyranosyl-*ent*-epicatechin-(2α→7, 4α→8)-epicatechin (132) [**46**]



Oritin-(4α→7, 5→6)-epioritin-4a-ol (**133**)

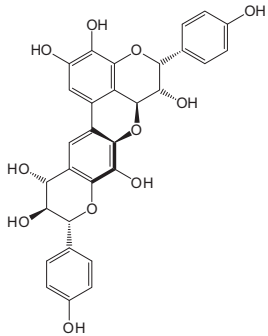


Oritin-(4β→7, 5→ 6)-epioritin-4α-ol (**134**)

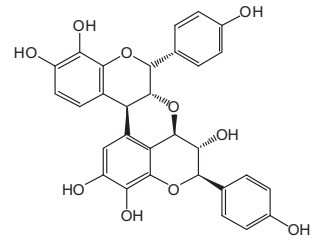


Epioritin-(4β→7, 5→6)-epioritin-4α-ol (**135**)

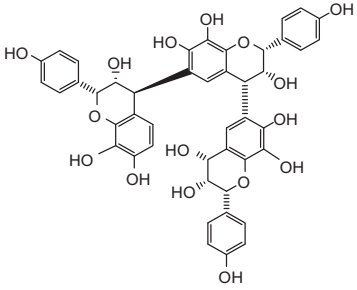
Figure 13.22 (Continued)



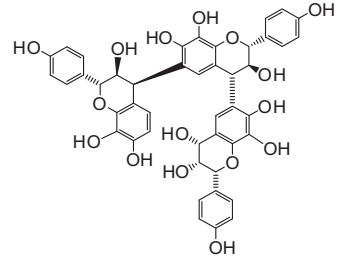
Epioritin-(4β→7, 5→ 6)-oritin-4α -ol (**136**)



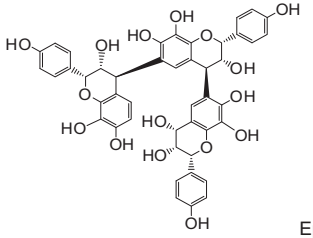
Epioritin-(4 β→5, 3→4)-oritin-4α -ol (**137**)



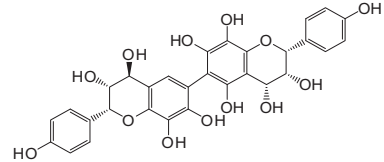
Epioritin-(4β→6)-oritin-(4α→6)-epioritin-4α-ol (**138**)



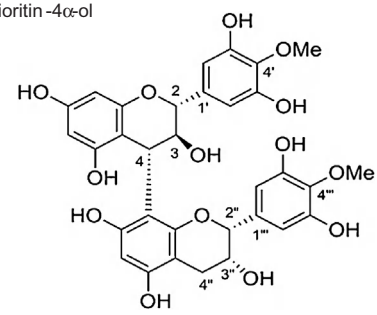
Oritin-(4β→6)-oritin-(4 α→6)-epioritin-4α-ol (**139**)



Epioritin-(4β→6)-epioritin -(4β→6)-epioritin -4α-ol (**140**)



Epioritin -4α-ol-(6→6)-epioritin -4β-ol (**141**)



4'-*O*-Methylgallocatechin-(4α→8)-4'-*O*-methylepigallocatechin (4', 4"'-di-*O*-methyl-prodelphinidin B_4) (**142**)

Figure 13.22 (Continued)

Table 13.4 Bioactive CTs and Related Compounds from African Medicinal Plants

Class/Compounds	Plants (Family)	Pharmacological Activities
CTs		
Epicatechin (**16**)	*Crataegus sinaica*	Anticomplement, [198], antiviral and antioxidant [196]
	Apple pomace	Antioxidant [199]
	Adansonia digitata	Antioxidant [200]
Epicatechin dimer (procyanidin B1) (**35**) Epicatechin dimer (procyanidin B3) (**37**) Epicatechin dimer (procyanidin B4) (**38**)	Green tea	Antibacterial [201]
Epicatechin dimer (procyanidin B2) (**36**)	*C. sinaica*	Antiviral and antioxidant [196,200]
Epicatechin dimer (procyanidin B5) (**39**) Proanthocyanidin A2	*A. digitata*	
Epicatechin trimer (C1)		
Epicatechin-(4β→8)]$_2$-epicatechin (procyanidin C1) (**45**)	*Cacao liquor*	LP and radical scavenging effects [202]
Epicatechin-(4β→8)]$_3$-epicatechin (cinnamtannin A2) (**50**)	*C. sinaica*	Anti-HIV [203]
Epicatechin pentamer epicatechin-(4β→8)]$_4$-epicatechin (**76**)	*A. digitata*	Antiviral and antioxidant [196,200]
Trimeric A-type epicatechin-(4β→8)-epicatechin-(4β→8,2β→*O*→7)-epicatechin (**77**)		
3T-*O*-α-L-Arabinopyranosylcinnamtannin B1 (**78**)	Cacao liquor (*Theobroma cacao*)	LP and radical scavenging effects [202]
3T-*O*-β-D-Galactopyranosylcinnamtannin B1 (**79**)		
3T-*O*-α-L-Arabinopyranosyl-ent-epicatechin-(2α→7,4α→8)-epicatechin (**80**)		
Procyanidin B5 (**39**)		
3T-*O*-β-D-Galactopyranosyl-*ent*-epicatechin-(2α→7,4α→8)-epicatechin (**82**)		
Cinnamtannin (**50**) (−)-Epicatechin 8-C-galactopyranoside (**84**)		
Cinnamtannin B-1 (**85**)		Antioxidant and antibacterial [197]
Ixoratannin A-2 (**86**)	*I. coccinea* leaves	

Table 13.5 New HTs Isolated in African Medicinal Plants

Compounds	Type	Plant Source	Parts	Area	References
1′-Decarboxy dehydrodigallic acid (**87**)	GTs	*Tamarix aphylla* (L.) Karst. (Tamaricaceae)	Bark	Egypt	[204]
Epilobamide A (**88**)	ETs	*Epilobium hirsutum* L. (Onagraceae)	Whole plant	Egypt	[205] [206]
2-*O*-Galloyl 3-*O*-valoneoyl dilactone-(α/β)-$^4C_1$-glucopyranose (**89**), 1′-monodecarboxyvaloneic acid dilactone (**90**), valoneic dilactone dioxine (**91**)					
Ellagic acid 3,3′-dimethyl ether 4-*O*-β-D-glucopyranoside (**92**)	ETs	*Tamarix nilotica* (Ehrenb.) Bunge. (Tamaricaceae)	Debarked roots	Egypt	[207]
1,2,4-tri-*O*-Galloyl-β-glucopyranose (**93**), 1,3,4-tri-*O*-galloyl-β-glucopyranose (**94**), 1,4-di-*O*-galloyl-3,6-(*R*)-hexahydroxydiphenyl-β-glucopyranose (**95**), brevifolin carboxylic acid 10-monopotassium sulfate (**96**)	HTs	*P. granatum* L. (Punicaceae)	Leaves	Egypt	[208]
3,6-di-*O*-Caffeoyl-(α/β)-glucose (**97**), 1-*O*-caffeoyl-β-xylose (**98**), 2,3-*O*-hexahydroxydiphenoyl-4,6-*O*-sanguisorboyl-(α/β)-glucose (**99**)	Caffetannins	*Rubus sanctus* Schrreb. (Rosaceae)	Aerial parts	Egypt	[209]
3′-*O*-Methyl-3,4-methylene-dioxyellagic acid (**100**)	ETs	*P. granatum* L. (Punicaceae)	Leaves	Egypt	[210]
2-(3,4-di-Hydroxyphenyl)ethyl-2-I-[6-deoxy-α-L-mannopyranosyl-4-(3,4-dihydroxyphenyl)-2-propenoate]-β-D-glucopyranoside (**101**)	Caffetannin	*T. stans* (L.) Juss. (Bignoniaceae)	Flowers and fruits	Egypt	[190]
6-Hydroxyeugenol 4-*O*-(6′-*O*-galloyl)-β-D-$^4C_1$-glucopyranoside (**102**), 3-(4-hydroxy-3-methoxyphenyl)-propane-1,2-diol-2-*O*-(2′,6′-di-*O*-galloyl)-β-D-$^4C_1$-gluco-pyranoside (**103**), grandininol (**104**)	HTs	*P. dioica* (Merr.) L. (Myrtaceae)	Leaves	Egypt	[191]

(*Continued*)

Table 13.5 (Continued)

Compounds	Type	Plant Source	Parts	Area	References
Puniciin (**105**)	ETs	*P. granatum* var. *nana* (L.) Pers. (Punicaceae)	Pericarp	Egypt	[211]
Jacraninoside-A (**106**)	Caffetannins	*Jacaranda mimosifolia* D. Don. (Bignoniaceae)	Leaves	Egypt	[212]
Gallic acid 4-*O*-(2′,3′,6′-tri-*O*-galloyl)-β-D-glucopyranoside (**107**)	HTs	*E. cotinifolia* L. (Euphorbiaceae)	Leaves		[213]
Nilotinin M_1 (**108**), nilotinins D_1 (**109**), D_2 (**110**), D_3 (**111**)	ETs	*T. nilotica* (Ehrenb.) Bunge. (Tamaricaceae)	Leaves	Egypt	[214]
3-Methoxyellagic acid 4,4′-disulfate (**112**)	ET	*R. vermiculata* L. (Tamaricaceae)	Aerial parts	Egypt	[214]

1′-decarboxy dehydrodigallic acid (**87**) was confirmed easily by MS from corresponding acid due to the difference in MW by less 44 amu in molecular ion [M-H]- as base peak in negative ESI-MS. In ^{1}H NMR, the free H-1 creates a new pattern of two O-doublets instead of two singlets in the case of the DHDG acid, and in ^{13}C, C-1 will become upfield as a protonated aromatic C-atom instead of carboxylated at about 120 ppm. This type of information was used for confirmation of the structure of **90** versus its acid **147**. While differentiation of the amide (**88**) from its acid (**147**) was achieved from molecular ion peak that was less by 1 mu and refer to an odd MW due the presence of one N-atom. In addition, ^{1}H NMR at different temperatures submits very interesting information from the pattern of NH_2 as an AB-spin system of diastereomeric protons disappeared completely at high temperatures (≈50°C) as an exchangeable type of protons. Confirmation of NH_2 signals was carried out by ^{3}J- and ^{2}J-cross peaks with aromatic C-1″ and carbonyl-C-7″, respectively. Compound **89** was differentiated from its positional isomer through HMBC ^{3}J-cross peaks between carbonyl carbon signals of valaneoyl and galloyl, with H-2 and H-3 on the glucose core. The identity of jacraninoside-A (**106**), isolated as the first phenylethanoid dimer in nature, was confirmed through negative HR-MS, and the molecular ion peak at 1245.3880 eliminated the probability of the mixture of two different monomeric isomers with molecular ion peak at 623.1989. HMBC correlations confirmed the connectivity between aglycones, rhamnosyls, and caffeoyls at C-1, C-3, and C-4 of the glucose core, respectively.

13.4.2 New CTs Isolated in African Medicinal Plants

A series of dimeric and trimeric PAs possessing one or two doubly linked interflavanyl linkages were isolated from stem bark of *P. owariensis* (Rubiaceae). Spectroscopic investigations and partial acid-catalyzed degradation established their structures as *ent*-epicatechin-(4α→8, 2α→7)-*ent*-catechin (pavetannin A) (**113**) [215], epicatechin-(4β→8,2β→O→7)-*ent*-catechin-(4β→8)-epicatechin-(4β→8)-epicatechin (pavetannin C2) (**114**), epicatechin-(4β→8,2β→O→7)-*ent*-epicatechin-(4α→8)-*ent*-epicatechin-(4α→8)-epicatechin (pavetannin C3) (**115**), epiafzelechin-(4β→8,2β→O→7)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (pavetannin C4) (**116**), epiafzelechin-(4β→8,2β→O→7)-*ent*-afzelechin-(4α→8)-*ent*-epicatechin-(4α→8,2α→O→7)-*ent*-catechin (pavetannin C5) (**117**), epiafzelechin-(4β→8,2β→O→7)-*ent*-catechin-(4α→8)-*ent*-epicatechin-(4α→8,2β→O→7)-*ent*-catechin (pavetannin C6) (**118**) [216], epicatechin-(4β→8, 2β→0→7)-*ent*-epicatechin-(4α→8, 2α→0→7)-*ent*-catechin (pavetannin B7) (**119**), epicatechin-(4β→8, 2β→0→7)-epicatechin-(4β→8, 2β→0→7)-*ent*-catechin (pavetannin B8) (**120**), epicatechin-(4β→8)-epicatechin-(4β→8, 2, β→0→7)-epicatechin-(4β→8)-epicatechin (cinnamtannin B2) (**121**), epicatechin-(4β→6)-epicatechin-(4β→8, 2β→0→7)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (pavetannin C1) (**122**), and epicatechin-(4β→8)-epicatechin-(4β→8, 2β→0→7)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (pavetannin D1) (**123**) [217].

Seventeen phenolics, including four new compounds, were isolated from cacao beans (*T. cacao* L.). The new compounds are (−)-epicatechin 8-C-β-D-galactoside (**124**), 3*T*-*O*-arabinopyranosyl-*ent*-epicatechin-(2α→7, 4α→8)-catechin (**125**), 3*T*-*O*-α-L-arabinopyranosyl cinnamtannin B_1 (**126**), and 3*T*-*O*-β-D-galactopyranosyl cinnamtannin B_1 (**127**). The new compounds were characterized as a C-glycosidic flavan, an *O*-glycoside of a dimeric, and two *O*-glycosides of trimeric A-linked PAs, on the basis of spectroscopic data [202].

A rare series of doubly linked proteracacinidin-type oligoflavonoids were isolated by Bennie et al. [218], who identified four new analogs, oritin-(4α→7, 5→6)- epioritin-4a-ol (**33**), oritin-(4β→7, 5→6)-epioritin-4α-ol (**134**), epioritin-(4β→7, 5→6)-epioritin-4α-ol (**135**), and epioritin-(4β→7, 5→6)-oritin-4α-ol (**136**), and a compound possessing a rare (4β→5)- as well as a unique (3→4)- ether linkage (**137**). In 2004, the same authors reported the structures of the first trimeric proteracacinidins with exclusive C−C interflavanyl linkages, epioritin-(4β→6)-oritin-(4α→6)-epioritin-4α-ol (**138**), oritin-(4β→6)-oritin-(4α→6)-epioritin-4α-ol (**139**), and epioritin-(4β→6)-epioritin-(4β→6)-epioritin-4α-ol (**140**), as well as the first naturally occurring bisleucoanthocyanidin with a biphenyl linkage, epioritin-4α-ol-(6→6)-epioritin-4β-ol (**141**) from the heartwoods of *A. caffra* and *Acacia galpinii* [219] and 4′-O-Methylgallocatechin-(4α→8)-4′-O-methylepigallocatechin (4′, 4″-di-O-methyl-prodelphinidin B4) (**142**) was isolated from green tea [220].

13.5 Other Tannins or Tannin Monomers from African Medicinal Plants

13.5.1 Other HTs Isolated in African Medicinal Plants

In Figure 13.21, the structures of some interesting known HTs were displayed to explain the very high structural diversity among the different types of tannins and related polyphenols which were isolated from African medicinal plants (Table 13.6).

13.5.2 Other CTs Isolated in African Medicinal Plants

Different types of procyanidins represent the dominant class of natural PAs. Among these the dimers procyanidins B1, B2, B3, and B4 (**35**−**38**) occur most frequently in plant tissues. Procyanidin B5 [epicatechin-(4β→6)-epicatechin] (**39**), B6 [catechin-(4α→6)-catechin] (**40**), B7 [epicatechin-(4β→6)-catechin] (**41**), and B8 [catechin-(4α→6)-epicatechin] (**42**)] are also widespread in plants. Analogs of procyanidins B1 and B2 with epicatechin chain extension units (2*R*,3*R*-2,3-*cis* configuration) are very commonly represented in the plant kingdom, and many plants also produce analogs of procyanidins B3−B8 [24,200] (Table 13.7).

Table 13.6 Other HTs Isolated in African Medicinal Plants

Compounds	Plant Source	Parts	Area	References
Gallic acid (**143**), gallic acid 4-methyl ether (**144**), ellagic acid (**145**), **54**	*T. aphylla* (Tamaricaceae)	Bark	Egypt	[204]
101, protocatechuic acid (**146**), **103**, valoneic acid dilactone (**147**), methyl gallate (**148**), *p*-methoxy-methylgallate (**149**), 6-*O*-galloyl-glucose (**150**), 1,6-di-*O*-galloyl-glucose (**151**), **54**, 1,2,6-tri-*O*-galloyl-glucose (**152**)	*Epilobium hirsutum* L. (Onagraceae)	Whole plant	Egypt	[205]
3,4-Digalloylquinate (**153**), 3,4,5-trigalloylquinate (**154**)	*Koelreuteria paniculata* Laxm. (Sapindaceae)	Leaves	Egypt	[221]
Brevifolin (**155**), brevifolin carboxylic acid (**156**), corilagin (**157**), 3,6-(*R*)-hexahydroxy-diphenoyl-(α/β)-$^{1}C_{4}$-glucopyranose (**158**), **110**, 1,4,6-tri-*O*-galloyl-β-$^{4}C_{1}$-glucopyranose (**159**), **103**, granatin-B (**160**), punicafolin (**161**)	*P. granatum* L. (Punicaceae)	Leaves	Egypt	[222]
6	*R. sanctus* (Rosaceae)	Aerial parts	Egypt	[209]
54, **101**−**103**	*Eugenia jambolana* Lam. (Myrtaceae)	Leaves	Egypt	[223]
54, **101**, **103**, **106**	*T. myriocarpa* Heurck	Leaves	Egypt	[187]
54, **101**, **103**, **108**, 1,2,3,4-Tetra-*O*-galloyl-β-D-glucopyranose (**162**), 1,2,3,6-tetra-*O*-galloyl-β-D-glucopyranose (**163**)	*C. lanceolatus* DC., (Myrtaceae)	Flowers and leaves	Egypt	[188,224]
54, **101**, **103**, 3-*O*-Methylellagic acid (**164**), 3,4,3′-tri-*O*-methylellagic acid (**165**), castalin (**166**)	*M. quinquenervia* (Clav.) S. T. Blake	Leaves	Egypt	[189]
53, **54**, **101**, **103**, Casuariin (**167**), casuarinin (**168**), vascalagin (**169**)	*P. dioica* (Merr.) L. (Myrtaceae)	Leaves	Egypt	[191]

(*Continued*)

Table 13.6 (Continued)

Compounds	Plant Source	Parts	Area	References
108–**110**, 1,2,6-Tetra-*O*-galloyl-β-D-allopyranose (**170**), 1,2,4,6-tetra-*O*-galloyl-β-D-glucopyranose (**171**), 1,2,4,6-tetra-*O*-galloyl-β-D-glucopyranose (**172**), chebulagic acid (**9**), euphormisin M_2 (**173**)	*E. cotinifolia* L. (Euphorbiaceae)	Leaves	Egypt	[213]
53, **58**, 1,3,6-tri-*O*-Galloyl-β-D-$^4C_1$-glucopyranose (**174**), **73**, ellagic acid 4-*O*-methyl ether (**175**)	*E. cotinifolia* L. (Euphorbiaceae)	Leaves and small branches	Egypt	[192]
53–**55**, Ellagic acid 3,3′-di-*O*-methyl ether **(176)**	*M. ericifolia* Sm. (Myrtaceae)	Leaves	Egypt	[193]
Hirtellin A (**177**), remurin A (**178**), remurin B (**179**), 1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-D-glucose (**180**), **56**, hippomanin A (**181**)	*T. nilotica* (Ehrenb.) Bunge. (Tamaricaceae)	Leaves	Egypt	[214]
7, Terflavin A (**182**), terflavin C (**183**), alnusiin (**184**)	*P. granatum* var. *nana* (L.) Pers. (Punicaceae)	Pericarp	Egypt	[211]
53–**55**, **127**, **136**, 2,6-Digalloylglucose (**185**), 3-*O*-methylellagic 4-sodium sulfate (**186**), dehydrodigallic acid (**187**)	*R. vermiculata* L. (Tamaricaceae)	Aerial parts	Egypt	[195]

Table 13.7 Other CTs Isolated in African Medicinal Plants

Class and Compounds	Plant Sources	References
(a) Procyanidins		
Monomers		
Epicatechin	*C. sinaica* leaves	[195]
	T. cacao beans	[202]
(+)-Catechin, (−)-epicatechin 3-*O*-gallate	*Anisophyllea dichostyla* roots	[225]
Dimers		
Epicatechin-(4β→8)-catechin (procyanidin B1)	*Lotus corniculatus* leaves	[226]
	Lotus pedunculatus unripe fruits	[227]
	Prunus amygdalus (almond)	[228]
	Vicia faba (fava bean) seed testa	[229]
	A. dichostyla	[225]
Epicatechin-(4β→8)-epicatechin (procyanidin B2)	*T. cacao* L.	[230]
	C. sinaica	[198]
	A. digitata pericarp of fruits	[200]
	Guazuma ulmifolia bark	[231]
	Humulus lupulus female inflorescences	[232]
	L. corniculatus leaves	[226]
	L. pedunculatus leaves	[227]
	P. amygdalus unripe fruits	[228]
	Vaccinium pahalae cell culture	[233]
	A. dichostyla	[225]
	Mesembryanthemum edule leaves	[234]

(*Continued*)

Table 13.7 (Continued)

Class and Compounds	Plant Sources	References
Catechin-(4α→8)-catechin (procyanidin B3)	*Hamamelis virginiana* bark	[235]
	Humulus lupulus female inflorescences	[236]
	Khaya senegalensis bark	[237]
	L. pedunculatus leaves	[227]
	Pinus densiflora bark	[238]
	P. amygdalus unripe fruits	[228]
	V. faba testa of fava beans	[229]
Catechin-(4α→8)-epicatechin (procyanidin B4)	*H. lupulus* female inflorescences	[236]
	L. pedunculatus leaves	[227]
	P. amygdalus unripe fruits	[228]
	V. faba seed testa	[229]
Epicatechin-(4β→6)-epicatechin (procyanidin B5)	*C. sinaica*	[198]
	A. digitata pericarp of fruits	[200]
	Guazuma ulmifolia bark, fruits	[231]
Catechin-(4α→6)-catechin (procyanidin B6)	*K. senegalensis* bark	[237]
Epicatechin-(4α→6)-catechin (procyanidin B7)	*P. amygdalus* unripe fruits	[228]
	Citrus incanus aerial parts	[239]
	P. amygdalus unripe fruits	[228]
ent-Epicatechin-(4α→6)-*ent*-epicatechin	*Byrsonima crassifolia* bark	[240]
ent-Epicatechin-(4α→8)-*ent*-epicatechin		
(b) Prodelphinidins		
Epigallocatechin-(4β→8)-catechin	*C. incanus* aerial parts	[239]
	H. virginiana bark	[235]
	L. pedunculatus leaves	[227]
Gallocatechin-(4α→8)-catechin	*V. faba* seed testa	[229]
Epigallocatechin-(4β→8)-epicatechin	*L. pedunculatus* leaves	[227]

Gallocatechin-(4α→8)-epicatechin	*V. faba* seed testa	[229]
Epigallocatechin-(4β→8)-gallocatechin	*C. incanus* aerial parts	[239]
	L. pedunculatus leaves	[227]
	Stryphnodendron adstringens stem bark	[241]
Gallocatechin-(4α→8)-gallocatechin	*Ziziphus spina-christi* leaves	[242]
Epigallocatechin-(4β→8)-epigallocatechin	*L. pedunculatus* leaves	[227]
Gallocatechin-(4α→8)-gallocatechin		
Epigallocatechin-(4β→8)-epigallocatechin	*V. faba* seed testa	[229]
(c) Proteracacinidin		
Epioritin-(4β→O→3)-epioritin-4β-ol	*A. caffra*	[243]
Epioritin-(4β→O→3)-epioritin-4α-ol	*A. galpinii*	[240]
Epioritin-(4β→O→3)-oritin-4α-ol		[244]
Epioritin-(4β→O→4)-epioritin-4α-ol		[245]
ent-Oritin-(4α→O→4)-epioritin-4α-ol		
Epioritin-(4β→6)-oritin-4α-ol-epioritin-(4β→6)-*ent*-oritin-4α-ol		
ent-Oritin-(4β→6)-epioritin-4α-ol		
ent-Oritin-(4β→6)-oritin-4α-ol		
ent-Oritin-(4α→6)-epioritin-4α-ol		
ent-Oritin-(4α→6)-oritin-4α-ol		
ent-Oritin-(4α→6)-epioritin-4β-ol		
(d) Proteracacinidins/melacinidins		
Epioritin-(4β→6)-epimesquitol-4α-ol	*A. galpinii* and *A. caffra* heartwood	[245]
Epioritin-(4β→6)-epimesquitol-4β-ol		
Epimesquitol-(4β→6)-epioritin-4α−ol		
(e) Promelacacinidin		
Epimesquitol-(4β→O→4)-epioritin-4β-ol	*A. caffra* heartwood	[243]
Epimesquitol-(4β→6)-epimesquitol-4β-ol	*A. galpinii* and *A. caffra* heartwood	[245]

(*Continued*)

Table 13.7 (Continued)

Class and Compounds	Plant Sources	References
bis-Leucoteracacinidin, epioritin-4α-ol-(6→6)-epioritin-4β-ol	*A. galpinii* and *A. caffra*	[219]
(f) Profisetinidins		
Fisetinidol-(4α→8)-catechin	*Colophospermum mopane*	[249]
Fisetinidol-(4β→8)-catechin		
Fisetinidol-(4α→8)-epicatechin		
Fisetinidol-(4α→6)-catechin		
Fisetinidol-(4β→6)-catechin		
ent-Epifisetinidol-(4α→6)-fisetinidol		
Trimers		
[Epicatechin-(4β→8)]$_2$-epicatechin (procyanidin C1) (**45**)	*T. cacao* L.	[230]
	C. sinaica	[198]
Epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin	*A. digitata* pericarp of fruits	[200]
Epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin	*G. ulmifolia* bark	[231]
[Epicatechin-(4β→8)]$_2$-catechin	*A. dichostyla*	[225]
[Epicatechin-(4β→6)]$_2$-epicatechin	*P. amygdalus* unripe fruits	[228]
[Catechin-(4α→8)]$_2$-catechin (procyanidin C2)	*G. ulmifolia* bark	[231]
Epicatechin-(4β→6)-epicatechin-(4β→8)-catechin	*P. amygdalus* unripe fruits	[228]
Epicatechin-(4β→8)-epicatechin-(4β→6)-catechin	*G. ulmifolia* bark	[231]
Epicatechin-(4β→8)-catechin-(4α→8)-catechin		[226]
[Gallocatechin-(4α→8)]$_2$-gallocatechin	*L. corniculatus*	[228]
Epioritin-(4β→6)-oritin-(4α→6)-epioritin-4α-ol	*P. amygdalus* unripe fruits	[228]
Oritin-(4β→6)-oritin-(4α→6)-epioritin-4α-ol	*P. amygdalus* unripe fruits	[232]
Epioritin-(4β→6)-epioritin-(4β→6)-epioritin-4α-ol	*H. lupulus* female inflorescences	[239]
	C. incanus aerial parts	[219]
	A. galpinii	
	A. caffra heartwood	

Tetramers		
[Epicatechin-(4β→8)]$_3$-epicatechin (cinnamtannin A2)	*T. cacao* L.	[230]
[Epicatechin-(4β→8)]$_3$-catechin	*C. sinaica*	[196]
	A. digitata pericarp of fruits	[200]
Pentamers		
[Epicatechin-(4β→8)]$_3$-epicatechin (**49**)	*G. ulmifolia* bark	[231]
	P. amygdalus unripe fruits	[228]
	C. sinaica	[196]
Proanthocyanidins A type		
Dimers		
Epicatechin-(4β→8, 2β→O→7)-epicatechin (procyanidin A2) (**47**)	*C. sinaica*	[198]
	A. digitata pericarp of fruits	[200]
	Parameria laevigata bark	[232]
Epicatechin-(4β→8, 2β→O→7)-catechin (procyanidin A1) (**48**)	*Pavetta owariensis* stem bark	[216]
Epicatechin-(4β→8, 2β→O→7)-*ent*-catechin (procyanidin A4)	*Arachis hypogaea* peanut skins	[247]
Epicatechin-(4β→6, 2β→O→7)-epicatechin (proanthocyanidin A6)	*V. macrocarpon* (cranberry) fruits	[131]
Epicatechin-(4β→8, 2β→O→7)-*ent*-epicatechin	Peanut skins	[247]
Epicatechin-(4β→6, 2β→O→7)-catechin	*Lupinus angustifolius* seeds	[216]
Epicatechin-(4β→6, 2β→O→7)-*ent*-catechin	*P. owariensis* stem bark	[232]
Epicatechin-(4β→6, 2β→O→7)-*ent*-epicatechin	*P. laevigata* bark	
ent-Epicatechin-(4α→8, 2β→O→7)-ent-catechin (pavetannin A1)	Peanut skins	
ent-Epicatechin-(4α→8, 2β→O→7)-catechin (pavetannin A2)	*P. owariensis* stem bark	[216]
Epicatechin-(4β→8, 2β→O→7)-*ent*-catechin-(4β→8)-epicatechin (aesculitannin B)	*P. laevigata* bark	[232]
Epicatechin-(4β→6)-epicatechin-(4β→8, 2β→O→7)-epicatechin	*V. macrocarpon* fruits	[132]
Epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-epicatechin		
Epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-*ent*-epicatechin (pavetannin B1)	*P. owariensis* stem bark	[217]
Epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin (pavetannin B2)		[216]
Epicatechin-(4β→6, 2β→O→7)-epicatechin-(4β→8)-epicatechin (pavetannin B3)		
Epicatechin-(4β→6, 2β→O→7)-ent-epicatechin-(4β→8)-epicatechin (pavetannin B4)		

(*Continued*)

Table 13.7 (Continued)

Class and Compounds	Plant Sources	References
Epicatechin-(4β→6, 2β→O→7)-catechin-(4β→8)-epicatechin (pavetannin B5)		
Epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-catechin (pavetannin B6)	*A. digitata* pericarp of fruits	[200]
Epicatechin-(4β→8, 2β→O→7)-*ent*-epicatechin-(4β→8, 2β→O→7)-*ent*-catechin (pavetannin B7)		
Epicatechin-(4β→8,2β→O→7)-epicatechin-(4β→8, 2β→O→7)-*ent*-catechin (pavetannin B8)		
Epicatechin-(4β→6, 2β→O→7)-epicatechin-(4β→8, 2β→O→7)-epicatechin		
Epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-epicatechin		
Tetramers		
Epicatechin-(4β→8, 2β→O→7) ent-epicatechin-(4α→8)-*ent*-epicatechin-(4α→8)-epicatechin (pavetannin C2)	*P. owariensis* stem bark	[216]
Epicatechin-(4β→8, 2β→O→7)-*ent*-catechin-(4β→8)-epicatechin-(4β→8)-Epicatechin (pavetannin C6, aesculitannin F)	*P. owariensis* stem bark	[216]
Epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin	*P. owariensis* stem bark	[248]
Epicatechin-(4β→6)-epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin (pavetannin C1)	*Malus pumilacv*	
Epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (pavetannin D1)		
Epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin-(4β→8)-catechin		
Epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin-(4β→6)-catechin		
Epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin		
Epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→8)-catechin		
Epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin-(4β→8)-catechin		
Epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin		

Epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin		
Epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin-(4β→8)-epicatechin		
Epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→6)-catechin		
Epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin		
Epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin		
Procyanidins/propelargonidins		
Epiafzelechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (pavetannin C3)	*P. owariensis* stem bark	[216]
Epiafzelechin-(4β→8, 2β→O→7)-*ent*-afzelechin-(4β→8)-*ent*-epicatechin-(4α→8, 2α→O→7)-*ent*-catechin (pavetannin C4)		
Epiafzelechin-(4β→8, 2β→O→7)-*ent*-catechin-(4β→8)-*ent*-epicatechin-(4β→8, 2β→O→7)-*ent*-catechin (pavetannin C5)		
ent-Epiafzelechin-(4α→8, 2α→O→7)-epicatechin	*P. armeniaca* roots	[249]
ent-Epiafzelechin-(4α→8, 2α→O→7)-catechin.		
ent-Epiafzelechin-(4α→8, 2s→O→7)-epiafzelechin (mahuannin A)	*P. armeniaca* roots	[250]
	P. armeniaca branches	[251]
ent-Epiafzelechin-(4α→8, 2α→O→7)-epicatechin	*P. armeniaca* branches	[250]
ent-Epiafzelechin-(4α→8, 2α→O→7)-afzelechin	*P. armeniaca* roots	
ent-Epiafzelechin-(4α→8, 2α→O→7)-*ent*-afzelechin	*P. armeniaca* aerial parts	[252]
ent-Epiafzelechin-(4α→8, 2α→O→7)-afzelechin		
ent-Epiafzelechin-(4α→8, 2α→O→7)-*ent*-epicatechin	*P. armeniaca* roots	[250]
ent-Epiafzelechin-(4α→8, 2α→O→7)-*ent*-epiafzelechin		
ent-Epiafzelechin-(4α→8, 2α→O→7)-catechin		
3-*O*-*p*-Hydroxybenzoate-*ent*-epiafzelechin-(4α→8, 2α→O→7)-epiafzelechin		

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14 Alkaloids from the Medicinal Plants of Africa

Jean Duplex Wansi[a], *Krishna Prasad Devkota*[b], *Emmanuel Tshikalange*[c] *and Victor Kuete*[d]

[a]Department of Chemistry, University of Douala, Douala, Cameroon, [b]Molecular Targets Laboratory, Center for Cancer Research, Frederick National Laboratory for Cancer Research, Frederick, MD, [c]Department of Plant Science, University of Pretoria, Pretoria, South Africa, [d]Department of Biochemistry, University of Dschang, Dschang, Cameroon

14.1 Introduction

Alkaloids are one of the most diverse groups of secondary metabolites found in plants, marine organisms, and microorganisms. They have an array of structural types, biosynthetic pathways, and pharmacological activities. Sertuerner in 1806 laid the foundation of alkaloid chemistry with the report of the isolation of semi-purified morphine from opium. Since then, more than 20,000 alkaloids have been isolated from natural sources. "Alkaloid" simply means alkali-like; however, there are several definitions that describe the term alkaloid. The well-accepted definition is "alkaloids are naturally occurring, nitrogen-containing organic compounds with the exception of amino acids, peptides, purines and derivatives, amino sugars, and antibiotics." The nitrogen atom remains as part of a heterocyclic ring, with some exceptions. Based on biogenesis, alkaloids are broadly classified as the *true alkaloids* and the *pseudo-alkaloids*. The majority of alkaloids are true alkaloids, which are derived from α-amino acid precursors. Other alkaloids, such as terpenes and steroids, are called pseudo-alkaloids because a relatively late amination process occurs in a transamination reaction by donating a nitrogen atom from an amino acid source.

14.1.1 Occurrence

Alkaloids have been well known for their biological activity since the beginning of human civilization. They were used to cure disease and at the tip of weapons as toxins. Alkaloids are widely distributed in higher plants such as those of the

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families Apocyanaceae, Ranunculaceae, Papaveraceae, Solanaceae, and Rutaceae. They are distributed in different parts of the plants, examples being nicotine in the leaves, cinchonine and quinine in bark, strychnine and nibidine in seeds, and rawelfinine and glycyrrhizin in roots. On average, the maximum amount of alkaloids are contained in leaves, followed by fruit/seeds, root, and bark. In recent years, alkaloids have also been reported in lower plants, insects, marine organisms, and microorganisms. The occurrences of such compounds are listed in Tables 14.1 and 14.2.

14.1.2 Classification and Nomenclature

Alkaloids are classified on the basis of taxonomy, pharmacology, biosynthetic path, and chemical structure. The classification based on chemical structure is popular among the readers who need to cover a broad range of compounds. Based on chemical structure, alkaloids are broadly classified into heterocyclic and nonheterocyclic alkaloids.

Heterocyclic alkaloids are those which contain a nitrogen atom in their heterocyclic ring. Based on the type of ring, they are further classified as pyrrole, pyrrolidizine, pyridine, piperidine, quinoline, isoquinoline, norlupinane, indole alkaloids, and so on (Figure 14.1).

Nonheterocyclic alkaloids are also sometimes called proto-alkaloids or biological amines. These are less commonly found in nature. These molecules have a nitrogen atom which is not a part of any ring system. Examples of these include ephedrine, cathinone, and colchicine (Figure 14.2).

When there was no systematic nomenclature, alkaloids were named based on different criteria such as their source or physiological response, according to their discovery and prefixes. Alkaloids named based on their sources include ephedrine and papaverine; those named according to their physiological response include morphine and emetine.

14.2 Biosynthesis and Structural Diversity

The majority of the alkaloids are derived from L-amino acid precursors, either alone or in combination with a steroidal, secoiridoid (e.g., secologanin), or other terpenoid-type moiety. It has been demonstrated that, for the large variety of alkaloids, only a few building blocks are needed. Structural variety is generated by special enzyme systems in the plant and animal cells. As expected, amino acids play the most important role among the nitrogen-containing precursors (e.g., tryptophan, tyrosine, phenylalanine, lysine and arginine, histidine, anthranilic acid, and ornithine). Scheme 14.1 shows the amino acids (without specification of their absolute configuration), together with their corresponding alkaloids derivatives. In the case of rutaecarpine, tryptophan is required in addition to anthranilic acid as a second amino acid precursor. The remaining plant bases are derived by addition of

Table 14.1 Known Alkaloids Identified in African Plants

Compounds and Ring Type	Plants (Family)	Pharmacological Activities
Acridone		
Arborinine (**1**)	*Teclea gerrardii* I.Verd. (Rutaceae) [1]	Antimicrobial [2,3], anti-inflammatory, and antioxidant [4,5]
1,3-Dimethoxy-*N*-methylacridone (**2**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	Antimicrobial [1]
Melicopicine (**3**)	*T. gerrardii* I.Verd. (Toddaloideae: Rutaceae) [6]	Antiplasmodial [2]
1,2,3-Trimethoxy-*N*-methylacridone (**4**)	*T. gerrardii* I.Verd. (Toddaloideae: Rutaceae) [6]	–
1-Hydroxy-3-methoxy-10-methyl-9-acridone (**5**)	*Zanthoxylum leprieurii* Guill. et Perr. (Rutaceae) [4]	Cytotoxicity [4]
1,3-Dihydroxy-2-methoxy-10-methyl-9-acridone (**6**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	–
1,2-Dihydroxy-3-methoxy-10-methyl-9-acridone (**7**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	–
1-Hydroxy-2,3-dimethoxy-9-acridone (**8**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	–
Evoxanthine (**9**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	–
Acridone precursor		
Tecleanone (**10**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	–
Belladine		
Belladine (**11**)	*Nerine filifolia* Baker (Amaryllidaceae) [7]	–
Benzo[*c*]phenanthridine		
Chelerythrine (**12**)	*Zanthoxylum davyi* (I.Verd.) Waterm. (Rutaceae) [8], *Zanthoxylum lemairei* (Rutaceae) [9]	Cytotoxicity [10,11], antiparasitic [9]
Dihydrochelerythrine (**13**)	*Z. davyi* (I.Verd.) Waterm. (Rutaceae) [8]	Antimicrobial [12,13], cytotoxicity [14]
Bocconoline (**14**)	*Z. davyi* (I.Verd.) Waterm. (Rutaceae) [8]	Antiparasitic [15]
6-Methoxy-7-demethyldihydrochelerythrine (**15**)	*Z. davyi* (I.Verd.) Waterm. (Rutaceae) [8]	–
6-Hydroxydihydrochelerythrine (**16**)	*Z. davyi* (I.Verd.) Waterm. (Rutaceae) [8]	–

(*Continued*)

Table 14.1 (Continued)

Compounds and Ring Type	Plants (Family)	Pharmacological Activities
Benzophenanthridine		
6-Acetonyl-*N*-methyl-dihydrodecarine (**17**)	*Z. lem lemairei* (Rutaceae) [9]	Antiparasitic [9]
Nitidine (**18**)	*Z. lem lemairei* (Rutaceae) [9]	Antiparasitic [9]
Carbazole		
Heptaphylline (**19**)	*Clausena anista* (Willd.) (Rutaceae) [16]	Antimicrobial, cytotoxicity [17]
Girinimbine (**20**)	*C. anista* (Willd.) (Rutaceae) [16]	–
Ekeberginine (**21**)	*C. anista* (Willd.) (Rutaceae) [16]	–
3-Methylcarbazole (**22**)	*C. anista* (Willd.) (Rutaceae) [16]	–
Cherylline		
Cherylline (**23**)	*Crinum moorei* (Amaryllidaceae) [18], *Crinum macowanii* Baker (Amaryllidaceae) [19]	Enzyme inhibitor [20], protein affinity [21]
Crinine		
6-Hydroxycrinamine (**24**)	*Crinum delagoense* (Amaryllidaceae) [22]	Enzyme inhibitor [20]
Hamayne (**25**)	*C. delagoense* (Amaryllidaceae) [22], *C. macowanii* Baker (Amaryllidaceae) [19], *Brunsvigia josephinæ* (Red.) Ker-Gall. (Amaryllidaceae) [23]	Cytotoxicity [24], antiplasmodial [25], enzyme inhibitor [20]
Crinine (**26**)	*C. moorei* (Amaryllidaceae) [18], *C. macowanii* Baker (Amaryllidaceae) [19], *C. macowanii* Baker (Amaryllidaceae) [26], *Boophone disticha* L. Herb (Amaryllidaceae) [27], *Ammocharis tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	Cytotoxicity [29], enzyme inhibitor [20], protein affinity [21]
Powelline (**27**)	*C. moorei* (Amaryllidaceae) [18], *C. macowanii* Baker (Amaryllidaceae) [26], *A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	Protein affinity [21]
Crinamidine (**28**)	*C. moorei* (Amaryllidaceae) [18], *C. macowanii* Baker (Amaryllidaceae) [26]	Enzyme inhibitor [20]

Epibuphanisine (**29**)	*C. moorei* (Amaryllidaceae) [18]*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	Enzyme inhibitor [20], protein affinity [21]
Buphanisine (**30**)	*B. disticha* L. Herb (Amaryllidaceae) [27]	Binding activity [27]
Epivittatine (**31**)	*C. moorei* (Amaryllidaceae) [18]	Enzyme inhibitor [20], protein affinity [21]
3-*O*-Acetyl hamayne (**32**)	*Crinum bulbispermum* (Amaryllidaceae) [30], *B. josephinæ* (Red.) Ker-Gall. (Amaryllidaceae) [23]	Enzyme inhibitor [20]
Crinamine (**33**)	*C. bulbispermum* (Amaryllidaceae) [30], *B. josephinæ* (Red.) Ker-Gall. (Amaryllidaceae) [23]	Enzyme inhibitor [20]
Bulbispermine (**34**)	*C. bulbispermum* (Amaryllidaceae) [30], *C. macowanii* Baker (Amaryllidaceae) [19].	Cytotoxicity [24,25], enzyme inhibitor [31]
Maritidine (**35**)	*Cyrtanthus falcatus* (Amaryllidaceae) [32]	Protein affinity [21]
O-Methylmaritidine (**36**)	*C. falcatus* (Amaryllidaceae) [32]	Protein affinity [21]
11-*O*-Acetylambelline (**37**)	*N. filifolia* Baker (Amaryllidaceae) [7]	Enzyme inhibitor [33]
Buphanamine (**38**)	*B. disticha* L. Herb (Amaryllidaceae) [27]	Binding activity [27]
Distichamine (**39**)	*B. disticha* L. Herb (Amaryllidaceae) [27,34]	Antimicrobial [34], binding activity [27]
Buphanidrine (**40**)	*B. disticha* (L.f.) Herb (Amaryllidaceae) [35], *A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28], *C. macowanii* Baker (Amaryllidaceae), *B. disticha* L. Herb (Amaryllidaceae) [26,27], *B. disticha* (L.f.) Herb (Amaryllidaceae), [34]	Binding activity, antimicrobial [34,35]
Haemanthamine (**41**)	*Cyrtanthus elatus* (Jacq.) Traub (Amaryllidaceae) [36]	Antiplasmodial [37]
Haemanthidine (**42**)	*C. elatus* (Jacq.) Traub (Amaryllidaceae) [36]	Cytotoxicity [38]
6α-Hydroxycrinamidine (**43**)	*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	–
6α-Hydroxyundulatine (**44**)	*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	–
Flexinine (**45**)	*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	–

(*Continued*)

Table 14.1 (Continued)

Compounds and Ring Type	Plants (Family)	Pharmacological Activities
1,2β-Epoxyambelline (**46**)	*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	–
11-*O*-Acetyl-1,2β-epoxyambelline (**47**)	*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	–
Criwelline (**48**)	*C. delagoense* (Amaryllidaceae) [22]	–
Undulatine (**49**)	*C. moorei*, *N. filifolia* Baker (Amaryllidaceae) [7,18]	–
3-*O*-Acetyl-crinine or krepowine (**50**)	*C. moorei* (Amaryllidaceae), *C. macowanii* Baker (Amaryllidaceae) [26,18]	–
1-Epideacetyl-bowdensine (**51**)	*C. moorei* (Amaryllidaceae) [18]	–
Ambelline (**52**)	*N. filifolia* Baker (Amaryllidaceae) [7], *A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28], *B. josephinæ* (Red.) Ker-Gall. (Amaryllidaceae) [23]	–
6α-Hydroxybuphanidrine (**53**)	*N. filifolia* Baker (Amaryllidaceae) [7]	–
Dinitrogenous		
(+)-Plicamine (**54**)	*Cyrtanthus obliquus* (L.f.) Ait (Amaryllidaceae) [39]	–
(−)-Secoplicamine (**55**)	*C. obliquus* (L.f.) Ait (Amaryllidaceae) [39]	–
Erythrinaline		
(+)-11α-hydroxyerysotrine (**56**); (+)-erysodine (**57**), (+)-11α-hydroxyerysodine (**58**), (+)-erysotrine *N*-oxide (**59**)	*Erythrina lysistemon* Hutch. (Fabaceae) [40]	Antioxidant [40]
(+)-11α-Hydroxyerysotrine *N*-oxide (**60**), (+)-11β-methoxyerysotrine *N*-oxide [(+)-*O*-methylerythrartine *N*-oxide] (**61**), (+)-erythrabine (**62**), (+)-erysotramidine (**63**), (+)-erysotrine (**64**), (+)-erythristemine (**65**)	*E. lysistemon* Hutch. (Fabaceae) [40]	–

Furoquinoline		
Evoxine (**66**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	Antimicrobial [1]
7-(γ,γ-Dimethylallyloxy)-γ-fagarine (**67**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	Cytotoxicity [41]
Flindersiamine (**68**)	*Teclea natalensis* (Sond.) Engl., (Rutaceae) [42], *Teclea nobilis* (Rutaceae) [43]	Antibacterial [42], cytotoxicity [44,45]
Dictamnine (**69**)	*T. natalensis* (Sond.) Engl., (Rutaceae) [42]	Antimicrobial [3,46], cytotoxicity [47,48]
Kokusaginine (**70**)	*Teclea afzelii* Engl. (Rutaceae) [49,50]	Antimicrobial [49], antiplasmodial [50]
Nkolbisine (**71**)	*T. afzelii* Engl. (Rutaceae) [49,50]	Antimicrobial [49], antiplasmodial [50]
Skimmianine (**72**)	*T. nobilis* (Rutaceae) [43], *T. gerrardii* I.Verd. (Toddaloideae: Rutaceae) [6], *Teclea simplicifolia* Verdoorn (Rutaceae) [51]	Antiplasmodial [52], cytotoxicity [53]
Maculine (**73**)	*T. nobilis* [43], *T. afzelii* (Rutaceae) [50]	Antiplasmodial [50]
Tecleaverdoornine (**74**)	*T. afzelii* (Rutaceae) [50]	Antiplasmodial [50]
Montrifoline (**75**)	*T. afzelii* (Rutaceae) [50], *T. nobilis* (Rutaceae) [43], *T. simplicifolia* Verdoorn (Rutaceae) [51]	Antiplasmodial [50]
4,7-Dimethoxy-8-[(3-methyl-2-butenyl)oxy]furo [2,3−b]quinoline (**76**)	*T. natalensis* (Sond.) Engl., (Rutaceae) [42]	–
Galanthamine		
Galanthamine (**77**)	*C. elatus* (Jacq.) Traub (Amaryllidaceae) [36]	Binding activity [20]
Indole		
Geissolosimine (**78**), geissospermine (**79**), geissoschizoline (**80**), geissoschizone (**81**), vellosiminol (**82**)	*Geissospermum vellosii* (Apocynaceae) [54]	Antiplasmodial [54]
Palicoside (**83**)	*Strychnos usambarensis* Gilg [55].	Antifungal [56]
Akagerine (**84**)	*S. usambarensis* Gilg [55].	–
Serotobenine (**85**)	*Campylospermum flavum* (Schum.) *Farron.* (Ochnaceae) [57].	–

(*Continued*)

Table 14.1 (Continued)

Compounds and Ring Type	Plants (Family)	Pharmacological Activities
Indolopyridoquinazoline		
l-Hydroxyrutaecarpine (**86**)	*Vepris louisii* (Rutaceae) [58]	–
7,8-Dehydro-1-hydroxyrutaecarpine (**87**)	*V. louisii* (Rutaceae) [58]	–
Indolosesquiterpene		
Greenwayo-dendrin-3-one (**88**), 3-*O*-acetyl greenwayodendrin (**89**), *N*-acetylpolyveoline (**90**), polyveoline (**91**)	*Polyalthia suaveolens* (Annonaceae) [59]	Antiparasitic, enzyme inhibitor [59]
Isoquinoline		
Ancistrotectorine (**92**)	*Ancistrocladus guineënsis* Oliv. (Ancistrocladaceae) [60]	Antiparasitic [61]
Crotsparine (**93**)	*Antizoma miersiana* (Menispermaceae) [62], *Antizoma angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [63]	Antiplasmodial [64]
Bulbocapnine (**94**)	*A. miersiana* (Menispermaceae) [62], *A. angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [63]	Enzyme inhibitor [65]
Cycleanine (**95**)	*A. miersiana* (Menispermaceae) [62]	Cytotoxicity [66]
Dicentrine (**96**)	*A. miersiana* (Menispermaceae) [62]	Anthelmintic [67], antiprotozoal [68], cytotoxicity [69,70], vasodilatative [71]
Glaziovine or *N*-methylcrotsparine (**97**)	*A. angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [63]	Antiprotozoal [72], antiviral, cytotoxicity [73,74]
Pronuciferine (**98**)	*A. angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [63]	Cytotoxicity [74]
Salutaridine (**99**)	*A. angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [63]	Cytotoxicity [75]
Cissacapine (**100**)	*A. miersiana* (Menispermaceae), *A. angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [62,63]	–

Cycleaneonine (**101**); insulanoline (**102**)	*A. miersiana* (Menispermaceae) [62]	–
Insularine (**103**)	*A. miersiana* (Menispermaceae), *A. angustifolia* (Burch.) Miers ex Harv. (Menispermaceae) [62,63]	–
Lycorine		
Lycorine (**104**)	*C. delagoense* (Amaryllidaceae) [22], *C. moorei* (Amaryllidaceae) [18], *C. macowanii* Baker (Amaryllidaceae) [19,26]	Antimicrobial [26,76,77], anti-inflammatory [78], enzyme inhibitor [20]
1-*O*-Acetyllycorine (**105**)	*C. moorei* (Amaryllidaceae) [18]	Enzyme inhibitor [20], protein affinity [21]
Sternbergine (**106**)	*B. josephinæ* (Red.) Ker-Gall. (Amaryllidaceae) [23]	Antiplasmodial [25]
9-*O*-Demethylpluviine (**107**)	*A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	–
Mesembrine		
Mesembrine (**108**)	*Sceletium tortuosum* (Mesembryanthemaceae) [79]	Enzyme inhibitor, inhibitor of 5-HT reuptake [79]
Mesembrenone (**109**)	*S. tortuosum* (Mesembryanthemaceae) [79]	Inhibitor of 5-HT reuptake [79]
Mesembrenol (**110**)	*S. tortuosum* (Mesembryanthemaceae) [79]	Inhibitor of 5-HT reuptake [79]
Monoterpenoid indole		
Δ^{14}-Vincanol (**111**)	*Voacanga africana* Stapf. (Apocyanaceae) [80]	–
O-Methyl-16-epi-Δ^{14}-vincanol (**112**)	*V. africana* Stapf. (Apocyanaceae) [80]	–
Δ^{14}-Vincamone (**113**)	*V. africana* Stapf. (Apocyanaceae) [80]	–
***N*-acetylnoraporphine**		
N-Acetylanonaine (**114**)	*Papaver aculeatum* (Papaveraceae) [81]	PAF inhibitor [82,83]
Naphthylisoquinoline		
Ancistrocladinium A (**115**), 5′-*O*-demethylhamatine (**116**), 5′-*O*-demethylhamatinine (**117**), 6-*O*-demethylancistroealaine A (**118**), 6,5′-*O,O*-didemethylancistroealaine A (**119**), 5-epi-6-*O*-methylancistrobertsonine A (**120**), 5-epi-4′-*O*-demethylancistrobertsonine C (**121**)	*Ancistrocladus congolensis* (Ancistrocladaceae) [84]	– Antiparasitic [84]

(*Continued*)

Table 14.1 (Continued)

Compounds and Ring Type	Plants (Family)	Pharmacological Activities
Phenanthridone		
Narciprimine (**122**)	*Cyrtanthus contractus* (Amaryllidaceae) [85]	Enzyme inhibitor [85]
Piperidine		
┐-Coniceine (**123**), coniine (**124**), methylconiine (**125**), conhydrine (**126**)	*Conium maculatum* (Umbelliferae) [86,87]	–
Pyrrolizidine		
7-Angelylplatynecine (**127**)	*Senecio chrysocoma* (Asteraceae) [88]	–
7-*O*-Senecioylplatynecine (**128**)	*Solanecio mannii* (Hook. f.) C. Jeffrey (Asteraceae) [89]	–
7-*O*-Trigloylplatynecine (**129**)	*S. mannii* (Hook. f.) C. Jeffrey (Asteraceae) [89]	–
9-Angelylplatynecine (**130**)	*S. chrysocoma* (Asteraceae) [88]	–
Acetylseneciphylline (**131**)	*Senecio pterophorus* (Asteraceae) [90]	–
Bulgarsenine (**132**), eruciflorine (**133**), erucifoline (**134**) integerrimine (**135**), jacobine (**136**), jaconine (**137**)	*Solanecio tuberosus* (Sch. Bip. ex A. Rich.) C. Jeffrey var. *tuberosus* (Asteraceae) [89]	–
Madurensine (**138**)	*Crotalaria capensis* (Fabaceae) [91]	–
Neoplatyphylline (**139**), retroisosenine (**140**), retrosine (**141**)	*S. tuberosus* (Sch. Bip. ex A. Rich.) C. Jeffrey var. *tuberosus* (Asteraceae) [89]	–
Sarracine (**142**)	*S. chrysocoma* (Asteraceae) [88]	–
Senecionine (**143**)	*S. pterophorus* (Asteraceae) [90], *Solanecio angulatus* (Vahl) C. Jeffrey, and *S. tuberosus* (Sch. Bip. ex A. Rich.) C. Jeffrey var. *tuberosus* (Asteraceae) [89]	–
Seneciphylline (**144**)	*S. tuberosus* (Sch. Bip. ex A. Rich.) C. Jeffrey var. *tuberosus* (Asteraceae) [89], *S. pterophorus* (Asteraceae) [90]	Receptor binding activity [92]
Spartioidine (**145**)	*S. pterophorus* (Asteraceae) [90]	–

Quinoline		
Cyclomegistine (**146**)	*T. gerrardii* I.Verd. (Toddaloideae: Rutaceae) [6]	–
Edulinine (**147**)	*T. nobilis* (Rutaceae) [43], *T. simplicifolia* Verdoorn (Rutaceae) [51]	Anticonvulsant [93]
Quinolinone		
4-Methoxy-1-methyl-2(1H)-quinolinone (**148**)	*Z. davyi* (I.Verd.) Waterm. (Rutaceae) [8]	Antimicrobial [94,95]
Quinolizidine		
3-Hydroxylupanine (**149**), calpumine (**150**), calpurmenine (**151**), calpurmenine pyrrolecarboxylic acid ester (**152**), epilupinine (**153**), lupinine (**154**), virgiline (**155**), virgiline pyrrolecarboxylic acid ester (**156**)	*Calpunia aurea* subsp. *aureus* (Leguminosae) [96]	–
Quinolone		
Isoplatydesmine (**157**)	*T. nobilis* (Rutaceae) [43], *T. simplicifolia* Verdoorn (Rutaceae) [43]	–
Ribalinine (**158**)	*T. nobilis* (Rutaceae), [43], *T. simplicifolia* Verdoorn (Rutaceae) [51]	–
Secobenzo[*c*]phenantridine		
10-*O*-Demethyl-17-*O*-methylisoarnottianamide (**159**)	*Z. lem lemairei* (Rutaceae) [9]	Antiparasitic [9]
10-*O*-Demethyl-12-*O*-methyl isoarnottianamide (**160**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	–
Tazettine		
Tazettine (**161**)	*C. falcatus* (Amaryllidaceae) [32], *C. obliquus* (L.f.) Ait (Amaryllidaceae) [39]	Enzyme inhibitor [20], protein affinity [21]
Triterpenoid		
Buxaminol A (**162**)	*Buxus natalensis* (Oliv.) Hutch (Buxaceae) [97]	Enzyme inhibitor [97]

5-HT, hydroxytryptamine; PAF, platelet-activating factor.

Table 14.2 New Alkaloids Isolated in African Plants

Compounds and Ring Type	Plants	Area of Plant Collection	Plant Part	Physical Properties
2-indolinone				
Isothomandersine (**163**), thomandersine (**164**)	*Thomandersia laurifolia* (Acanthaceae) [98]	Cameroon	Leaves	–
2-quinolinone				
N-Methylpreskimmianine (**165**)	*V. louisii* (Rutaceae) [58]	Cameroon	Stem bark	mp 88–89°C [58]
Veprisine or 7,8-dimethoxy-*N*-methylflindersine (**166**)	*V. louisii* (Rutaceae) [58]	Cameroon	Stem bark	mp 89–90°C [58]
2-quinolone				
Veprisilone (**167**)	*V. louisii* (Rutaceae) [58]	Cameroon	Trunk bark	mp 135–136°C [58]
Acridone				
Helebelicine A or 3-hydroxy-1,4-dimethoxy-10-methyl-9-acridone (**168**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	Cameroon	Fruits	mp 122–123°C [4]
Helebelicine B or 3-hydroxy-1,2-dimethoxy-10-methyl-9-acridone (**169**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	Cameroon	Fruits	Yellow amorphous powder [4]
Oriciacridone A (**170**)	*Oriciopsis glaberrima* Engl. (Rutaceae) [99]	Cameroon	Stem bark	mp 249°C; $[\alpha]^{25}_{D}$ −45.7° (*c* 0.075, DMSO) [99]
Oriciacridone B (**171**)	*O. glaberrima* Engl. (Rutaceae) [99]	Cameroon	Stem bark	mp 309°C; $[\alpha]^{25}_{D}$ −85.3° (*c* 0.075, DMSO) [99]
Tegerrardin A (**172**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	South Africa	Stem bark	mp 158–159°C [1]
Tegerrardin B (**173**)	*T. gerrardii* I.Verd. (Rutaceae) [1]	South Africa	Stem bark	Pale yellow gum [1]
Toddaliopsins A (**174**), B (**175**), C (**176**), and D (**177**)	*Toddaliopsis bremekampii* I.Verd. (Rutaceae) [100]	South Africa	Leaves	Yellow glass [100]

Aporphine				
6a,7-Dehydro-1,2-dimethoxy-7-hydroxy-*N*-methylaporphine (**178**)	*Enantia chlorantha* (Apocyanaceae) [101]	Cameroon	Stem bark	mp 258−260°C [101]
6a,7-Dehydro-1,2-dimethoxy-7-hydroxyaporphine (**179**)	*E. chlorantha* (Apocyanaceae) [101]	Cameroon	Stem bark	mp 256−257°C [101]
Aristolactam				
Piperumbellactams A (**180**), B (**181**), C (**182**), and D (**183**)	*Piper umbellatum* (Piperaceae) [102]	Cameroon	Branches	–
Belladine				
N-Demethylbelladine (**184**)	*N. filifolia* Baker (Amaryllidaceae) [7]	South Africa	Bulbs	–
Benzophenanthridine				
Buesgeniine (**185**)	*Zanthoxylum buesgenii* (Rutaceae) [103]	Cameroon	Stem bark	mp 141−142°C [103]
Turraeanthin B (**186**)	*Turraenthus africanus* (Meliaceae) [104]	Cameroon	Stem bark	mp 270−272°C [104]
Carbazole				
Atanisatin (**187**)	*C. anista* (Rutaceae) [105]	Nigeria	Stems	–
Clausamtin (**188**)	*C. anista* (Rutaceae) [105]	Nigeria	Roots	mp 154−156°C [105]
O-Demethylmurrayanine or 3-formyl-1-hydroxycarbazole (**189**)	*C. anista* (Willd.) (Rutaceae) [16]	Cameroon	Stem bark and roots	mp 74−75°C [16]
Crinine				
3-[4'-(8'-Aminoethyl)phenoxy] bulbispermine (**190**)	*C. moorei* (Amaryllidaceae) [19].	South Africa	Whole plant	$[\alpha]^{29}_{D}$ +53.3° (*c* 0.045, $CHCl_3$) [18]
6α-Methoxybuphanidrine (**191**)	*N. filifolia* Baker (Amaryllidaceae) [7]	South Africa	Bulbs	$[\alpha]^{20}_{D}$ +34.6° (*c* 0.13, $CHCl_3$) [7]
Delagoenine (**192**)	*C. delagoense* (Amaryllidaceae) [22]	South Africa	Bulbs	mp 120−122°C; $[\alpha]^{20}_{D}$ +34.2° (*c* 0.48, MeOH) [22]

(*Continued*)

Table 14.2 (Continued)

Compounds and Ring Type	Plants	Area of Plant Collection	Plant Part	Physical Properties
Delagoensine (**193**)	*C. delagoense* (Amaryllidaceae) [22]	South Africa	Bulbs	mp 132−134°C; $[\alpha]^{20}_{D}$ +28.2° (*c* 0.475, MeOH) [22]
Filifoline (**194**)	*N. filifolia* Baker (Amaryllidaceae) [7]	South Africa	Bulbs	mp 191−193°C; $[\alpha]^{20}_{D}$ +12° (*c* 0.85, MeOH) [7]
Josephinine (**195**)	*B. josephinæ* (Red.) Ker-Gall. (Amaryllidaceae) [23]	South Africa	Bulbs	mp 230−232°C; $[\alpha]^{22}_{D}$ −30.9° (*c* 0.5, EtOH) [23]
Macowine (**196**)	*C. macowanii* Baker (Amaryllidaceae) [26]	South Africa	Bulbs	mp 115−117°C; $[\alpha]^{20}_{D}$ −34° (*c* 0.235, $CHCl_3$)
Dinitrogenous				
Obliquine (**197**)	*C. obliquus* (L.f.) Ait (Amaryllidaceae) [39]	South Africa	Bulbs	mp 136−139°C; $[\alpha]^{20}_{D}$ +20.5° (*c* 0.6, MeOH) [39]
Erythrinaline				
(+)-11β-Hydroxyerysotrine (**198**)	*E. lysistemon* Hutch. (Fabaceae) [40]	Botswana	Flowers and pods	Yellowish crystals [40]
(+)-11β-Hydroxyerysotrine *N*-oxide (**199**)	*E. lysistemon* Hutch. (Fabaceae) [40]	Botswana	Flowers and pods	$[\alpha]_D$ +25° (*c* 0.04, MeOH) [40]
(+)-11β-Methoxyerysotramidine (**200**)	*E. lysistemon* Hutch. (Fabaceae) [40]	Botswana	Flowers	$[\alpha]_D$ +60° (*c* 0.11, MeOH) [40]
(+)-11β-Hydroxyerysotramidine (**201**)	*E. lysistemon* Hutch. (Fabaceae) [40]	Botswana	Flowers and pods	$[\alpha]_D$ +100° (*c* 0.14, MeOH) [40]
Furoquinoline				
Isohaplopine 3′,3′-dimethylallylether (**202**)	*T. simplicifolia* Verdoorn (Rutaceae) [51]	Ethiopia	Leaves	mp 118−119°C [51]

Isohaplopine or 8-hydroxy-4,7-dimethoxyfuroquinoline (**230**)	*T. simplicifolia* Verdoorn (Rutaceae) [51]	Ethiopia	Leaves	mp 121−123°C [51]
Nobiline (**204**)	*T. nobilis* (Rutaceae) [43]	Ethiopia	Leaves and fruits	mp 117−119°C [43]
Quinosuaveoline A (**205**)	*Oricia suaveolens* (Engl.) Verd. (Rutaceae) [44].	Cameroon	Stems and leaves	Yellow amorphous powder [44]
Quinosuaveoline B (**206**)	*O. suaveolens* (Engl.) Verd. (Rutaceae) [44].	Cameroon	Stems and leaves	Colorless amorphous powder [44]
Tecleanatalensine A (**207**)	*T. natalensis* (Sond.) Engl. (Rutaceae) [42]	South Africa	Leaves	Pale yellow gum $[\alpha]_D$ +11° (*c* 0.19, CH_2Cl_2) [42]
Tecleanatalensine B (**208**)	*T. natalensis* (Sond.) Engl. (Rutaceae) [42]	South Africa	Leaves	Pale yellow gum [42]
Guanidine				
Millettonine (**209**)	*Millettia laurentii* (Leguminosae) [106]	Cameroon	Stem bark	mp 170°C; $[\alpha]^{21}_D$ +46.2° (*c* 0.71, MeOH) [106]
Millaurine A (**210**)	*M. laurentii* De Wild. (Fabaceae) [107]	Cameroon	Seeds	mp 136−137°C; $[\alpha]^{25}_D$ +46.7° (*c* 0.2, MeOH) [107]
Indole				
Flavumindole (**211**)	*C. flavum* (Schum.) *Farron* (Ochnaceae) [57]	Cameroon	Stem bark	mp 157−158°C; $[\alpha]^{20}_D$ +32° (*c* 0.05, MeOH) [57]
Indoloquinazoline				
Orisuaveoline A (**212**)	*O. suaveolens* (Engl.) Verd. (Rutaceae) [44]	Cameroon	Stems and leaves	Yellow amorphous powder [44]
Orisuaveoline B (**213**)	*O. suaveolens* (Engl.) Verd. (Rutaceae) [44]	Cameroon	Stems and leaves	Yellow amorphous powder [44]

(*Continued*)

Table 14.2 (Continued)

Compounds and Ring Type	Plants	Area of Plant Collection	Plant Part	Physical Properties
Indolosesquiterpene				
Polysin (**214**)	*P. suaveolens* (Annonaceae) [59]	Cameroon	Stem bark	–
Isoquinoline				
Ancistroguineine A (**215**)	*A. guineëensis* Oliv. (Ancistrocladaceae) [60]	South Africa	Leaves	mp 202–204°C; $[\alpha]^{25}_{D}$ +191.4° (*c* 0.52, $CHCl_3$) [60]
Ancistroguineine B (**216**)	*A. guineëensis* Oliv. (Ancistrocladaceae) [60]	South Africa	Leaves	$[\alpha]^{25}_{D}$ +141.2° (*c* 0.04, $CHCl_3$) [60]
Lycorine				
1,2-*O*-Diacetylzephyranthine (**217**)	*C. elatus* (Jacq.) Traub (Amaryllidaceae) [36]	South Africa	Bulbs	mp 157–159°C; $[\alpha]^{20}_{D}$ −13.5° (*c* 0.20, MeOH) [36]
Zephyranthine (**218**)	*C. elatus* (Jacq.) Traub (Amaryllidaceae) [36], *A. tinneana* (Kotschy & Peyr.) Milne-Redh. & Schweick. (Amaryllidaceae) [28]	South Africa	Bulbs	mp 115–118°C; $[\alpha]^{20}_{D}$ −30.6° (*c* 0.56, MeOH) [36]
Monoindole				
12-Methoxyicajine (**219**)	*Strychnos icaja* (Loganiaceae) [77]	Cameroon	Stem bark	White amorphous powder [77]
15-Hydroxyvomicine (**220**)	*S. icaja* [77]	Cameroon	Stem bark	White amorphous powder [77]
Phenanthridine				
Mooreine (**221**)	*C. moorei* (Amaryllidaceae) [18].	South Africa	Whole plant	Amorphous [18]
Piperidine				
N-Methylpseudoconhydrine (**222**)	*C. maculatum* (Umbelliferae) [87]	South Africa	Whole plant	mp 157°C; $[\alpha]^{25}_{D}$ +25° (MeOH) [87]

Pyrrolizidine				
Globiferine (**223**)	*Crotalaria globifera* E. Mey. (Leguminosae) [108]	South Africa	Seeds	mp 156–129°C; $[\alpha]^{18}_{D}$ −8.6° (*c* 0.0232, $CHCl_3$) [108]
Isorosmarinine (**224**)	*S. pterophorus* (Asteraceae) [90]	South Africa	–	mp 137–142°C [90]
Merenskine *N*-oxide (**225**)	*Senecio latifolius* DC (Asteraceae) [109]	South Africa	Whole plant	mp 146°C; $[\alpha]^{20}_{D}$ +26.1° (*c* 0.33, EtOH) [109]
Neosarracine (**226**)	*S. chrysocoma* (Asteraceae) [88]	South Africa	–	–
trans-Anacrotine (**227**)	*C. capensis* (Fabaceae) [91]	South Africa	Seeds	$[\alpha]^{22}_{D}$ +11° (*c* 1.7, $CHCl_3$) [91]
Pyrrolizidine (macrocyclic diesters)				
Oxypterine (**228**)	*Lotononis oxyptera* (Fabaceae) [110]	South Africa	Leaves and seeds	mp 127–129°C; $[\alpha]^{22}_{D}$ +19.6° (*c* 2.6, $CHCl_3$) [110]
Quinolinone				
2,6-Dihydro-9-methoxy2,2,6-trimethyl-5H-pyrano[3,2c]quinolin-5-one (**229**)	*Agathosma* sp. (Rutaceae) [111]	South Africa	Aerial part	Yellow oil [111]
4,6-Dimethyl-1-methyl-2-(1H)-quinolinone (**230**)	*Agathosma* sp. (Rutaceae) [111]	South Africa	Aerial parts	mp 143–144°C [111]
N-Methylswietenidine-B or 1-methyl-3,4-dimethoxy-2-quinolone (**231**)	*C. anista* (Willd.) (Rutaceae) [16]	Cameroon	Stem bark and roots	mp 237–239°C [16]
Quinolizidine				
13-*O*-(2′-Pyrrolylcarbonyl)calpurmenine (**232**)	*Calpurnia aurea* (Ait.) Benth. subsp. *sylvatica* (Leguminosae) [112]	South Africa	Leaves	–
3β,4α,13α-Trihydroxylupanine (**233**), calpaurine or 3β,4α-dihroxy 13α-*O*-(2′-pyrrolylcarbonyl) lupanine (**234**)	*C. aurea* subsp. *aureus* (Leguminosae) [96]	Ethiopia	Leaves	–
Calpurmenine (**235**)	*Calpurnia aurea* (Ait.) Benth. subsp. *sylvatica* (Leguminosae) [112]	South Africa	Leaves	–

(*Continued*)

Table 14.2 (Continued)

Compounds and Ring Type	Plants	Area of Plant Collection	Plant Part	Physical Properties
Secobenzo[*c*]phenanthridine				
10-*O*-Demethyl-12-*O*-methylarnottianamide (**236**)	*Z. leprieurii* Guill. et Perr. (Rutaceae) [4]	Cameroon	Roots	Brown amorphous powder [4]
Turraeanthin A (**237**)	*T. africanus* (Meliaceae) [104]	Cameroon	Stem bark	mp 237−239°C [104]
Tazettine				
8α-Ethoxyprecriwelline (**238**)	*C. bulbispermum* (Amaryllidaceae) [30]	South Africa	Whole plant	Amorphous $[\alpha]^{28}_{D}$ +116.6° (*c* 0.06, $CHCl_3$) [18]
N-Desmethyl 8α-ethoxy pretazettine (**239**)	*C. bulbispermum* (Amaryllidaceae) [30]	South Africa	Whole plant	Amorphous $[\alpha]^{28}_{D}$ +160.63° (*c* 0.09, $CHCl_3$) [18]
N-Desmethyl-8β-ethoxy pretazettine (**240**)	*C. bulbispermum* (Amaryllidaceae) [30]	South Africa	Whole plant	Amorphous $[\alpha]^{28}_{D}$ +34° (*c* 0.14, $CHCl_3$) [18]
Triterpenoid				
O(2)-Natafuranamine (**241**)	*B. natalensis* (Oliv.) Hutch (Buxaceae) [97]	South Africa	Stem bark	Yellow gum $[\alpha]^{20}_{D}$ +5.3° (*c* 0.75, $CHCl_3$) [97]
O(10)-Natafuranamine (**242**)	*B. natalensis* (Oliv.) Hutch (Buxaceae) [97]	South Africa	Stem bark	Yellow solid $[\alpha]^{20}_{D}$ +20.7° (*c* 0.75, $CHCl_3$) [97]
31-Demethylbuxaminol A (**243**)	*B. natalensis* (Oliv.) Hutch (Buxaceae) [97]	South Africa	Stem bark	While amorphous powder $[\alpha]^{20}_{D}$ +59.4° (*c* 0.09, $CHCl_3$) [97]
Cyclonataminol (**244**)	*B. natalensis* (Oliv.) Hutch (Buxaceae) [97]	South Africa	Stem bark	Yellow amorphous powder $[\alpha]^{20}_{D}$ −70° (*c* 0.05, $CHCl_3$) [97]

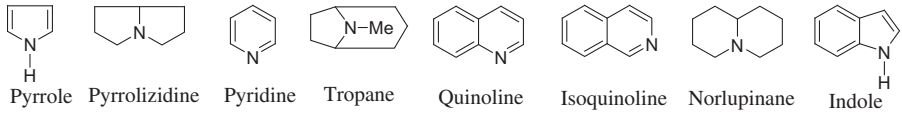


Figure 14.1 Different classes of heterocyclic alkaloids.

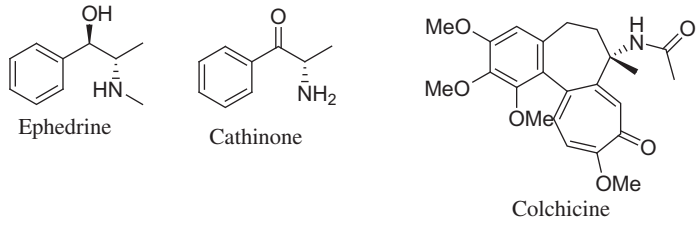
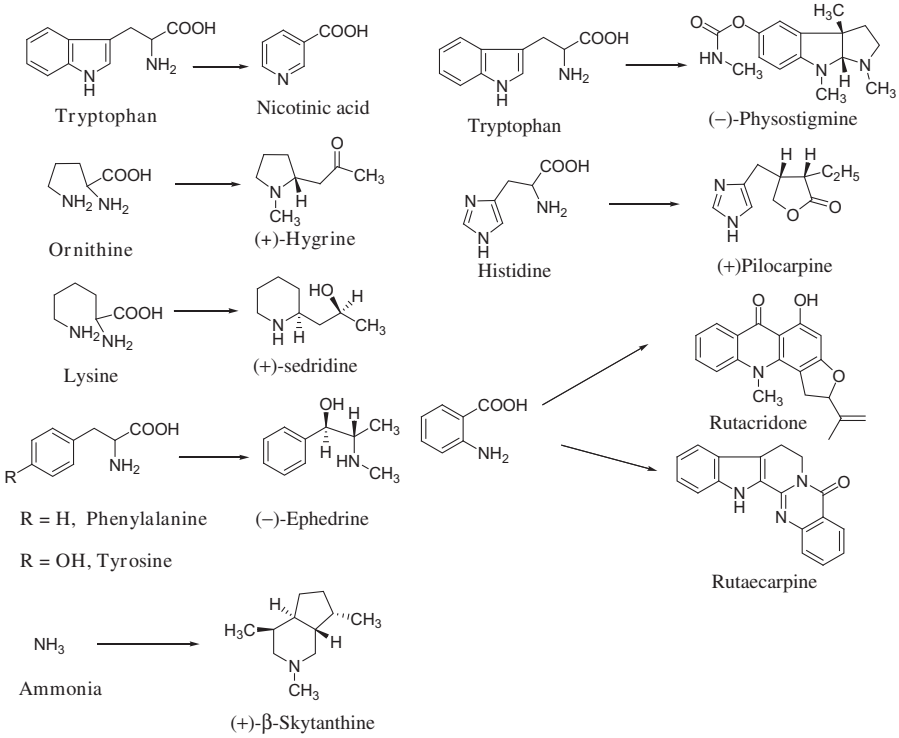


Figure 14.2 Nonheterocyclic alkaloids.



Scheme 14.1 Example of alkaloids and their corresponding amino acid precursors.

ammoniac or alkylamine to nonbasic precursors. Among the nitrogen building blocks of alkaloids are terpenoids, fatty acids, and cinnamic acid derivatives. Small carbon fragments, such as methyl acetate, and carbonate complete the peripheral functionalities. Carbon−carbon bond formation, oxidation, and reduction reactions are typical enzyme reactions.

14.3 Detection of Alkaloids

Isolation of alkaloids from a plant is always a difficult process due to the fact that an alkaloid-bearing plant generally contains a complex mixture of several alkaloids with other secondary metabolites. There are several methods to detect the presence of alkaloids in plant material. The best way to detect an alkaloid is to test with Dragendorff's reagent [solution A: bismuth nitrate (0.17 g) in AcOH (2 mL) and H_2O (8 mL); solution B: KI (4 g) in AcOH (10 mL) and H_2O (20 mL); mix solutions A and B and dilute to 100 mL with H_2O], the Mayer (cream color) test, the Marquis (conc. HCHO) test, and the Erdmann (conc. HNO_3) test. Since alkaloids are basic in nature, the extraction of plant material with acidic and alkaline solvents is very common. The extraction is basically done with organic solvents, organic acid such as acetic acid at pH 3−4 and an organic base such as ammonium hydroxide at pH 9−10. For quick detection of alkaloid in plant extract, 1 mg plant extract can be added to 1 mL methanol, then a 2 mL portion of extract is mixed with 1% HCl, then steamed, and 1 mL filtrate is further mixed with six drops of Mayer's reagents/Dragendorff reagent. A creamish or orange precipitate indicates the presence of alkaloids.

14.4 Pharmacological Activity of Alkaloids Isolated from African Medicinal Plants

All compounds described in this section were identified in African medicinal plants; their origin is summarized in Tables 14.1 and 14.2, while the chemical structures are found in Figures 14.3 and 14.4. They have displayed various types of biological activities, which are also reviewed below.

14.4.1 Antimicrobial Activity of Alkaloids Identified in African Medicinal Plants

Acridone alkaloids: Melicopicine (**3**) showed antiplasmodial activity against *Plasmodium falciparum*, with an IC_{50} value of 100 μg/mL [2]. The antimicrobial activity of arborinine (**1**) was reported against *Escherichia coli* and *Salmonella typhimurium* (minimal inhibitory concentration (MIC) of 128 μg/mL) [3]. Compound **1** was also active against *P. falciparum* strain HB3 (IC_{50} of 3.85 μM) [2], and displayed moderate antiplasmodial activity against the CQS D10 strain of *P. falciparum*, with IC_{50} values of 12.3 μM [1]. Tegerrardin A (**172**) and 1,3-dimethoxy-*N*-methylacridone (**2**) were

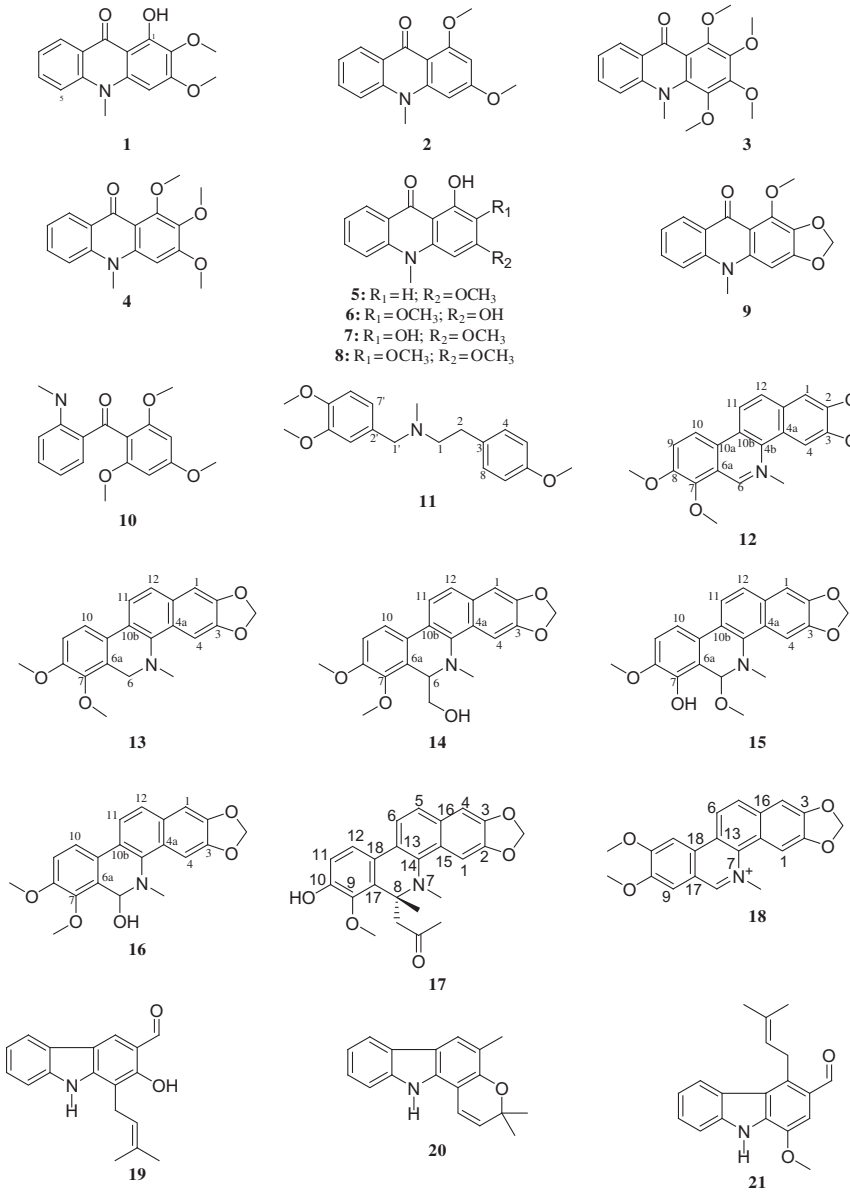
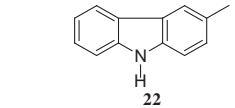


Figure 14.3 Known alkaloids identified in African plants: arborinine (**1**); 1,3-dimethoxy-*N*-methylacridone (**2**); melicopicine (**3**); 1,2,3-trimethoxy-*N*-methylacridone (**4**); 1-hydroxy-3-methoxy-10-methyl-9-acridone (**5**); 1,3-dihydroxy-2-methoxy-10-methyl-9-acridone (**6**); 1,2-dihydroxy-3-methoxy-10-methyl-9-acridone (**7**); 1-hydroxy-2,3-dimethoxy-10-methyl-9-acridone (**8**); evoxanthine (**9**); tecleanone (**10**); belladine (**11**); chelerythrine (**12**); dihydrochelerythrine (**13**); bocconoline (**14**); 6-methoxy-7-demethyldihydrochelerythrine



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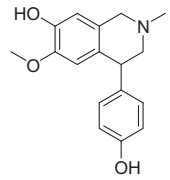

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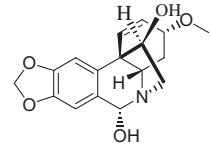

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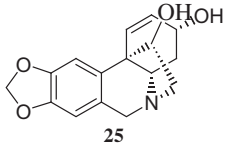

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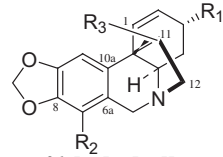
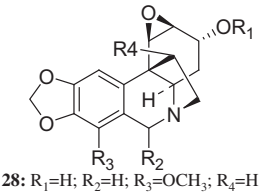
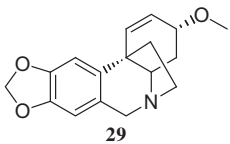


26: R_1=R_2=R_3=H
27: R_1=R_3=H; R_2=OCH_3
30: R_1=CH_3; R_2= R_3=H
40: R_1=CH_3; R_2=OCH_3; R_3=H
52: R_1=CH_3; R_2=OCH_3; R_3=OH



28: R_1=H; R_2=H; R_3=OCH_3; R_4=H
43: R_1=H; R_2=OH; R_3=OCH_3; R_4=H
44: R_1=CH_3; R_2=OH; R_3=OCH_3; R_4=H
45: R_1=H; R_2= H; R_3=H ; R_4= H
46: R_1=CH_3; R_2=OCH_3; R_3=OCH_3; R_4=OCH_3
47: R_1=CH_3; R_2=H; R_3=OCH_3; R_4= OAc
49: R_1=CH; R_2=H; R_3=OCH_3; R_4=H



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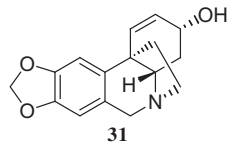

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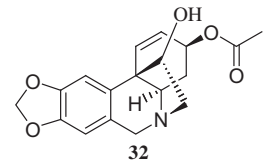

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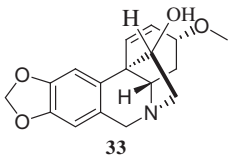

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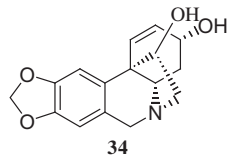

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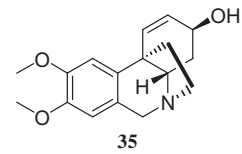

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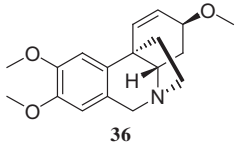

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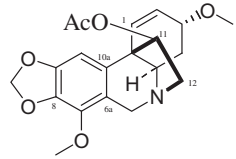

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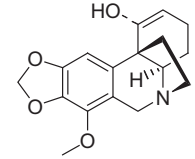
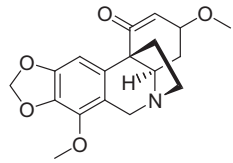


38

Figure 14.3 (Continued)

◀ (**15**); 6-hydroxydihydrochelerythrine (**16**); 6-acetonyl-*N*-methyl-dihydrodecarine (**17**); nitidine (**18**); heptaphylline (**19**); girinimbine (**20**); ekeberginine (**21**); 3-methylcarbazole (**22**); cherylline (**23**); 6-hydroxycrinamine (**24**); hamayne (**25**); crinine (**26**); powelline (**27**); crinamidine (**28**); epibuphanisine (**29**); buphanisine (**30**); epivittatine (**31**); 3-*O*-acetyl hamayne (**32**); crinamine (**33**); bulbispermine (**34**); maritidine (**35**); *O*-methylmaritidine (**36**); 11-*O*-acetylambelline (**37**); buphanamine (**38**); distichamine (**39**); buphanidrine (**40**);



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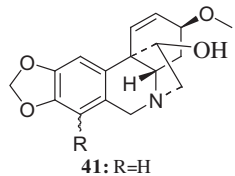

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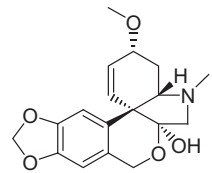
42: R=OH



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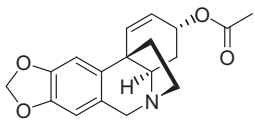

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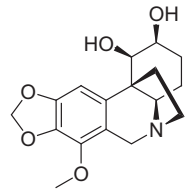

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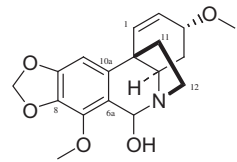

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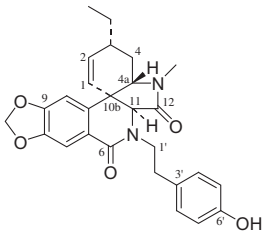

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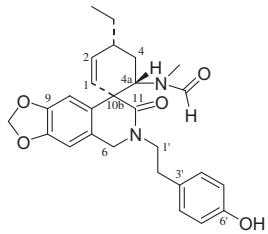

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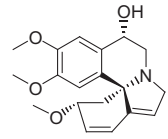

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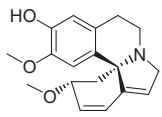

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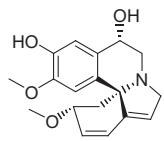

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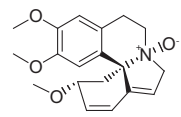

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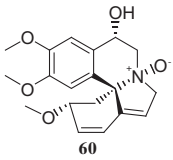

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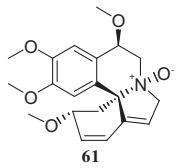

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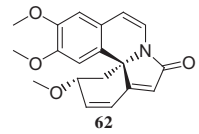


62

Figure 14.3 (Continued)

◀ haemanthamine (**41**); haemanthidine (**42**); 6α-hydroxycrinamidine (**43**); 6α-hydroxyundulatine (**44**); flexinine (**45**); 1,2β-epoxyambelline (**46**); 11-*O*-acetyl-1,2β-epoxyambelline (**47**); criwelline (**48**); undulatine (**49**); 3-*O*-acetyl-crinine (**50**); 1-epideacetyl-bowdensine (**51**); ambelline (**52**); 6α-hydroxybuphanidrine (**53**); (+)-plicamine (**54**); (−)-secoplicamine (**55**); (+)-11α-hydroxyerysotrine (**56**); (+)-erysodine (**57**); (+)-11α-hydroxyerysodine (**58**); (+)-erysotrine *N*-oxide (**59**);

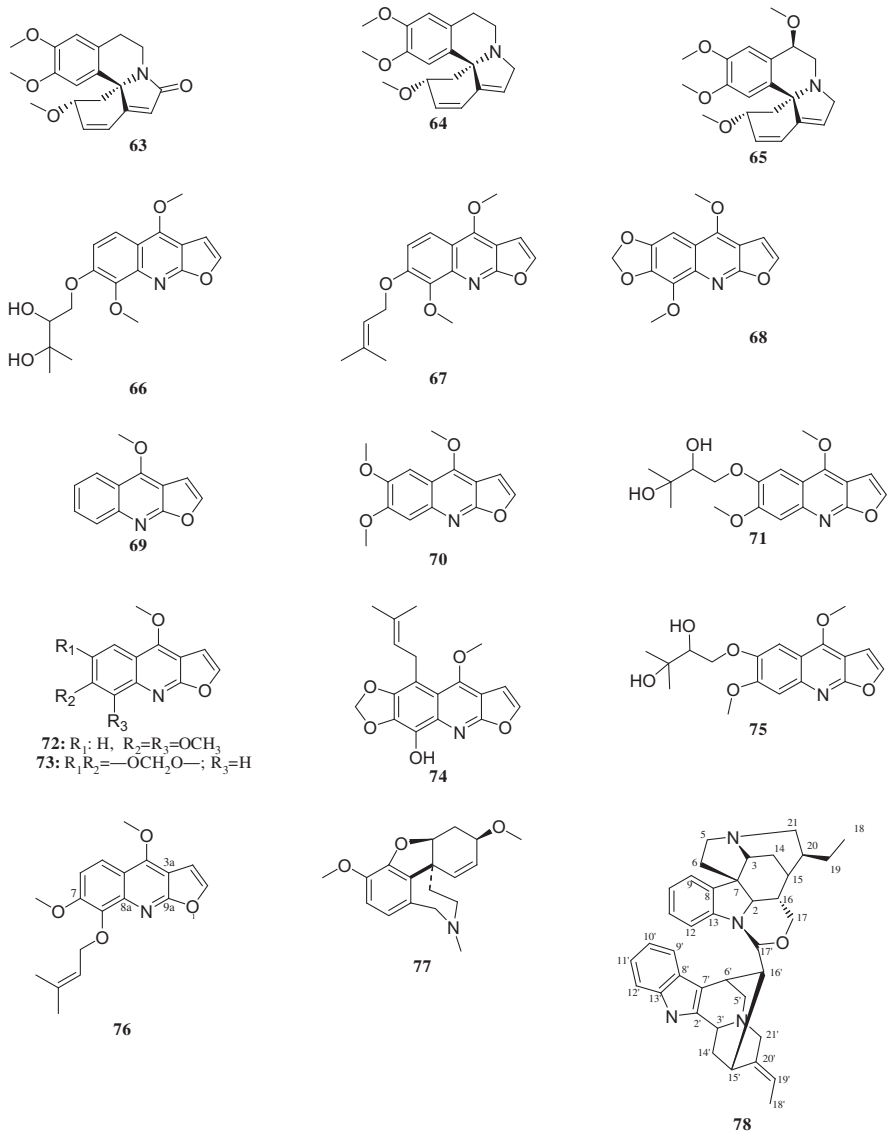
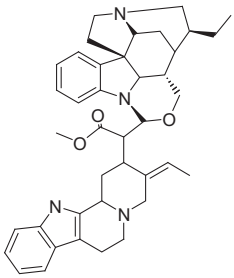


Figure 14.3 (Continued)

◀ (+)-11α-hydroxyerysotrine *N*-oxide (**60**); (+)-11β-methoxyerysotrine *N*-oxide [(+)-*O*-methylerythrartine-*N*-oxide] (**61**); (+)-erythrabine (**62**); (+)-erysotramidine (**63**); (+)-erysotrine (**64**), (+)-erythristemine (**65**); evoxine (**66**); 7-(γ,γ-dimethylallyloxy)-γ-fagarine (**67**); flindersiamine (**68**); dictamnine (**69**); kokusaginine (**70**); nkolbisine (**71**); skimmianine (**72**); maculine (**73**); tecleaverdoornine (**74**); montrifoline (**75**); 4,7-dimethoxy-



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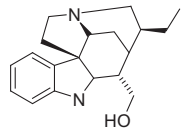

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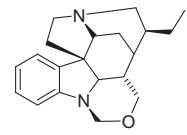

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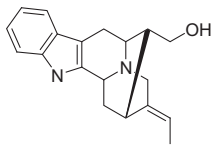

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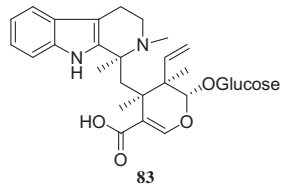

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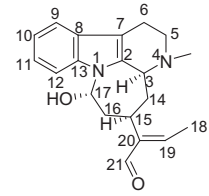

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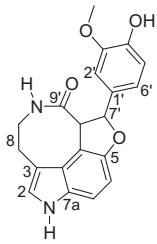

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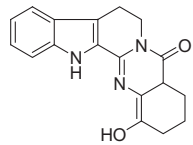

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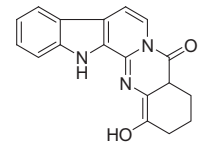

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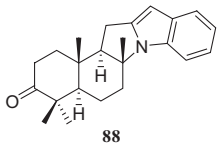

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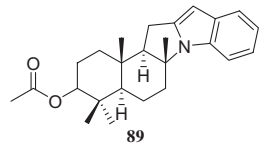

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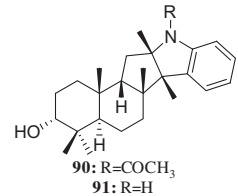
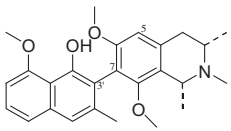


90: R=$COCH_3$
91: R=H



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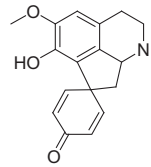

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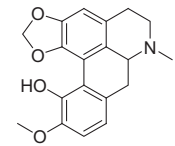
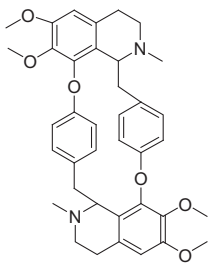


94

Figure 14.3 (Continued)

◀ 8-[(3-methyl-2-butenyl)oxy]furo[2,3-b]quinoline (**76**); galanthamine (**77**); geissolosimine (**78**); geissospermine (**79**); geissoschizoline (**80**); geissoschizone (**81**); vellosiminol (**82**); palicoside (**83**); akagerine (**84**); serotobenine (**85**); 1-hydroxyrutaecarpine (**86**); 7,8-deydro-1-hydroxyrutaecarpine (**87**); greenwayo-dendrin-3-one (**88**); 3-*O*-acetyl greenwayodendrin (**89**); *N*-acetylpolyveoline (**90**); polyveoline (**91**); ancistrotectorine (**92**); crotsparine (**93**);



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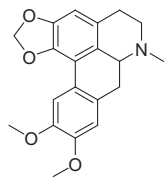

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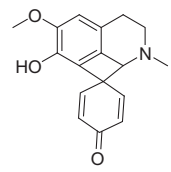

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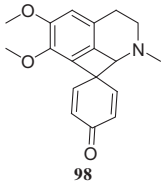

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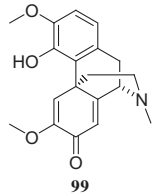

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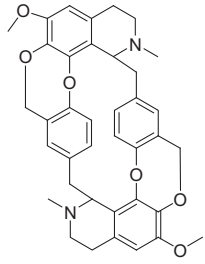

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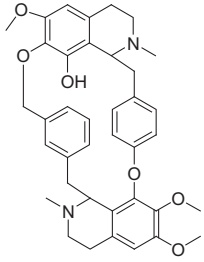

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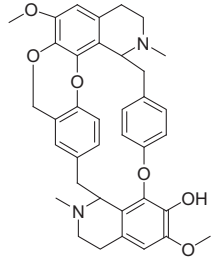

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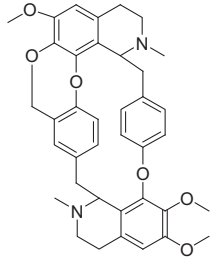

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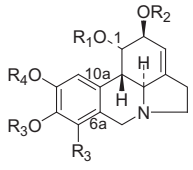
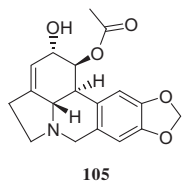


104: R_1=H; R_2=OH; R_3=+; R4=CH_2
106: R_1=Ac; R_2=OH; R_3=H; R_4=CH_3
107: R_1=H; R_2=H; R_3=CH_3; R_4=H



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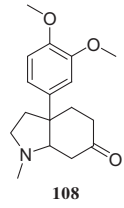
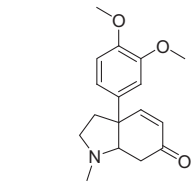


108

Figure 14.3 (Continued)

◀ bulbocapnine (**94**); cycleanine (**95**); dicentrine (**96**); glaziovine (**97**); pronuciferine (**98**); salutaridine (**99**); cissacapine (**100**); cycleaneonine (**101**); insulanoline (**102**); insularine (**103**); lycorine (**104**); 1-*O*-acetyllycorine (**105**); sternbergine (**106**); 9-*O*-demethylpulviine (**107**); mesembrine (**108**); mesembrenone (**109**); mesembrenol (**110**); Δ^{14}-vincanol (**111**); *O*-methyl-16-epi-Δ^{14}-vincanol (**112**); Δ^{14}-vincamone (**113**); *N*-acetylanonaine (**114**);



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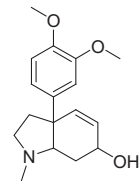

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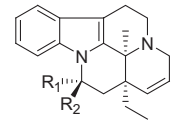
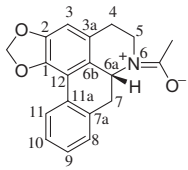


111: R1=H, R2=OCH_3
112: R1=OH, R2=H
113: R1+R2=O



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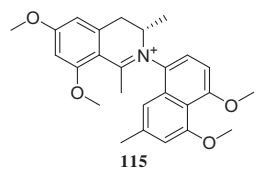

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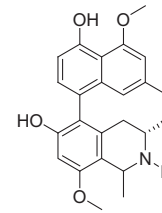

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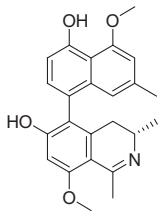

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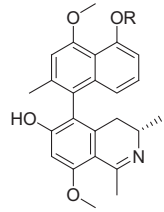
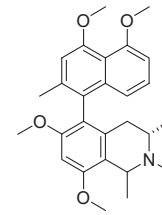


118: R=CH_3
119: R=H



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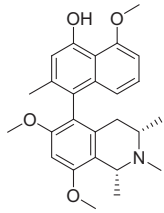

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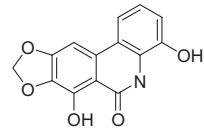

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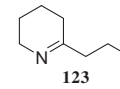

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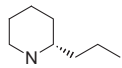

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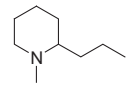

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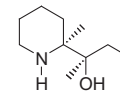


126

Figure 14.3 (Continued)

◀ ancistrocladinium A (**115**); 5′-*O*-demethylhamatine (**116**); 5′-*O*-demethylhamatinine (**117**); 6-*O*-demethylancistroealaine A (**118**); 6,5′-*O,O*-didemethylancistroealaine A (**119**); 5-epi-6-*O*-methylancistrobertsonine A (**120**); 5-epi-4′-*O*-demethylancistrobertsonine C (**121**); narciprimine (**122**); γ-coniceine (**123**); coniine (**124**); methylconiine (**125**); conhydrine (**126**); 7-angelylplatynecine (**127**); 7-*O*-senecioylplatynecine (**128**); 7-*O*-tigloylplatynecine (**129**);

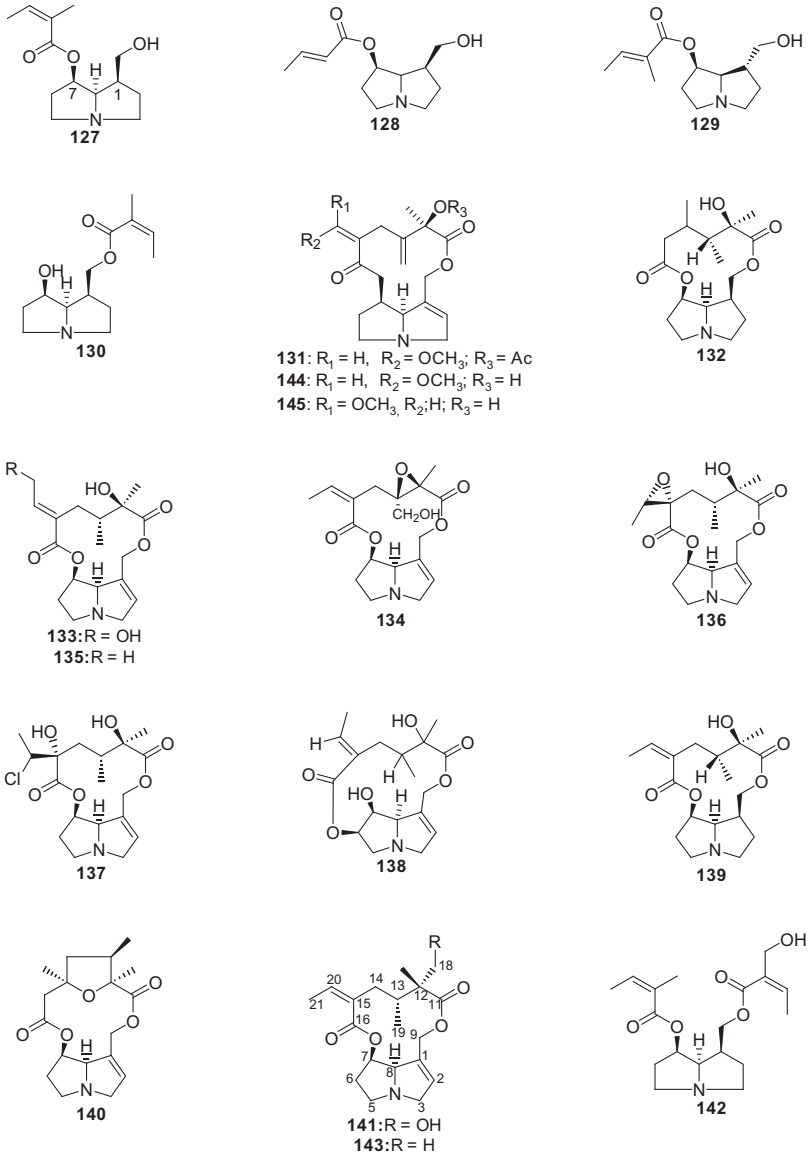
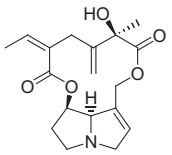


Figure 14.3 (Continued)

◀ 9-angelylplatynecine (**130**); acetylseneciphylline (**131**); bulgarsenine (**132**); eruciflorine (**133**); erucifoline (**134**); integerrimine (**135**); jacobine (**136**); jaconine (**137**); madurensine (**138**); neoplatyphylline (**139**); retroisosenine (**140**); retrosine (**141**); sarracine (**142**); senecionine (**143**); seneciphylline (**144**); spartioidine (**145**); cyclomegistine (**146**); edulinine (**147**); 4-methoxy-1-methyl-2(1*H*)-quinolinone (**148**); 3-hydroxylupanine (**149**);



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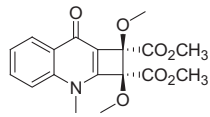

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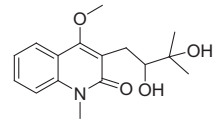

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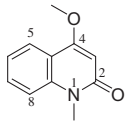

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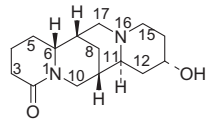

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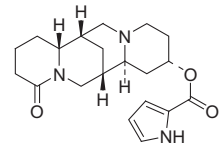

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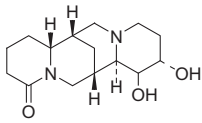

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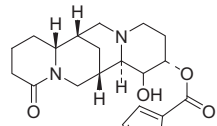

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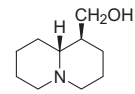

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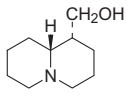

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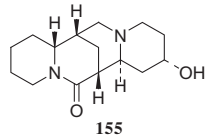

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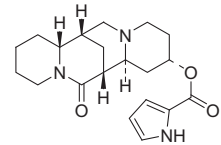

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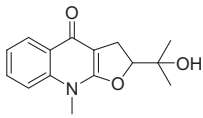

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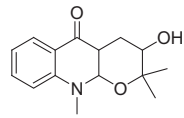

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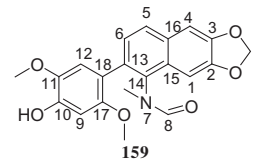

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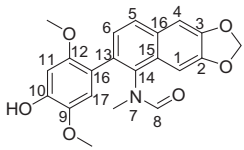

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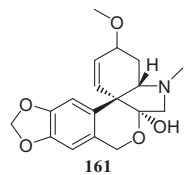

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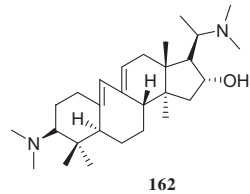


162

Figure 14.3 (Continued)

◀ calpumine (**150**); calpurmenine (**151**); calpurmenine pyrrolecarboxylic acid ester (**152**); epilupinine (**153**); lupinine (**154**); virgiline (**155**); virgiline pyrrolecarboxylic acid ester (**156**); isoplatydesmine (**157**); ribalinine (**158**); 10-*O*-demethyl-17-*O*-methylisoarnottianamide (**159**); 10-*O*-demethyl-12-*O*-methyl isoarnottianamide (**160**); tazettine (**161**); buxaminol A (**162**).

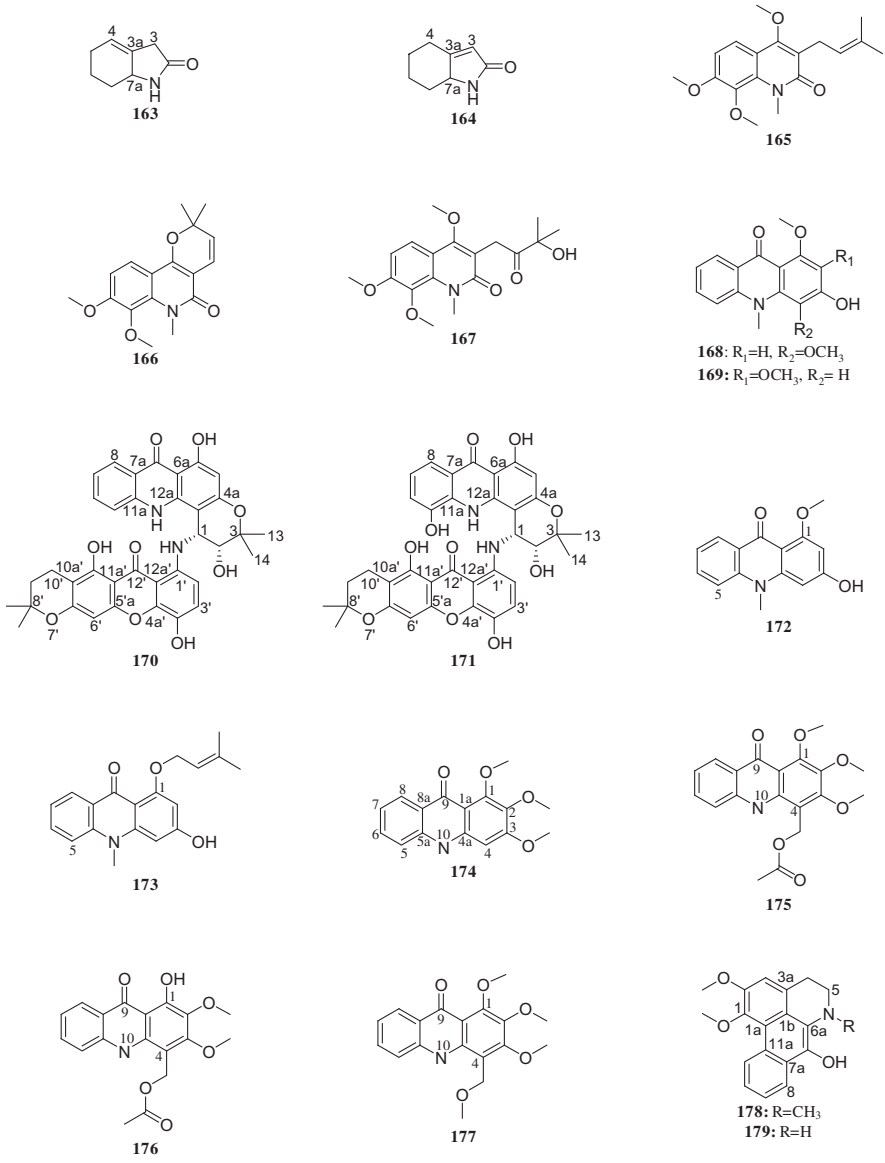
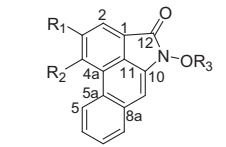
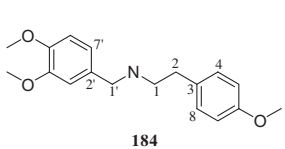


Figure 14.4 Alkaloids isolated as new compound in African medicinal plant: thomandersine (**163**); isothomandersine (**164**); *N*-methylpreskimmianine (**165**); veprisine or 7,8-dimethoxy-*N*-methylflindersine (**166**); veprisilone (**167**); helebelicine A (**168**); helebelicine B (**169**); oriciacridone A (**170**); oriciacridone B (**171**); tegerrardin A (**172**); tegerrardin B (**173**); toddaliopsin A (**174**); toddaliopsin B (**175**); toddaliopsin C (**176**); toddaliopsin D (**177**); 6a,7-dehydro-1,2-dimethoxy-7-hydroxy-*N*-methylaporphine (**178**); 6a,7-dehydro-1,2-dimethoxy-7-hydroxyaporphine (**179**); piperumbellactam A (**180**); piperumbellactam B (**181**); piperumbellactam C (**182**); piperumbellactam D (**183**); *N*-demethylbelladine (**184**);



180: R_1=R_2=OCH_3, R_3=H
181: R_1=OCH_3, R_2=OH, R_3=H
182: R_1=R_2=OH, R_3=CH_3
183: R_1+R_2=OCH_2O, R_3=CH_3



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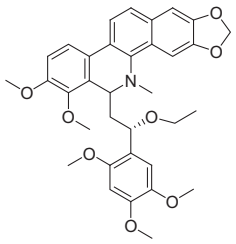

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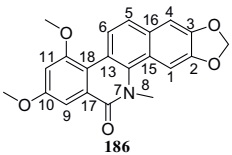

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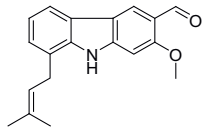

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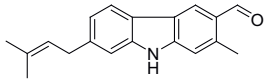

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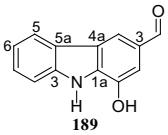

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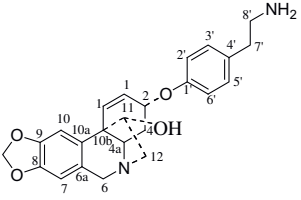

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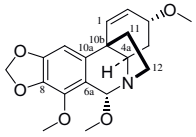

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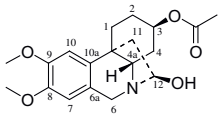

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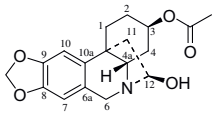

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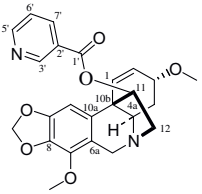

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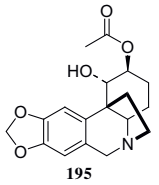

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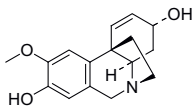

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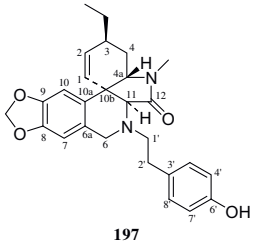


197

Figure 14.4 (Continued)

◀ buesgeniine (**185**); turraeanthin B (**186**); atanisatin (**187**); clausamtin (**188**); *O*-demethylmurrayanine or 3-formyl-1-hydroxycarbazole (**189**); 3-[4′-(8′-aminoethyl) phenoxy] bulbispermine (**190**); 6α-methoxybuphanidrine (**191**); delagoenine (**192**); delagoensine (**193**); filifoline (**194**); josephinine (**195**); macowine (**196**); obliquine (**197**); (+)-11β-hydroxyerysotrine (**198**); (+)-11β-hydroxyerysotrine *N*-oxide (**199**); (+)-11β-methoxyerysotramidine (**200**); (+)-11β-hydroxyerysotramidine (**201**); isohaplopine 3′,3′-dimethylallylether (**202**); isohaplopine or 8-hydroxy-4,7-dimethoxyfuroquinoline (**203**);

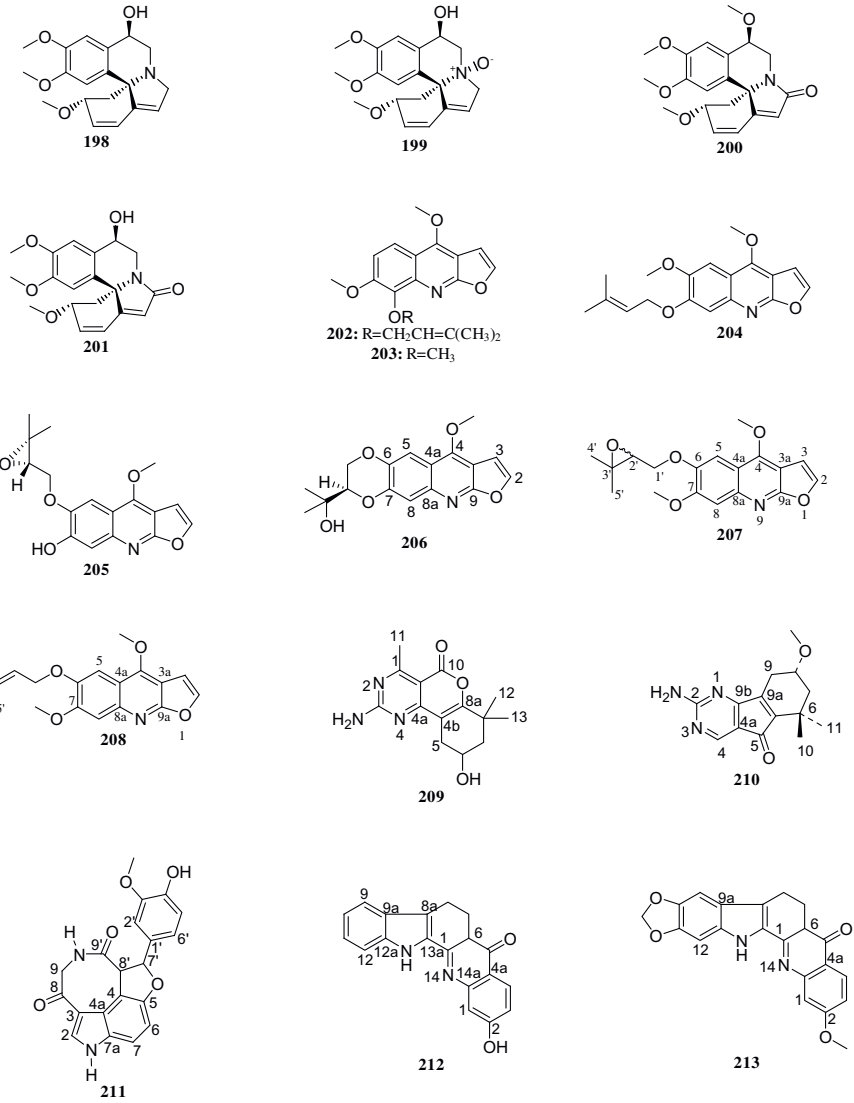
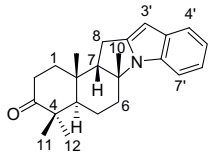


Figure 14.4 (Continued)

◀ nobiline (**204**); quinosuaveoline A (**205**); quinosuaveoline B (**206**); tecleanatalensine A (**207**); tecleanatalensine B (**208**); millettonine (**209**); millaurine A (**210**); flavumindole (**211**); orisuaveoline A (**212**); orisuaveoline B (**213**); polysin (**214**); ancistroguineine A (**215**); ancistroguineine B (**216**); 1,2-*O*-diacetylzephyranthine (**217**); zephyranthine (**218**); 12-methoxyicajine (**219**); 15-hydroxyvomicine (**220**); mooreine (**221**); *N*-methylpseudoconhydrine (**222**); globiferine (**223**); isorosmarinine (**224**); merenskine *N*-oxide (**225**); neosarracine (**226**); *trans*-anacrotine (**227**); oxypterine (**228**); 2,6-dihydro-9-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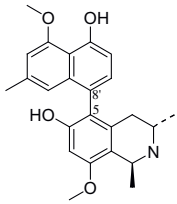
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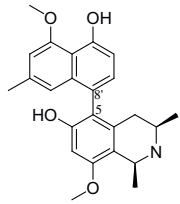
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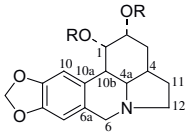
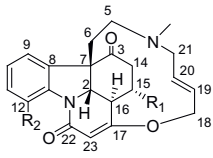
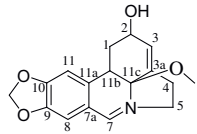

217: R=Ac
218: R=H


219: R_1=H, R_2=OCH_3
220: R_1=R_2=OH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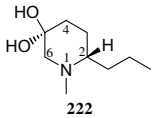
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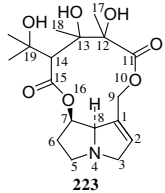
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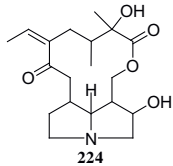
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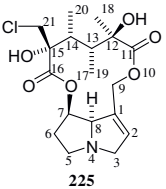
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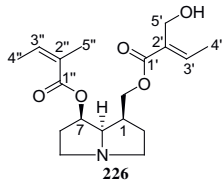
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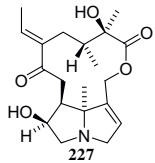
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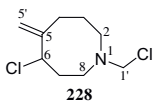
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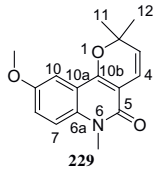
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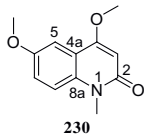
230

Figure 14.4 (Continued)

◀ methoxy2,2,6-trimethyl-5H-pyrano[3,2c] quinolin-5-one (**229**); 4,6-dimethyl-1-methyl-2-(1*H*)-quinolinone (**230**); *N*-methylswietenidine-B or 1-methyl-3,4-dimethoxy-2-quinolone (**231**); 13-*O*-(2′-pyrrolylcarbonyl)calpurmenine (**232**); 3β,4α,13α-trihydroxylupanine (**233**); calpaurine (**234**); calpurmenine (**235**); 10-*O*-demethyl-12-*O*-methylarnottianamide (**236**); turraeanthin A (**237**); 8α-ethoxyprecriwelline (**238**); *N*-desmethyl 8α-ethoxy pretazettine (**239**); *N*-desmethyl-8β-ethoxy pretazettine (**240**); *O*(2)-natafuranamine (**241**); *O*(10)-natafuranamine (**242**); 31-demethylbuxaminol A (**243**); cyclonataminol (**244**).

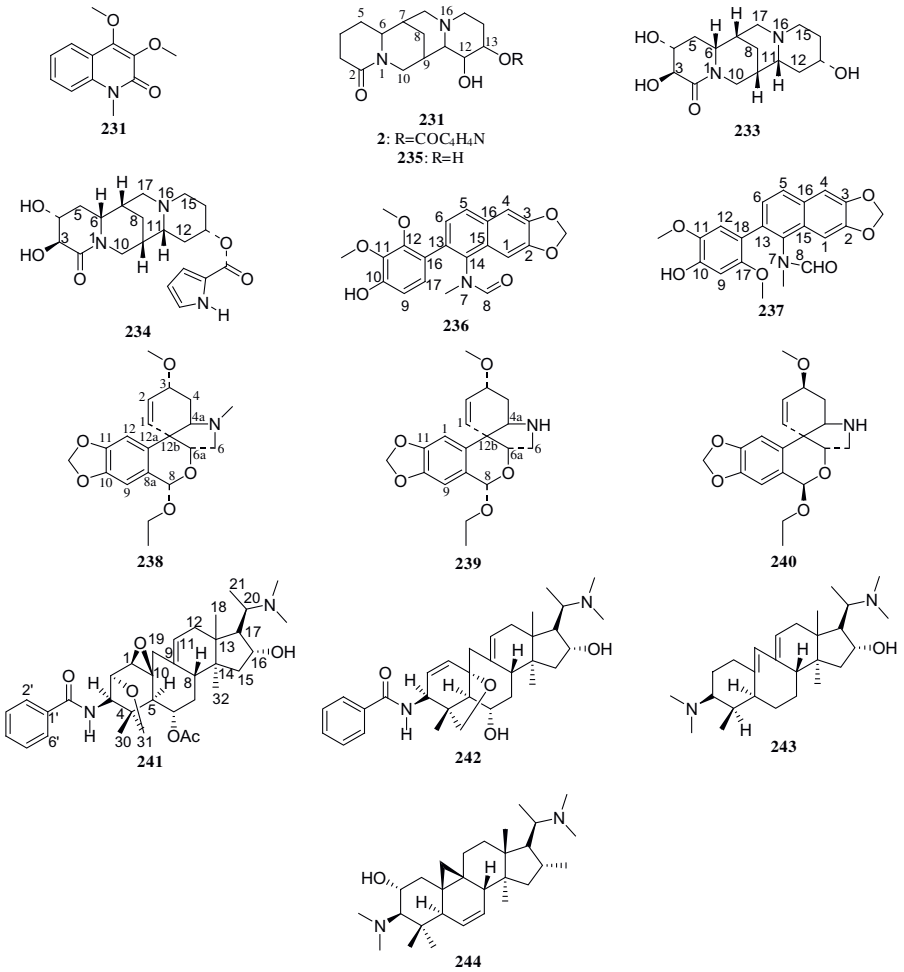

Figure 14.4 (Continued)

active against the chloroquine-sensitive (CQS) *P. falciparum* D10 strain (IC_{50} of 95.3 and 46.8 μM, respectively) [1]. It was found that the substitution of the *O*-methyl group in C-1 of compound **172** by the *O*-prenyl group to yield tegerrardin B (**173**) leads to the loss of this antiplasmodial activity [1].

Benzo[c]phenanthridine alkaloids: Dihydrochelerythrine (**13**) inhibited the growth of *Staphylococcus aureus* (MIC of 50 μg/mL) [12], as well as the germination of the spore of the gray mold of *Botrytis cinerea* (IC_{50} of 56.35 μg/mL) and that of the northern leaf blight, *Exserohilum turcicum* (IC_{50} of 70.66 μg/mL) [13]. The leishmanicidal effect of bocconoline (**14**) was also reported against the promastigotes of *Leishmania major* (IC_{50} of 0.29 μg/mL) [15].

Furoquinoline alkaloids: Evoxine (**66**) displayed moderate antiplasmodial activity against the CQS D10 strain of *P. falciparum*, with IC_{50} values of 24.5 μM [1]. Flindersiamine (**68**), identified in the leaves of the South African plant *T. natalensis* [42], was active against *S. aureus* and *Streptococcus faecalis*, with the respective MIC of 50 and 100 μg/mL [113], but antiprotozoal activity was not detected against *P. falciparum* FCM29 at up to 64 μg/mL [114]. Dictamnine (**69**), another furoquinoline alkaloid reported in the leaves *T. natalensis* [42], displayed antibacterial activity against *S. typhimurium* (MIC of 128 μg/mL) [3] and *M. tuberculosis* H37Rv (MIC of 30 μg/mL) [46], and poor antifungal effects against *Leucoagaricus gongylophorus* (MIC of 1000 μg/mL) [115]. Skimmianine (**72**) showed antiplasmodial activity against *P. falciparum* FcB1 (IC_{50} of 77.3 μg/mL) [52], as well as antibacterial activity against *E. coli*, *S. typhimurium*, and *S. aureus* (MIC of 128 μg/mL) [3], *Shigella dysenteriae* (MIC of 16 μg/mL) [116], and antifungal inhibitory effects against *L. gongylophorus* (MIC_{80} of 1000 μg/mL) [115].

Benzo[c]phenanthridine-type alkaloids: Compound **13** exhibited antiparasitic activity against *Leishmania donovani* (IC_{50} of 2.0 μM) and *Trypanosoma brucei* (IC_{50} of 0.8 μM) [117]. Chelerythrine (**12**), 6-acetonyl-*N*-methyl-dihydrodecarine (**17**), and nitidine (**18**), as well as the secobenzo[*c*]phenantridine 10-*O*-demethyl-17-*O*-methylisoarnottianamide (**159**), isolated from the Cameroonian plant *Z. lemairei* (Rutaceae), displayed antilarvicidal activity against the malaria vector *Anopheles gambiae* [9]. Compounds **159** and **17** produced mortality rates of 96.7% and 98.3%, respectively, at a concentration of 250 μg/mL, while the corresponding percentage was 28.3% for compound **18** [9].

Carbazole alkaloid: Heptaphylline (**19**) displayed antimicrobial activity against *E. coli* and *S. typhimurium* (MIC of 128 μg/mL) [17].

Crinine alkaloids: Buphanidrine (**40**) was active against *Bacillus subtilis* (MIC of 13 μg/mL), *S. aureus*, *E. coli*, and *Klebsiella pneumoniae* (MIC of 63 μg/mL) [34]. Antiparasitic activity of crinine-type alkaloids was also documented for hamayne (**25**) against *P. falciparum* strains FAC8 and D10 (IC_{50} of 18.2 and 9.4 μg/mL, respectively), bulbispermine (**34**) against *P. falciparum* strain FAC8 (IC_{50} of 18.2 μg/mL), and haemanthamine (**41**) against *T. brucei rhodesiense* (IC_{50} of 1.62 μM) [37], and for several compounds from the South African plant *G. vellosii*, geissolosimine (**78**) (IC_{50} of 0.55 μM), geissospermine (**79**) (IC_{50} of 3.17 μM), geissoschizoline (**80**) (IC_{50} of 4.16 μM), geissoschizone (**81**) (IC_{50} of 3.19 μM), and vellosiminol (**82**) (IC_{50} of 46.16 μM) against the *P. falciparum* D10 strain [54].

Furoquinoline alkaloids: Kokusaginine (**70**), nkolbisine (**71**), and maculine (**73**), isolated from the bark of the Cameroonian plant *T. afzelii*, displayed antibacterial and antifungal activities against a panel of bacteria and fungi, but were found inactive or moderately active (**73**) against *Mycobacterium smegmatis* [49]. Compound **70** inhibited the growth of *E. coli*, *B. subtilis*, and *Microsporum audouinii* (MIC of 4.88 μg/mL), *S. typhi*, *Candida albicans*, and *Candida glabrata* (MIC of 9.76 μg/mL), and *S. aureus* (MIC of 39.06 μg/mL) [49]. Compound **73** was active against *B. subtilis* (MIC of 2.44 μg/mL), *M. audouinii* (MIC of 4.88 μg/mL), *S. typhi*, *C. albicans*, and *C. glabrata* (MIC of 9.76 μg/mL), as well as against *Pseudomonas aeruginosa* (MIC of 39.06 μg/mL) [49]. Inhibitory activities of compound **71** were

recorded against *M. audouinii* and *B. subtilis* (MIC of 4.88 μg/mL), S. *typhi*, *C. albicans*, and *C. glabrata* (MIC of 9.76 μg/mL) [49]. However, *in vitro* treatment of the CQS strain of *P. falciparum* NF-54 with 3 μM of compounds **70**, **73**, **74**, and **75** resulted in a very low inhibitory effect [44].

Lycorine-type alkaloids: Lycorine (**104**) did not show a good antimicrobial spectrum; inhibitory activity was, however, reported against *Flavobacterium columnare* (MIC range of 27−108 μg/mL) [76] and *C. albicans* (MIC of 39 μg/mL) [118]. Compound **104** also displayed anti-HIV activity in human MT4 T cells, with an IC_{50} value of 0.4 μM [119]. The lycorine-type alkaloids with antiparasitic activities include sternbergine (**106**) against *P. falciparum* strains D10 and FAC8 (IC_{50} of 4.8 and 3.9 μg/mL, respectively) [25], lycorine (**104**) against *P. falciparum strain* NF-54 (IC_{50} of 0.34 μg/mL) [26] and *P. falciparum* F-32 Tanzania strain (IC_{50} of 0.13 μM) [77], and the monoindole alkaloid 15-hydroxyvomicine (**220**) against the CQS 3D7 strain of *P. falciparum* (IC_{50} of 51.09 mg/mL) [120].

Isoquinoline, naphthylisoquinoline, and quinolinone alkaloids: The anthelmintic activity of isoquinoline alkaloid dicentrine (**96**) was recorded *in vitro* on the larvae of *Haemonchus contortus* (IC_{90} of 6.3 μg/mL) [67]. This activity was also obtained *in vivo* in the Swiss Webster mouse, as this compound exhibited up to 67% reduction of worm count in mice when dosed orally at 25 mg/kg [67]. Compound **96** also showed antiprotozoal activity against *T. brucei* (IC_{50} of 14.6 μM) [68]. The antiviral activity of glaziovine (**97**) was reported *in vivo* against *Herpes simplex* virus type 2 (HSV-2) (IC_{50} of 6.7 μM) using Vero monkey kidney cells [73]. Antiparasitic activity was also documented for crotsparine (**93**) against chloroquine-resistant *P. falciparum* FcB1 (IC_{50} of 2.1 μg/mL) and Thai CQS (IC_{50} of 3.4 μg/mL) strains [64], ancistrotectorine (**92**) against *T. brucei rhodesiense*, *Trypanosoma cruzi*, and *P. falciparum* 3D7 with respective IC_{50} values of 4.3, 4.3, and 9.1 μg/mL [84], glaziovine (**97**) against *Leishmania braziliensis*, *Leishmania amazonensis*, and *L. donovani* (IC_{50} of 100 μg/mL) [72]. The naphthylisoquinolines 5′-*O*-demethylhamatine (**116**), 6-*O*-demethylancistroealaine A (**118**), 5-epi-6-*O*-methylancistrobertsonine A (**120**), 6,5′-*O,O*-didemethylancistroealaine A (**119**), 5-epi-4′-*O*-demethylancistrobertsonine C (**121**), and 5′-*O*-demethylhamatinine (**117**) displayed antiplasmodial activity against the *P. falciparum* K1 strain with respective IC_{50} values of 1.0, 1.8, 1.9, 2.1, 2.6, and 2.8 μg/mL [84]. The quinolinone alkaloid 4-methoxy-1-methyl-2(1H)-quinolinone (**148**) was reported for its antimicrobial activity against methicillin-resistant *S. aureus* (MIC of 8 μM) [94], as well as anti-HIV activity in H9 lymphocyte T cells (IC_{50} of 0.625 μg/mL) [95].

Indole alkaloids: A mixture of the indolosesquiterpene alkaloid polysin (**214**) and its epimer greenwayo-dendrin-3-one (**88**) (IC_{50} of 18 μM), as well as *N*-acetylpolyveoline (**90**) (IC_{50} of 32 μM) and polyveoline (**91**) (IC_{50} of 54 μM), displayed antiparasitic activity against *T. brucei* [59]. Palicoside (**83**) showed antifungal activity against *C. glabrata* (MIC of 1.48 mg/mL) and *C. glabrata* (MIC of 140 μg/mL) [56].

14.4.2 Cytotoxicity of Alkaloids Identified in African Medicinal Plants

The antiproliferative activity of various types of alkaloids identified in African plants has been documented. Many of these belong to acridone-type, benzo[*c*] phenanthridine-type, crinine-type, and other ring types of alkaloids.

Acridone alkaloids: Compounds **1** and **172** displayed antiproliferative activity against human cancer cell lines such as lung carcinoma A549 cells (IC_{50} of 36 and 35 μM, respectively), colorectal adenocarcinoma DLD-1 cells (IC_{50} of 71 and 74 μM, respectively), and skin fibroblast WS1 cells (IC_{50} of 42 and 56 μM, respectively) [4]. The cytotoxicity of compound **1** was also reported against ovarian carcinoma A2780 cells (IC_{50} of 12 μg/mL) [121], skin epidermoid carcinoma A431 cells (IC_{50} of 12.95 μM), breast adenocarcinoma MCF-7 (IC_{50} of 11.74 μM), and cervix adenocarcinoma HeLa (IC_{50} of 1.84 μM) [122]. 1-Hydroxy-3-methoxy-10-methyl-9-acridone (**5**) (IC_{50} of 31 μM) and 3-hydroxy-1,2-dimethoxy-10-methyl-9-acridone (**169**) (IC_{50} of 52 μM) also displayed cytotoxic activity against the A549 cell line [4].

Benzo[c]phenanthridine-type alkaloids: Compound **12** induced cytotoxic effects on a panel of cancer cell lines such as A549 cells (IC_{50} of 0.9 μM), lung undifferentiated adenocarcinoma PC-14 cells (IC_{50} of 15.5 μM), lung adenocarcinoma RERF-LC-KJ cells (IC_{50} of 5.2 μM) [10], human lymphoblast tumor cell line CPT-K5 (IC_{50} of 4 μM), leukemia U937 (IC_{50} of 0.8 μM) and U937/CR (IC_{50} of 3.5 μM), the KB3-1 tumor cell line (IC_{50} of 0.06 μM), CEM cells (IC_{50} of 0.16 μM), CEM/V1 cells (IC_{50} of 1.0 μM), and CEM/V5 cells (IC_{50} of 0.8 μM) [11]. Dihydrochelerythrine (**13**) displayed a cytotoxic effect against colon cancer HCT-8 cells (IC_{50} of 1.4 μM), A2780 cells (IC_{50} of 3.5 μM), stomach cancer BGC-823 cells (IC_{50} of 0.4 μM) [14], and was hopefully not as toxic against Vero cells (IC_{50} of 35.4 μM) [117] as on malignant cells.

Carbazole alkaloid: Compound **19** showed antiproliferative activity against KB cells (IC_{50} of 94.2 μM), MCF-7 cells (IC_{50} of 171 μM), and NCI-H187 small lung cancer cells (IC_{50} of 20.2 μM) [17].

Crinine-type alkaloids: Crinine (**26**) suppressed the viability of several cancer cell lines, including breast carcinoma MDA-MB-231 (IC_{50} of 68.11 μM), T-cell leukemia SKW-3 (IC_{50} of 16.95 μM), and acute myeloid leukemia HL-60 and HL-60/Dox (IC_{50} of 20.86 and 14.04 μM, respectively) [29]. Another crinine-type alkaloid, compound **25**, suppressed the proliferation of U373 cells (IC_{50} of 38 μM), anaplastic oligodendroglioma Hs683 cells (IC_{50} of 11 μM), cervical adenocarcinoma HeLa cells (IC_{50} of 8 μM), glioblastoma T98G and U87 cells (IC_{50} of 9 μM) [24], and BL6 mouse melanoma cells (IC_{50} of 9.4 μg/mL) [25]. Compound **34** exhibited cytotoxic effects against U373 cells (IC_{50} of 38 μM), anaplastic oligodendroglioma Hs683 cells (IC_{50} of 11 μM), HeLa cells (IC_{50} of 8 μM), glioblastoma T98G and U87 cells (IC_{50} of 9 μM) [24], and BL6 mouse melanoma (IC_{50} of 9.4 μg/mL) [25]. Another crinine-type alkaloid with documented cytotoxic activity was haemanthidine (**42**) against mouse lymphoma L5178 cells (IC_{50} of 0.41 μg/mL) [38].

Lycorine-type alkaloids: The cytotoxicity of compound **104** was reported against a panel of cancer cell lines, including T98G and U373 (IC_{50} of 3 μM), A549 (IC_{50} of

0.9 μM), pancreatic PC3 and breast MCF-7 (IC_{50} of 4 μM), melanoma SKMEL-28 and B16-F10 (IC_{50} of 4 and 2 μM, respectively) [123], esophageal cancer OE21 cells (IC_{50} of 4.5 μM), Hs683 (IC_{50} of 6.9 μM), U373 (IC_{50} of 7.6 μM), SKMEL-28 and B16-F10 (IC_{50} of 8.4 and 6.3 μM, respectively) [124], and leukemia HL-60 and 6T-CEM (IC_{50} of 0.17 and 1.42 μg/mL, respectively) [125].

Furoquinoline alkaloids: Compound **68** significantly inhibited the proliferation of A549 cells (IC_{50} of 8.9 μM) [44] and A2780 cells (IC_{50} of 3.3 μg/mL) [45]. 7-(γ,γ-dimethylallyloxy)-γ-fagarine, also known as 7-isopentenyloxy-gamma-fagarine (**67**), displayed cytotoxic effects against Raji cells (IC_{50} of 1.5 μg/mL), Jurkat cells (IC_{50} of 3.6 μg/mL), and MCF-7 cells (IC_{50} of 15.5 μg/mL) [41]. The cytotoxicity of compound **69** was documented on a panel of cancer cell lines such as the hepatocarcinoma HepG2 (IC_{50} of 55.2 μM) [47], HeLa (IC_{50} of 65 μM), HCT-116 (IC_{50} of 85 μM) [126], Jurkat (IC_{50} of 245 μM) [127], lung adenocarcinoma A549 (IC_{50} of 25.43 μg/mL), and human colon adenocarcinoma HT-29 (IC_{50} of 26.07 μg/mL) [48].

Indole alkaloids: Flavumindole (**211**), identified for the first time in the Cameroonian plant *C. flavum*, showed 90% inhibition of the proliferation of the brine shrimp *Artmia salina* at 10 μg/mL [57].

Isoquinoline alkaloids: The antiproliferative activity of cycleaneonine (**101**) was reported against murine colon 26-L5 and 26-L5 adenocarcinoma cell lines (IC_{50} of 23.1 and 29.3 μg/mL, respectively) [66]. Compound **96** exhibited cytotoxic activity against many human cancer cell lines, including larynx carcinoma Hep-2 (IC_{50} of 21.8 μg/mL), MCF-7 (IC_{50} of 25.2 μg/mL), melanoma B16-F10 (IC_{50} of 11.2 μg/mL), kidney carcinoma 786-0 (IC_{50} of 16.3 μg/mL) [69], and glioblastoma U87MG and U87MG deletion-activated delta epidermal growth factor receptor (ΔEGFR) expression vector (IC_{50} of 43 and 4.73 μM, respectively) [70]. Other cytotoxic isoquinoline alkaloids include glaziovine (**97**) (IC_{50} of 7−8 μM), pronuciferine (**98**) (IC_{50} of 42−50 μM) [74], and salutaridine (**99**) (IC_{50} of 0.43−0.45 μM) against HepG2 cells [75].

Mesembrine-type alkaloids: Mesembrenone (**109**) inhibited the proliferation of the human T-cell lymphoma line Molt4 (IC_{50} of 0.6 μg/mL), HepG2, and the mouse fibroblast cell line LMTK (IC_{50} of 10 μg/mL) [128].

14.4.3 Enzymatic Inhibitory Activity of Alkaloids Identified in African Medicinal Plants

Several enzymes were identified as targets of some alkaloids identified in African plants. Acetylcholine esterase (AChE) was one of the most frequently investigated enzymes; its biological functions are discussed in Chapter 11. In summary, this enzyme is involved in Alzheimer's disease (AD), which is characterized by a progressive alteration of cognitive functions such as loss of memory and the ability to perform basic life activities [129]. It has been shown that these symptoms occur as a result of the decrease in brain acetylcholine activity due to catabolism of acetylcholine by AChE [130]. AChE inhibitors inhibit the activity of AChE, and thus maintaining the level of acetylcholine in the brain [131].

Elgorashi et al. [20] reported the AChE inhibitory activity of a panel of Amaryllidaceae alkaloids having several different ring types (Figures 14.1 and 14.2; Tables 14.1 and 14.2). These include 1-*O*-acetyllycorine (**105**) (IC_{50} of 0.96 μM), which showed strong activity, as well as *N*-desmethyl-8α-ethoxypretazettine (**239**) (IC_{50} of 234 μM), epivittatine (**31**) (IC_{50} of 239 μM), crinamidine (**28**) (IC_{50} of 300 μM), cherylline (**23**) (IC_{50} of 407 μM), crinine (**26**) (IC_{50} of 461 μM), 6-hydroxycrinamine (**24**) (IC_{50} of 490 μM), (**239**) (IC_{50} of 419 μM), lycorine (**104**) (IC_{50} of 213 μM), epibuphanisine (**29**) (IC_{50} of 547 μM), hamayne (**25**) (IC_{50} of 553 μM), 3-*O*-acetylhamayne (**32**) (IC_{50} of 594 μM), crinamine (**33**) (IC_{50} of 697 μM), tazettine (**161**) (IC_{50} of 705 μM), and 8α-ethoxyprecriwelline (**238**) (IC_{50} of 1145 μM), all of which exhibit weak activity. In that study, Elgorashi et al. [20] demonstrated that the lycorine-type alkaloids were the most active alkaloids, with compound **105** exhibiting inhibitory effects twofold better than the reference drug galanthamine (**77**) (IC_{50} of 1.9 μM). Other reports documented the IC_{50} values of compounds **25** and **104** as 250 [31] and 155 μM [132], respectively. Though such values were different from those of Elgorashi et al. [20] for the two compounds, it should be noted that both studies concluded that compounds **25** and **104** were poor AChE inhibitors. Other alkaloids acting as AChE inhibitors identified in African plants include bulbispermine (**34**) (IC_{50} of 250 μM) [31], 11-*O*-acetylambelline (**37**) (IC_{50} of 1160 μM) [33], narciprimine (**122**) (IC_{50} of 78.9 μM) [85], and skimmianine (**72**) (IC_{50} of 1.4 mM) [53].

It should also be noted that compound **77** was isolated in the South African medicinal plant *C. elatus* (Jacq.) Traub (Amaryllidaceae) [36]. Compound **77**, a selective, reversible, and competitive AChE inhibitor for the treatment of AD, is the first commercial natural product from the Amaryllidaceae family and was launched onto the market in the EU and USA in 2001. Due to its biological activity and limited availability from natural sources, many synthetic analogs have been developed for this natural medicine [133].

The aristolactam alkaloids piperumbellactams A (**180**), B (**181**), C (**182**), and D (**183**), isolated from branches of *P. umbellatum*, showed weak to moderate and selective alpha-glucosidase inhibitory activity, with IC_{50} values of 98.07, 43.80, and 29.64 μM, respectively [102].

The indolosesquiterpene alkaloids (**88**) and (**214**) (as a mixture), 3-*O*-acetyl greenwayodendrin (**89**), *N*-acetylpolyveoline (**90**), and polyveoline (**91**) showed inhibitory activities on *T. brucei* glycolytic enzymes glyceraldehyde 3-phosphate dehydrogenase (GAPDH), phosphofructo kinase (PFK), and aldolases [59]. The best enzyme inhibitory activity was recorded with alkaloid (**90**) (IC_{50} of 0.5 μM) [59]. A mixture of **214** and **88** showed a moderate GAPDH inhibitory activity, but was more specific for the parasite enzyme. Better effects were obtained with compounds **89** and **91**, which were respectively 19 times and twofold more active on *T. brucei* GAPDH (IC_{50} of 110 and 310 μM, respectively) than on its rabbit muscle homolog (IC_{50} of 2050 and 620 μM, respectively) [59]. The mixture of **214** and **88** also inhibited the PFK of the parasite (IC_{50} of around 20 μM) [59].

The mesembrine alkaloids, mesembrine (**108**), mesembrenone (**109**), and mesembrenol (**110**), were reported in the South African plant *S. tortuosum* [79].

Compound **108** behaved as a potent inhibitor of the enzyme phosphodiesterase 4 (PDE4) [79], and thus may have antidepressant effects [134].

The triterpenoid alkaloids *O*(2)-natafuranamine (**241**), *O*(10)-natafuranamine (**242**), 31-demethylbuxaminol A (**243**), cyclonataminol (**244**), and buxaminol A (**162**), isolated from the South African plant *B. natalensis*, also inhibited the activity of AchE, with respective IC_{50} values of 3.0, 8.5, 22.9, 25.8, and 29.5 μM [97]. However, under similar experimental conditions, such activities were lower than that of the reference compounds huperzine A (IC_{50} of 1.7 μM) and galanthamine (IC_{50} of 0.53 μM) [97].

14.4.4 Anti-Inflammatory Activity of Alkaloids Identified in African Medicinal Plants

Many alkaloids identified in African plants were documented for their antiproliferative effects. Toddaliopsins A (**174**), B (**175**), C (**176**), and D (**177**) were tested for anti-inflammatory activity by the chemiluminescence assay and displayed moderate activity, with mean IC_{50} values of 27.3, 48.3, 4.21, and 79.1 μg/mL, respectively [100]. Of these, **176** had the greatest activity, and it was suggested that the presence of a hydroxy group at C-1 may enhance the anti-inflammatory properties of these compounds [100]. The *C. delagoense* alkaloid (**104**) inhibited LPS-induced TNF-α production (IC_{50} of 0.9 μM) [78]. The isoquinoline alkaloid bulbocapnine (**94**) inhibited the human recombinant cytochrome P450 enzyme CYP3A4 ($IC_{50} < 1$ μM) [65].

14.4.5 Antioxidant Activity of Alkaloids Identified in African Medicinal Plants

Some alkaloids identified in African plants were also reported to have antioxidant properties. Compounds **180** and **182** exhibited DPPH radical scavenging activity, with IC_{50} values of 17.4 and 8.1 μM, respectively [102]. It was postulated that the effectiveness of **182** could be due to the presence of an ortho-dihydroxy group, which, by donating hydrogen radicals, gives greater stability to their radical forms [102]. Compound **1** inhibited the heme-mediated protein oxidation (IC_{50} of 42 μM) [5], while compound **104** inhibited LPS-induced nitric oxide production (IC_{50} of 1.2 μM) in the mouse macrophage cell line RAW264 [78].

A panel of 14 erythrinaline-type alkaloids, namely (+)-11α-hydroxyerysotrine (**56**), (+)-erysodine (**57**), (+)-11α-hydroxyerysodine (**58**), (+)-erysotrine *N*-oxide (**59**), (+)-11α-hydroxyerysotrine *N*-oxide (**60**), (+)-11β-methoxyerysotrine *N*-oxide [(+)-*O*-methylerythrartine *N*-oxide] (**61**), (+)-erythrabine (**62**), (+)-erysotramidine (**63**), (+)-erysotrine (**64**), (+)-erythristemine (**65**), (+)-11β-hydroxyerysotrine (**198**), (+)-11β-hydroxyerysotrine *N*-oxide (**199**), (+)-11β-methoxyerysotramidine (**200**), and (+)-11β-hydroxyerysotramidine (**201**), were isolated from different parts of *E. lysistemon*. Of these, **57** (IC_{50} of 90 μg/mL), **58** (IC_{50} of 160 μg/mL), **59** (IC_{50} of 700 μg/mL), **64** (IC_{50} of 210 μg/mL), and **298** (IC_{50} of 280 μg/mL) showed 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity [135].

14.4.6 Other Pharmacological Activities of Alkaloids Identified in African Medicinal Plants

Apart from antimicrobial, cytotoxic, anti-inflammatory, and antioxidant properties, several other attributes were reported for alkaloids identified in African plants. Reduction of serotonergic neurotransmission is strongly implicated in the neuropathology of depression [40]. Thus, it has been shown that the inhibition of serotonin reuptake is an important principle in antidepressant treatment [21]. Citalopram is one of the most selective serotonin reuptake inhibitors [21]. Some alkaloids reported in African plants also acted as serotonin reuptake inhibitors. Elgorashi et al. [21] demonstrated that a panel of alkaloids from the family Amaryllidaceae, including **23** (IC_{50} of 3.4 μM), **26** (IC_{50} of 267.2 μM), **29** (IC_{50} of 78.2 μM), **31** (IC_{50} of 12.1 μM), **33** (IC_{50} of 608.7 μM), **27** (IC_{50} of 20.7 μM), **35** (IC_{50} of 20.8 μM), **36** (IC_{50} of 40.1 μM), **105** (IC_{50} of 452.1 μM), and **161** (IC_{50} of 99.6 μM), showed affinity to serotonin reuptake transport protein. Four crinine-type alkaloids isolated from *B. disticha* harvested in South Africa, buphanamine (**38**), buphanidrine (**40**), buphanisine (**30**), and distichamine (**39**), also showed affinity to serotonin transporter (SERT), with IC_{50} values of 55, 62, 199, and 65 μM, respectively [27]. Affinity to SERT was also reported for compound **40** (IC_{50} of 274 μM) [35].

The *N*-acetylnoraporphine *N*-acetylanonaine (**114**), identified in the seeds, fruit capsules, leaves, and stems of *P. aculeatum* Thunb. harvested in South Africa, also inhibited platelet aggregation of human blood (IC_{50} of 64 μM) [82] and showed dose-dependent inhibition of the platelet-activating factor receptor binding to platelets (IC_{50} of 52.4 μM) [83].

Compound **108** was also shown to be a potent inhibitor of 5-hydroxytryptamine (5-HT) reuptake [136], and this was confirmed with synthetic (−)-mesembrine. Its IC_{50} against 5-HT uptake was 27 nM, with much weaker effects on noradrenaline uptake ($IC_{50} \sim 10$ μM) and no effect on dopamine uptake, at 10 μM [137]. Compound **109** was also active against the 5-HT transporter and PDE4 ($IC_{50} < 1$ μM), this effect being 87 times greater than that of compound **110** [79]. 5-HT active binding alkaloids also include the pyrrolizidine alkaloid seneciphylline (**131**) (IC_{50} of 608.6 μM) [92]. The quinoline alkaloid edulinine (**147**) showed anticovulsant activity in mice, as it protects the animals from seizures produced by electroshock [93].

14.5 Some Particular Aspects of New Alkaloids Isolated in African Medicinal Plants

Toddaliopsins (**175** and **177**) were the first reported acridone alkaloids with substituted *N*-methyl groups, showing the chemotaxonomic relationship of *Toddaliopsis* and *Vepris* [100]. Delagoenine (**192**) and delagoensine (**193**), isolated from *C. delagoense* (Amaryllidaceae), are the first reported crinane-type alkaloids with a hydroxyl

group in the C-12 position, as opposed to the usual 11-substitution [22]. When the 5,8'-coupled naphthylisoquinolines, ancistroguineines A (**215**) and B (**216**), were isolated from *A. guineëensis*, they constituted the first example of a pair of 3-epimeric naphthylisoquinoline alkaloids [60]. In addition, before the isolation of ancistrotectorine (**92**) in *A. guineëensis*, the only 7,3'-coupled alkaloid previously known was from the Southeast Asian species *Ancistrocladus tectorius* [60]. Though the two crinine alkaloids 6α-hydroxycrinamidine and 6α-hydroxyundulatine were known, they were isolated for the first time as natural compounds from the South African plant *A. tinneana* (Amaryllidaceae) [28]. The triterpenoid alkaloids buxaminol A (**162**) was isolated for the first time as a natural product in the South African plant *B. natalensis* [97].

14.6 Conclusion

In this chapter, we inventoried as much as possible the alkaloids isolated from African plants. We also identified many alkaloid-producing families in plants of the continent, the Amaryllidaceae being widely represented. Several documented compounds exhibited various potentially useful activities such as enzyme inhibitory effects and anticancer, antimicrobial, and anti-inflammatory activity. This chapter also highlighted the importance of the flora of the continent as a source of pharmacologically active alkaloids and brought out the advances made in the search for alkaloids from African plants, especially in South Africa, Egypt, and Cameroon.

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15 Ceramides, Cerebrosides, and Related Long Chains Containing Derivatives from the Medicinal Plants of Africa

Louis Pergaud Sandjo[a] *and Victor Kuete*[b]

[a]Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon, [b]Department of Biochemistry, University of Dschang, Dschang, Cameroon

15.1 Introduction

Ceramides are natural products formed by a fatty acid bound to a long chain amine called a sphingoid through an amide function. The base including the sphingosine (**1**) and sphinganine (**2**) can contain several carbon−carbon double bonds according to the fatty acids involved in the biosynthesis (Figure 15.1). These amides are found in the cytoplasmic membrane, where they play a crucial role in the development and growth of cells [1,2]. Thus, a decrease in quantity may cause some skin diseases, cancers, and other dysfunctional cell diseases [2]. Based on the structural activity relationship, sphingolipids would require a 4,5-*trans* carbon−carbon double bond to induce apoptosis [2,3]. The predominant long chain base in animal ceramides is sphingosine, which is present only in trace amounts in plant ceramides. In contrast, sphinganine, 4-hydroxysphinganine, and 4-hydroxy-8-sphingenine are the prevalent long chain bases in plants. The acyl chain of plant ceramides usually contains an α-hydroxylated very long chain fatty acid [4]. More than 200 structurally distinct molecular species of ceramides have been characterized from mammalian cells. In plants, 2-hydroxy acids predominate, sometimes accompanied by small amounts of 2,3-dihydroxy acids [5]. However, in this chapter, we will focus on ceramides isolated from African medicinal plants.

15.2 Biosynthesis and Structural Diversity

In general, the first step in biosynthesis is the condensation of L-serine and fatty acyl-CoA, yielding 3-ketodihydrosphingosine, which is reduced to dihydrosphingosine. This component is then *N*-acylated, followed by a dehydrogenation in order to form

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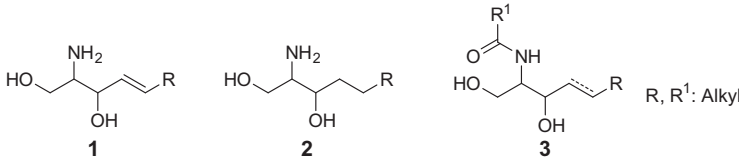


Figure 15.1 General structure of sphingosine (**1**), sphinganine (**2**), and ceramide (**3**).

a ceramide. The variety of saturated, unsaturated, and polyunsaturated fatty acids in plants, as well as the length of their side chains, allows the synthesis of different dihydrosphingosines (**2**), sphingosines (**1**), phytosphingosines, and subsequently, ceramides (**3**). Glycosylceramide synthase can further catalyze the conversion of ceramides to glycosylceramides or polysaccharide ceramides (Figure 15.2).

15.3 Structure Elucidation and Nomenclature of Ceramides

Usually, ceramides containing one olefinic function at an undefined position on both side chains (fatty acid or long chain base part) show similar nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR). Further work, such as high-resolution mass spectrometry analysis, hydrolysis followed by the HPLC-MS analysis, and oxidative cleavage, is required to determine the molecular weight and molecular formula and to identify the fatty acid and the long chain base as well as the position of the carbon−carbon double bond. This information leads to the structure determination of several of these molecules (Figure 15.3).

The ^{1}H and ^{13}C NMR spectra are characterized by signals corresponding to a fatty acid at δ_H 0.88/δ_C 14.8 integrating for six protons of both terminal methyl groups; in the range of δ_H 1.20−2.40/δ_C 23.4−32.6, resonances of methylene group sequences are observed, and at δ_C 174.4 is found the chemical shift of the carbonyl of amide. In addition, a signal of an exchangeable proton attached to nitrogen is present around δ_H 8.00, depending on the solvent used for the analysis (Figure 15.4).

The stereochemistry of the olefinic function is deduced from coupling constants of olefinic protons and carbon chemical shifts of allylic methylene groups; if the chemical shifts of the allylic carbons are more than δ_C 30.0 and the coupling constant of the olefinic proton is $J = 15.0$ Hz, then the configuration is *trans*. A coupling constant of the olefinic proton of $J = 8.0$ Hz and chemical shifts of the allylic methylene at δ_C 26.0 suggest a *cis* configuration [7].

The nomenclature of ceramides is based on the part of the molecule chosen as the principal chain. In some cases, the long chain base is used as the main core to name the molecule; in other cases, the fatty acid part is considered as the principal chain. Consequently, compound **4** was named 1,3,4,5-tetrahydroxy-2-octadecanoylaminopentacosene [8], while compound **5** was named (2*R*,6*Z*)-hydroxy-*N*-((2*S*,3*S*,4*R*)-1,3,4-trihydroxyhexacosan-2-yl)heptadec-6-enamide (Figure 15.5) [9].

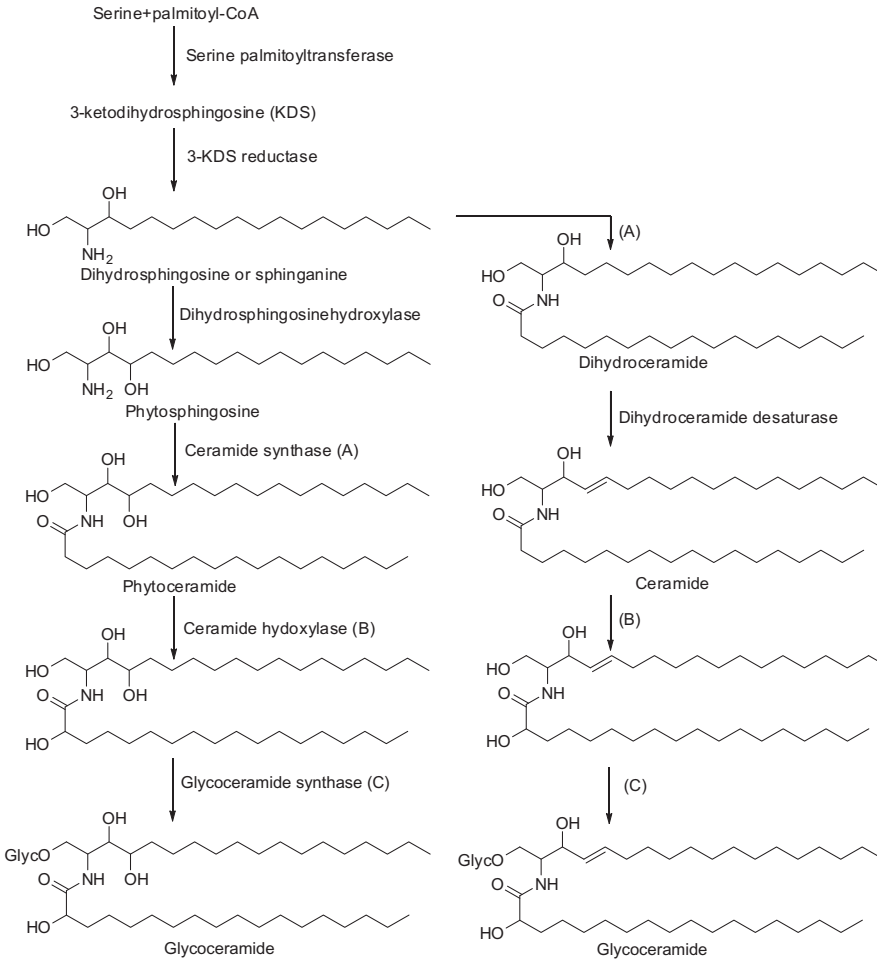


Figure 15.2 Biosynthetic pathway of ceramide and cerebroside [6].

15.4 Pharmacological Activity of Ceramides and Cerebrosides Isolated from African Medicinal Plants

The most widely studied biological activity of ceramides is the ability to induce apoptosis, a programmed cell death that is essential for the maintenance of normal cellular homeostasis and an important physiological response to many forms of cellular stress. Ceramide accumulation has been found following treatment of cells with many apoptotic agents, including ionizing radiation UV light, tumor necrosis factor alpha, and chemotherapeutic agents [10–13]. Several studies have attempted to further define the specific role of ceramides in cell death, and

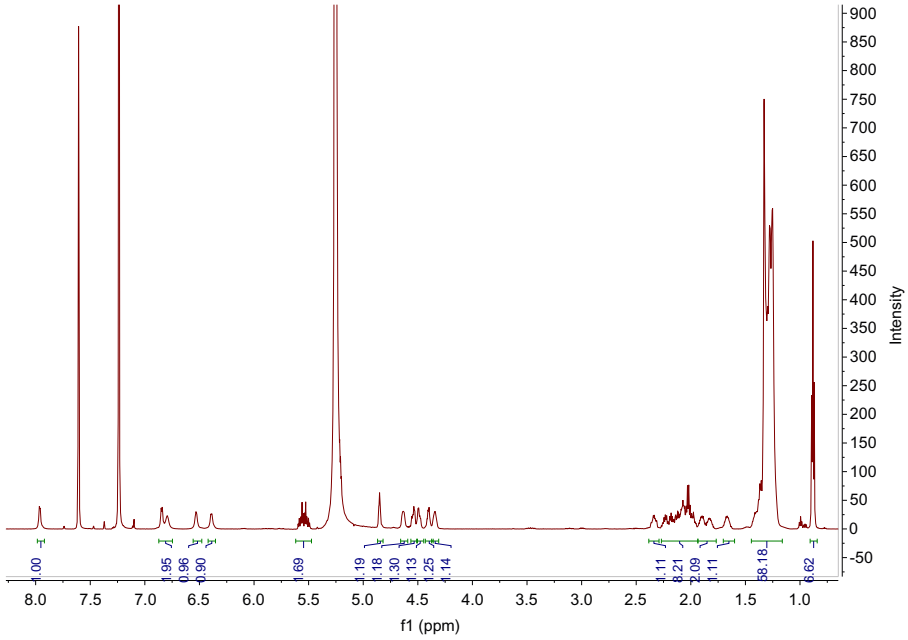


Figure 15.3 ^{1}H-NMR spectrum (C_5H_5N, 600 MHz) of a ceramide (personal unpublished data).

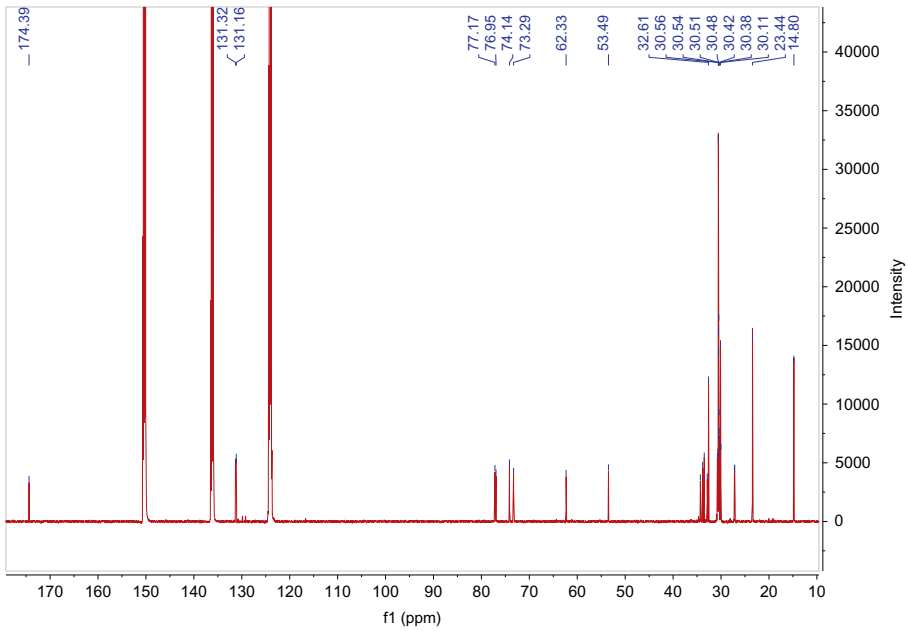
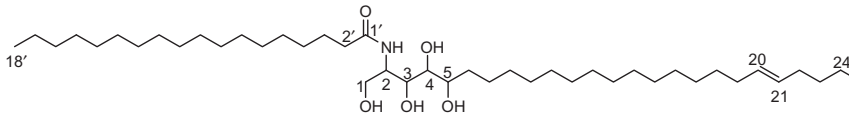


Figure 15.4 ^{13}C-NMR spectrum (C_5H_5N, 150 MHz) of a ceramide (personal unpublished data).



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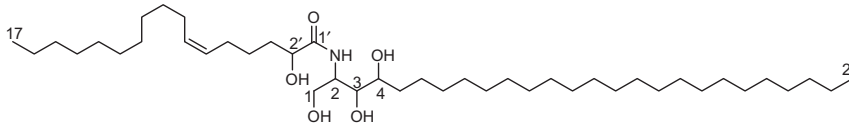

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Figure 15.5 Chemical structures of 1,3,4,5-tetrahydroxy-2-octadecanoyl-aminopentacosene (**4**) and (2*R*,6*Z*)-hydroxy-*N*-((2*S*,3*S*,4*R*)-1,3,4-trihydroxyhexacosan-2-yl)heptadec-6-enamide (**5**).

there is some evidence suggesting that ceramides function in the upstream regulation of the mitochondria in inducing apoptosis. However, owing to the conflicting and variable nature of studies into the role of ceramides in apoptosis, the mechanism by which they regulate apoptosis remains elusive [14]. A limited number of ceramides and cerebrosides have been isolated from African medicinal plants, and very few of these have been submitted to the pharmacological studies (Figure 15.6). However, a new ceramide, lutaoside (**17**), and benjaminamide (**6**), isolated from the twigs of *Ficus benjamina* [15] and from the wood of *Ficus lutea* [16] harvested in Cameroon, inhibited the growth of several microorganisms, including the bacteria *Scenedesmus subspicatus*, *Chlorella sorokiniana*, *Mucor miehei*, *Bacillus subtilis*, and the fungus *Candida albicans*, with inhibition zone diameters (IZ) ranging from 11 to 17 mm [16]. Interestingly, the activity on *C. albicans* (IZ of 12 mm) was close to that of the reference drug nystatin (15 mm) under similar experimental conditions of 40 μg/disk [16]. Nonetheless, compound **17** was found inactive on other microorganisms such as *Streptomyces viridochromogenes*, *Escherichia coli*, and *Staphylococcus aureus* [16].

Newboudiamide (**7**), newly isolated from another Cameroonian plant, *Newbouldia laevis* [17], displayed a wide range of antimicrobial activities, its inhibitory effects being observed in fungi and in both Gram-negative and Gram-positive bacteria (Table 15.1) [18]. This compound was significantly active (minimal inhibitory concentration (MIC) < 10 μg/mL) against the Gram-negative bacteria *Enterobacter cloacae*, *E. coli*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Shigella flexneri*, *Salmonella typhi*, the Gram-positive bacteria *Streptococcus faecalis*, *S. aureus*, *Bacillus cereus*, *Bacillus megaterium*, *Bacillus stearothermophilus*, *B. subtilis*, and the yeasts *Candida krusei* and *Candida glabrata* [18]. Pancoviamide (**10**), isolated as a new compound from the Cameroonian medicinal plant *Pancovia laurentii* [18], showed low activity against the causal agent of African trypanosomiasis, *Trypanosoma brucei rhodesiense*, with an IC_{50} value of 53.45 μg/mL, as well as

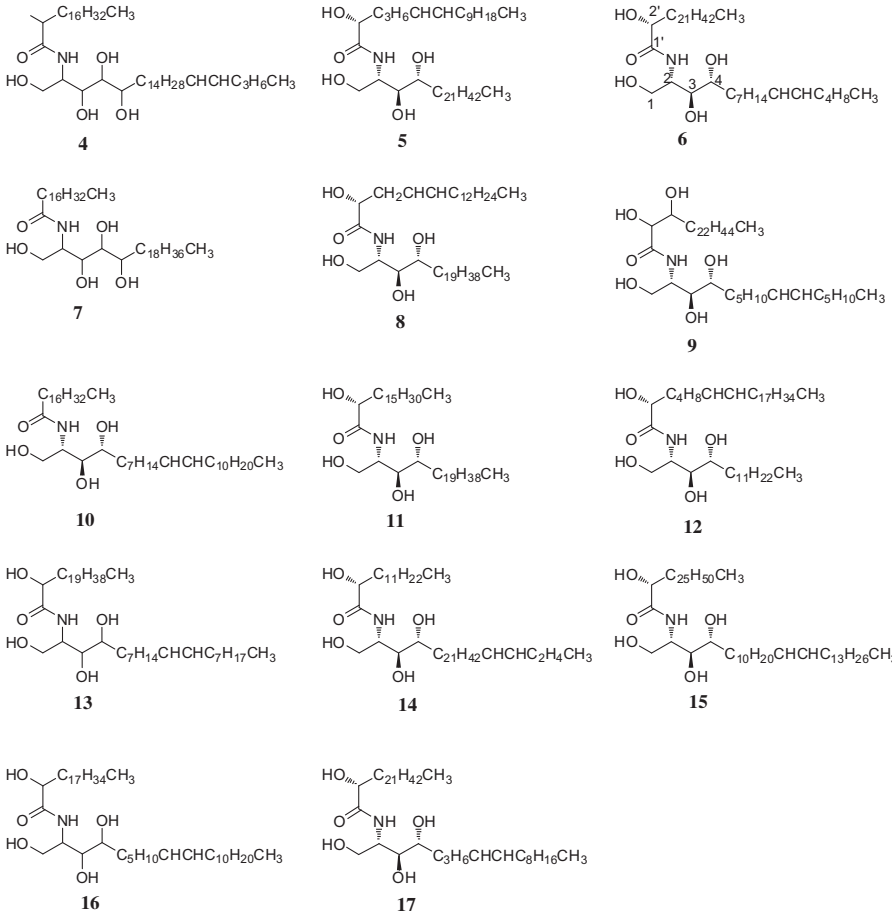


Figure 15.6 Ceramides newly isolated from African medicinal plants: tithoniamide (**4**); triumfettamide (**5**); benjaminamide (**6**); newbouldiamide (**7**); pancoviamide (**8**); ficusamide (**9**); paullinomide A (**10**); citropremide (**11**); glumoamide (**12**); cameroonemide A (**13**); triumfettamide A (**14**); (2*R*)-2-hydroxy-*N*-[(2*S*,3*S*,4*R*,15*Z*)-1,3,4-trihydroxy-15-triaconten-2-yl] octacosamide (**15**); laportomide A (**16**); (2*S*,3*S*,4*R*,8*E*)-2*N*-[(2′*R*)-2′-hydroxy-tetracosanoyl]-8(*E*)-octadecene-1,3,4-triol (**17**).

Table 15.1 Bioactivity of Ceramides and Cerebrosides from African Medicinal Plants

Compounds	Plant Source	Biological Activity
Benjaminamide (**6**)	*F. benjamina* [15] and *F. lutea* [16]	Antimicrobial [16]
Newboudiamide (**7**)	*N. laevis* [17]	Antimicrobial [18]
Pancoviamide (**8**)	*P. laurentii* [19]	Antiprotozoal, cytotoxic [19]
Ficusamide (**9**)	*Ficus exasperata* [20]	Antimicrobial [20]
Lutaoside (**18**)	*F. lutea* [16]	Antimicrobial [16]

low cytotoxicity on the normal rat L6 skeletal muscle cell line ($IC_{50} > 90$ μg/mL) [18].

15.5 New Ceramides and Cerebrosides Isolated in African Medicinal Plants

Most of the sphingolipids reported in this chapter do not show any interesting biological activity. Formed by ceramides and cerebrosides, this family of compounds structurally involves different fatty acids in their biosynthetic pathway. Some of them may or may not contain an α-hydroxylated acyl, and the long chain base can have two or three oxymethine groups. The sugar moiety in cerebrosides is mostly β-D-glucopyranose and is always attached to the oxymethylene C-1.

15.5.1 New Ceramides

Several new ceramides have been isolated from African medicinal plants (Table 15.2; Figure 15.7). This section reports such compounds with unreported biological activity.

15.5.2 New Cerebrosides

Several cerebrosides have been isolated as new compounds from African medicinal plants, but their pharmacological activities have not been evaluated. The African plant sources of these compounds are summarized in Table 15.3 and their chemical structures shown in Figure 15.7.

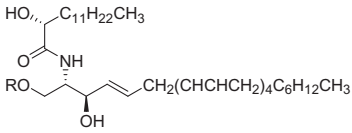
15.5.3 Related Compounds

Plants can produce or modify some secondary metabolites in response to stress [31]. Thus, a piperidinic cerebroside, (2*R*,8*Z*)-2-hydroxy-{(2*S*,3*R*,5*R*,6*S*)-3,5-dihydroxy-6-[(1*E*,5*Z*)-hexadeca-1,5-dienyl]-2-(β-D-glucopyranosyloxy)methylpiperidine-1-yl}tetracos-8-enamide (**28**),was isolated from the cultivated species *Triumfetta cordifolia* (Figure 15.8) [25]. Furthermore, several long chain−derived secondary metabolites were isolated and identified from several African plants, namely, two glycerides: glyceryl-1-eicosanoate (**29**) from the Egyptian medicinal plant *Sida spinosa* L. [32] and (2*S*)-3-[(10*Z*)-tetradec-10-enoyloxy]-2-hydroxypropanoic acid (**30**) from *Alchornea laxiflora* collected in Cameroon [26]. A known cerebroside (**31**) was obtained from *S. spinosa* L. [32], while the phytochemical studies of *Hyoseris lucida*, another Egyptian medicinal plant, led to the isolation of two structurally interesting polyacetylenic chains (**32**, **33**). In the same way, (4*R**,5*S**,6*E*,8*Z*)-ethyl-4-((*E*)-but-1-enyl)-5-hydroxypentdeca-6,8-dienoate (**34**), a ramified fatty acid ethyl ester, was obtained from *Cassia obtusifolia* harvested in the Yaoundé Centre region of Cameroon [33].

Table 15.2 Ceramides Newly Isolated from African Medicinal Plants with No Reported Activity

Compounds	Plant Source	Physical Properties	References
Tithoniamide (**4**)	*Tithonia diversifolia*	mp 129°C; $[\alpha]_D$ +9.67° ($CHCl_3$/MeOH)	[6]
Triumfettamide (**5**)	Wild *T. cordifolia*	mp 135−13°C; $[\alpha]_D$ −7.36° (C_5H_5N)	[7]
Benjaminamide (**6**)	*F. benjamina*	mp 142°C; $[\alpha]_D$ +12.3° ($CHCl_3$/MeOH)	[15]
Newbouldiamide (**7**)	*N. laevis*	mp 129°C; $[\alpha]_D$ +12° ($CHCl_3$/MeOH)	[16]
Pancoviamide (**8**)	*P. laurentii*	mp 145.4°C; $[\alpha]_D$ +16.7° ($CHCl_3$/MeOH)	[19]
Ficusamide (**9**)	*F. exasperata*	$[\alpha]_D$ +15.35° (MeOH)	[20]
Paullinomide A (**10**)	*Paullinia pinnata*	mp 174°C; $[\alpha]_D$ +17.1° ($CHCl_3$/MeOH)	[21]
Citropremide (**11**)	*Citropsis gabunensis*	mp 139°C; $[\alpha]_D$ +10.0° ($CHCl_3$/MeOH)	[22]
Glumoamide (**12**)	*Ficus glumosa*	mp 127.0−127.3°C; $[\alpha]_D$ +10.5° (THF)	[23]
Cameroonemide A (**13**)	*Helichrysum cameroonense*	mp 173°C	[24]
Triumfettamide A (**14**)	Cultivated *T. cordifolia*	mp 136−138°C; $[\alpha]_D$ −12.86° (C_5H_5N)	[25]
(2*R*)-2-Hydroxy-*N*-[(2*S*,3*S*,4*R*,15*Z*)-1,3,4-trihydroxy-15-triaconten-2-yl] octacosamide (**15**)	*A. laxiflora*	mp 139.5−140.5°C; $[\alpha]_D$ −8.05° (C_5H_5N)	[26]
Laportomide A (**16**)	*Laportea ovalifolia*	mp 119°C; $[\alpha]_D$ +8.17° ($CHCl_3$/MeOH)	[27]
(2*S*,3*S*,4*R*,8*E*)-2*N*-[(2′*R*)-2′-Hydroxy-tetracosanoyl]-8(*E*)-octadecene-1,3,4-triol (**17**)	*Cordia platythyrsa*	$[\alpha]_D$ +30.3° (MeOH)	[28]

Chemical compounds containing strong conjugated systems showed anti-inflammatory activity and other biological properties [38,39]. (2*S*)-3-[(10*Z*)-Tetradec-10-enoyloxy]-2-hydroxypropanoic acid (**30**), from *Alchornea cordifolia*, exhibited a moderate cytotoxicity against the leukemia HL60 cancer line, while a new fatty aldol, 17-*O*-triacontanoylheptadecanal (**35**), isolated from *Mimosa invisa*, showed antimicrobial activity against *E. coli*, *E. aerogenes*, *S. aureus*, *P. aeruginosa*, *K. pneumiae*, *S. typhi*, and *C. albicans*, with MICs varying between 64 and 256 μg/mL [35]. More fatty metabolites, including two glucolipids (**36**, **37**) and four polyacetylenic chains (**38**−**41**) were obtained from Cameroonian medicinal plants. The biological activity of



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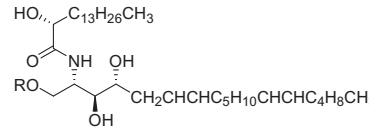

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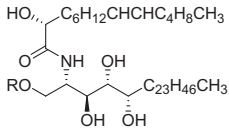

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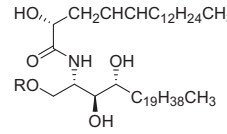

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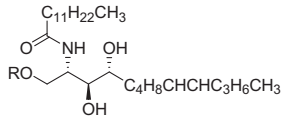

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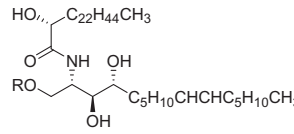

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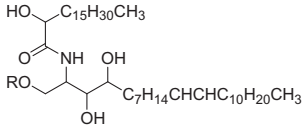

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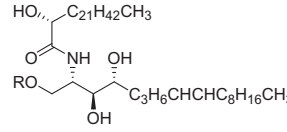

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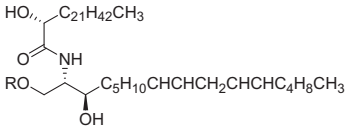

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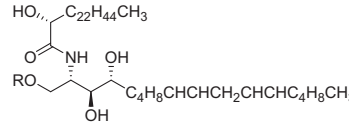

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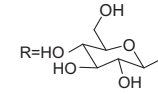


Figure 15.7 Cerebrosides newly isolated from African medicinal plants: triumfettoside Ic (**18**); lutaoside (**19**); politamide (**20**); pancovioside (**21**); paullinoside A (**22**); glumoside (**23**); laportoside A (**24**); 1-*O*-(β-D-glucopyranosyl)-(2*S*,3*S*,4*R*,8*E*)-2*N*-[(2′*R*)-2′-hydroxytetracosanoyl]-8(*E*)-octadecene-1,3,4-triol (**25**); 1-*O*-β-D-glucopyranosyl-(2*S*,3*R*,9*E*,12*E*)-2-*N*-[(2*R*)-hydroxytetracosanoyl]-octadecasphinga-9,12-dienine (**26**); 1-*O*-β-D-glucopyranosyl-(2*S*,3*S*,4*R*,9*E*,12*E*)-2-*N*-[(2*R*)-hydroxy pentacosanoyl] octadeca sphinga-9,12-dienine (**27**).

compound **40** was evaluated, but no effect was noted against the Gram-negative bacteria *B. subtilis*, Gram-negative *Pseudomonas fluorescens*, or the fungus *Cladosporium cucumerinum* [37]. Nevertheless, this compound exhibited an antimolluscicidal activity against *Biomphalaria glabrata*, with a total lethal dose (LD_{100}) of 25 μg/mL [37]. It has also been reported that compound **39** was able to prevent the growth of a panel of microorganisms, including the fungi *Epidermophyton floccosum*, *Microsporum canis*,

Table 15.3 Cerebrosides Newly Isolated from African Medicinal Plants with No Reported Activity

Compounds	Plant Source	Physical Properties	References
Triumfettoside Ic (**18**)	Wild *T. cordifolia*	mp 172−173°C; $[\alpha]_D$ +35.64 (MeOH)	[9]
Lutaoside (**19**)	*F. lutea*	mp 203−205°C; $[\alpha]_D$ +8.12° (MeOH)	[16]
Politamide (**20**)	*Ficus polita*	mp 168.5−170.5°C; $[\alpha]_D$ +0.009° (DMSO)	[29]
Pancovioside (**21**)	*P. laurentii*	mp 178°C, $[\alpha]_D$ +10.56° ($CHCl_3$/MeOH)	[19]
Paullinoside A (**22**)	*P. pinnata*	mp 137°C; $[\alpha]_D$ +13.23° ($CHCl_3$/MeOH)	[21]
Glumoside (**23**)	*F. glumosa*	mp 199.6−199.8°C; $[\alpha]_D$ +17° (THF)	[23]
Laportoside A (**24**)	*L. ovalifolia*	No data found	[27]
1-*O*-(β-D-Glucopyranosyl)-(2*S*,3*S*,4*R*,8*E*)-2*N*-[(2′*R*)-2′-hydroxy tetracosanoyl]-8(*E*)-octadecene-1,3,4-triol (**25**)	*C. platythyrsa*	$[\alpha]_D$ +53° (MeOH)	[28]
Hylodendroside-I (**26**)	*Pteleopsis hylodendron*	$[\alpha]_D$ +1.21° (CH_2Cl_2/MeOH)	[30]
Hylodendroside-II (**27**)	*P. hylodendron*	$[\alpha]_D$ +4.2° (CH_2Cl_2/MeOH)	[30]

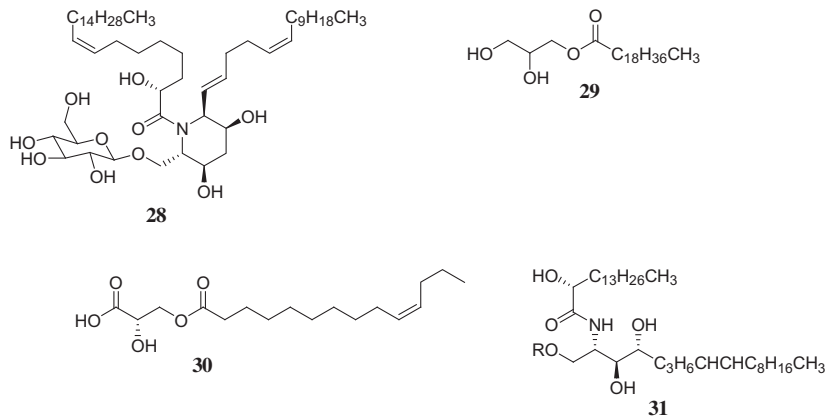
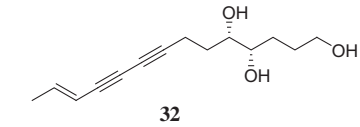


Figure 15.8 Chemical structures of some rare long chains isolated from African medicinal plants: (2*R*,8*Z*)-2-hydroxy-{(2*S*,3*R*,5*R*,6*S*)-3,5-dihydroxy-6-[(1*E*,5*Z*)-hexadeca-1,5-dienyl]-2-(β-D-glucopyranosyloxy) methylpiperidine-1-yl}tetracos-8-enamide (**28**) [25]; glyceryl-1-eicosanoate (**29**) [32]; (2*S*)-3-[(10*Z*)-tetradec-10-enoyloxy]-2-hydroxypropanoic acid (**30**) [26]; 1-*O*-β-D-glucopyranosyl-(2*S*,3*S*,4*R*,8*Z*)-2-[(2′*R*)-2′-hydroxypalmitoylamino]-8-octadecene-1,3,4-triol (**31**)



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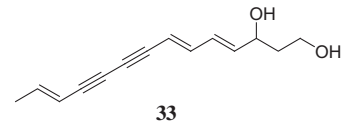

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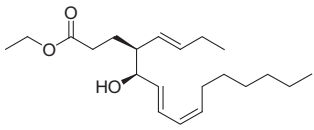

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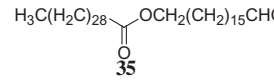

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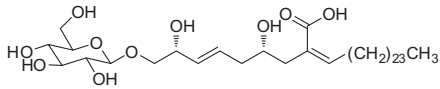

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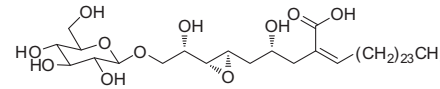

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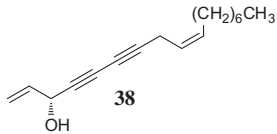

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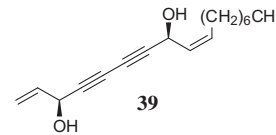

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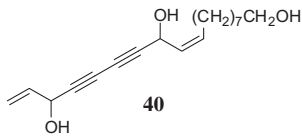

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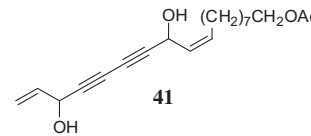

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Figure 15.8 [32]; 1,4,5-trihydroxytetradec-12*E*-en-8,10-diyne (**32**) [34]; 1,3-dihydroxytetradec-4*E*,6*E*,12*E*-trien-8,10-diyne (**33**) [34]; (4*R**,5*S**,6*E*,8*Z*)-ethyl-4-((*E*)-but-1-enyl)-5-hydroxy pentdeca-6,8-dienoate (**34**) [33]; 17-*O*-triacontanoylheptadecanal (**35**) [35]; (3*E*,8*Z*)-8-carboxy-1-(*O*-β-D-glucopyranosyl)-2,6-dihydroxytritriaconta-3,8-diene (**36**) [36]; (8*Z*)-8-carboxy-1-(*O*-β-D-glucopyranosyl)-3,4-epoxy-2,6-dihydroxytritriacont-8-ene (**37**) [36]; falcarinol (**38**) [37]; falcariridiol (**39**) [37]; (+)-9(*Z*),17-octadecadiene-12,14-diyne-1,11,16-triol (**40**) [37]; (+)-9(*Z*),17-octadecadiene-12,14-diyne-1,11,16-triol triacetate (**41**) [37].

Microsporum gypseum, *Microsporum nanum*, *Trichophyton erinacei*, *Trichophyton mentagrophytes*, *Trichophyton mentagrophytes* var. *interdigitale*, and the bacteria *B. subtilis*, *E. coli*, and *S. aureus* [40]. The activities of compounds **38** and **39** were also observed on microbial spore germination, with more than 50% inhibition at 10 ppm recorded against *Alternaria brassicicola*, *Botrytis cmerea*, *Glomerella cingulata*, and *Fusarium culmorum* [41].

15.6 Conclusions

The gluco- and sphingolipids presented above, in most cases, have not yet been evaluated for their pharmacological properties, although a number of such compounds

are key elements in cells' life cycle. Ceramides and cerebrosides remain interesting as many reports have presented some of them as potent anti-inflammatory agents [42]. Their association with paclitaxel, a well-known antineoplasic compound, enhanced apoptosis in the head and neck squamous carcinoma cell line Tu138 [43]. Mixtures of cerebrosides showed weak antifungal and antimycobacterial activity, but the effects were rather better than those recorded with a single compound, which showed weak or no activity in some cases [44]. Additionally, some cerebrosides exhibited anti-HIV-1 [45] activity, although unfortunately some side effects were noted on the liver [46]. The fact that ceramides seem to be less active than cerebrosides may be due to their high lipophilicity. Ceramides are among the most important ingredients in cosmetic products. As a result, many scientific documents have revealed their role in the water-retention capacity of the skin [47].

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16 Antibacterial, Antifungal, and Antiviral Activities of African Medicinal Plants

Ashwell R. Ndhlala, Stephen O. Amoo, Bhekumthetho Ncube, Mack Moyo, Jerald J. Nair and Johannes Van Staden

Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

16.1 Introduction

Traditional medicine (TM) is defined as "the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses" [1]. Its significance and impact on the African continent is huge, with an estimated 80% of the population depending on TM and medical practices, referred to as complementary or alternative medicine for primary health care purposes [1]. The reliance of such a large proportion of these populations on TM for primary health care needs has been attributed to a number of factors, including availability and accessibility, affordability, and extensive traditional knowledge and expertise within local communities [2]. Herbal medicines, which include herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants or other plant materials as active ingredients, are the most popular and lucrative forms of TM [1]. Figure 16.1 illustrates different forms and species of medicinal plants used in TM in South Africa.

Africa is home to two floral kingdoms: the Paleotropical Kingdom of Central Africa and the Capensis Kingdom of the Western Cape province of South Africa, the latter of which contains around 10,000 species, representing roughly 20% of Africa's floral biodiversity, forming the Cape herbal medicine [3]. This southern tip, together with the northwestern part of Africa, is characterized by winter rainfall. The southern tip of Africa also forms part of the traditional home of the Khoi/San, who have a long history of medicinal plant usage. Another important culture to mention is the Arab medicine, which is practiced in the northeastern parts of Africa. Arab medicine is, however, greatly influenced by Greek scientific and philosophical works.

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Figure 16.1 Illustration of different forms and types of medicinal plants used in traditional medicine in South Africa. Pictures were taken at an open markert in Nongoma, Zululand, South Africa. (A) *W. salutaris* and other species bark. (B) *Hypoxis hemerocallidea* corms under display. (C) An assortment of fresh and dried plant material on sale. (D) Semiprocessed (by drying and chopping) and raw wild-harvested plant materials.

Given the popularity of TMs on the African cultural landscape and its abundant floral biodiversity, allied to the chemotherapeutic potential of many of its representatives, the continent presents a relatively untapped reservoir for phytochemical prospecting and drug discovery. Microbial infections, including bacterial, fungal, and viral infections, are among the most commonly encountered diseases worldwide.

Despite the extensive use of antibiotics and vaccination programs, these diseases continue to be a leading cause of morbidity and mortality worldwide [4]. This is exacerbated by widespread antibiotic resistance, the emergence of new pathogens in addition to the resurgence of old ones, and the lack of effective new therapeutics [4]. In this regard, African traditional medicines (ATMs) provide an exciting frontier to ease this particular burden of disease on the conventional health care sector. ATMs used specifically for these purposes (i.e., microbial infections) are too numerous to categorize for a single report, and thus, for the purpose of this chapter, we chose a collection selected as "Africa's top 50 medicinal plants" as outlined in the *African Herbal Pharmacopoeia* edited by Brendler et al. [5] to survey for such properties. These plants, which were chosen based on their widespread traditional appeal and medicinal usage, were seen to be endemic to eight distinct geographical zones within Africa, namely, Sahara; Sub-Sahara; West Africa; East Africa; Central Africa; Southern Africa; Madagascar, Mauritius, and the Mascarenes as a collective; and Continental Africa itself [5]. Furthermore, 31 plant families are represented in the list, of which the Apocynaceae (5 species), Asclepiadaceae (4 species), Asteraceae (3 species), Fabaceae (3 species), and Leguminosae (3 species) are the most represented [5]. Information gathered on the plants during this review include their medicinal uses, plant parts used in TM, extracts used in the microbial assays, microbial activity, and constituents responsible for activity. As given in Table 16.1, most of these plants are exploited in ethnic medicine for treatment of wounds and infections. In addition, some of these plants are administered for viral-borne diseases such as influenza, measles, chicken pox, and, importantly, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). The literature also revealed that the majority of these plants have been pharmacologically examined for microbial activity, especially against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* [5]. Figure 16.2 presents some of the medicinal plants commonly used for bacterial, fungal, and viral infections throughout Africa. Based on these findings, it was possible to graphically compare activities for the 10 most efficacious plants within the list against these pathogens, which provides insights into their potential for clinical development. Furthermore, given the scourge of the HIV/AIDS pandemic on the continent, this survey also sheds light on the ethnic usage and pharmacological investigation of plants used for this disease, which may prove significant in the strategies directed at identifying possible chemotherapeutic candidates.

16.2 Distribution and Diversity

With only a few exceptions, Africa's flora is either tropical or subtropical [96]. This is primarily because none of the African continents extends far from the equator, and there are only a few high-elevation regions that support more temperate plants [96]. The three main biomes discernible on the continent, in order of increasing land area, are tropical forest, tropical savanna, and subtropical desert [96]. The

Table 16.1 Antibacterial Activity of Some African Medicinal Plants Recorded from Various Research Projects

Family	Species	Medicinal Uses	Plant Part Tested	Extract Tested	Activity		Bioactivity of Isolated Compounds	References
					Gram-Positive Bacteria	Gram-Negative Bacteria		
Annonaceae	*Centella asiatica* (Linn.) Urban	Skin diseases, dyspeptic complaints, worms, wound healing, fever, insomnia	Leaves	Ethanol	S.a. 10 mg/mL (MIC)	–	–	[6,7]
			Leaves	Water	S.a. 5 mg/mL (MIC)	–	–	
	X. aethiopica A. Rich	Antiseptic, bronchitis, cough, dysentery, female sterility, hypoglycemia, rheumatism	Fruits	Water	S.a. 27 mm (ZI), B.c. 27 mm (ZI)	E.c. 32 mm (ZI), E.f. 25.5 mm (ZI)	–	[8,9]
Apocynaceae	*C. roseus* (L.) G. Don f. albus Pich	Venereal diseases, leukemia, diabetes, fever, diarrhea, stomach problems	Leaves	Ethanol	S.a. 256 μg/mL (MIC)	K.p. 1024 μg/mL (MIC)	–	[10–12]
			Leaves	Methanol	S.a. 512 μg/mL (MIC)	–	–	
			Stems	Ethanol	S.a. 512 μg/mL (MIC)	E.c. 1024 μg/mL (MIC)	–	
			Roots	Ethanol	S.a. 512 μg/mL (MIC)	–	–	
			Roots	Methanol	S.a. 256 μg/mL (MIC)	–	–	
			Roots	Dichloromethane: methanol	–	O.u. 500 μg/mL (MIC), N.g. 4 mg/mL (MIC)	–	
	Mondia whitei (Hook.f.) Skeels	Abdominal pains, nausea, fever, bilharzia, sexual dysfunction, induce labor, anthelmintic, asthma, skin diseases	Roots	Water	S.h. 50 mg/mL (MIC)	–	–	[13–15]

	R. vomitoria Afz.	For treating venereal disease, neuropsychiatry disorders, jaundice, gastrointestinal problems, sexual complaints, measles, fever, malaria	Leaves	Methanol	–	–	3β-Hexadecanoyloxy-lup-20(29)-en-21-ol (E.c. 256 μg/mL MIC; S.a, S.t. 512 μg/mL MIC)	
			Roots	Methanol	S.a. 17.5 mm (ZI at 10 mg/mL)	P.a., P.m 20, 28 mm, respectively (ZI at 10 mg/mL)	–	[16,17]
	V. africana Stapf ex Scott-Elliot	Poison, stimulant, leprosy, diarrhea, mental disorders, ulcers, gonorrhea, psychedelic	Root bark	Water	S.a. 31.3 μg/mL (MIC)	E.c. 31.3 μg/mL, E.p. 31.3 μg/mL, C.d. 62.5 μg/mL, K.p. 62.5 μg/mL, P.a. 62.5 μg/mL, S.e. 62.5 μg/mL, S.f. 31.3 μg/mL (MIC)	–	[18,19]
Asclepiadaceae	*C. sanguinolenta* (Lindl.) Schlechter	Diarrhea, fever, malaria, respiratory and urinary tract infections, venereal diseases, rheumatism	Roots	Ethanol	–	–	Cryptolepine (E.c., C.j. 25 μg/mL; M.a. 2 μg/mL; M.b. 12.5 μg/mL; M.f. 16 μg/mL; M.s. 8 μg/mL; S.a. 62.5 μg/mL; S.p. <8 μg/mL MIC)	[20–23]
Asphodelaceae	*Bulbine frutescens* (L.) Willd.	Wounds, cuts, grazes, burns, sores, rashes, itches, cracked lips, mosquito bites, ringworm, herpes	Leaves	Water	B.s., M.k. 2.0, 3.0 mg/mL, respectively (MIC)	–	Phenylanthraquinones knipholone, aloctin A and B (also found in *Aloe arborescens*)	[24,25]
			Roots	Water	B.s., M.k. 3.0, 4.0 mg/mL, respectively (MIC)	–	–	

(*Continued*)

Table 16.1 (Continued)

Family	Species	Medicinal Uses	Plant Part Tested	Extract Tested	Activity		Bioactivity of Isolated Compounds	References
					Gram-Positive Bacteria	Gram-Negative Bacteria		
			Rhizomes	Water	M.k. 5.0 mg/mL (MIC)	–	–	
Asteraceae	*Artemisia afra* Jacq. ex Willd.	Respiratory tract infections, cold, influenza, stomach ailments, analgesic, anthelmintic, blocked nose	Leaves	Ethanol	B.s. 0.2 mg/mL, S.a. 0.25 mg/mL (MIC)	–	–	[26–29]
			Leaves	Dichloromethane	M.t. 1.9 μg/mL (MIC)	M.a. IC_{50} 0.25 mg/mL, M.t. IC_{50} 0.27 mg/mL (MIC)	–	
	Vernonia amyg-dalina Delile	Diarrhea, dysentery, gastroenteritis, malaria, hepatitis, worms	Roots	Water	S.g. 9.5 mm (ZI)	P.a. 9 mm (ZI), P.g. 13.5 mm (ZI), P.n. 14.5 mm (ZI)	–	[30,31]
		Cough, pneumonia, diarrhoea, boils, tonic	Leaves	Ethanol	S.a. 1.56 mg/mL (MIC), B.s. 0.78 mg/mL (MIC)	E.c. 1.56 mg/mL (MIC), K.p. 0.78 mg/mL (MIC)	Sesquiterpene lactones, vernolide, vernodalin (MIC 0.1–0.5 mg/mL against S.a. and B.s.)	[32,33]
Balanitaceae	*B. aegyp-tiaca* (L.) Delile	Whooping cough, wound healing, leucoderma, skin diseases	Leaves	Ethanol	–	S.t. 6.5 mg/mL	–	[34]
Bignoniaceae	*K. africana* (Lam.) Benth	Dysentery, sores, stomach ailments, wounds, rheumatism, skin care, cosmetic	Bark	Ethyl acetate	B.s. 10 μg/mL (MIC)	E.c.78 μg/mL, K.p. 78 μg/mL (MIC)	–	[35–37]
			Bark	Dichloromethane	–	E.c.78 μg/mL, K.p. 78 μg/mL (MIC)	–	
Bombacaceae	*A. digitata* L.	Diarrhea, dysentery, wound healing, venereal diseases; malaria, tuberculosis, toothache, anemia, fever, influenza	Stem bark	Water/ethanol	S.a.mr 78 μg/mL (MIC)	–	–	[38]
			Stem bark	Dichloromethane	S.a.mr 156 μg/mL (MIC)	–	–	
			Stem bark	Methanol	S.a.mr 78 μg/mL (MIC)	–	–	

Burseraceae	*B. sacra* Flueck	Wound healing, skin diseases, urinary tract infections, gynecological disorders, anti-inflammatory agent	Seeds	Essential oils	S.a. 4 mg/mL, B.c. 2 mg/mL (MIC)	E.c. 4 mg/mL, P.v. 3 mg/mL (MIC)	–	[11]
	C. myrrha Engl.	Trauma, arthritis, fractures, diseases caused by blood stagnation, wounds, worms, sepsis, cough, snakebite, infections in mouth, teeth, and eyes	Leaves	Ethanol	S.a. 0.4 mg/mL (MIC)	E.c. 0.18 mg/mL (MIC)	–	[39–41]
Canellaceae	*W. salutaris* (G. Bertol.) Chiov.	Fever, malaria, cold, influenza, venereal diseases, abdominal pain, toothache, constipation, cancer, ulcers, headache, cough, chest infections	Bark	Methanol	B.s., S.a., S.e. 0.78, 0.38, 0.15 mm, respectively (ZI) at 10 μL of crude plant extract	–	–	[27,42,43]
			Bark	Water	S.a., S.e. 1.34, 0.25 mm, respectively (ZI) at 10 μL of crude plant extract	B.s. 0.36 mm (ZI) at 10 μL of crude plant extract	–	
Clusiaceae	*H. madagascariensis* Lam. ex Poir	As an abortifacient and antiseptic for treating anemia, asthma, tuberculosis, fever, angina, diarrhea, dysentery, STDs, malaria, parasitic skin diseases, wounds	Leaves	Water	B.s. 1.9 mg/mL (MIC)	E.c. 1.9 mg/mL (MIC)	Harunmadagascarin D (B.m. 10 mm ZI at 5 μg/μL) and astilbin (M.l, S.e. 25, 50 μg MIC, respectively)	[44–48]
				Ethyl acetate	M.l., M.s., S.h., S.x. 50, 250, 100, 25 μg/mL, respectively (MIC)	–	–	
				Ethanol	S.a. 94 μg/mL (IC_{100})	–	–	

(*Continued*)

Table 16.1 (Continued)

Family	Species	Medicinal Uses	Plant Part Tested	Extract Tested	Activity		Bioactivity of Isolated Compounds	References
					Gram-Positive Bacteria	Gram-Negative Bacteria		
			Stem bark	Ethanol	S.a., E.f. 94, 188 μg/mL, respectively (IC_{100})	–	–	
				Acetone	E.f., S.a. 0.31, 0.62 mg/mL, respectively (MIC)	E.c., P.a. 0.62, 0.31 mg/mL, respectively (MIC)	–	
				Water	E.f., S.a. 2.5 mg/mL each (MIC)	E.c., P.a. 2.5 mg/mL each (MIC)	–	
				Hexane	E.f, S.a. 1.25, 0.62 mg/mL, respectively (MIC)	E.c., P.a. 1.25, 2.5 mg/mL, respectively (MIC)	–	
				Dichloromethane	E.f, S.a. 0.15 mg/mL each (MIC)	E.c., P.a. 0.83, 0.31 mg/mL, respectively (MIC)	–	
				Chloroform	E.f, S.a. 0.15 mg/mL each (MIC)	E.c., P.a. 0.62, 0.15 mg/mL, respectively (MIC)	–	
				Ethyl acetate	E.f, S.a. 0.15, 0.31 mg/mL, respectively (MIC)	E.c., P.a. 0.62, 0.31 mg/mL, respectively (MIC)	–	
				Methanol	E.f, S.a. 0.31 mg/mL each (MIC)	E.c., P.a. 0.62, 0.31 mg/mL, respectively (MIC)	–	
Combretaceae	*C. micranthum* G. Don.	Wound healing, sores, cough, bronchritis, malaria, fever, smallpox, chicken pox, measles	Leaves	Acetone	S.a. 400 μg/mL (MIC)	–	–	[49]

	T. sericea Burch. ex DC.	Tuberculosis, diarrhea, wounds, infections, inflammation, STDs, diabetes, gonorrhea, menorrhagia, bilharzia	Roots	Ethyl acetate	S.a. 1.5 mg/mL (MIC), B.s. 0.3 mg/mL (MIC)	E.c. 1.5 mg/mL (MIC), K.p. 0.7 mg/mL (MIC)	Anolignan B (IC_{50} 3.8 μg/mL against B.s.)	[50−52]
Euphorbiaceae	*A. madagascariense* Lam.	Dysentery, fever, diabetes, boils, muscle pain	Leaves	Water	S.a. 4.0 mg/mL (MIC)	E.c., P.a., S.t. 8.0 mg/mL each (MIC)	–	[53,54]
	E. hirta Linn.	Galactagogue, venereal discharges, dysentery, diarrhea, asthma, bronchitis, hay fever, cough, cold	Leaves	Ethanol	S.a. 2.2 mg/mL (MIC)	E.c., P.a. 5.9, 7.4 mg/mL, respectively (MIC)	Diterpenes, triterpenes, afzelin, quercitrin, myricitrin	[55]
Fabaceae	*A. senegal* (L.) Willd.	Roots: constipation, diarrhea, stomach disorders, gonorrhea; bark, leaves, and gum: cold, cough, dysentery, sore throat, typhoid, urinary tract infection	Bark	Methanol	S.a. 8.0 mm (ZI) at 100 mg/mL	P.a., P.v., S.t., S.d. 8.0, 10.0, 8.0, 8.0 mm, respectively (ZI) at 100 mg/mL	Arabic acid	[56]
			Bark	Methanol	K.p. 8.0 mm (ZI) at 100 mg/mL	P.a., P.v., S.t., S.d. 8.0, 10.0, 8.0, 8.0 mm, respectively (ZI) at 100 mg/mL	–	
	Aspalathus linearis (Brum.f) R. Dahlgr.	Herbal (rooibos) tea for neutraceutical, health, and beauty products; relief of vomiting, nausea, stomach cramps, heartburn, dermatological problems	Leaves, stems	Water	S.a. 57% growth inhibition at 2 mg/mL, B.c, L.m. S. m. 45%, 55%, and 48% growth decrease, respectively, at 2 mg/mL	E.c. 69% growth inhibition at 5 mg/mL	–	[57−59]

(*Continued*)

Table 16.1 (Continued)

Family	Species	Medicinal Uses	Plant Part Tested	Extract Tested	Activity		Bioactivity of Isolated Compounds	References
					Gram-Positive Bacteria	Gram-Negative Bacteria		
				Ethanol	–	E.c. 60% growth inibition at 10 mg/mL	–	
	C. cajan (L.) Millsp.	Treatment or relief of cough, bronchitis, fever, hepatitis, diabetes, measles, urinary infections, dysentery, menstrual disorders, inflammation, pain, ulcers	Leaves	Methanol	B.c. 39 μg/mL (MIC)	S.t., P.a. 2.5 mg/mL each (MIC), S.s. 5 μg/mL (MIC)	–	[60–62]
				Ethanol	B.s., S.a., S.e. 2.5 mg/mL each (MIC), 10.0 mg/mL (MBC)	–	Cajanuslactone (S.a. 31 μg/mL MIC; B.s., S.e. 125 μg/mL each MIC), cajaninstilbene acid (S.e. 13 μg/mL MIC; B.s., S.a. 25 μg/mL each MIC)	
				Water	–	E.c., S.t. 0.125 mg/mL each (MIC)	–	
				Petroleum ether	S.a. 0.125 mg/mL (MIC)	S.t. 62.5 μg/mL (MIC)	–	
			Seeds	Methanol	B.c. 625 μg/mL (MIC)	K.p., P.a., S.t. 5 mg/mL each (MIC)		
	Cyclopia genisto-ides (L.) R. Br.	Herbal (honeybush) tea for neutraceutical, health, and beauty products; as a restorative and expectorant in chronic catarrh and pulmonary tuberculosis; relief of nausea, heartburn	Leaves, stems	Ethanol	–	E.c. 80% growth inhibition at 10 mg/mL	–	[58,59]
	Cyclopia subternata Vog.	Herbal (honeybush) tea for neutraceutical, health, and beauty products	Leaves, stems	Ethanol	–	E.c. 85% growth inhibition at 10 mg/mL	–	[58,59]

	S. frutescens R. Br.	Dysentery, diarrhea, wounds, infections, pustules, influenza, chicken pox, fever	Leaves	Acetone	S.a. 10.0 mg/mL (MIC)	E.c. 1.25 mg/mL, P.a. 1.25 mg/mL, E.f. 1.25 mg/mL (MIC)	–	[63–65]
Flacourtiaceae	*A. theiformis* Benn.	Dysentery, fever, gastrointenstinal infections, ulcers, jaundice, stomach pains, skin infections	Leaves	Methanol	S.a. 500 μg/mL	S.e. 500 μg/mL	–	[66]
Geraniaceae	*Pelargonium sidoides* DC.	Gonorrhea, diarrhea, dysentery	Roots	Hexane	M.a. 64 mg/mL (MIC)	–	Coumarins, umckalin, gallic acid, flavonoids (quercetin)	[36,67,68]
Hypoxidaceae	*H. hemero-callidea* Fisch. & Avé-Lall.	Bladder disorders, dizziness, insanity, tonic, prostate hyperplasia	Leaves/corms	Water	S.a. 0.39 mg/mL (MIC)	K.p. 0.25 μg/mL (MIC)	–	[26,69,70]
Malvaceae	*Hibiscus sabdariffa* L.	Calyx: aphrodisiac; leaves: diuretic, diaphoretic, cholagogic, cough, childbirth, wounds, boils, mouthwash, toothache	Calyces	80% Methanol	S.a., M.l. 0.3 mg/mL each (MIC)	P.a., E.c. 1.3 mg/mL each (MIC)	Mucilage polysaccharides, pectin; ascorbic, citric, malic, tartaric acids	[71,72]
Meliaceae	*Trichilia emetica* Vahl.	Hepatic diseases, purgative, antiepileptic, antipyretic, antimalarial, intestinal worms, jaundice, skin diseases	Leaves	Acetone	S.a. 0.60 mg/mL (MIC)	E.c. 0.40 mg/mL, P.a. 0.40 mg/mL, E.f. 0.26 mg/mL (MIC)	Limonoids, trichilins	[73,74]
Moringaceae	*Moringa oleifera* Lam.	Malaria, wound healing	Seeds	Methanol	–	S.t. 76.5% at 2.5% concen-tration, E.c. 36.8% at 2.5% concen-tration (disc diffusion)	–	[75,76]

(*Continued*)

Table 16.1 (Continued)

Family	Species	Medicinal Uses	Plant Part Tested	Extract Tested	Activity		Bioactivity of Isolated Compounds	References
					Gram-Positive Bacteria	Gram-Negative Bacteria		
Pedaliaceae	*H. procum-bens* (Burch.) DC. ex Meisn.	Allergies, analgesia, arteriosclerosis, boils, skin injuries, ulcers, sores, childbirth, dysmenorrhea, edema, fever, gastrointestinal disorders, headache, migraine, malaria, myalgia, neuralgia, tendonitis, urinary tract infections	Tubers	50% Ethanol	S.a., M.l. 10, 100 μg/mL, respectively (MIC)	E.c., M.m., B.s., P.m. 100, 100, 100, 20 μg/mL, respectively (MIC)	Iridoid glycosides, harpagoside, pagoside, cinnamic acid, caffeic acid, procumbide, procumboside, flavonoids, fatty acids, harpagoquinone, stigmasterol, sitosterol (compounds not tested for antibacterial properties)	[77]
Rosaceae	*P. africana* (Hook. f.) Kalkm.	For treating chest pain, diarrhea, fever, genitourinary complaints, allergies, inflammation, kidney diseases, malaria, stomachache	Bark	Ethanol	B.s., S.a. 3.12, 1.56 mg/mL, respectively (MIC)	K.p. 2.9 mg/mL (MIC)	–	[78–80]
			Bark	Water	B.s., S.a. 2.9 mg/mL each (MIC)	–	–	
			Leaves	Ethanol	B.s., S.a. 1.56, 2.9 mg/mL, respectively (MIC)	–	–	
			Stem bark	Methanol	S.a., E.h., S.p. 0.073, 0.625, 0.3 mg/mL, respectively (MIC)	P.a. 0.3125 mg/mL (MIC)	–	

Rubiaceae	*N. latifolia* Sm.	Malaria, sterility, female fertility, stomachache, urinary retention, hernia, leprosy, diarrhea, dysentery	Leaves, stem bark	Methanol	S.a. 64 μg/mL, B.c. 128 μg/mL (MIC)	E.c. 32 μg/mL (MIC), P.a. 64 μg/mL (MIC), S.f. 32 μg/mL (MIC), S.t., cr 32 μg/mL (MIC)	–	[81,82]
Rutaceae	*A. betulina* (P. J. Bergius) Pillans.	Urinary tract infections, stomach ailments, cough	Aerial parts	Methanol: dichloro-methane (1:1)	B.c. 4.0 mg/mL, S.a. 4.0 mg/mL (MIC)	K.p. 4.0 mg/mL (MIC)	–	[83]
			Leaves	Ethanol		E.c. > 1.0 mg/mL (MIC)	–	[84]
			Leaves, flowers (essential oils)	Steam distilled	S.a. 5.8 mm, E.h. 4 mm (ZI) at 10 μL of undiluted extract	E.c. 6 mm, P.a. 4 mm (ZI) at 10 μL of undiluted extract	–	[85]
	T. asiatica Lam.	Diaphoretic, stomachic, antipyretic, antimalarial, lung diseases, rheumatism, snakebite	Leaves	Ethyl acetate	S.a. 0.039 mg/mL, S.e. 0.078 mg/mL, B.s. 0.156 mg/mL (MIC)	E.f. 2.5 mg/mL (MIC)	Flindersine (MIC 31.25 μg/mL against B.s.)	[19,86]
Sterculiaceae	*G. kola* Heckel	Antihepatotoxic drug extract, bronchitis, diarrhea, throat infections, aphrodisiac, cough	Leaves	Ethanol	S.a. 13 mm (ZI) at 0.1 mL of crude extract	E.c. 12 mm, P.a. 13 mm (ZI) at 0.1 mL of crude extract	–	[87]
Xanthorrhoeaceae	*A. ferox* Mill.	As a laxative, emetic, relief of arthritis, sinusitis, conjunctivitis, and opthalmia, skin and wound healing, treatment of infection-related	Leaves	Methanol	–	N.g. 0.5 mg/mL (MIC)	Aloe emodin (B.c., E.c. 62.5 μg/mL each (MIC); B.s., S.a. 125 μg/mL each (MIC); S.e., S.s. 250 μg/mL each (MIC)), chrysophanol (S.e., E.c., B.s. 31.25, 125, 250 μg/mL, respectively, (MIC)), aloin A (B.c., B.s., S.a. 62.5 μg/mL each	[88–91]

(*Continued*)

Table 16.1 (Continued)

Family	Species	Medicinal Uses	Plant Part Tested	Extract Tested	Activity		Bioactivity of Isolated Compounds	References
					Gram-Positive Bacteria	Gram-Negative Bacteria		
		ailments including sexually transmitted infections					(MIC); E.c., S.e. 125 μg/mL each (MIC); S.s. 250 μg/mL (MIC))	
Zingiberaceae	*Aframomum melegueta* (Roscoe) K. Schum.	Wound healing, skin rushes, mouth sores, boils, fractures, stomachache, cough remedy, measles, yellow fever	Seeds	Methanol (3% w/v)	S.a. 11.8 mm, B.s. 15.2 mm (ZI)	E.c.15.4 mm P.a. 5.7 mm (ZI)	–	[92,93]
				n-Hexane (10 mg/mL)	S.a. 11.5 mm (ZI)	E.c. 30 mm, P.a. 23 mm (ZI)	–	[17]
				Methanol (10 mg/mL)		P.a. 25 mm (ZI)	–	
	S. aethiop-icus (Schweinf.) B. L. Burtt	Treatment or relief of cold, cough, influenza, sore throat, pain, asthma, dysmeno-rrhea, hysteria	Leaves	Ethyl acetate	B.c., B.s., S.a. 3.0, 1.56, 1.56 mg/mL, respectively (MIC)	E.c., K.p. 3.13, 6.25 mg/mL, respectively (MIC)	–	[94,95]
				Ethanol	B.s., S.a. 3.13, 1.56 mg/mL, respectively (MIC)	E.c., K.p. 3.13 mg/mL each (MIC)	–	
			Roots	Ethyl acetate	B.s., S.a. 0.78, 1.56 mg/mL, respectively (MIC)	E.c., K.p. 6.25, 12.5 mg/mL, respectively (MIC)	–	
				Ethanol	B.s., S.a. 1.56, 0.78 mg/mL, respectively (MIC)	E.c., K.p. 6.25 mg/mL each (MIC)	–	

Rhizomes	Ethyl acetate	B.c., B.s., M. k., S.a. 3, 1.56, 4, 1.56 mg/mL, respectively (MIC)	E.c., K.p. 6.25 mg/mL each (MIC)	–
	Ethanol	B.s., S.a. 1.56 mg/mL each (MIC)	E.c., K.p. 3.13, 6.25 mg/mL, respectively (MIC)	–
	Acetone	B.c., B.s., M. k., S.a., S.e. 4, 3, 3, 3, 2 mg/mL, respectively (MIC)	E.c., P.v. 3, 4 mg/mL, respectively (MIC)	–
Roots	Ethyl acetate	B.s., S.a. 0.78, 1.56 mg/mL, respectively (MIC)	E.c., K.p. 6.25, 12.5 mg/mL, respectively (MIC)	–
	Ethanol	B.s., S.a. 1.56, 0.78 mg/mL, respectively (MIC)	E.c., K.p. 6.25 mg/mL (MIC)	–

B.c., *Bacillus cereus*; B.m., *Bacillus megaterium*; B.s., *Bacillus subtilis*; C.j., *Campylobacter jejuni*; C.d., *Citrobacter diversus*; E.f., *Enterococcus faecalis*; E.h., *Enterococcus hirae*; E.c., *Escherichia coli*; E.p., *Escherichia paracoli*; K.p., *Klebsiella pneumoniae*; L.m., *Listeria monocytogenes*; M.k., *Micrococcus kristinae*; M.l., *Micrococcus loteus*; M.r., *Micrococcus roseus*; M.s., *Micrococcus sedentarius*; M.k., *Mocuria kristinae*; M.m., *Morganella morganii*; M.a., *Mycobacterium aurum*; M.b., *Mycobacterium bovis*; M.f., *Mycobacterium fortuitum*; M.s., *Mycobacterium smegmatis*; M.t., *Mycobacterium tuberculosis*; N.g., *Neisseria gonorrhoeae*; O.u., *Oligella ureolytica*; P.g., *Porphyromonas gingivalis*; P.n., *Porphyromonas nigrescens*; P.m., *Proteus mirabilis*; P.v., *Proteus vulgaris*; P.a., *Pseudomonas aeruginosa*; P.m., *Pseudomonas maltophilia*; S.e., *Salmonella enteritidis*; S.tp., *Salmonella typhi*; S.t., *Salmonella typhimurium*; S.h., *Schistosoma haematobium*; S.f., *Shigella flexnerii*; S.d., *Shigella dysenteriae*; S.s., *Shigella sonnei*; S.a., *Staphylococcus aureus*; S.a.mr, *Staphylococcus aureus* methicillin resistant; S.e., *Staphylococcus epidermidis*; S.h., *Staphylococcus haemolyticus;* S.t.cr., *Salmonella typhi - Chloramphenicol resistant*; S.s., *Staphylococcus saprophytious*; S.x., *Staphylococcus xylosus*; S.g., *Streptococcus gordonii*; S.m., *Streptococcus mutans*; S.p., *Streptococcus pyogenes*; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; STDs, sexually transmitted diseases; ZI, zone of inhibition; (−), no data.

Figure 16.2 Some of the widely used medicinal plants used for bacterial, fungal, and viral infections throughout Africa: (A) *B. frutescens*, (B) *W. salutaris*, (C) *H. hemerocallidea* (African potato), (D) *P. sidoides*, (E) *A. ferox.*

subtropical desert biome includes some of the driest locations on earth. The largest desert region is the Sahara in northern Africa, which extends from the west coast of Africa to the Arabian Peninsula, and is part of the largest desert system in the world, which extends into southern Central Asia [96]. Plants that grow in this region include succulents, water-dependent plants, and ephemerals [96]. Where moisture is available, grasslands predominate, and as rainfall increases, grasslands gradually become tropical savanna [96]. The grassland/tropical savanna biome forms a broad swath across much of Central Africa and dominates much of eastern and southern Africa [96]. Plants found in these regions include savanna grasses and herbs, as well as savanna shrubs and trees [96]. Tropical forests make up a much smaller area of Africa than the other two biomes and are most abundant in portions of Central Africa [96]. Scattered tropical forest regions also occur along major river systems of West Africa, from the equator down to southern Africa [96]. Typical plants of these regions are lianas and epiphytes, as well as forest floor plants [96].

It is thus apparent that Africa's top 50 medicinal plants are to be found among the most diverse habitats on the planet. These habitats are further divisible into eight distinct regions over which the plants are preeminent: Sahara; Sub-Sahara; West Africa; East Africa; Central Africa; Southern Africa; and Madagascar, Mauritius, and the Mascarenes. *Balanites aegyptiaca* (Balanitaceae) is the only representative that thrives in the Saharan region but also extends to dry lands south of the Sahara, including Sudan [5]. It is a multibranched, spiny shrub or tree that stands between 10 and 12 m tall, with a spherical crown, obovate leaflets, and yellow-green flowers.

The Sub-Saharan region is home to 14 of these medicinal plants (Table 16.1), including *Acacia senegal* and *Euphorbia hirta*, genera of which both are universally known. *A. senegal* (Fabaceae), also referred to as "gum Arabic tree," is a deciduous shrub or small tree that can reach a height of 15 m, with alternate bipinnate leaves and white flowers [5]. The papery bark is yellow-brown to purple-black and is commonly seen peeling off in strips. Seven representatives of these medicinal plants are endemic to West Africa, including *Combretum micranthum*, *Cryptolepis sanguinolenta*, *Garcinia kola*, *Griffonia simplicifolia*, *Nauclea latifolia*, *Strophanthus gratus*, and *Xylopia aethiopica*. Also referred to as "negro pepper" or "moor pepper," *X. aethiopica* (Annonaceae) is an evergreen, aromatic tree, growing up to 20 m high, 50 cm wide, with a straight bole [5]. Flowers are greenish-white, solitary or occurring in small clusters of 3−5. Fruits are peppery and occur as monocarp with orange-red to black cylindrical seeds. It is native to the lowland rainforest and moist fringe forests in the savanna zones of West Africa, from Senegal in the north to Angola in the south [5].

The East African region harbors three of these medicinal plant representatives, *Boswellia sacra*, *Commiphora myrrha*, and *Toddalia asiatica*. Of these, *T. asiatica* (Rutaceae) is a scandent shrub or woody liana with trifoliolate-palmate leaves and axillary yellowish-white flowers. Also referred to as "ajua" or "patte poule," the plant is distributed through the eastern regions of Africa from Sudan in the north to South Africa in the south [5].

Central Africa provides fertile ground for *Harungana madagascariensis* and *Voacanga africana*, both of which are included among Africa's top medicinal

plants. The "voacanga tree" (*V. africana*) is a small evergreen tree or shrub reaching up to 6 m in height, with a low, widely spreading crown. The leaves are opposite, obovate, and acuminate, and flowers are white, borne in loosely branched glabrous, auxiliary, or terminal inflorescences [5]. The spherical, mettled green fruits occur in pairs, with seeds wrapped in a yellow pulp. Geographically, the plant is widespread in mainland tropical Africa, ranging from Senegal across to Kenya and reaching south as far as Zimbabwe and Mozambique [5].

The Southern African region is home to at least 10% of the global floral biodiversity of around 300,000 species. Not surprisingly, therefore, the majority of Africa's top medicinal plants are resident in this region. Of the 18 listed for this region, *Aloe ferox* (Asphodelaceae) is best known for its many ethnobotanical and medicinal uses [5]. It is a single-stemmed succulent with broad, spiny leaves and distinctive orange or red flowers, blooming between May and August.

The Madagascar−Mauritius−Mascarenes zone is exclusively home to four of Africa's top medicinal plants, including *Antidesma madagascariense*, *Aphloia theiformis*, *Danais fragrans*, and *Ravenala madagascariensis. D. fragrans* (Rubiaceae) is a woody, scandent plant with stems of 1−4 m in length, elliptical or oval leaves, and fragrant orange-red flowers. Also referred to as "bongonomby," the plant is restricted in its distribution, being found only in Madagascar and the Mascarenes [5]. *Cajanus cajan* (Fabaceae) and *Catharanthus roseus* (Apocynaceae) are unique within the African medicinal plant list as they are the only representatives found throughout Continental Africa [5].

16.3 Antibacterial Activity

The antibacterial activity of the top 50 African medicinal plants is presented in Table 16.1. Although the majority of these plants are used traditionally for treating infection-related ailments, some plant species such as *G. simplicifolia* and *S. gratus* are yet to be evaluated for their potential antibacterial activity. In other cases, only zonal inhibition diameters were recorded as a measure of antibacterial activities. This measure makes it difficult to compare reported activity to others in the literature. The pitfalls associated with the use of the diffusion technique for determining antibacterial activity of medicinal plant extracts have been highlighted by many researchers. For example, nonpolar or lipophilic extracts are known to not easily diffuse into agar. The differences in solubility, volatility, and diffusion characteristics are among the factors that may affect the antimicrobial potency of medicinal plant extracts [97]. Therefore, the microdilution method of quantifying minimum inhibitory concentrations (MICs) has become the most preferred technique for evaluating antibacterial potency of plant extracts or compounds. In order to standardize many "hits" reported in the literature, some researchers have suggested using stringent endpoint criteria for describing interesting antibacterial activity. Thus, plant extracts having MIC values below 1 mg/mL have been considered in some cases as constituting "good activity" [98]. Other researchers recommend MIC values below

100 μg/mL and 10 μg/mL as criteria for describing the activity of a plant crude extract and isolated compound, respectively, as noteworthy or potent [97,99].

Among the top 50 African medicinal plants, extracts obtained from *Adansonia digitata*, *C. cajan*, *C. sanguinolenta*, *Harpagophytum procumbens*, *H. madagascariensis*, *Kigelia africana*, *N. latifolia*, *Prunus africana*, *T. asiatica*, and *V. africana* exhibited potent antibacterial activity (MIC < 100 μg/mL) against Gram-positive and/or Gram-negative bacteria. *Bacillus* sp. and *Staphylococcus* sp. were the most commonly used Gram-positive strains employed in evaluating the antibacterial activity of plant extracts, while *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella* sp. were the most frequently used Gram-negative strains. In general, lower MIC values against Gram-positive bacteria are often reported for plant extracts, as compared to the Gram-negative ones. This has been attributed to the thick outer murein layer in the structure of Gram-negative bacteria, which prevents the entry of inhibitors [100]. Although clinical isolates have been used in some studies, the American Type Culture Collection (ATCC) strains have been widely used as a standard [97]. It is important that clinical isolates be well characterized for them to be useful in evaluating antibacterial activity. Of particular note is *A. digitata*, stem bark methanolic extracts of which have demonstrated potent activity against methicillin-resistant *S. aureus*. However, of these medicinal plants, very few have had their antibacterial compounds isolated and evaluated. Indeed, there is a gap in knowledge when it comes to the isolation of antibacterial compounds from plants whose extracts have demonstrated strong activity. Figure 16.3 presents some of the antimicrobial compounds isolated from the most utilized African plants. Of course, it must be noted that some of the activities recorded for plant extracts may be due to

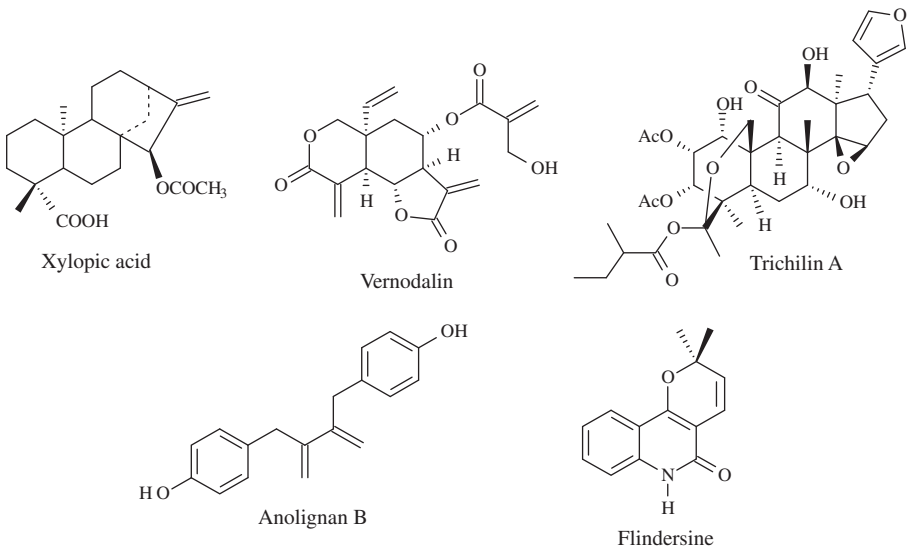

Figure 16.3 Miscellaneous antimicrobial agents identified in African medicinal plants.

synergistic actions between two or more of the constituent compounds rather than a single pure compound. Nevertheless, antibacterial investigation of African medicinal plants needs to be taken beyond the preliminary screening for benefits in drug development. Factors such as season and location of plant collection are known to affect antibacterial activity of plant extracts [99,101]. It is therefore expedient that such details be recorded when reporting antimicrobial activity of plant extracts.

S. aureus and *E. coli* are perhaps the most widely used test organisms used for performing activities against Gram-positive and Gram-negative bacteria, respectively. This is largely because of their significant contribution to human health. Figures 16.4 and 16.5 present the bioactivity of the top 10 African medicinal plants with the best recorded MIC values against the Gram-positive *S. aureus* and Gram-negative *E. coli*. For the Gram-positive *S. aureus*, all 10 extracts had MICs < 300 μg/mL, with *H. procumbens* (tuber, 50% ethanol) recording the best MIC value of 10 μg/mL. For the Gram-negative *E. coli*, the top 10 plant extracts presented a wider MIC value range, with the highest (*Sutherlandia frutescens*) having an MIC of 1250 μg/mL and the lowest and most potent (*X. aethiopica*) recording 31 μg/mL.

16.4 Antifungal Activity

Besides bacterial infections, people are also battling with the challenges of fungal infections. In developed countries, the number of deaths due to fungi largely surpasses that by parasites [102]. As opposed to bacteria, very few fungal pathogens

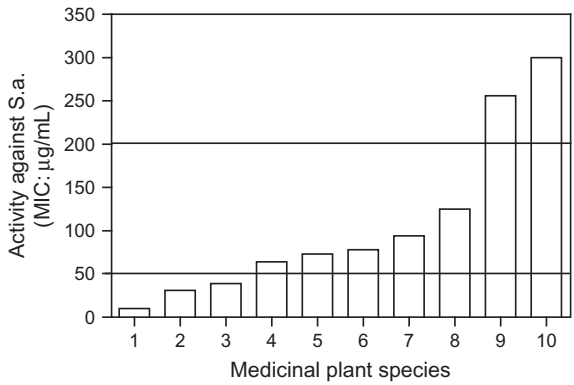

Figure 16.4 Antibacterial activity against Gram-positive *S. aureus* of the top 10 African medicinal plants recorded by various researchers. 1. *H. procumbens* (tubers, 50% ethanol); 2. *X. aethiopica* (roots, water); 3. *T. asiatica* (leaves, ethyl acetate); 4. *N. latifolia* (leaves, methanol); 5. *P. africana* (stems, methanol); 6. *A. digitata* (bark, water); 7. *H. madagascariensis* (leaves, ethanol); 8. *C. cajan* (leaves, petroleum ether); 9. *C. roseus* (leaves, ethanol); 10. *H. sabdariffa* (calyces, 80% methanol).
Source: The data used to plot the graph were obtained from Refs. [8,10,38,44,52,71,77,78,81,86].

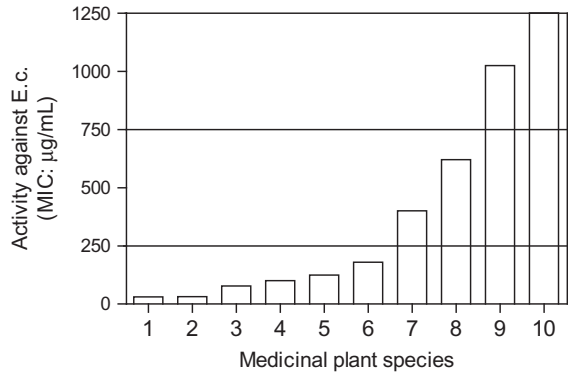

Figure 16.5 Antibacterial activity against Gram-negative *E. coli* of the top 10 African medicinal plants recorded by various researchers. 1. *X. aethiopica* (roots, water); 2. *N. latifolia* (leaves, methanol); 3. *K. africana* (bark, ethyl acetate, dichloromethane); 4. *H. procumbens* (tubers, ethanol); 5. *C. cajan* (leaves, water); 6. *C. myrrha* (leaves, ethanol); 7. *T. emetica* (leaves, acetone); 8. *H. madagascariensis* (stems, acetone, dichloromethane, chloroform); 9. *C. roseus* (stems, acetone); 10. *S. frutescens* (leaves, acetone). *Source*: The data used to plot the graph were obtained from Refs. [8,10,35,39,44,60,63,73,77,81].

are causative agents of infectious diseases. Among these, *C. albicans*, which forms part of the normal flora of the respiratory, gastrointestinal, and female genital tracts in humans, is thought to be responsible for up to 90% of fungal infections [103]. Immunosuppression is the key factor that triggers the establishment and dissemination of fungal infections. The establishment of an infection by a fungal pathogen and its invasion and growth in host tissues require that the fungus be aggressive at a time when the host's immune response is debilitated [102]. Opportunistic pathogens are normally eradicated by the innate immunity of the immunocompetent host. Up to 90% of all HIV/AIDS patients suffer fungal infections at some point during the course of the disease, with up to 20% of them dying as a direct consequence of such infections [103,104].

Infectious diseases due to pathogenic fungi are still a significant cause of mortality and morbidity in most developing countries [105]. To these populations, plants offer a unique resource that provides a diverse array of natural products, which they exploit in the treatment of a diverse range of ailments. Not only are these plants used to treat human ailments, but also domestic animals and even crops. In order to fully exploit the potential medicinal value of these plants, several traditionally used species have been subjected to robust and multiple pharmacological screening for biological activity against selected animal, plant, and human pathogenic fungi (Table 16.2). From these screenings, different extracting solvents and plant parts have been or are being used, with varying levels of efficacy being recorded from case to case.

The hexane leaf extracts of *T. asiatica* tested against *Epidermorphyton floccosum* (MIC: 0.62 µg/mL), *Trichophyton rubrum* 296 (MIC: 0.125 µg/mL), *T. rubrum*

Table 16.2 Antifungal Activity of Some African Medicinal Plants Recorded from Various Research Projects

Family	Species	Plant Part Tested	Extract Examined	Best Activity Recorded	Bioactive Compounds Isolated and Activity	References
Annonaceae	*X. aethiopica* A. Rich	Leaves	Water	C.a. 15.17 mm (ZI)	Essential oils (C.a., A.fl. 15.17, 21 mm, respectively (ZI))	[8,9]
		Fruits	Water	A.fl. 21 mm (ZI)	–	
Apocynaceae	*C. roseus* (L.) G. Don f. albus Pich	Roots	Water	C.a. 500 μg/mL (MIC)	–	[11]
	R. vomitoria Afz.	Bark	Dichloromethane	A.n., C.a., C.n. 0.4, 12.5, 6.3 μg/mL, respectively (MIC)	–	[16,17,106]
		Leaves	Methanol	–	3β-Hexadecanoyloxy-lup-20(29)-en-21-ol (C.a. 64 μg/mL (MIC))	
		Roots	Methanol	A.n., C.a. 20, 19 mm, respectively (ZI)++ at 10 mg/mL	–	
Asclepiadaceae	*C. sanguinolenta* (Lindl.) Schlechter	Roots	Ethanol	C.a., S.c. 62.5, 5 μg/mL, respectively (MIC)	–	[22,23]
Asteraceae	*A. afra* Jacq. ex Willd.	Leaves	Ethanol	C.a., C.n. 0.25, 0.5 mg/mL, respectively (MIC)	–	[107]
Bignoniaceae	*K. africana* (Lam.) Benth	Fruits	Methanol	C.n. 1 mg/mL	–	[108]
Bombacaceae	*A. digitata* L.	Seeds	Essential oils	F.g., F.p. 0.95, 0.78 mg/mL, respectively (MIC)	–	[109]
		Flowers	Methanol	M.c., E.p., T.r. 1.0, 0.125, 1.0 mg/mL, respectively (MIC)	–	[110]
Burseraceae	*B. sacra* Flueck	Gum resin	Essential oils	C.a. 8 mg/mL (MIC)	–	[111]
	C. myrrha Engl.	Leaves	Chloroform	C.n. 2.8 μg/mL	–	[39,41]
Canellaceae	*W. salutaris* (G. Bertol.) Chiov	Bark	Ethanol	C.a. 256 μg/mL (MIC)	–	[112,113]
		Leaves	Dichloromethane	F.m. 15 mm (ZI)	–	
		Bark	Methanol/hexane	F.m. 12 mm (ZI)	–	
Clusiaceae	*H. madagascariensis* Lam. ex Poir	Stem bark	Hexane	A.f., C.a., C.n., M.c., S.s. 1.25, 1.25, 0.31, 0.15, 1.25 mg/mL, respectively (MIC)	–	[47]
			Dichloromethane		–	

				A.f., C.a., C.n., M.c., S.s. 0.62, 0.62, 0.31, 0.15, 0.62 mg/mL, respectively (MIC)		
			Chloroform	A.f., C.a., C.n., M.c., S.s. 0.62, 0.62, 0.31, 0.15, 0.62 mg/mL, respectively (MIC)	–	
			Ethyl acetate	A.f., C.a., C.n., M.c., S.s. 0.62, 0.62, 0.62, 0.31, 0.62 mg/mL, respectively (MIC)	–	
			Acetone	A.f., C.a., C.n., M.c., S.s. 0.31, 0.15, 0.15, 0.15, 0.15 mg/mL, respectively (MIC)	–	
			Methanol	A.f., C.a., C.n., M.c., S.s. 2.5, 2.5, 1.25, 0.31, 0.62 mg/mL, respectively (MIC)	–	
			Water	A.f., C.a., C.n., M.c., S.s. 2.5, 0.62, 0.62, 0.62, 2.5 mg/mL, respectively (MIC)	–	
Combretaceae	*T. sericea* Burch. ex DC++	Leaves	Dichloromethane	C.a. 0.08 mg/mL (MIC)	–	[50−52]
			Hexane	A.f., C.n. 0.16 mg/mL, 80 μg/mL, respectively (MIC)	–	
			Ethyl acetate	S.s., M.c. 20 μg/mL each (MIC)	–	
Euphorbiaceae	*E. hirta* Linn.	Leaves	Methanol	C.a. 0.033 mg/mL (MIC)	–	[114]
Fabaceae	*A. linearis* (Brum.f) R. Dahlgr.	Leaves, stems	Water	C.a., S.c. 8.5 mm each (ZI), 53% growth inhibition at 2 mg/mL	–	[57,58,115]
		Leaves, stems	Ethanol	B.c. 36% spore viability reduction at 100 mg/mL	–	
	C. cajan (L.) Millsp.	Leaves	Ethanol	C.a., C.k., C.t. 256, 512, 256 μg/mL, respectively (MIC)	–	[116]
		Roots	Ethanol	C.a., C.k., C.t. 512 μg/mL each (MIC)	–	
	C. genistoides (L.) R. Br.	Leaves, stems	Ethanol	B.c. 19% spore viability reduction at 100 mg/mL	–	[58]
Geraniaceae	*P. sidoides* DC	Roots	Acetone	A.n., F.o., R.s. 53, 47, 35 mm, respectively, (ZI) at 0.5 mg/mL	–	

(*Continued*)

Table 16.2 (Continued)

Family	Species	Plant Part Tested	Extract Examined	Best Activity Recorded	Bioactive Compounds Isolated and Activity	References
Hypoxidaceae	*H. hemerocallidea* Fisch. & Avé-Lall.	Leaves/corms	Water	C.a. 0.39 mg/mL (MIC)	–	[69]
Leguminosae	*A. senegal* (L.) Willd.	Bark	Hexane	C.a. 15 mm (ZI)	–	[117]
Meliaceae	*T. emetica*	Leaves	Hexane	C.a., C.n., S.s., M.c., A.fl. 0.3, 1.25, 0.15, 1.25, 0.45 mg/mL, respectively (MIC)	–	[73,74]
Pedaliaceae	*H. procumbens* (Burch.) DC. ex Meisn.	Whole plant	Water	C.a., C.k. 100 μg/mL (MIC)	Harpagoside	[77]
Rosaceae	*P. africana* (Hook. f.) Kalkm.	Stem bark	Methanol	M.g., T.m. 0.078, 0.04 mg/mL, respectively (MIC)	–	[80]
Rubiaceae	*N. latifolia* Sm.	Stem bark	Methanol	C.a. 2 μg/mL (MIC)	–	[81]
Rutaceae	*A. betulina* (P.J. Bergius) Pillans.	Aerial parts	Methanol: dichloro-methane (1:1)	C.a. 2 mg/mL (MIC)	–	[83]
	T. asiatica Lam.	Leaves	Hexane	E.f., T.r., 0.62, 0.125 μg/mL (MIC)	Flindersine (E.f. 31.25 μg/mL MIC)	[19,86]
Sterculiaceae	*G. kola* Heckel	Seeds	Ethanol	C.a. 9 mm (agar gel diffusion)	–	[87]
Xanthorrhoeaceae	*A. ferox* Mill.	Leaves	Juice	C.n. 1.2 cm (ZI) at 1 mL	–	[91,118]
		Leaves	Acetone	A.a., M.h., P.n., S.co. 2.53, 5.18, 9.51, 8.99 mg/mL, respectively (LC_{50})	–	
Zingiberaceae	*A. melegueta* (Roscoe) K. Schum.	Seeds	Methanol (3% w/v)	A.n., C.a. 6.9, 12.8 mm, respectively (ZI)	–	[93]
	S. aethiopicus (Schweinf.) B.L. Burtt	Bulbs	Ethanol/ethyl acetate/ hexane	C.a. 1.03 mg/mL (MIC)	–	[119]

A.a., *Alternaria alternaria*; A.f., *Aspergillus fumigatus*; A.fl., *Aspergillus flavus*; A.n., *Aspergillus niger*; B.c., *Botrytis cinera*; C.a., *Candida albicans*; C.k., *Candida krusei*; C.n., *Cryptococcus neoformans*; C.t., *Candida tropicalis*; E.f., *Epidermorphyton floccosum*; F.g., *Fusarium graminearum*; F.m., *Fusarium moniliforme*; F.o., *Fusarium oxysporum*; F.p., *Fusarium proliferatum*; M.c., *Microsporum canis*; M.g., *Microsporum gypseum*; M.h., *Mucor hiemalis*; P.n., *Penicillium notatum*; R.s., *Rhizopu stolonifer*; S.c., *Saccharomyces cerevisiae*; S.co., *Schizophyllum commune*; S.s., *Sporotrichum schenckii*; T.m., *Trichophyton mentagrophytes*; T.r., *Trichophyton rubrum*; MIC, minimum inhibitory concentration; ZI, zone inhibition; (–), no data.

57/01 (MIC: 0.62 μg/mL), and *Scopulariopsis* sp. (MIC: 0.125 μg/mL) [86] were, remarkably, the most active of all extracts tested using the microdilution technique (Table 16.2). The quinoline alkaloid flindersine, from leaf extracts of the plant, was found to be active against *E. floccosum* (MIC: 31.25 μg/mL). This activity is far better than that of most of the isolated pure compounds, making these extracts promising potentials for the future discovery of novel therapeutics. The plant belongs to the Rutaceae family. Notwithstanding the excellent bioactivity displayed by the extracts from this plant species, methanol−dichloromethane (1:1) extracts of *Agathosma betulina*, a member of the same family (Rutaceae), was recorded among the lowest bioactivity when it was tested against *C. albicans* [120]. Of notable interest among the plants screened against *C. albicans* is the recently reported excellent MIC of 2 μg/mL from the methanol stem bark extracts of *N. latifolia* [81], a plant belonging to the Rubiaceae family. Other extracts that showed excellent activity include *C. myrrha* chloroform leaf extract (MIC: 2.8 μg/mL), *Terminalia sericea* leaf ethyl acetate (MIC: 20 μg/mL), *Rauvolfia vomitoria* bark dichloromethane (MIC: 0.4 μg/mL), and *E. hirta* leaf methanol extract (MIC: 33 μg/mL) against *Cryptococcus neoformans*, *Sporotrichum schenckii*, *Alternaria alternaria*, and *C. albicans*, respectively (Table 16.2). Dichloromethane bark extracts of *R. vomitoria* also showed consistently good activity against both *C. albicans* and *C. neoformans*, with MIC values of 12.5 μg/mL and 6.3 μg/mL, respectively, compared to the methanol isolated pure compound (3β-hexadecanoyloxy-lup-20(29)-en-21-ol) (Table 16.2), with an MIC of 64 μg/mL. Essential oils from the gum resin of *B. sacra* recorded the least (8 mg/mL) bioactivity against *C. albicans* of all the plant extracts tested using the microdilution method (Table 16.2). Compared to the other methods such as agar dilution and paper disc diffusion, the microdilution method offers a better qualitative and quantitative measure of extract activity and has become the most widely used technique for modern pharmacological screenings.

C. albicans has been the most widely used test organism for antifungal activity, largely because of its significant contribution to human health. Figure 16.6 shows the bioactivity of the top 10 African medicinal plants with best recorded MIC values against *C. albicans*. All 10 extracts had MICs ≤ 0.3 mg/mL, with *N. latifolia* stem bark methanol extract recording the best MIC of 2 μg/mL. Although *C. albicans* remains the most common opportunistic yeast pathogen in HIV/AIDS and other immunocompromised patients, other *Candida* species such as *Candida dubliniensis*, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida guilliermondii* are also common. Among these, only *C. krusei* has been screened for bioactivity (Table 16.2). In addition, other common fungi used in test models include *Aspergillus niger*, *Aspergillus fumigatus*, *C. neoformans*, *E. floccosum*, *Fusarium graminearum*, *Fusarium proliferatum*, *Microsporum canis*, *T. rubrum*, and *Saccharomyces cerevisiae*.

Despite their widespread use in TM against fungal infections, some plant species have not been extensively studied, and some show very poor bioactivity when screened against some of the causative agents. A notable example in this regard is *Warburgia salutaris*, one of the most important and popular TMs of tropical

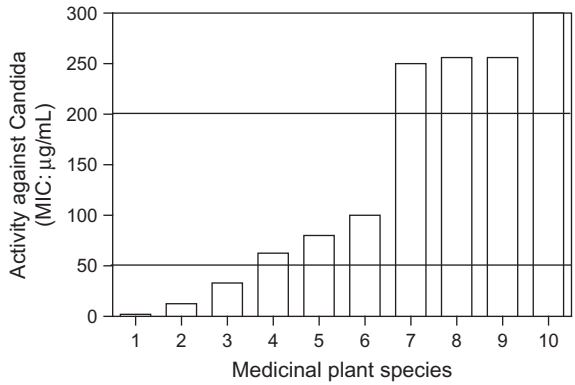

Figure 16.6 Anticandidal activity of the top 10 African medicinal plants recorded by various researchers. 1. *N. latifolia* (bark, methanol); 2. *R. vomitoria* (leaves, ethanol); 3. *E. hirta* (leaves, methanol); 4. *C. sanguinolenta* (roots, ethanol); 5. *T. sericea* (leaves, dichloromethane); 6. *H. procumbens* (whole plant, water); 7. *A. afra* (leaves, ethanol); 8. *C. cajan* (bark, dichloromethane); 9. *W. salutaris* (bark, ethanol); 10. *T. emetica* (leaves, hexane).
Source: The data used to plot the graph were obtained from Refs. [17,22,23,51,73,77,81,107,113,114,116].

Africa. Surprisingly, the documented knowledge about this plant does not match its wide usage and popularity [5]. As indicated in Table 16.1, the tree is widely used to treat abdominal pain, cancer, constipation, cold, cough, fever, headache, influenza, malaria, rheumatism, and venereal diseases. This has put immense pressure on the tree, which has subsequently become rare and endangered, particularly in South Africa. The bark is chemically similar to the leaves and is used to produce a branded product (tablets), marketed by Phyto Nova as a natural antibiotic to treat oral and esophageal thrush [121].

16.5 Antiviral Activity

Apart from bacterial and fungal infections, the world, and Africa in particular, has to deal with the ruthless devastation of viral diseases, which in most cases are the most difficult to deal with. Unlike bacterial and fungal cells, which exist as free-living entities, viruses are small infectious intracellular parasites, which contain little more than wads of genetic material in the form of either RNA or DNA, surrounded by a lipid-carbohydrate-containing envelope [122]. Viruses can infect all types of organisms, humans, animals, and plants alike.

The spread of viruses is achieved in many ways, but the major one is through vectors, often insects. Viruses that affect humans and animals are often transmitted through contact and/or exposure to infected fluid. The HIV is transmitted through

sexual contact and/or exposure to infected blood. Some viruses are airborne (e.g., influenza viruses) and are spread by coughing or sneezing. Rotaviruses are transmitted by the faecal−oral route and are passed from person to person by contact, entering the body through food or water. Viruses in plants are often transmitted from plant to plant by insects (e.g., aphids that feed on plant sap).

The first line of virus control is therefore control of the spreading methods. This includes control of virus vectors and prevention of contact with infected hosts. This has, however, failed, especially when it comes to the human-infecting viruses such as HIV, which is spread mostly through sexual contact. As it stands, according to the WHO and UNAIDS, more than 34 million people worldwide are infected with HIV. More than two-thirds (69%, or 23−25 million) of these reside in Sub-Saharan Africa, which harbors roughly 91% of the world's HIV-positive children. However, some unconfirmed reports have surfaced, claiming that HIV infection rates have leveled out and fertility has begun to recover. South Africa, one of the countries with high HIV prevalence, recently reported a drop in HIV/AIDS statistics [123], thus "turning the tide" in the HIV/AIDS war. To cite an example, in the year 2010, in Gauteng, South Africa's most populous province, where life expectancy is 57 years, HIV-related deaths have dropped by 20% [123]. This could be due to the far-reaching changes in govenment policies on the epidemic, geared toward support of the infected and vigorous educational programs meant to educate the general populace on prevention of infection and caring for the infected. Other reasons for the drops or leveling of HIV statistics could be improved quality of life. Most people in Africa are now beginning to experience good living, all owed to interventions from different govenments and aid from Western countries to deal with poverty, unemployment, food insecurity, and inequality. This, however, may not be true for some pockets of Africa which are still ravaged by war, malnutrition, and bad governance. Another important point to make is the current availability of therapies meant to improve the lives of the infected and reduce the possibility of new infections. Such therapies include the use of synthetic antiretroviral drugs and natural remedies such as extracts from medicinal plants, all thanks to the scientific advances that may eventually put a major dent on the epidemic.

Table 16.3 presents the medicinal plants most used within the top 50 list on the African continent that have been tested against a range of viruses including HIV, feline herpes, *Herpes simplex*, human cytomegalovirus, respiratory syncytial, and yellow fever viruses. It is surprising that the knowledge and research on plants used for viral conditions are poorly documented, considering the wide use of medicinal plants in Africa. Medicinal plants make up an important resource for drug discovery, yet documented information is scarce. This could be attributed to the high cost involved in antiviral assays, most of which are based on manufactured kits. Very few research groups and institutions have research grants sufficient to fund the purchase of these expensive kits. A solution to this would be an increase in government and institutional funding toward promoting programs based on effectiveness and efficiency in order to optimize the use of resources. Equally useful would be the establishment of research centers throughout Africa, with the aim of research on different aspects of different viruses. Examples of such centers are

Table 16.3 Antiviral Activity of Some African Medicinal Plants Recorded from Various Research Projects

Family	Species	Plant Part	Extract	Activity	Chemical Constituents	References
Apiaceae	*C. asiatica* (Linn.) Urban	Aerial parts	Water	HSV-1, 362.40 μg/mL (ED_{50})	Asiaticoside	[124]
Apocynaceae	*Carissa edulis* (Forssk.) Vahl	Roots, bark, leaves	Water, hexane, dichloromethane, acetone	HSV-1 60 μg/mL (MIC), 97.8% (ZI); HSV-2 60 μg/mL (MIC), 97.8% (ZI) CDV; FHV-1 $EC_{50} < 70$ μg/mL (MIC)	–	[125–127]
	V. africana Stapf ex Scott-Elliot	Root bark	Water	Chikungunya viral disease	–	[18,19]
Asteraceae	*Vernonia colorata* Drake	Leaves	Water	Fever	–	[32,33]
Bombacaceae	*A. digitata* L.	Leaves	Methanol	Flu 0.72 μg/mL (MIC)	–	[128]
			DMSO	Flu 0.12 μg/mL (MIC); HSV 1.0 μg/mL (MIC); RSV 16.2 μg/mL (MIC)	–	
		Bark	Water	HIV-1 RT 0.1 mg/mL (IC_{50})	–	[129]
Combretaceae	*C. micranthum*	Leaves	Methanol	HSV-1 2 μg/mL; HSV-2 4 μg/mL (EC_{50})	Alkaloids (combretine and betonicine)—not tested	[130]
	T. sericea Burch. ex DC	Leaves	Methanol	HIV-1 RDDP inhibition (98%); HIV-1 RNase inhibition (99.3%); methanol leaf extract	–	[50–52]
Euphorbiaceae	*E. hirta* Linn.	Aerial parts	50% Methanol	HIV-1, 5 ± 0.5 μg/mL (IC_{50})	–	[131]
Fabaceae	*A. linearis* (Brum.f) R. Dahlgr.	Leaves	Alkaline water	HIV 38.9 μg/mL (EC_{50})	Polysaccharide (HIV inhibition at 250 μg/mL)	[132]
	C. cajan (L.) Millsp.	Leaves, stems, roots	Water, ethanol	Absence of cytopathic effect at 250 mg/mL (MV)	–	[133]
	S. frutescens R.Br.	Leaves	Water	HIV, chicken pox, influenza	Catechin	[63–65]
Geraniaceae	*P. sidoides* DC	Roots	Water	HSV-1 40 μg/mL (IC_{50})	–	[134]
Hypoxidaceae			Water	Unconfirmed uses against HIV	–	[70]

	H. hemerocallidea Fisch. & Avé-Lall.	Leaves/ corms				
Malvaceae	*H. sabdariffa* L.	Leaves	Ethanol	MV	–	[135]
Moringaceae	*M. oleifera* Lam.	Leaves	Water	50% reduction of HSV-1 100 μg/mL (MIC)	–	[136]
Rosaceae	*P. africana* (Hook.f.) Kalkm.	Stem bark	Water	HCMV 80 μg/mL (EC_{50} plaque inhibition)	–	[137]
Rutaceae	*T. asiatica* Lam.	Leaves	Hexane	Measles virus, influenza	–	[19,86]
Xanthorrhoeaceae	*A. ferox* Mill.	Leaves	Water	HSV-1 (detectable activity at 1 mg/mL)	Aloin (significant against HSV-1 at 63 μg/mL)	[138]
Zingiberaceae	*A. melegueta* (Roscoe) K. Schum.	Seeds	Ethanol	MV 125 μg/mL (MIC); YFV 250 μg/mL (MIC)	–	[17,139]

CDV, canine distemper virus; DMSO, dimethyl sulfoxide; FHV-1, feline herpesvirus-1; HSV, *Herpes simplex* virus; HSV-1, *Herpes simplex* virus-1; HSV-2, *Herpes simplex* virus-2; HCMV, human cytomegalovirus; HIV, human immunodeficiency virus; MV, measles virus; Flu, influenza virus; RSV, respiratory syncytial virus; YFV, yellow fever virus; (–), no data.

the Botswana–Harvard AIDS Institute and Centre for the AIDS Programme of Research in South Africa (CAPRISA).

Some small-scale projects have also been launched, as in rural KwaZulu-Natal in South Africa, encouraging the use of medicinal plants to manage HIV/AIDS-related illnesses. An HIV/AIDS support clinic was started at Ngwelezana Hospital, near Empangeni in Zululand, in 1997 by Dr Peter Haselau, with the objectives of providing support and clinical care, as well as identifying affordable and effective management protocols for people living with HIV/AIDS. Indigenous plants that have been introduced in the program include *Sutherlandia* sp., *Warburgia* sp., and *Siphonochilus aethiopicus* as remedies in various forms, from creams to tablets, all of which have been reported to have therapeutic qualities beneficial to those with HIV.

Despite the lack of scientific data on the potency of medicinal antiviral plant extracts, some notable results have been reported (Table 16.3). For the last several years, testing plants based on ethnopharmacological data for antiviral activity has been successful in many studies, highlighting the importance of this approach as a guide in finding biologically active plant material [140]. As evident from Table 16.3, most plants are screened against different types of HIV, followed by the *Herpes simplex* virus. In relation to its usage for HIV/AIDS, clinical studies have shown that *S. frutescens* taken on a daily basis can improve appetite, facilitate weight gain, and improve the CD4 counts of HIV-positive patients [63]. Catechin isolated from *S. frutescens* was shown to have moderate activity on HIV-1 integrase [63]. Of significance for its antiviral potential, *T. sericea* was strongly active against the HIV-1 RNA dependent DNA polymerase (RDDP) and HIV-1 RNase enzymes, with 98% and 99.3% inhibition, respectively [50].

V. africana in combination with *Euphorbia tirucalli* is known to be effective in the treatment of chikungunya viral disease [18,19], while *T. asiatica* is known to be effective in measles and influenza patients [141]. However, there is still a gross lack of information on the activity of any isolated compounds from such promising medicinal plants.

16.6 Concluding Remarks

The African continent is universally recognized as the epicenter for the use, practice, and trade in TM. This status is drawn out of several contributing factors, including an abundant floral biodiversity platform with two resident floral kingdoms, affordability, a fragmented conventional health care sector, and extensive traditional knowledge and expertise within local communities. Infectious diseases borne by bacterial, fungal, and viral pathogens have long been recognized as the leading causes of morbidity and mortality worldwide, and this has been exacerbated by more recent concerns such as multidrug resistance and the lack of effective new therapeutic regimens. The use of traditional remediation for such purposes is, as expected, extensive on the African continent and, thus, too widely encompassing for the framework of a single review. For this reason, we selected “Africa’s top 50

medicinal plants" as a category in which the status of research in the field could be quantified. These plants, which are representative of 31 plant families, are endemic to 8 distinct geographical zones on the continent, and are widely used in ethnic medicine for wounds and infections, as well as viral-borne diseases such as influenza, measles, chicken pox, and HIV/AIDS. Based on the available pharmacological literature, it was possible to select the 10 most efficacious plants against the commonplace *E. coli*, *S. aureus*, *C. albicans*, and HIV/AIDS infections. Of these, *X. aethiopica* was seen to be the most potent against *E. coli*, the root water extract of exhibiting an MIC of 31 μg/mL. Against *S. aureus*, *H. procumbens* was the most active, with an MIC of 10 μg/mL for tuber 50% ethanol extracts. *N. latifolia* was the most potent plant against *C. albicans*, with methanol stem bark extract exhibiting an MIC of 2 μg/mL against each fungal strain. Although many of these plants are administered for viral-borne diseases, we focused our attention on the HIV/AIDS virus due to its impact and prevalence on the African continent. As such, *S. frutescens* was seen to be the most potent against this virus, with 98% and 99.3% inhibition of the HIV-1 RDDP and HIV-1 RNase enzymes, respectively. Together, these findings correlate well with the traditional medicinal uses of the plants, and should go some way in steering programs aimed at elucidating potential candidates for clinical development.

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17 Antimalarial and Other Antiprotozoal Products from African Medicinal Plants

Denis Zofou[a], *Victor Kuete*[b] *and Vincent P.K. Titanji*[a]

[a]Biotechnology Unit, University of Buea, Buea, Cameroon,
[b]Department of Biochemistry, University of Dschang, Dschang, Cameroon

17.1 Introduction

Protozoan parasites are unicellular organisms that are morphologically and functionally distinct and can perform almost all functions of life. They live, however, at the expense of their animal hosts. Most parasitic protozoans of public health importance in tropical regions can be grouped into four major classes: Sporozoa, Flagellates, Rhizopoda, and Ciliates. This chapter focuses more on diseases caused by Plasmodia (malaria) and three major trypanosomatid diseases, leishmaniasis, human African trypanosomiasis (HAT), and Chagas disease.

Malaria is alleged to be one of the oldest human diseases, and it remains the world's most important parasitic disease, especially when *Plasmodium falciparum* is the causative agent [1,2]. The scourge is endemic in over 100 developing countries, accounting for about 40–45 million disability adjusted life years (DALYs), and kills an estimated 1.2 million people each year in Africa [3]. In Sub-Saharan Africa, one in five children dies before they are 5 years old, and 75% of the deaths are attributed to malaria [4]. The other important protozoan diseases include leishmaniasis, African trypanosomiasis, and Chagas disease, which have been classified among the "neglected tropical diseases (NTDs)" by WHO. As the wording implies, the NTDs have attracted little attention, whether at the community, national, or international levels, despite their heavy burden. Like malaria, all three trypanosomatid diseases are vector-borne and mostly affect populations living in poverty [5].

In the absence of effective vaccines, the fight against these infections mainly relies on chemotherapy and vector control through the use of insecticide-treated bed nets, insecticides, and environmental care. Unfortunately, the phenomenon of resistance has been a constant threat to chemotherapies and insecticides. On the

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other hand, the funding of drug research is yet to be given the priority it deserves at the local level in most malaria-endemic countries, which cannot afford the heavy investment for research and development (R&D) in the pharmaceutical sector. Therefore, it is necessary to devise new ways of developing cost-effective medicines for the NTDs [6], preferably from the abundantly rich flora of the African continent.

With a disproportionately large share of the global burden of communicable and noncommunicable diseases in sub-Saharan Africa, it is reasonable to expect that the solutions to these problems would be home grown [7].

For thousands of years, plants have constituted the basis of traditional medicine systems, and recently, natural products have provided lead compounds for drug development. The discovery of quinine and its subsequent isolation from *Cinchona* in 1820 is considered one of the most significant medical discoveries, and malaria treatment with quinine marked the first successful use of a chemical compound to treat an infectious disease [8,9]. Africa is the world's second largest continent after Asia; it possesses a rich flora, with an estimated 68,000 plant species, of which at least 35,000 are endemic to the continent. Medicinal plants and the drugs derived from them are the most important and readily available sources of health care remedies to rural people in Africa, with an estimated 80% of African population relying on them [10,11].

Generally, there exist two types of traditional pharmacopoeia: the specialized pharmacopoeia, which is practiced by traditional healers for difficult health problems, and the popular or general pharmacopoeia, which is common knowledge in a given community and is used by individuals mostly for treating common ailments such as fever, headaches, wounds, and diarrhea [9,12]. Traditional medicinal preparations are commonly sold in markets and public places or administered by healers in their homes, which serve as traditional clinics. Whole plants or parts of them are usually prepared and administered as oral decoctions, steam baths, infusions, or enemas. Most remedies are a concoction of two or more plant species; solvents used include water, palm wine, or oils. Health problems are often self-treated first with the popular pharmacopoeia, also called self-aid or auto-medication [9,12–14].

Drug R&D from natural products has regained the interest of African and international researchers in recent decades, certainly thanks to increasing combined efforts from local governments and regional and international organizations. A good number of plant species have been screened against *P. falciparum* and other protozoa, and promising leads have been identified from several plant species locally employed in African folk medicines.

In this chapter, we report on the plants that have been identified as antiprotozoal plants and the evaluation of their biological activities. The present report updates previous reviews [9,15] and extends to three other diseases, namely leishmaniasis, HAT, and Chagas disease. The review covers plant identification and screening for related diseases up to 2012.

The data on the medicinal plants were collected through a review of published articles available on the Internet, books previously released on the target diseases,

and information from various research groups. The chapter reviews the prevalence and burden of malaria and other protozoan diseases in Africa and discusses the current control strategies and their limitations, as well as the progress made in the control of these diseases in Africa. The chapter ends with a review of the major strategies used in drug R&D, with particular reference to pharmacological activities of African medicinal plants that have been explored as potential sources of new drug candidates or phytomedicines in the African continent and abroad. This last section is structured according to plant families and is restricted to products with highly significant pharmacological activity. Preference is given to plant species that have undergone full investigation leading to the identification of active pure compounds ($IC_{50} < 20$ μg/mL) isolated and extracts or essential oils with good activity ($IC_{50} < 5$ μg/mL).

17.2 The Costs of Malaria and Other Protozoan Diseases to the African Population

17.2.1 Malaria

Malaria is a mosquito-borne disease caused by protozoans belonging to the genus *Plasmodium*. More than 200 species cause the disease in vertebrates, among which *Plasmodium knowlesi* and *Plasmodium cynomolgi* infect monkeys, *Plasmodium gallinaceum* targets birds, *Plasmodium berghei* and *Plasmodium chabaudi* parasitize rodents, and *Plasmodium basilisci* infects reptiles [16]. Today, five *Plasmodium* species are known to cause the disease in humans, namely *P. falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae*, and most recently, *P. knowlesi*. *P. falciparum* is by far the most deadly, accounting for 98% of malaria cases in Sub-Saharan Africa. However, *P. vivax* is thought to cause about 25−40% of the global malaria burden, particularly in Southeast Asia and South America [17]. *Anopheles* mosquitoes represent the main transmission vector of malaria. Mosquitoes breed in stagnant water, the seasonal transitions being favorite periods for their development and multiplication. There exist about 500 different species of *Anopheles*, and up to 60 of them transmit the disease. The most frequent species that malaria are *Anopheles gambiae*, *Anopheles arabiensis*, *Anopheles obscursus*, *Anopheles guadrimacutus*, *Anopheles nili*, and *Anopheles moucheti*[18]. The vector distribution therefore determines the distribution and endemicity of malaria. For example, in the United States and Europe, where climatic factors are not favorable to *Anopheles*, malaria is very rare or absent. However, it important to note that malaria was endemic and extremely common in the eastern and southern US until widespread vector control in the 20th century. Sporadic cases occur in these regions among recent immigrants or visitors. The term "airport" malaria refers to malaria caused by infected mosquitoes that are transported rapidly by aircraft from a malaria-endemic region to a nonendemic country.

According to the World Health Organization, an estimated 3.3 billion people were at risk of malaria in 2011, with populations living in Sub-Saharan Africa having the highest risk of acquiring malaria. Approximately 80% of cases and 90% of

deaths are estimated to occur in the WHO African region, where children under 5 years of age and pregnant women are most severely affected. The disease remains endemic in 104 countries (99 of which have ongoing malaria transmission). There were about 219 million cases of malaria in 2010 and an estimated 660,000 deaths in 2011 [19].

Almost 2000 African children succumb to malaria every day [20]. With increased effort in controlling malaria in Africa in recent years, it is reported that between 2000 and 2010, malaria mortality rates fell by 26% around the world, and decreased up to 33% in the WHO African region during the same period. Fifty countries are on track to reduce their malaria incidence rates by 75%, in line with the World Health Assembly and Roll Back Malaria targets for 2015. However, these countries account only for 3% (7 million) of malaria cases around the world [19]. Africa continues to bear the heaviest burden of malaria, with close to 80% (174 million) of total estimated yearly cases, among which 98% are caused by the most deadly *P. falciparum* parasite. The disease kills about 600,000 people (91% of total deaths worldwide) on the continent every year. More than 80% of estimated malaria deaths worldwide occur in just 14 countries, and 80% of estimated cases happen in 17 countries, with the Democratic Republic of the Congo and Nigeria together accounting for >40% of the estimated global deaths. At the World Health Organization, it is therefore judiciously thought that international targets for reducing malaria cases and deaths will not be attained unless considerable progress can be made in these 17 most affected countries [18].

17.2.2 Leishmaniasis

Leishmaniasis is caused by four different species of flagellate protozoan parasites of the genus *Leishmania*, all transmitted to humans by sand flies (*Lutzomyia* and *Phlebotomus* spp.), with many animals (rodents, cats, dogs, etc.) serving as reservoirs. *Leishmania donovani* is the worst species responsible for visceral leishmaniasis, which is characterized by a systemic infection accompanied by nausea, vomiting, chills, fever, and hepatosplenomegaly. *Leishmania braziliensis* (from Brazil) causes a deforming mucocutaneous disease deforming the nose and palate. *Leishmania tropica* and *Leishmania mexicana* are fairly benign, causing ulceration at the bite site. Leishmaniasis affects more than 12 million people worldwide, with 2 million new cases each year [21,22]. Infections vary from simple cutaneous leishmaniasis to serious disfigurement as well as fatal visceral leishmaniasis, called "kala-azar" in India. This severe form is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, progressive anemia, and complicated by coinfection with diseases such as HIV, TB, or malaria [23,24]. Visceral leishmaniasis affects poor populations living in remote areas of over 80 countries across Asia, East Africa, South America, and the Mediterranean region. The most affected countries (Bangladesh, Brazil, India, Ethiopia, Kenya, Nepal, and Sudan) account for over 90% of new cases detected. Cutaneous leishmaniasis has a wider geographic range, with the majority of cases occurring in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, Sudan, Costa Rica, and Peru.

17.2.3 Human African Trypanosomiasis (HAT)

HAT, also called sleeping sickness, is another neglected tropical disease with a fatal outcome if untreated, which still affects hundreds of thousands of people per year [5,24]. The causative agents are *Trypanosoma brucei gambiense* (95% of cases) and *Trypanosoma brucei rhodesiense* in West, Central, East, and Southern Africa. These protozoan parasites are both transmitted by the bite of the tsetse fly. The typical somnolence (sleeping sickness) usually progresses to coma as a result of demyelinating encephalitis. In the acute form, cyclical fever spikes occur approximately every 2 weeks, corresponding to the appearance of new antigenic variants of the parasite within the human host. In fact, specific immune responses, antibody- or T-cell-mediated, are directly dependent on epitope types. Antigenic variation sequences therefore cause fluctuations in the efficacy of the immune response, which is responsible for the spikes often observed in HAT [5,24].

Tsetse infestation and disease transmission are more common in poor rural populations. Of the 36 countries considered endemic for HAT, the seven most affected countries represent 97% of all reported cases, with the Democratic Republic of the Congo alone accounting for two-thirds of reported cases. HAT occurs primarily in the poorest, most rural areas in Africa, where the difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain [5].

17.2.4 Chagas Disease

American trypanosomiasis, also known as Chagas disease, is an infection caused by *Trypanosoma cruzi*; the main transmission mode is vectorial, through infected dejections of triatomine bugs ("kissing bugs"), a blood-sucking insect that feeds on humans and animals. The disease can also be transmitted congenitally or through blood transfusion or organ transplantation, and rarely through contaminated food or drink [5]. Chagas disease can be a lifelong infection if left untreated. The majority of infected persons are asymptomatic, but about 30% suffer irreversible cardiovascular, gastrointestinal, and/or neurological problems. Although both the numbers of cases and deaths have dropped significantly in the past two decades, Chagas disease remains an important public health problem, especially in Latin America, where it currently affects an estimated 8 million people in 21 countries. The disease is spreading to a number of nonendemic regions, including Africa and developed countries, due to increased migration of Latin Americans unknowingly carrying the parasites in their blood [5,25].

17.3 Pharmacological Activity of Medicinal Plants

Drug R&D is a long and tedious process requiring funding, good infrastructure, qualified manpower, and a conducive political/institutional environment. The starting product from diverse sources (plants, marine flora, and microorganisms) may

be chosen and screened at random, or the source materials may be selected based on previous knowledge (ethnobotanical or ethnopharmacological surveys) of their use in local communities. A wide range of technologies are available for the extraction of active components and essential oils from medicinal and aromatic plants. The choice depends on the nature of the source material, the nature of the experiment and models employed, as well as economic feasibility and suitability of the process to the particular situation [26]. Crude extracts with promising activity undergo bioassay-guided fractionation toward detection and isolation of potentially active pure ingredients. The systematic isolation and testing of molecules from plant parts against the different parasites is not a feasible option because of the prohibitive cost of such a vast enterprise. The use of ethonobotanic information to select plants for screening has proved to be a fruitful and cheaper approach to drug discovery. Once identified, active principles can be optimized by chemical synthesis to obtain more active products at affordable cost. The entire molecular suite of the plant parts can also be isolated and randomly tested against different parasite types in the search for potential active compounds. Pink et al. [27] extensively discussed the major *in vitro* and animal models that are commonly used in antiprotozoan drug discovery (Figure 17.1). However, the cost of the naturally occurring drug molecules may be prohibitive, and so efforts to design fully synthetic analogs with lower product cost are an important priority.

In this section, we focus only on plant extracts and compounds that have exhibited considerably high activity, using cutoff points proposed by various authors working in the field [15,28−30]. We propose cutoff point values summarized in Table 17.1 based on previous proposals by Rasoanaivo et al. [28] and Willcox et al. [29] for the activity of crude extracts, and Mahmoudi et al. [30] for pure compounds.

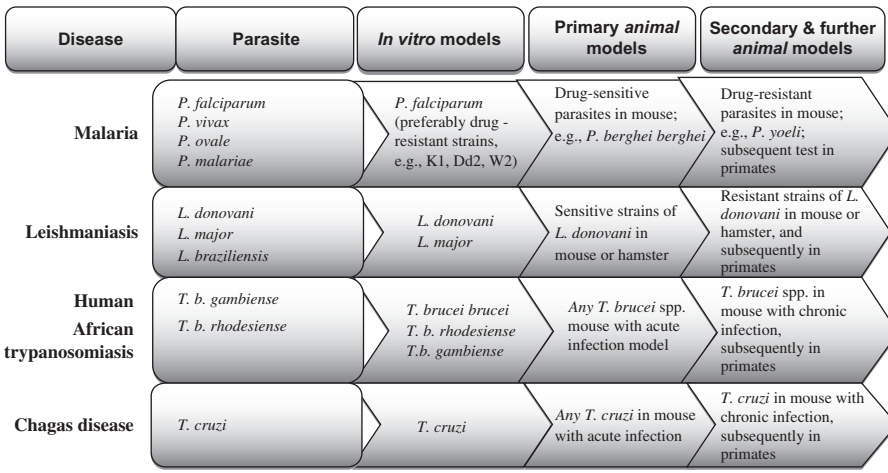

Figure 17.1 Commonly used *in vitro* and *in vivo* models in antiprotozoan drug discovery and development.
Source: Adapted from Pink et al. [27]

Table 17.1 Standard Cutoff Point Values for *In Vitro* and *In Vivo* Antiprotozoal Activity

Samples and Ranges			
Range	**Activity**	**Range**	**Activity**
Crude extract and fractions			
In vitro (IC_{50} value)		*In vivo* (inhibition by fixed dose at fixed dose of 250 mg/kg/day) inhibition of parasite growth, and recovery from disease	
<0.1 μg/mL	Highly potent	100–90%	Very active
0.1–1 μg/mL	Very active	90–50%	Active to moderately active
1.1–5 μg/mL	Active	50–10%	Mildly to weakly active
5.1–10 μg/mL	Moderately active	>10%	Inactive
11–25 μg/mL	Mildly active	–	–
26–100 μg/mL	Weakly to very weakly active	–	–
>100 μg/mL	Inactive	–	–
Pure compounds			
In vitro (IC_{50} value)		*In vivo* (inhibition by fixed dose at fixed dose of 100 mg/kg/day)	
0.06 μM (0.03 μg/mL)	Highly active	100–90%	Very active
0.06–5 μM (0.03–2.5 μg/mL)	Active	90–50%	Active to moderately active
5–10 μM (2.5–5 μg/mL)	Weakly active	50–10%	Mildly to weakly active
>10 μM (>5 μg/mL)	Inactive	>10%	Inactive

Assuming an average molecular weight of 500 Da for a typical drug molecule, the values proposed by Mahmoudi et al. in micromolar were converted to microgram per milliliter. According to Pink et al. [27], at the start of a screening campaign for antiprotozoan drugs, a product is considered a hit from *in vitro* testing if it has an $IC_{50} \leq 1$ μg/mL and the inhibitory effects targeting selectively parasite cells (at least 10-fold more active against a parasite than against a mammalian cell line). Such a compound can be further submitted to *in vivo* screening in various animal models in order to move from the hit stage to the level of lead compound. A lead should be significantly active in animal model, preferably against a relevant parasite (drug-resistant strain, for example), at a daily dose ≤100 mg/kg, with no overt toxicity at efficacious concentrations [27]. Nwaka and Hudson [31] proposed more specific standards for each disease type. According to these criteria, the hit compound should have an $IC_{50} < 0.2$ μg/mL against drug-resistant strains for malaria and HAT. In addition, the compound should have a selectivity index (SI)

of at least 100. For Chagas disease, the highest IC_{50} is 1.0 μg/mL, SI > 50, whereas a valid antileishmanial hit is expected to have an $IC_{50} < 0.5$, and 1 μg/mL against *L. donovani* axenic amastigotes and amastigotes in macrophage, respectively. In both cases, the compound should be at least 20-fold more toxic against the parasite than against mammalian cells. Lead compounds are hit molecules with significant *in vivo* activity (Table 17.1) and no toxicity on the animal model used (rodents or monkeys).

Furthermore, we will take into consideration up to $IC_{50} < 20$ μg/mL to report on the activity of compounds isolated from African medicinal plants. Despite their relatively low activity, such compounds could still be used as good templates for synthesis of more active molecules. For the sake of clarity, we present the data according to the families of African medicinal plants that have been investigated so far.

17.3.1 Antimalarial Activity of African Medicinal Plants

Over a thousand plant species are used by traditional healers across Africa to prevent and/or treat malaria symptoms; the parts employed can be the fruits, barks, roots, and/or leaves of a wide range of trees and shrubs [32], and the Research Initiative on Traditional Antimalarial Methods (RITAM) is currently constructing a database of ethnobotanical studies of herbal antimalarial products [33]. Many of these plants have been subjected to laboratory investigation in an attempt to establish their actual efficacy. However, most often these efforts have been limited to determine the activity of crude extracts and/or essential oils of plants against malaria parasites *in vitro* and/or *in vivo* even though a limited number of pure molecules have been isolated and screened for antimalarial activity [9,32,33].

17.3.1.1 Anacardiaceae

Pseudospondias microcarpa (Anacardiaceae) is widely used in African traditional medicine to treat various ailments. Ethanol was used to extract the roots and stem bark of the plant harvested in Tanzania. Both extracts exhibited good antiplasmodial activity, with IC_{50} of 1.13 μg/mL for the roots and 4.33 μg/mL for the stem bark [34].

17.3.1.2 Annonaceae

Nkunya et al. investigated nine Tanzanian species of the genus *Uvaria*, namely *U. dependens*, *U. faulknerae*, *U. kirkii*, *U. leptocladon*, *U. lucida*, *U. pandensis*, *U. scheffleri*, and *U. tanzaniae*. The most active extracts prepared from these plants were subjected to further fractionation, and several active compounds were isolated, among which the most active components were uvaretin and 3-(8,9-dihydroxyfarnesyl) indole, with 3.49 and 2.86 μg/mL on K1, respectively [35]. The seeds of *Xylopia parviflora*, a shrub growing in the savanna region of western Cameroon, are locally used as a condiment and for the treatment of fevers. Six diterpenes isolated from the seeds of this plant have shown antimalarial activity [36]. Four

other species from this family (*Xylopia phloiodora*, *Xylopia aethiopica*, *Pachypodanthium confine*, and *Hexalobus crispiflorus*) were also investigated by Boyom et al. [37]. Essential oils from these plants were active against the W-2 strain of *P. falciparum* in culture. The most effective was the oil of *H. crispiflorus*, with an IC_{50} of 2 μg/mL.

17.3.1.3 Apocynaceae

Many research groups have investigated *Picralima nitida*, using organic and aqueous extracts of the roots, stem bark, fruit rind, seeds, and leaves, for antiplasmodial activity [38,39]. The dichloromethane extract of the roots was highly active (IC_{50} of 0.2 μg/mL), followed by stem bark dichloromethane extract (IC_{50} of 0.5 μg/mL) and fruit rind aqueous extract (IC_{50} of 1.5 μg/mL). Kapadia et al. [38] isolated the alkaloid akuamine (**1**) from the seeds of *P. nitida*, which Zirihi et al. [40] showed had activity against *P. falciparum* (Figure 17.2). The stem bark alcoholic extract of *P. nitida* also presented a significant inhibitory activity on *P. berghei* in mice [39]. Fotie et al. investigated the extracts of the stem bark of *Holarrhena floribunda*, which is used by Baka pygmies of Cameroon to treat malaria [41]. The aqueous extract showed the highest activity on the Indochina (W-2) strain of *P. falciparum*, with an IC_{50} of 1 μg/mL, while the ethanol extract was most active against the Sierra Leone *P. falciparum* (D-6) strain, with an IC_{50} of 4.3 μg/mL. Lupeol and its derivatives, -3-*O*-(3'hydroxyeicosanoyl) lupeol, (5) 3-*O*-(2'tetracosyloxy) acetyllupeol, and 3-*O*[(1″-hydroxyoctadecyloxy) 2-hydroxypropanoyl] lupeol were isolated from this plant and exhibited a significant antimalarial activity *in vitro*.

17.3.1.4 Asparagaceae

Asparagus africanus (Asparagaceae), a medicinal plant commonly used by the Akamba tribe in Kenya to treat malaria and other fevers, was investigated using a bioassay-guided fractionation of the root extract. These efforts yielded two active compounds, muzanzagenin (IC_{50} of 7.07 μg/mL against *P. falciparum* Dd2) and nyasol (IC_{50} of 3.02 μg/mL on Dd2) [42].

17.3.1.5 Asphodelaceae

The plant species *Kniphofia foliosa* Hochst (Asphodelaceae), widely used across the continent as an antimalarial, was found to be a source of two antimalarial compounds, namely 10-(chrysophanol-7′-yl)-10-(x)-hydroxychrysophanol-9-anthrone (**2**) and chryslandicin (**3**), isolated from the dichloromethane extract of the roots. These compounds showed good activity against 3D7, with IC_{50} of 0.5 and 1.0 μM, respectively [43].

17.3.1.6 Asteraceae

For well over a millennium, the Chinese herb *qing hao*, *Artemisia annua*, has been used traditionally for the treatment of fevers, but it was with the discovery and

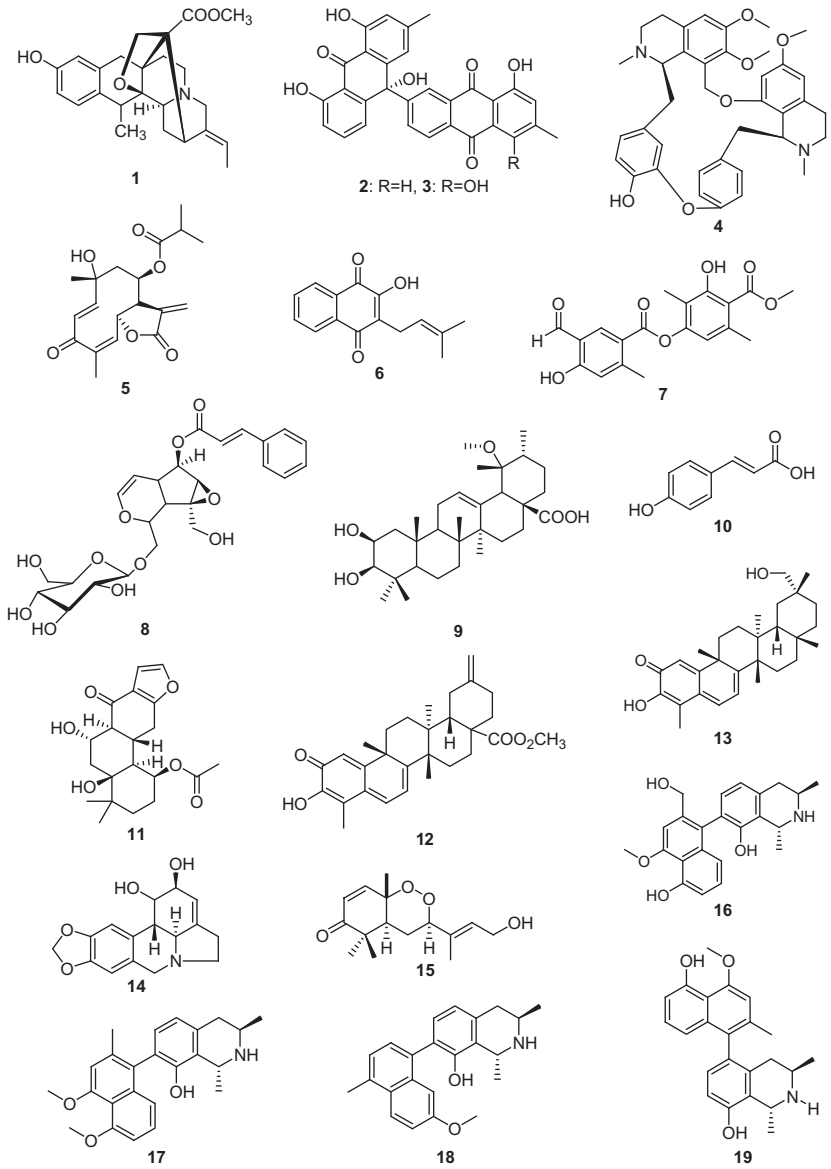

Figure 17.2 Chemical structures of selected antimalarial compounds identified in African plants: akuamine (**1**); 10-(chrysophanol-7′-yl)-10-(x)-hydroxychrysophanol-9-anthrone (**2**); chryslandicin (**3**); pycnamine (**4**); tagitinin C (**5**); lapachol (**6**); atranorin (**7**); specicoside (**8**); 2β,3β,19α-trihydroxy-urs-12-20-en-28-oic acid (**9**); *p*-hydroxy-cinnamic acid (**10**); norcaesalpinin E (**11**); methoxycarbonyl-28-norisoiguesterin (**12**); isoiguesterol (**13**); lycorine (**14**); okundoperoxide (**15**); dioncopeltine A (**16**); dioncophyllines A (**17**), B (**18**), and C (**19**); korundamine A (**20**); betulinic acid (**21**); 5-hydroxy-3-methoxyxanthone (**22**),

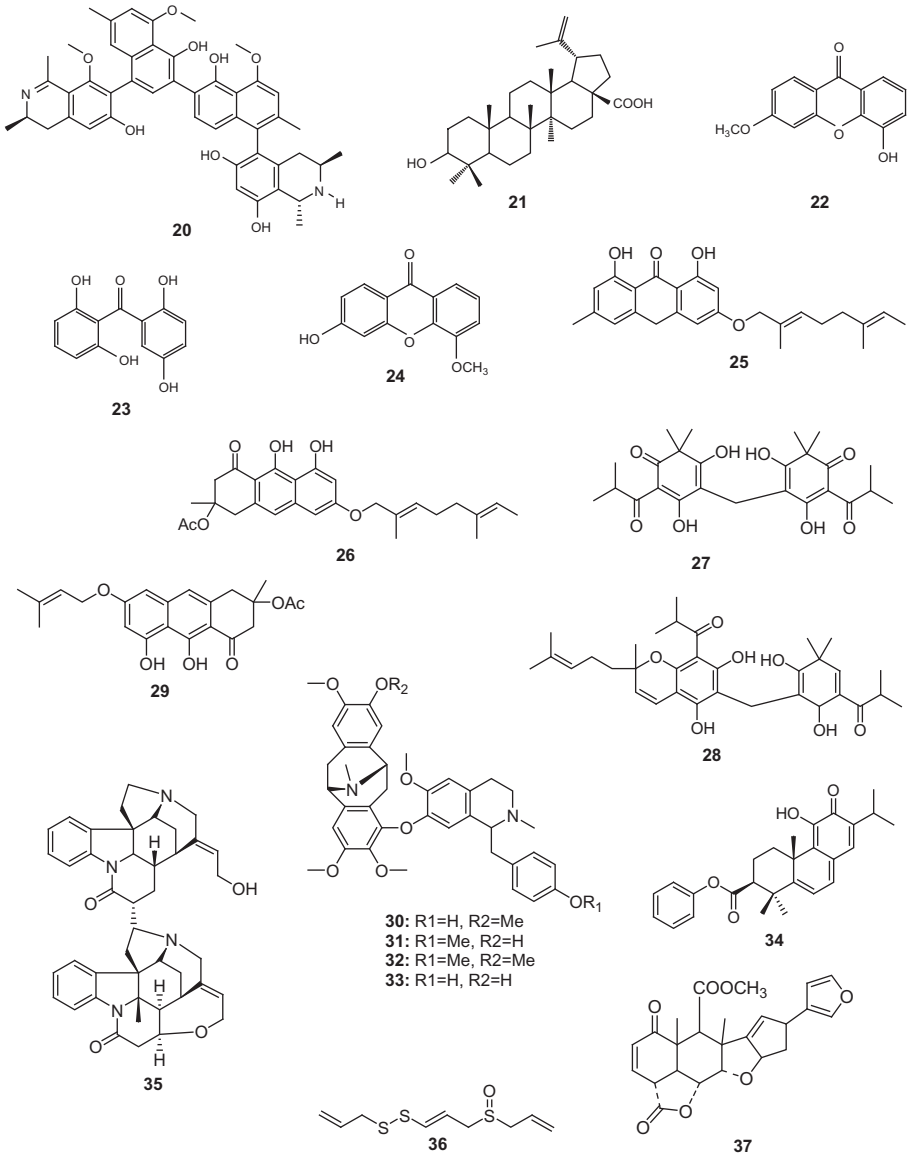

Figure 17.2 (Continued)

◀ 2,5,2′,6′-tetrahydroxybenzophenone (**23**); 3-hydroxy-5-methoxyxanthone (**24**); 3-geranyloxyemodin anthrone (**25**); acetylvismione D (**26**); japonicins A (**27**) and B (**28**); vismione H (**29**); hervelines A(**30**), B(**31**), C (**32**), and D (**33**); 3-*O*-benzoylhosloppone (**34**); strychnogucine B (**35**); ajoene (**36**); nimbolide (**37**); gedunin (**38**); azadirachtin (**39**); palmatine (**40**); jatrorrhizine (**41**); bartericin A (**42**); stipulin (**43**); 4-hydroxylonchocarpin

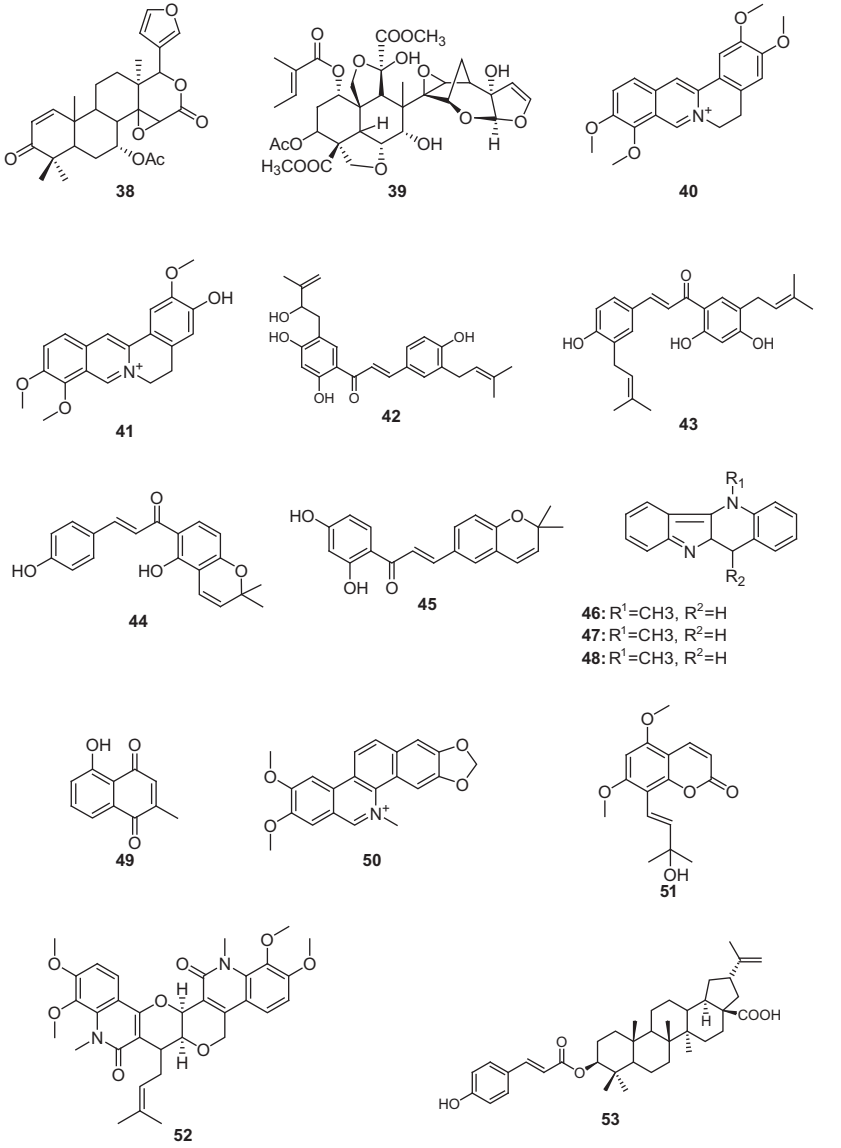

Figure 17.2 (Continued)

◀ (**44**); kanzonol B (**45**); cryptolepine (**46**); 11-hydroxycryptolepine (**47**); quindoline (**48**); plumbagin (**49**); nitidine (**50**); 5,7-dimethoxy-8-(3′-hydroxy-3′-methyl-1′-buteneyl)-coumarin (**51**); araliopdimerine A (**52**); 3-*O*-betulinic acid-*p*-coumarate (**53**); ailanthinone (**54**); zambesiacolactones B (**55**); 1(10)*E*,5*E*-germacradien-4β-ol (**56**); 5*E*,10 (14)-germacradien1β,4β-diol (**57**); oplodiol (**58**).

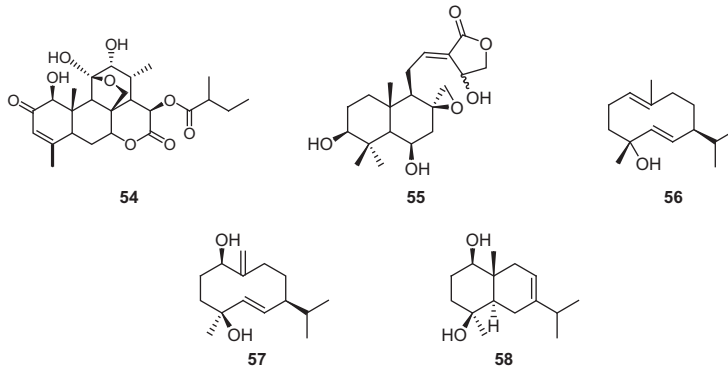

Figure 17.2 (Continued)

isolation of the most active molecule, artemisinin, from this plant in 1972 that the plant gained its international reputation. This herb has been widely exported, and today it commonly grows across Africa, together with several other indigenous species of the same genus. Probably stimulated by the detection of artemisinin in *A. annua*, several additional *Artemisia* species have been screened as part of malaria drug discovery research. However, the results obtained so far are well below expectations. For example, exiguaflavanones A and B, isolated from *Artemisia indica*, exhibited *in vitro* activity against *P. falciparum*, with IC_{50} of 4.6 and 7.1 μg/mL, respectively [44]. Karioti et al. [45] isolated a linear sesquiterpene lactone, 4-hydroxyanthecotulide, from *Anthemis auriculata* Boiss. (Asteraceae). This compound was tested against K1 and had an IC_{50} of 7.6 μM.

Kayser et al. [46] reported work on *Trichilia* sp. (Asteraceae), from which pycnamine (**4**) was isolated and found to have an IC_{50} of 0.15 μg/mL. Many *Vernonia* species have been investigated for their antimalarial potential and were found to be source of active molecules. For example, the macrocyclic germacrane dilactone 16,17-dihydrobrachy-calyxolide, from *Vernonia brachycalyx*, showed antiplasmodial activity (IC_{50} of 17 μg/mL against *P. falciparum*) but was also found to be significantly toxic against human lymphocytes at the same concentration [32,47]. The antiplasmodial activity of 2′-epicycloisobrachycoumarinone epoxide and its stereoisomer, isolated from *V. brachycalyx*, was also reported; the two stereoisomers show similar *in vitro* activity against chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* [32,48]. *Tithonia diversifolia*, a multipotential medicinal plant widely known in Cameroon, has been reported for its antimalarial properties. The macerated leaves are used for the treatment of fevers in children in the western region of the country [9]. Goffin et al. [49] investigated this plant *in vitro* against three strains of *P. falciparum*. The ether extract from aerial parts of the plant, collected in São Tomé e Príncipe, demonstrated good antiplasmodial activity (IC_{50} of 0.75 μg/mL against the FCA strain), and fractionation of this extract yielded the known sesquiterpene lactone tagitinin C (**5**) as an active

compound against *Plasmodium* (IC_{50} of 0.33 μg/mL against the FCA strain). This compound was also shown to possess interesting anticancer properties [49].

Another member of this family, *Garcinia cowa*, was shown to be a good source of prenylated xanthones with antiplasmodial activity, of which cowaxanthone had an IC_{50} of 1.5 μg/mL, compared to pyrimethamine (IC_{50} of 2.8 μg/mL) [50].

17.3.1.7 Bignoniaceae

The plant family Bignoniaceae has been shown to be one of the most promising sources of antimalarial compounds. For example, lapachol (**6**), a hydroxynaphthoquinone with antimalarial, antifungal, antibacterial, and anticancer activities, which is present in virtually all members of the Bignoniaceae, was used as template for the synthetic antimalarial atovaquone [51], which is now a prescription drug. The "savage tree," *Kigelia africana* (Lam.) Benth. syn. *Kalanchoe pinnata* (Jacq.) DC, a member of this family, is widely used in South, Central, and West Africa, and has a long history of use by rural and African countries, particularly for medicinal purposes. Several parts of the plant are employed to treat a wide range of skin ailments, dysentery, ringworm, tapeworm, postpartum hemorrhage, and malaria [52]. Clarkson et al. [53] described a moderate activity of methylene chloride crude extract of leaves (IC_{50} of 51 μg/mL) on the chloroquine-sensitive strain (D-10) of *P. falciparum*. In Cameroon, Zofou et al. [54,55] identified four compounds in *K. africana* stem bark with considerable antiplasmodial activity, namely atranorin (**7**) (1.65 and 0.67 μg/mL on W2 and W2mef, respectively), specicoside (**8**) (0.79 and 0.0.52 μg/mL on W2 and W2mef, respectively), 2β,3β,19α-trihydroxy-urs-12-20-en-28-oic acid (**9**) (0.78 and 0.90 μg/mL on W2 and W2mef, respectively), and *p*-hydroxy-cinnamic acid (**10**) (8.83 and 2.11 μg/mL on W2 and W2mef, respectively). The authors further studied the interactions of these compounds among themselves and their combination effects with quinine and artemether. A slight synergistic effect was observed between atranorin and 2β,3β,19α-trihydroxy-urs-12-en-28-oic acid [combination index (CI) of 0.82], whereas the interaction between specicoside and *p*-hydroxy-cinnamic acid was antagonistic (CI of 2.67). All three compounds showed synergistic effects with artemether (CI of 0.42−0.71). Interestingly, these molecules did not show any significant sign of toxicity against the monkey kidney cell strain LLC-MK2, except for 2β,3β,19α-trihydroxy-urs-12-en-28-oic acid, which was slightly toxic ($CC_{50} = 9.37$, with a SI of 5.98). *K. africana* compounds are therefore likely to serve as leads in the development of new partner drugs in artemether-based combination therapy.

The leaves and stem bark of *Spathodea campanulata* are widely used by the Bamoun community of western Cameroon as an antimalarial remedy. The aqueous, chloroform, and hexane extracts of stem bark were investigated by Makinde et al. [56]. When tested against *P. berghei* in mice with chloroquine as the control, the hexane and chloroform extracts were the most effective. Amusan et al. [57] isolated ursolic acid and its two derivatives, tomentosolic acid and 3β,20β-(dichloroxyurs 12−28)oic acid, from stem bark, which suppressed malaria and prolonged the survival time of mice infected with *P. berghei*. Elsewhere, the aqueous, chloroform,

and hexane extracts of the stem bark of *S. campanulata* (Bignoniaceae) were investigated [58]. Each extract was tested against *P. berghei berghei* in mice using chloroquine as the control. The hexane and chloroform extracts showed good activity, while the aqueous extract showed little or no activity.

17.3.1.8 Buddlejaceae

Manbu et al. [59] isolated seven new and two known compounds from an ethyl acetate extract of the leaves of *Nuxia sphaerocephala* Baker (Buddlejaceae), of which two were moderately active, namely 3-oxolupenal and 3β-hydroxy-lupenal, with IC_{50} of 3.6 and 7.2 μM, respectively, against the FcB1 parasite strain.

17.3.1.9 Caesalpiniaceae

The plant species *Caesalpinia crista* is widely employed across the African continent and Asia for the treatment of various diseases and disorders such as malaria fever, leucorrhea, abdominal pain, rheumatoid arthritis, diabetes, cystic fibrosis, and amenorrhea. Kalauni et al. [60] investigated the antimalarial potential of 44 cassane- and norcassane-type diterpenes isolated from cultivars harvested in Myanmar and Indonesia, using the FCR-3/A2 *falciparum* clone *in vitro*. Most of the tested diterpenes displayed antimalarial activity, and norcaesalpinin E (**11**) showed the most potent activity, with an IC_{50} of 90 nM, more potent than the clinically used drug chloroquine (IC_{50} of 0.29 μM).

17.3.1.10 Celastraceae

Salacia kraussii (Celastraceae) is a small shrub growing on the dunes, bushy steppes, and open woods of Mozambique and KwaZulu-Natal Province, South Africa. In Mozambique, where this plant is used to treat bilharzia and dysentery [51], bioassay-guided fractionation of the roots resulted in the isolation of several compounds, of which methoxycarbonyl-28-norisoiguesterin (**12**) and isoiguesterol (**13**) showed greater activity than chloroquine on the chloroquine-resistant K1 strain of *P. falciparum*. In addition, these compounds showed very high selectivity (CI of 30−50) with reference to HT-29 cell line [61]. The ethanol extract from the root bark of *Maytenus senegalensis* (Celastraceae) also displayed significant antiplasmodial property, with an IC_{50} of 2.05 μg/mL on the K1 strain [45].

17.3.1.11 Clusiaceae

Lenta et al. [62] carried out a detailed phytochemical and pharmacological investigation of *Harungana madagascariensis*, leading to the isolation of bazouanthrone, a new anthrone derivative, from the root bark, together with known compounds, feruginin A, harunganin, harunganol A, harunganol B, friedelan-3-one, and betulinic acid. The antiplasmodial activity of the isolated compounds was evaluated against the W2 strain of *P. falciparum*, and all the compounds were found to be active, with bazouanthrone showing particular potency (IC_{50} of 1.80 μM). *Allanblackia monticola* is a large forest

tree found in West and South provinces of Cameroon, where it is used as a medicinal plant to treat several diseases including respiratory infections, toothache, and diarrhea. The methanol extract of the stem bark of this plant yielded a new prenylated xanthenedione, designated as allanxanthone C (IC_{50} on FcM29 of 1.3 μM and IC_{50} on F32 of 6.9 μM), together with the known compounds norcowanin (IC_{50} on F32 of 6.3 μM) and mangostin (IC_{50} on FcM29 of 4.1 μM and IC_{50} on F32 of 7.8 μM) [59]. Azebaze et al. [63] also investigated this plant, and isolated from the methanol extract of the stem bark a new prenylated xanthenedione, allanxanthone C; five known xanthones, garciniafuran, tovophyllin A, rubraxanthone, norcowanin, and mangostin; and one saponin, stigmasterol-3-*O*-β-D-glucopyranoside. The methanol extract and pure compounds showed IC_{50} of 0.6−8.9 μg/mL on *P. falciparum*, F32 (chloroquine sensitive), and FcM29 (chloroquine resistant). Their cytotoxicity was estimated on human melanoma cells A375, and the cytotoxicity/antiplasmodial ratio were found to be high (between 15.45 and 30.46), indicating their possible safety.

17.3.1.12 Combretaceae

The plant genus *Combretum* (Combretaceae) is widely distributed and is used by populations of various Southern African countries (Botswana, Mozambique, South Africa, Swaziland, Zambia, Zimbabwe) for medicinal purposes. Extracts prepared from *Combretum erythrophyllum* were shown to display significant antiplasmodial activity (IC_{50} ranging from 0.70 to 10.68 μg/mL), with the leaves being most active (IC_{50} 0.87 μg/mL). Clarkson et al. [53] reported a particularly potent activity of the ethyl acetate extract of *C. bulbispermum* bulbs, showing an IC_{50} of 0.08 μg/mL against the parasite strain. Lycorine (**14**), a compound isolated from this plant and other species, also displayed highly significant antiplasmodial activity, with an IC_{50} of 0.03, 0.6, and 0.7 mg/mL against the chloroquine-resistant strain (FCR-3), W-2, D-10, and FAC8 strains of *P. falciparum*, respectively [62−67].

17.3.1.13 Cucurbitaceae

The plant species *Cogniauxia podolaena* Baill. (Cucurbitaceae) is well known in Congo Brazzaville folk medicine for its use as an antimalarial. Three triterpenes were isolated from the stem bark, cucurbitacins B and D and 20-epibryonolic acid, with moderate antimalarial activity against FcM29 (IC_{50} of 2.9, 7.8, and 3.7 μM, respectively) [68]. *Momordica balsamina* is widely used in Guinea-Bissau and Mozambique to cure vomiting with bile and fever. Work conducted by Ramalhete et al. [69] and Silva et al. [70] with material collected in Mozambique showed significant antiplasmodial activity for the ethyl acetate extract from aerial parts of *M. balsamina* (1.0 μg/mL). Subsequent bioassay-guided fraction led to the isolation of four major active compounds, with significant inhibitory properties against the 3D7 *P. falciparum* strain: Balsaminoside A (IC_{50} of 4.6 and 4.0 μM against 3D7 and Dd2, respectively) and karavilagenin E (IC_{50} of 7.4 and 8.2 μM, against 3D7 and Dd2, respectively) [71].

17.3.1.14 Cupressaceae

Three known compounds were isolated from the dried fruits of *Juniperus seravschanica* Komarov (Cupressaceae) by Okasaka et al. [66] and exhibited a wide range of antimalarial activity: cedrol, with IC_{50} of 2.65, 1.4, and 10.2 μM; sugiol, with IC_{50} of 1.6, 3.4, and 1.4 μM; and 12,15-dihydroxylabda-8 (17),13-dien-19-oic acid with IC_{50} of 2.2, 4.1, and 4.6 μM against D6, TM91C235, and W-2, respectively.

17.3.1.15 Cyperaceae

Scleria striatinux de Wild (syn. *S. striatonux*) (Cyperaceae) is a local spice in parts of Cameroon. The roots are also used as an herbal tea for fevers. The *S. striatinux* roots harvested in Oku in the Northwest Region of Cameroon were extracted and screened for antimalarial activity, showing significant activity *in vitro* against the W-2 and D-6 strains, with IC_{50} of 0.08 and 0.89 μg/mL, respectively. Bioassay-guided fractionation of this promising extract yielded okundoperoxide (**15**), which displayed consistent antiplasmodial activity on three different *P. falciparum* strains, with IC_{50} of 0.47, 0.48, 1.49, and 1.30 μg/mL on W-2, D-6, K1, and NF 54, respectively [72]. In an attempt to investigate Tanzanian medicinal plants, Weenen et al. [73,74] tested *Cyperus rotundus*, a plant used traditionally to treat malaria. The dichloromethane extract had *in vitro* activity against *P. falciparum*, and the active components were identified as α-cyperone and β-selinene. However, the activity of β-selinene fluctuated, and it was suggested that the parent compound is not active, but that it forms peroxides readily by autoxidation, and that these decomposition products were active [60,74]. The same species (*C. rotundus*), obtained from Thailand, was extracted following bioassay-guided fractionation by Thebtaranonth et al. [75], who obtained four active compounds, of which the most active was 10,12-peroxycalamenene (IC_{50} of 2.33 μM), a sesquiterpene with an endoperoxide group similar in structure to artemisinin.

17.3.1.16 Dioncophyllaceae

Some remarkably active antimalarial alkaloids, dioncopeltine A (**16**) (IC_{50} of 0.021 μM on NF 54), dioncophyllines A (**17**) (IC_{50} of 0.086 μM on K1), B (**18**) (IC_{50} of 0.063 μM on K1), and C (**19**) (IC_{50} of 0.014 μM on NF 54), were isolated from *Triphophyllum peltatum*[39,76]. When tested *in vivo*, compound **16** was able to suppress parasitemia almost totally, while dioncophylline C cured infected mice completely after oral treatment with 50 mg/kg of body weight for 4 days without noticeable toxic effects [77]. Subsequently, a novel heterodimeric napthylisoquinoline alkaloid, korundamine A (**20**), was isolated from another species of Dioncophyllaceae, *Ancistrocladus korupensis*. Comprised of two monomeric biaryl halves, this compound exhibited significant antiplasmodial activity, with an IC_{50} of 1.1 μg/mL against *P. falciparum*, and considerable inhibitory effect against HIV-1. Despite a lack of information about its safety profile, this compound is one of the most potent naturally occurring antiplasmodial napthylisoquinoline dimers yet identified by *in vitro* screening [78].

17.3.1.17 Euphorbiaceae

The young shoots of *Alchornea cordifolia* are used to treat malaria by Baka pygmies of the East and South provinces of Cameroon. Banzouzi et al. [79] isolated ellagic acid from the leaves, which showed good activity against *P. berghei* in mice, with an IC_{50} in the range of 0.2−0.151 μg/mL. *Drypetes natalensis*, another member of Euphorbiaceae, showed good antimalarial activity, with ethanol extracts of the root bark and stem bark showing IC_{50} of 1.06 and 1.42 μg/mL, respectively, when tested against the chloroquine-reisitant K1 strain of *P. falciparum*[34].

17.3.1.18 Hypericaceae

The African Saint John's wort *Hypericum lanceolatum* subsp. *revolutum*, also known as *Norysca lanceolata*, *Campylosporus angustifolius*, *Campylosporus madagascariensis*, *Campylosporus reticulatus*, *Hypericum angustifolium*, *Hypericum madagascariense*, and *H. lanceolatum*, is a multipurpose plant, commonly used in Cameroon and other areas to treat several ailments, including malaria, skin infections, venereal diseases, gastrointestinal disorders, tumors, infertility, and epilepsies [80,81]. The antiplasmodial activity of this plant extract was assayed by against the multidrug-resistant W2mef laboratory strain and a local field isolate of *P. falciparum* from Cameroon; its cytotoxicity tests were carried out using the LLC-MK2 monkey kidney epithelial cells [81]. Four well-known and active compounds were isolated from the ethyl acetate extract, namely betulinic acid (**21**), 5-hydroxy-3-methoxyxanthone (**22**), 2,5,2′,6′-tetrahydroxybenzophenone (**23**), and 3-hydroxy-5-methoxyxanthone (**24**), and shown to be active on W2mef strain of *P. falciparum*, with IC_{50} of 4.50 (2.05 μg/mL), 13.56 μg/mL, 3.26 μM (0.79 μg/mL),and 8.28 μg/mL,respectively.

Compound **21** (betulinic acid) is a multipotential molecule shown to be anti-inflammatory, antitumor, anti-angiogenesis [82], antiviral, including anti-HIV [83,84], and antineoplastic [85]. The molecule, isolated from the root bark of the Tanzanian tree *Uapaca nitida*, was previously screened *in vitro* for antiplasmodial activity against CQ-resistant K1 and CQ-sensitive T9−96 *P. falciparum*, and exhibited weak activity against both strains, with IC_{50} of 19.6 and 25.9 μg/mL, respectively. But it was shown to be inactive when tested *in vivo* against *P. berghei*, even at high concentration of 250 mg/kg/day in mice [86]. Compound **21** was also isolated from another Cameroonian plant, *Psorospermum glaberrimum*, and tested for its activity against the W-2 strain of *P. falciparum*[87], with an IC_{50} of 5.10 μM (2.33 μg/mL), which is very close to the results obtained by Zofou et al. [81].

Lenta et al. [87] also isolated glaberianthrone, a new bianthrone, from the hexane extract of the stem bark of *P. glaberrimum*, together with 13 known compounds: 3-geranyloxyemodin anthrone, friedelan-3-one, 3-prenyloxyemodin anthrone, 3-geranyloxyemodin, 3-prenyloxyemodin, friedelan-3-ol, acetylvismione D, 2-geranylemodin, bianthrone A2b, bianthrone 1a, emodin, and 2-prenylemodin. The isolated compounds were tested *in vitro* for antiplasmodial activity against *P. falciparum* (chloroquine-resistant strain W-2). Of these compounds,

3-geranyloxyemodin anthrone (**25**) and acetylvismione D (**26**) showed the highest potencies against *P. falciparum* W-2, with IC_{50} of 1.68 and 0.12 μM, respectively. Investigation of the Chinese species *Hypericum japonicum* resulted in the isolation of four new acylphloroglucinol derivatives, two of which were active against *P. berghei* in mice, japonicins A (**27**) and B (**28**) [88]. *Vismia guineënsis* is well known in Cameroonian traditional medicine for its use on malaria, skin diseases, and bacterial infections. Stimulated by the good activity previously obtained with the *V. guineënsis* extracts, Francois et al. [89] carried out a further investigation of this plant and succeeded in isolating a highly active molecule, the prenylated preanthraquinone vismione H (**29**), with an IC_{50} of 88 ng/mL.

17.3.1.19 Hernandiaceae

The stem bark of *Hernandia voyronii* is used in Madagascar in combination with chloroquine to treat malaria [90,91]. An investigation of the stem bark by Rasoanaivo et al. [91] led to the isolation and screening of hervelines A, B, C, and D (**30**) to (**33**) on FCM29, with IC_{50} of 2.13, 1.09, 1.87, and 1.41 μg/mL, respectively. Encouraged by the moderate activity observed with all four compounds, the authors went ahead to investigate the interaction patterns of these molecules with chloroquine (as traditionally used by Madagascan people). Compounds **31** and **32** were shown to enhance chloroquine activity, while herveline D was shown to be a chloroquine antagonist [92].

17.3.1.20 Lamiaceae

Hoslundia opposita (Lamiaceae) is used in East and West Africa to treat malaria [93]. The hexane extract of the root bark showed good activity *in vitro* against *P. falciparum*, with an IC_{50} of 5.6 μg/mL. Bioassay-directed fractionation led to the isolation of an active ester of an abietane-type quinomethane alcohol, 3-*O*-benzoylhosloppone (**34**), IC_{50} of 0.4 μg/mL [51,93]. The activity was attributed to the presence of an α,β-unsaturated carbonyl moiety in this compound. In South Africa, several members of the *Salvia* genus, if not all, form an integral part of traditional healing, particularly in regions where they occur in abundance. Several species are used to treat microbial infections, cancer, malaria, inflammation, loss of memory, and to disinfect homes after sickness. A compound was isolated from the active fraction of *Salvia radula* Epling and identified as betulafolientriol oxide, displaying moderate antimalarial activity (IC_{50} of 10.4 μM) [94].

17.3.1.21 Leguminosae

A bioassay-guided fractionation of extracts of roots and leaves of *Cajanus cajan* yielded three compounds, logistylin A and C and betulinic acid, with a moderately high *in vitro* activity against the chloroquine-sensitive *P. falciparum* strain 3D7 [95].

Adjanohoun et al. [12] reported the use of some plants of this family for the treatment of malaria symptoms in Cameroonian folk medicine. These include *Senna* sp. (*S. occidentalis* and *S. hirsute*), whose leaves are used as a decoction,

and *Guibourtia tessmannii* (stem bark). *G. tessmannii* was tested by Tantchou et al. [96] on the Viet Nam Smith strain of *P. falciparum*. The aqueous extract of the bark exhibited remarkable activity, with a minimum inhibitory concentration (MIC) of 2.4 μg/mL when using the Giemsa slide method, versus 3.8 μg/mL for the hypoxanthine technique. Compound 6a,7b-diacetoxyvouacapane was isolated from the seeds of *Bowdichia nitida* Spruce ex Benth., another member of the Leguminosae family, showing promising antiplasmodial activity against 3D7 (IC_{50} of 0.96 μM) and a good SI with regard to mammalian cells ($CC_{50} > 250$ μM) [97].

17.3.1.22 Loganiaceae

An investigation of *Strychnos icaja* roots resulted in the isolation of two tertiary quasi-symmetric bisindole alkaloids, named strychnogucines A and B. Both compounds were considerably active against four strains of *P. falciparum*, with strychnogucine B (**35**) having an IC_{50} of 80 nM against the chloroquine-resistant W-2 strain. In addition, this compound showed a selective antiplasmodial activity with 25−180 times greater toxicity toward *P. falciparum*, relative to cultured human cancer cells (KB) or human fibroblasts (WI38) [98].

17.3.1.23 Liliaceae

Allium sativum is widely used as a spice in Cameroon and has been investigated for its antimalarial activity. Perez et al. [99] isolated ajoene (**36**) from this plant, which reduced considerably the severity of *P. berghei* infection in mice and was nontoxic. Ajoene was further tested for antimalarial activity *in vivo* in a well-characterized murine model by Perez et al. [99]. A single ajoene oral dose of 50 mg/kg, on the day of infection, suppressed the development of parasitemia with no obvious acute toxicity. A single-dose combination of ajoene (50 mg/kg) and chloroquine (4.5 mg/kg), given on the day of the infection, completely prevented the subsequent development of parasitemia in infected mice.

17.3.1.24 Malpighiaceae

Seven crude extracts were prepared and tested from different parts of the Tanzanian variety of *Acridocarpus chloropterus* (Malpighiaceae). Among these, two were moderately active, including the dichloromethane extracts of the root bark (IC_{50} of 5.06 μg/mL) and the stem bark (IC_{50} of 7.23 μg/mL) [34].

17.3.1.25 Malvaceae

Gossypol is abundant in cottonseed (*Gossypium* spp.) oil and exhibits a variety of biological activities, including antispermatogenic, anticancer, antiparasitic, and antiviral activity. It also showed antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*, with an IC_{50} of 10 μg/mL. But it is cytotoxic, and its synthetic analogs retained the biological effects, including the antimalarial activity [51].

17.3.1.26 Meliaceae

Members of the Meliaceae have been used for generations in Africa, India, and tropical America. The highest activity against the chloroquine-sensitive strain was found in the leaves of *Azadirachta indica*, *Cedrela salvadorensis*, and *Chukrasia tabularis*, the bark of *Trichilia glabra*, and the wood of both *Cedrela odorata* and *Dysoxylum fraserianum*[100]. The neem tree, *A. indica*, which is widely used as an antiplasmodial in Africa, was investigated by several teams for its antimalarial properties. Nimbolide (**37**) (IC_{50} of 0.95 μg/mL, *P. falciparum* K1 strain) was the first agent to be identified as an active antiplasmodial principle from this species [101]. Later, gedunin (**38**) was also found to be active *in vitro* against *P. falciparum*, with IC_{50} in the range of 0.7−1.7 μg/mL [32,100,102]. Further investigation on *A. indica* has been carried out by Jones et al. [103]. Jones's team isolated azadirachtin (**39**) and studied the molecule together with a series of 17 semisynthetic derivatives *in vitro* on male gamete production from malarial microgametocytes. Azadirachtin and three of the semisynthetic derivatives were shown to inhibit the formation of mobile male gametes *in vitro*. Dhar et al. [104], working with the seeds of *A. Indica*, found that in addition to inhibiting the asexual stages of the parasite, the neem extracts also revealed a gametocytocidal effect. All stages of maturation of the gametocytes were affected, unlike artemisinin and primaquine, which only affect the immature stages [104].

The antimalarial properties of the crude water extract from *Khaya grandifoliola* stem bark in mice have been reported by Bickii et al. [105]. Bioassay-guided fractionation of stem bark and leaf extracts led to four main active compounds, namely methylangolensate, 7α-acetoxydihydronomilin, 7α-obacunylacetate, and 22-hydroxyhopan-3-one.

Ngemenya et al. [106] investigated the antimalarial properties of *Turreanthus africanus.* A phytochemical analysis of the methylene chloride/methanol (1:1) extract of the seeds of the plant yielded seven compounds. Of four compounds tested, one (16-oxolabda-8 (17), 12(*E*)-dien-15-oic acid), showed mild antiplasmodial activity (IC_{50} of 26 μg/mL) on chloroquine-sensitive *P. falciparum* F32, *in vitro*; two others, namely methyl-14,15-epoxylabda-8 (17), 12(*E*)-diene-16-oate, and turreanin A, had moderate activity and one, 17,20-dihydroxypregn-4-ene-3,16-dione, was inactive. These results appear to justify the use of *T. africanus* as an antimalarial in Cameroonian folk medicine.

17.3.1.27 Melianthaceae

The methanol extract of the leaves of *Bersama engleriana* was investigated by Ngemenya et al. [107] and showed highly significant activity, with IC_{50} of 2.7 μg/mL, and was also highly active on schizonts. Tapondjou et al. [108] isolated eight compounds, including five 3-*O*-glucuronide triterpene saponins, from the stem bark, but there are no reports on the antiplasmodial activity of these compounds.

17.3.1.28 Menispermaceae

Peniantus longifolius was reported by Bidla et al. [109] as an antimalarial plant in Cameroonian folk medicine. Two compounds, palmatine (**40**) and jatrorrhizine

(**41**), isolated from the stem bark methylene chloride/methanol (1:1) extract, showed promising *in vitro* activity on *P. falciparum*: IC_{50} of 350 ng/mL on the D-6 chloroquine-sensitive strain from Sierra Leone and 284.3 ng/mL on the W-2 chloroquine-resistant strain from Indochina.

17.3.1.29 Monimiaceae

A phytochemical study of the methylene chloride/methanol (1/1) extract of the leaves of *Glossocalyx brevipes* Benth. led to four active compounds, namely two new derivatives of homogentisic acid, methyl-2 (1′β-geranyl-5′β-hydroxy-2-oxocyclohex-3′enyl)acetate and 2-(1′β-5′β-hydroxy-2′-oxocyclohexyl)acetate, and two known alkaloids, aristalolatam BII and liriodenine. These phytochemicals showed a modest *in vitro* activity against *P. falciparum*[110].

17.3.1.30 Moraceae

Ngameni et al. [111] studied the antimalarial activity of *Dorstenia barteri* harvested in Cameroon. A prenylated chalcone, bartericin A (**42**), and three known natural products, stipulin (**43**), 4-hydroxylonchocarpin (**44**), and kanzonol B (**45**), were isolated from the twigs of *D. barteri* var. *subtriangularis* (Engl.) Hijman & C. C. Berg (Moraceae). All compounds showed moderate activity against W-2 *in vitro* (IC_{50} of 2.2, 5.1, 3.4, and 9.6 μM, respectively) [111,112].

17.3.1.31 Myrtaceae

Ethanol extract from *Eucalyptus robusta* leaves revealed good antimalarial activity, and robustadial B was isolated from this plant [113]. *Psidium guajava* is a widespread plant in Cameroon. Its fruit is consumed and the leaves used to treat diarrhea in some parts of the country. Nundkumar and Ojewole [114] investigated this plant using the parasite lactate dehydrogenase (pLDH) assay method, a recently developed *in vitro* enzymatic method for evaluating antiplasmodial activity. The aqueous extracts of the leaf, stem bark, and fruit were tested on the chloroquine-sensitive *P. falciparum* D-10 strain. The stem bark extract was the most active, with IC_{50} of 10−20 μg/mL. Phytochemical analysis revealed the presence of anthraquinones, flavonoids, seccoirridoids, and terpenoids. Thus, further studies including isolation and screening of individual compounds, as well as further toxicity studies, are highly suggested.

17.3.1.32 Periplocaceae

Cryptolepis sanguinolenta a plant that is used by traditional healers in Central and West Africa to treat infectious diseases, amoebiasis, and fever, including malaria [51,69]. Three bioactive alkaloids were isolated from the root bark, exhibiting higher *in vitro* antiplasmodial activity than chloroquine. These are cryptolepine (**46**), 11-hydroxycryptolepine (**47**), and quindoline (**48**), with IC_{50} of 33, 45, and 87 ng/mL, respectively, on K1 [51]. Several cryptolepine analogs have been synthesized

that have promising *in vitro* and *in vivo* antimalarial activity. Further investigations into the mechanism of action of this molecule are highly encouraged. Kayser et al. [46] also reported the indole **1**−**46** and related indolequinolines from *C. sanguinolenta* (Periplocaceae) to have significant antiplasmodial activity *in vitro* against the W-2, D6, and K1 strains of *P. falciparum*, with IC_{50} ranging from 27 to 41 ng/mL [46].

17.3.1.33 Poaceae

Cymbopogon citratus is one of the most commonly used herbs in Cameroon to treat malaria and other fevers. The essential oils extracted from fresh leaves of this plant were found to be active in a 4-day suppressive *in vivo* test on *P. berghei* in mice, giving IC_{50} from 6 to 9.5 μg/mL [115].

17.3.1.34 Plumbaginaceae

Plumbagin (**49**), a cytotoxic napthoquinone isolated from *Plumbago zeylanica* by Lin et al. [116], was shown to exhibit significant activity against chloroquine-sensitive (D6) and resistant (W2) strains of *P. falciparum* (IC_{50} of 178 and 189 ng/mL, respectively) [32]. However, because of its high toxicity, it is unlikely to be used for malaria treatment.

17.3.1.35 Rubiaceae

Coffea arabica, a source of caffeine, is an important cash crop in Cameroon, and a decoction of the leaves in water is used as an antimalarial remedy [12]. Many authors have investigated the antimalarial potential of this plant. A bioassay-guided fractionation of leaf extract resulted in the isolation of two known triterpenic acids, ursolic acid and oleanolic acid. These two compounds showed weak to moderate antimalarial activity, with IC_{50} of 19.8 and 32.3 μM for oleanolic acid and 6.8 and 10.7 μM for ursolic acid. *In vivo*, oleanolic acid at a daily dose of 200 mg/kg produced 37.4% inhibition in mice [117,118].

17.3.1.36 Rutaceae

Gakunju et al. [119] also reported antimalarial activity in *Toddalia asiatica*, a plant used by the Pokot tribe of Kenya to treat fevers. The highest potency was observed in the basic chloroform extract, which had an IC_{50} of <1 mg/mL. According to the authors, the activity observed was mainly due to the presence of the alkaloid nitidine (**50**), as proven by the high activity of the fractions containing this compound, with IC_{50} ranging from 9 to 108 ng/mL on both chloroquine-susceptible and resistant strains. However, the purified molecule was less active (42−165 ng/mL) than some of the fractions, showing that there may exist other compounds acting in synergy with nitidine in *T. asiatica.* This compound was recently tested against different strains of *falciparum* and showed IC_{50} ranging from 0.49 to 0.80 μM [120]. *T. asiatica* was also investigated by Oketch-Rabah et al. [47], leading to the isolation of a

new coumarin derivative, 5,7-dimethoxy-8-(3′-hydroxy-3′-methyl-1′-buteneyl)-coumarin (**51**), which was found to show IC_{50} of 16.2 and 8.8 μg/mL against chloroquine-sensitive and resistant strains of *P. falciparum*, respectively. Also in the Rutaceae family, Pierre Tane et al. [121] investigated *Araliopsis tabuensis*. The stem bark of this plant showed a good *in vitro* activity against *P. falciparum*, with an IC_{50} of 0.89 and 1.04 μg/mL for the D6 and W-2 strains, respectively. The bioassay-guided fractionation yielded 13 alkaloids, of which araliopdimerine A (**52**) was the most active, with IC_{50} of 34.1 ng/mL and 17.4 ng/mL for D6 and W-2, respectively.

17.3.1.37 Sapotaceae

The plant species *Baillonella toxisperma*, also called "moabi," is a tree occurring only in the humid tropical forests of West and Central Africa. The plant is used for the treatment of abscesses, infertility, stomach troubles, convulsion, rheumatism [12,122], and malaria. The methylene chloride extract from the stem bark of *B. toxisperma* was screened [123] and found to display promising antiplasmodial activity (IC_{50} of 2.43 μg/mL on D6). To identify the bioactive constituents, the extract was subjected to column chromatography, leading to the isolation of three compounds, the known betulinic acid, 3-*O*-betulinic acid-*p*-coumarate (**53**) (IC_{50} of 1.647 μM), and stigmasterol (IC_{50} of 38.37 μM).

17.3.1.38 Simaroubaceae

The methanol extract of the leaves of *Odyendyea gabonensis* was highly active, with IC_{50} of 1.8 μg/mL on trophozoites, and was also highly active on schizonts [106]. Tane et al. [122] also investigated the stem bark and observed remarkable activity on two *P. falciparum* clones, with IC_{50} of 111.9 ng/mL on the Sierra Leone D-6 strain and 101.5 ng/mL on the Indochina W-2 strain. They then isolated three indole alkaloids with moderate activity and one quassinoid, ailanthinone (**54**). This compound, isolated from stem bark, displayed high activity against D-6 and W-2 strains, with IC_{50} of 2.5 and 2.1 ng/mL, respectively. Compared to the IC_{50} of the reference molecules, chloroquine (IC_{50} of 4.6 ng/mL) and mefloquine (IC_{50} of 2 ng/mL), this molecule is a potential lead for development of a new antimalarial agent.

17.3.1.39 Zingiberaceae

Some four *Aframomum* species (*A. melegueta*, *A. zambesiacum*, *A. Latifolium*, and *A. sceptrum*) are used by traditional healers in different regions of Cameroon for the treatment of malarial symptoms [9,14,124–127]. Duker-Eshum et al. [124] investigated *A. latifolium* and *A. sceptrum*. Both showed significant antiplasmodial activity. Some active compounds were isolated from their fruits: (+)-(*S*)-nerolidol and 7 labdanes, coranarin B, galanal A and B, galanolactone, (*E*)-8β,17-epoxylabd-12-ene-15,16-dial, (+)-(*E*)-labda-8(17),12-diene-15,16 dial. The labdanes showed a modest *in vitro* activity on chloroquine-sensitive *P. falciparum* strains. Kenmogne et al. [125] isolated five labdane diterpenoids from *A. zambesiacum*. Zambisiacolactone B (**55**) was the most active, with an IC_{50} of 4.97 μM *in vitro*

against *P. falciparum*. Powdered fruits of *Reneilmia cincinnata* are one of the major constituents of the ingredients of a steam bath used to treat fevers. A bioassay-guided fractionation of dichloromethane extract of the fruits led to the isolation of six sesquiterpenoids, including 1(10)*E*,5*E*-germacradien-4β-ol (**56**) (IC_{50} of 1.54 μM), 5*E*,10(14)-germacradien1β,4β-diol (**57**) (IC_{50} of 1.63 μM), and oplodiol (**58**) (IC_{50} of 4.17 μM) [126] (Table 17.2).

17.3.2 Antileishmanial Activity of African Medicinal Plants

Drug R&D stakeholders in Africa working on medicinal plants have paid less attention to leishmaniasis and trypanosomiasis, as compared to malaria. This may be due to the relatively lower burden (fewer people affected in Africa, as compared to malaria). Herein, similar cutoff points as for antimalarials have been considered for activity against leishmania and trypanosomes.

The antileishmanial activity of hexane, dichloromethane, ethyl acetate, and methanol extracts of *Warburgia ugandensis* (Canellaceae), collected in Kenya, was assessed by Ngure et al. [116]. Among these, the hexane extract scored the best activity against *Leishmania major* promastigotes and amastigotes, with IC_{50} of 9.95 μg/mL for promastigotes and 8.65 μg/mL for amastigotes, and minimum inhibition concentrations of 62.5 μg/mL. According to the authors, the activity of the hexane extract on amastigotes was comparable to that of pentostam and amphotericin B. Similar results were obtained on *L. donovani*, with IC_{50} of 8.67 μg/mL for promastigotes and a 100-fold reduction of amastigotes in macrophage cultures. Considering the safety aspects, the authors concluded that *W. ugandensis* preparation had lower levels of toxicities compared to pentostam and amphotericin B. This report thus seems to scientifically justify the use of *W. ugandensis* in the treatment of leishmaniasis in Kenya [116].

Compounds with good antileishmanial activities were also isolated from *Garcinia lucida* (Clusiaceae), with IC_{50} of 2.0 and 6.6 μg/mL, respectively, for dihydrochelerythrine and 6-acetonyldihydrochelerythrine against *L. donovani*[15,129].

Khaya senegalensis (Desr.) A. Jus. (Meliaceae) is well known in Cameroonian folk medicine for its leaves, which are widely used for the treatment of urinary tract infections, dysmenorrhea, and irregular menstruation, while the seeds are employed for treating dermatitis [12]. This tree was also revealed as a potential source of antileishmanial compounds by Kayser and Abreu [130]. Two dimeric proanthocyanidins, catechin-(4a,6)-catechin (**59**) and catechin-(4a,8)-catechin (**60**), with immunostimulative activity were isolated from the bark, following bioassay-guided fractionation (Figure 17.3) [130]. The screening of the extracts and pure compounds against *L. donovani*, *L. major*, and *Leishmania infantum* promastigotes showed that the isolated compounds **59** and **60** were not active against promastigotes ($IC_{50} > 25.0$ mg/mL), but exhibited significant effects when tested against amastigotes, suggesting an indirect immunostimulative mechanism (IC_{50} of 3.85 and 3.98 μg/mL, respectively). Interestingly, no cytotoxicity was observed.

Khalid et al. [102] investigated the antileishmanial activity of crude methanol extracts of four Sudanese plants, of which three species had a considerable *in vitro*

Table 17.2 Selected Hit Antimalarial Compounds from Medicinal Plants of Africa

Plant and Family	Traditional Use with References	Countries of the Studies	Potentially Active Compounds	Activities
P. nitida (Apocynaceae)	Malaria [38]	Ghana/India	Akuamine (**1**)	IC_{50} of 0.001 μg/mL (W2) [38]
K. foliosa (Asphodelaceae)	Fevers [43]		10-(Chrysophanol-7′-yl)-10-(x)-hydroxychrysophanol-9-anthrone (**2**)	IC_{50} of 0.5 μM (3D7) [43]
			Chryslandicin (**3**)	IC_{50} of 1 μM (3D7) [46]
Trichilia sp. (Asteraceae)	Malaria, other parasitic infections [32]	South Africa	Pycnamine (**4**)	IC_{50} of 27−41 ng/mL (W2, D6, and K1) [47]
T. diversifolia (Asteraceae)	Antimalarial, mosquito repellency properties [49]	São Tomé e Príncipe	Tagitinin C (**5**)	IC_{50} of 0.33 μg/mL (CFA) [49]
P. zeylanica (Plumbaginaceae)	Malaria [49]	China	Plumbagin (**49**)	IC_{50} of 178 and 189 ng/mL (D6, W2, respectively) [127]
K. africana (Bignoniaceae)	Skin ailments, dysentery, intestinal worm, postpartum hemorrhage, malaria [55]	Cameroon	Specicoside (**8**)	IC_{50} of 1.02 μM (W2mef) [55]; synergy with artemether [56]
			Atranorin (**7**)	IC_{50} of 1.65 and 0.67 μg/mL (W2, W2mef, respectively) [55]; synergy with artemether [56]
			2β,3β,19α-Trihydroxy-urs-12-20-en-28-oic acid (**9**)	IC_{50} of 0.78 and 0.90 μg/mL (W2, W2mef, respectively) [55]; synergy with artemether [56]
			p-Hydroxy-cinnamic acid (**10**)	IC_{50} of 8.83 and 2.11 μg/mL (W2, W2mef, respectively) [55]; synergy with artemether [56]

C. crista (Caesalpiniaceae)	Antispasmodic, malarial fever, leucorrhea, abdominal pain, rheumatoid, arthritis, diabetes, cystic fibrosis, amenorrhea [60]	Myanmar/ Indonesia	Norcaesalpinin E (**11**)	IC_{50} of 0.090 μM (FCR-3/A2) [60]
S. kraussii (Celastraceae)	Bilharzia, dysentery	South Africa	Methoxycarbonyl-28-norisoiguesterin (**12**)	IC_{50} of 0.090 μM (FCR-3/A2) [38]
			Isoiguesterol (**13**)	IC_{50} of 0.090 μM (FCR-3/A2) [38]
C. erythrophyllum (Combretaceae)	Malaria [65]	South Africa	Lycorine (**14**)	IC_{50} of 0.03, 0.6, 0.7 mg/mL (FCR-3, W2, D-10) [65]
S. striatinux (Cyperaceae)	Fevers [72]	Cameroon	Okundoperoxide (**15**)	IC_{50} of 0.47, 0.48 μg/mL (W2, D-6) [72]
T. peltatum (Dioncophyllaceae)	Malaria [76]	South Africa	Dioncopeltine A (**16**), dioncophyllines A (**17**), B (**18**), C (**19**)	IC_{50} of 0.021 μg/mL (NF 54) [76] IC_{50} of 0.086 μg/mL (K1) [76] IC_{50} of 0.063 μg/mL (K1) [76] IC_{50} of 0.014 μg/mL (FCR-3, W2, D-10) [76]
A. korupensis (Dioncophyllaceae)	–	Cameroon	Korundamine A	IC_{50} of 1.1 μg/mL (W2) [78]
H. lanceolatum (Hypericaceae)	Malaria, skin diseases, tumors [81]	Cameroon	Betulinic acid	IC_{50} of 2.05 μg/mL (W2mef) [81]
			5-Hydroxy-3-methoxyxanthone	IC_{50} of 0.79 μg/mL (W2mef) [81]
H. opposita (Lamiaceae)	–	India	3-*O*-Benzoylhosloppone (**34**)	IC_{50} of 0.4 μg/mL (K1) [93]
S. icaja (Loganiaceae)	–	India	Strychnogucine B (**35**)	IC_{50} of 80 nM (FCR-3, W2) [112]

(*Continued*)

Table 17.2 (Continued)

Plant and Family	Traditional Use with References	Countries of the Studies	Potentially Active Compounds	Activities
A. sativum (Liliaceae)	Antivenomous, hypertension, malaria [11,99]	Cameroon	Ajoene (**36**)	ED of 50 mg/kg (*P. berghei*) [99]
A. indica (Meliaceae)	Systemic poison, insect repellent [11]	India	Nimbolide	IC_{50} of 0.95 μg/mL (K1) [101]
			Gedunin (**38**)	IC_{50} of 0.7 to 1.7 μg/mL (FCR-3, W2, D-10) [32,33,102]
			Azadirachtin (**39**)	Gametocidal activity *in vitro* [103]
P. longifolius (Menispermaceae)	Malaria [109]	Cameroon	Palmatine (**40**)	IC_{50} of 0.28−0.35 μg/mL (W2, D6) [121]
			Jatrorrhizine (**41**)	IC_{50} of 0.28−0.35 μg/mL (W2, D6) [121]
C. sanguinolenta (Periplocaceae)	Amoebiasis, fever [51]	South Africa	Cryptolepine	IC_{50} of 33 ng/mL (K1) [64,128]
			11-Hydroxycryptolepine	$IC_{5\ 0}$of 45 ng/mL (K1) [51]
			Quindoline	IC_{50} of 87 ng/mL (K1) [51]
			Neocryptolepine	IC_{50} of 0.51 μg/mL (K1) [51]
T. asiatica (Rutaceae)	Fevers [119]	Kenya	Nitidine (**50**)	IC_{50} of 9−108 ng/mL (K1) [119]
A. tabuensis (Rutaceae)	Malaria, dysentery [121]	Cameroon	Araliopdimerine-A (**52**)	IC_{50} of 34.1 and 17.4 ng/mL (D6, W2, respectively) [121]
O. gabonensis (Simaroubaceae)	Fevers [121]	Cameroon	Ailanthinone (**54**)	IC_{50} of 2.5 and 2.1 ng/mL (D6, W2, respectively) [121]

activity against *L. major* promastigotes: *A. indica* (Meliaceae) (IC_{50} of 10.2 μg/mL), *A. sativum* (Liliaceae) (IC_{50} of 4.94 μg/mL), and *Acacia nilotica* (Meliaceae) (IC_{50} of 89.38 μg/mL).

17.3.3 Antitrypanosomial Activity of African Medicinal Plants

Several medicinal plants harvested in Africa have displayed various ranges of antitrypanosomial activities [131–138]. The leaves of *P. guajava*, collected from a local farm in Ilorin, Kwara State, Nigeria, were evaluated for antitrypanosomal activity in the bloodstream species of *T. brucei brucei* (BS427). The different extracts prepared from the leaves inhibited growth of *T. b. brucei* with an IC_{50} of 6.3 and 48.9 μg/mL for 80% and 20% ethanolic preparations, respectively, showing that ethanol was the best solvent in extracting active ingredients from *P. guajava.* Additionally, none of these preparations was considerably toxic against HEK293 cell line, even at the highest screening dose of 238.10 μg/mL. This lack of cytotoxicity at the doses screened and the direct activity against *T. b. brucei* whole cells are very encouraging for further chemical elucidation and biological profiling [137]. Significant antitrypanosomal activity was also reported for the stigmastane derivatives vernoguinosterol (**61**) and vernoguinoside (**62**), isolated from *Vernonia guineensis* (Asteraceae), against bloodstream trypomastigotes of *T. b. rhodesiense*, with IC_{50} ranging from 3 to 5 μg/mL [129].

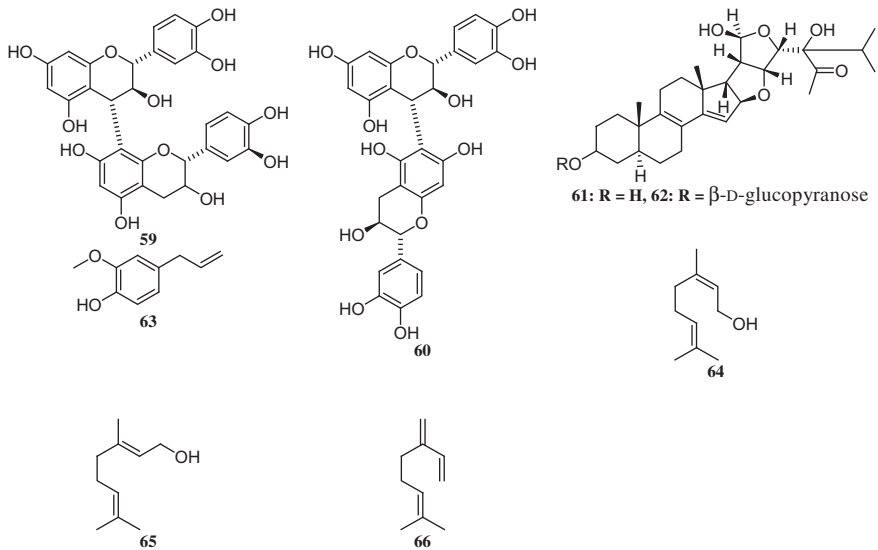

Figure 17.3 Chemical structures of selected antileishmanial (**59**, **60**) and antitrypanosomial (**61**–**63**), and other antiparasitic compounds identified in African plants: catechin-(4a,6)-catechin (**59**); catechin-(4a,8)-catechin (**60**); vernoguinosterol (**61**); vernoguinoside (**62**); eugenol (**63**); neral (**64**); geranial (**65**); myrcene (**66**).

Adamu et al. [139] investigated the inhibitory effects of the aqueous extract of the leaf of *Ocimum gratissimum* both *in vitro* and *in vivo* against *T. brucei*. Parasite survival was completely inhibited within 2 h of incubation in various concentrations of the extract at MLCs of 25−12.5 μg/mL. For *in vivo* assay, infected rats treated with the extract had less dramatic clinical manifestations and mortality, survived longer, and showed higher PCV values than their untreated counterparts (mean survival time of 11.6 ± 2.4 days as against 22.44 ± 3.5 days for the group infected with the extract). However, parasitemia was not significantly reduced [131]. Eugenol (**63**), a compound isolated from *O. gratissimum* essential oil, was tested on the growth, viability, and ultrastructural alterations of the amastigote and promastigote forms of *Leishmania amazonensis*, as well as on the interaction of these flagellates with mouse peritoneal macrophages, concomitant with nitric oxide production stimulation by the infected macrophages [131,132]. Essential oil was observed to cause considerable alteration, notably at the level of parasite mitochondria, including swelling, disorganization of the inner membrane, and an increase in the number of cristae [133]. Root and stem bark extracts of *Terminalia avicennioides* were shown to completely immobilize *T. b. brucei* in mice within 30 min of incubation at 20 mg/mL concentration, with the aqueous root extract displaying the highest activity. These results were confirmed *in vivo* by significant suppression of parasitemia, alleviation of anemia, and prolongation of life span observed in a dose-dependent fashion in mice [133].

Maikai et al. [134] demonstrated the *in vitro* and *in vivo* antitrypanosomal activity of aqueous and methanolic extracts of *Ximenia americana*. From the results obtained, *in vitro* incubation of infected blood with methanolic extract immobilized the parasites at a concentration of 9 μg/mL. *In vivo* study also showed the aqueous extract at 50, 100, 200, and 300 mg/kg body weight was parasite free for 1, 5, 7, and 14 days, respectively. However, this suppression of parasite growth was followed by a relapse [134].

From *in vitro* screening of crude extracts of eight medicinal plants from Nigeria, including *Anthocleista vogelii*, *Blighia unijugata*, *Cussonia arborea*, *Gardenia erubescens*, *Hymenocardia acida*, *Lophira lanceolata*, *Stereospermum kunthianum*, and *Uapaca togoensis*[135]. *H. acida* extract was found active against *T. b. brucei* at a MIC of 2.5 mg/mL.

The sacred garlic pear tree, *Crateva adansonii* DC, syn. *Crateva religiosa*, *Crateva adansonii* (Capparaceae) is used in traditional medicines in West Africa for the treatment of ear infections, syphilis, jaundice, and yellow fever. Crude hexane and ethyl acetate extracts were evaluated for *in vitro* bioactivity against African trypanosome *T. b. brucei* (S427) bloodstream forms and showed moderate antitrypanosomal activity (MIC of 12.5 μg/mL) [136].

Based on previous findings from ethnobotanical survey carried out in the central and western regions of Burkina Faso, *Xeoderris sthulmannii* (Fabaceae), *Parinari curatellifolia* (Chrysobalanaceae), *Ozoroa insignis* (Anacardiaceae), and *Ficus platyphylla* (Moraceae) were investigated for probable antileishmanial and antitrypanosomal activities. All four extracts showed significant antitrypanosomal activities, with minimum lethal concentrations (MLCs) between 1.5 and 25 μg/mL, the *L.*

ukambensis extract being the most active; it was also active against *Leishmania* [24]. The very low MLC values recorded in this study suggest a promising outcome for further bioassay-guided fractioning of these extracts.

17.3.4 Medicinal Plants with Multiactivity

Some medicinal plants used in African folk medicine have been shown to exhibit activity against more than one parasitic disease (Table 17.3). The pluripotency of such plants, herein termed multiactivity, makes them particularly attractive for drug R&D [137].

From work carried out by Ehata et al. [138], an 80% methanol extract of *Brucea sumatrana* Roxb. (Simaroubaceae), collected from the Democratic Republic of the Congo, exhibited significant activity against both *T. cruzi* (IC_{50} of 1.52 μg/mL) and *L. infantum* (IC_{50} of 2.41 μg/mL), *T. b. brucei* ($IC_{50} < 0.25$ μg/mL), and the chloroquine- and pyrimethamine-resistant K1 strain of *P. falciparum* ($IC_{50} < 0.25$ μg/mL). However, this extract was highly cytotoxic (IC_{50} of 0.54 μg/mL on MRC-5 cell lines). Fractionation of this interesting plant extract successfully separated the alkaline aqueous-soluble fraction, which exhibited pronounced antiprotozoal activity against *T. cruzi*, *T. b. brucei*, *L. infantum*, and the K1 strain of *P. falciparum* (IC_{50} of 0.33, <0.25, 0.25, and <0.25 μg/mL, respectively). The chloroform-soluble fraction, rich in alkaloid, was cytotoxic against MRC-5 cell lines (CC_{50} of 27.09 μg/mL), maintaining moderate activity against *T. b. brucei* (IC_{50} of 8.36 μg/mL) and weak activity against *T. cruzi*, *L. infantum*, and K1 strain ($20 < IC_{50} < 30$ μg/mL) [140].

Malebo et al. [34] evaluated the antiplasmodial, antitrypanosomal, and antileishmanial activity of 25 crude extracts obtained from seven Tanzanian medicinal plants: *Annickia kummeriae* or *Enantia kummeriae* (Annonaceae), *A. annua* (Asteraceae), *Pseudospondias microcarpa* (Anacardiaceae), *D. natalensis* (Euphorbiaceae), *A. chloropterus* (Malpighiaceae), *M. senegalensis* (Celastraceae), and *Neurautanenia mitis* (Papilonaceae). Out of the 25 extracts tested, 17 were reported to have good antiplasmodial activity (IC_{50} of 0.04−5.0 μg/mL), seven exhibited moderate antitrypanosomal activity (IC_{50} of 2.3−2.8 μg/mL), and five displayed mild antileishmanial activity (IC_{50} of 8.8−9.79 μg/mL). Five of these extracts, all from *A. kummeriae*, exhibited both antiplasmodial (K1 strain) and antitrypanosomial (*T. b. rhodesiense*) activity; the *n*-hexane extract of *A. annua* leaves showed antiplasmodial and antileishmanial potential, while the dichloromethane extract of *A. kummeriae* was highly active on *Plasmodium* and *Trypanosoma*, and moderately active on *Leishmania*. Similarly, ethyl acetate prepared from *N. mitis* was highly active against the malaria parasite and mildly active on *Trypanosome* and *Leishmania*.

Teclea trichocarpa (Engl.) Engl. (Rutaceae) is used traditionally by Akamba tribe in Kenya to treat malaria and other ailments. Fractionation of the methanol extract of its leaves yielded three acridone alkaloids, a furoquinoline alkaloid, and two triterpenoids, which were tested against *P. falciparum*, *T. b. rhodesiense*, *T. cruzi*, and *L. donovani*. Among the melicopicines, normelicopicine, arborinine, and α-amyrin showed the best

Table 17.3 Selected Antileishmanial Hits from Medicinal Plants of Africa

Plant and Family	Traditional Use with References	Countries of the Studies	Potentially Active Compounds	Activities with References
W. ugandensis (Canellaceae)	Stomach ache, constipation, toothache, venereal diseases, cough, fever, pains [116]	Kenya	None identified	IC_{50} of 9.95 μg/mL for promastigotes and 8.65 μg/mL for amastigotes (*L. major*); IC_{50} of 8.67 μg/mL for promastigotes and 100-fold reduction of amastigotes (*L. donovani*) [116]
G. lucida (Clusiaceae)	Poisoning [12]	South Africa	Dihydrochelerythrine	IC_{50} of 2.0 μg/mL (*L. donovani*) [15,41]
			6-Acetonyldihydro chelerythrine	IC_{50} of 6.6 μg/mL (*L. donovani*) [15,41]
K. senegalensis (Desr.) A. Jus. (Meliaceae)	Dysmenorrhea, irregular menstruation, dermatitis [12]	Guinea-Bissau	Catechin-(4a,6)-catechin (**59**)	IC_{50} of 0.85 μg/mL against amastigote (*L. donovani*) [102]
			Catechin-(4a,8)-catechin (**60**)	IC_{50} of 3.98 μg/mL against amastigote (*L. donovani*) [102]
A. indica (Meliaceae)	Malaria [129]	Sudan	None identified	IC_{50} of 10.2 μg/mL against promastigote (*L. major*) [129]
A. sativum (Liliaceae)	Muscle cramp [12]		None identified	IC_{50} of 4.94 μg/mL against promastigote (*L. major*) [139]

antiplasmodial activity (IC_{50} of 0.96 μg/mL); normelicopicine and skimmianine showed the best antitrypanosomal activity against *T. b. rhodesiense* (IC_{50} of 5.24 μg/mL) and *T. cruzi* (IC_{50} of 14.50 μg/mL), respectively. Normelicopicine also exhibited best antileishmanial activity (IC_{50} of 1.08 μg/mL) [140].

In a search for new antiparasitic agents from medicinal plants used in Burkina Faso folk medicine, one study [24] investigated *Lantana ukambensis* (Verbenaceae) and recorded multiactivity on both *T. b. brucei* GVR − 35 (MLC of 1.5 μg/mL) and *L. donovani* LV9WT (IC_{50} of 6.9 μg/mL).

The aerial parts of *Acanthospermum hispidum* DC are often used by traditional healers in Benin for various diseases, especially malaria. Ganfon et al. [141] investigated the traditional remedy in an attempt to identify and characterize active ingredients that could be used for malaria, leishmaniasis, and/or trypanosomiasis. From this ambitious project, the authors succeeded in isolating two known sesquiterpenic lactones, 15-acetoxy-8β-[(2-methylbutyryloxy)]-14-oxo-4,5-*cis*-acanthospermolide and 9α-acetoxy-15-hydroxy-8β-(2-methylbutyryloxy)-14-oxo-4,5-*trans*-acanthospermolide. Both compounds showed remarkable cross-activity against the three parasitic diseases *in vitro*, with IC_{50} of 2.9 and 2.23 μM, respectively, on the 3D7 *falciparum* strain; 2.45 and 6.36 μM, respectively, against *T. b. brucei*, and 0.94 and 2.54 μM, respectively, on *L. mexicana*.

Lemon grass, *C. citratus* (Poaceae), a well-known antimalarial herbal medicine [142] and mosquito repellent [143], was investigated by Machado et al. [144] for antileishmanial activity. The essential oil and two monoterpenic aldehydes, mrycene and citral, were screened *in vitro* against several species of *Leishmania*. The essential oil and citral (its main constituent) displayed mild activity, targeting several *Leishmania* species. They were most active in inhibiting *L. infantum*, *L. tropica*, and *L. major* growth at IC_{50} concentrations ranging from 25 to 52 μg/mL and from 34 to 42 μg/mL, respectively. *L. infantum* promastigotes exposed to essential oil and citral underwent considerable ultrastructural alteration, namely mitochondrial and kinetoplast swelling, autophagosomal structures, disruption of nuclear membrane, and nuclear chromatin condensation [143]. Citral, at the same concentration, killed about 45% of *L. infantum* and *L. tropica* promastigotes and about 60% of *L. major* promastigotes. In *C. citratus* oil, citral (90% of total oil) exists in three forms, two isomeric aldehydes, *cis*-citral neral (**64**) and *trans*-citral geranial (**65**), which together represent around 81% of the oil, and myrcene (**66**), which represents 6.4%. Microscopic observation revealed that *L. infantum* promastigotes exposed to essential oil and citral underwent considerable ultrastructural alteration, namely mitochondrial and kinetoplast swelling, autophagosomal structures, disruption of nuclear membrane, and nuclear chromatin condensation [143]. Citral has also been shown to exhibit an inhibitory effect on *T. cruzi*, with IC_{50} of about 31 μg/mL on metacyclogenesis and 24.5 μg/mL on metacyclic trypomastigotes after 24 h [144]. From this study, the authors thought citral could be a good drug candidate and suggested that further studies analyzing the *T. cruzi* metacyclogenesis process be considered.

Sakirigui et al. [145] recently generated five semisynthetic derivatives from citral isolated from *C. citratus* leaves collected in Benin, and tested their

antitrypanosomial activities. When tested *in vitro* on *T. b. brucei*, 4-phenyl-3-thiosemicarbazone had the highest activity (IC_{50} of 1.96 μM), followed by thiosemicarbazone (IC_{50} of 7.6 μM), while the remaining three were inactive. Based on these findings, it can be reasonably concluded that citral can serve as template for the development of new drugs targeting simultaneously the three trypanosomatid diseases, leishmaniasis, HAT, and Chagas disease (Table 17.4).

17.4 Antiprotozoal Herbal Medicine from African Medicinal Plants: Clinical Safety and Efficacy Research

Compared to synthetic drugs, there has been very little clinical research on herbal antiprotozoals, and these studies have been limited to malaria [146–149]. A total of 18 case reports, 14 of them on *falciparum*; 34 cohort studies, 17 *falciparum*, 12 *vivax*, 5 undefined; and 10 controlled trials, 4 *falciparum*, 6 *vivax* were reported by Willcox and Bodeker [146] in a systematic review. One of the major obstacles encountered is that there is often limited information about the method of preparation of remedies in their traditional forms, which makes them very difficult to replicate. This is often the deliberate intention of traditional healers, in order to protect intellectual property rights [146]. Nevertheless, the innovative approach of "reverse pharmacology" has been instrumental in the development of a new antimalarial phytomedicine from African medicinal plants. The concept of reverse pharmacology originated in India to develop pharmaceutical products from traditional medicines, and was also implemented by Chinese in the 1950s [147]. This approach was recently applied in Mali, resulting in new standardized herbal antimalarial products after 6 years of research activity. The first step is to select remedies for development, through a retrospective treatment–outcome study. The second step consists of a dose-escalating clinical trial that helps select the safest and most efficacious dose. The third step is a randomized controlled trial to compare the phytomedicine to the standard first-line treatment. The final step is to identify active compounds that can be used as markers for standardization and quality control [147]. The most promising example of herbal medicine developed using this approach is Phyto-Laria™, produced from *C. sanguinolenta*. The roots of this plant, also known by Ghanaian communities as nibima, kadze, gangamau, Ghanaian quinine, and yellow-dye root were extracted and developed into an herbal tea formulation trademarked as Phyto-Laria™, and the clinical evaluation of its potential as an herbal drug treatment for malaria was conducted [148]. From this trial, the overall antimalarial cure rate in patients was 93.5%, suggesting that Phyto-Laria™ could be used as a safe and effective treatment of acute uncomplicated malaria, and may also be useful in the treatment of patients infected with chloroquine-resistant strains of *P. falciparum* as well [149]. Also of great interest is the case of "malarial"; parasite clearance was not complete, but there was a good clinical response, even after 3 weeks of follow-up. An *Argemone mexicana* aerial part decoction also underwent clinical trial and is currently in the process of being approved by the Malian

Table 17.4 Some Medicinal Plants with Multiactivity on Protozoan Parasites

Plant and Family	Traditional Use	Countries of the Studies	Potentially Active Compounds	Antiplasmodial Activity	Antitrypanosomial Activity	Antileishmanial Activity
B. sumatrana (Simaroubaceae)	Malaria, amoebic dysentery, cancer, repellent [140]	D.R. Congo	None identified	$IC_{50} < 0.25$ μg/mL (K1) [140]	$IC_{50} < 0.25$ μg/mL (*T. b. brucei*) [140] IC_{50} of 1.52 μg/mL (*T. cruzi*) [140]	IC_{50} of 2.41 μg/mL (*L. infantum*) [140]
Lantana ukambensis (Verbenaceae)	Parasitic infections [24]	Burkina Faso	None identified	Not done	IC_{50} of 1.5 μg/mL (*T. b. brucei*) [24]	IC_{50} of 6.9 μg/mL (*L. infantum*) [24]
E. kummeriae (Annonaceae)	Malaria [34]	Tanzania	(None identified) L (MeOH)	IC_{50} of 0.12 μg/mL (K1) [34]	IC_{50} of 9.25 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 2.5 μg/mL (*L. donovani*) [34]
			ST (DCM)	IC_{50} of 0.31 μg/mL (K1) [34]	IC_{50} of 2.50 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 18.00 μg/mL (*L. donovani*) [34]
			ST (MeOH)	IC_{50} of 0.31 μg/mL (K1) [34]	IC_{50} of 2.50 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 19.41 μg/mL (*L. donovani*) [34]
			RT (PE)	IC_{50} of 2.51 μg/mL (K1) [34]	IC_{50} of 14.10 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 14.55 μg/mL (*L. donovani*) [34]
			RT (DCM)	IC_{50} of 0.36 μg/mL (K1) [34]	IC_{50} of 2.80 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 9.79 μg/mL (*L. donovani*) [34]
			RT (DCM)	IC_{50} of 0.35 μg/mL (K1) [34]	IC_{50} of 2.30 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 12.38 μg/mL (*L. donovani*) [34]

(*Continued*)

Table 17.4 (Continued)

Plant and Family	Traditional Use	Countries of the Studies	Potentially Active Compounds	Antiplasmodial Activity	Antitrypanosomial Activity	Antileishmanial Activity
A. chloropterus (Malpighiaceae)	Fever	Tanzania	L (EthOH)	IC_{50} of 5.50 μg/mL (K1) [34]	IC_{50} of 29.40 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 11.66 μg/mL (*L. donovani*) [34]
Pseudospondias microcarpa (Anacardiaceae)	Heart palpitation [34]	Tanzania	ST (EtOH)	IC_{50} of 4.33 μg/mL (K1) [34]	IC_{50} of 5.40 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 29.90 μg/mL (*L. donovani*) [34]
			RT (EthOH)	IC_{50} of 1.13 μg/mL (K1) [34]	IC_{50} of 11.60 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} >30 μg/mL (*L. donovani*) [34]
D. natalensis (Euphorbiaceae)	Rheumatism and filariasis [34]	Tanzania	ST (EtOH)	IC_{50} of 1.42 μg/mL (K1) [34]	IC_{50} of 10.70 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 19.00 μg/mL (*L. donovani*) [34]
			RT (EthOH)	IC_{50} of 1.06 μg/mL (K1) [34]	IC_{50} of 12.10 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 29.70 μg/mL (*L. donovani*) [34]
N. mitis (Papilonaceae)	Fish poison [34]	Tanzania	T (EthOH)	IC_{50} of 0.1.58 μg/mL (K1) [34]	IC_{50} of 12.4 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 8.8 μg/mL (*L. donovani*) [34]
M. senegalensis (Celastraceae)	Malaria and bacterial infections [34]	Tanzania	RT (EthOH)	IC_{50} of 2.05 μg/mL (K1) [34]	IC_{50} of 12.2 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 16.5 μg/mL (*L. donovani*) [34]

A. annua (Asteraceae)	Malaria and other protozoal diseases [34]	Tanzania	L (n-C_6H_6)	IC_{50} of 0.04 μg/mL (K1) [34]	IC_{50} of 15.3 μg/mL (*T. b. rhodesiense*) [34]	IC_{50} of 6.4 μg/mL (*L. donovani*) [34]
T. trichocarpa (Rutaceae)	Malaria [140]	Tanzania	Melicopicine	IC_{50} of 12.45 μg/mL (K1) [34]	IC_{50} of 15.56 μg/mL (*T. b. rhodesiense*) [140] IC_{50} >30 μg/mL (*T. cruzi*) [140]	$IC_{50} > 30$ μg/mL (*L. donovani*) [140]
			Normelicopicine	IC_{50} of 3.35 μg/mL (K1) [34]	IC_{50} of 5.24 μg/mL (*T. b. rhodesiense*) [34] IC_{50} of 30 μg/mL (*T. cruzi*) [140]	IC_{50} of 1.08 μg/mL (*L. donovani*) [34]
			Arborinine	IC_{50} of 1.61 μg/mL (K1) [34]	IC_{50} of 23.52 μg/mL (*T. b. rhodesiense*) [34] $IC_{50} > 30$ μg/mL (*T. cruzi*) [140]	IC_{50} of 5.20 μg/mL (*L. donovani*) [34]
			Skimmianine	IC_{50} of 5.60 μg/mL (K1) [34]	IC_{50} of 15.78 μg/mL (*T. b. rhodesiense*) [34] IC_{50} of 14.50 μg/mL (*T. cruzi*) [141]	IC_{50} of 9.40 μg/mL (*L. donovani*) [34]
			α-Amyrin	IC_{50} of 0.96 μg/mL (K1) [34]	IC_{50} of 11.21 μg/mL (*T. b. rhodesiense*) [34] $IC_{50} > 30$ μg/mL (*T. cruzi*) [140]	IC_{50} of 7.90 μg/mL (*L. donovani*) [34]

(*Continued*)

Table 17.4 (Continued)

Plant and Family	Traditional Use	Countries of the Studies	Potentially Active Compounds	Antiplasmodial Activity	Antitrypanosomial Activity	Antileishmanial Activity
A. hispidum (Asteraceae)	Malaria [141]	Benin	15-Scetoxy-8β-[(2-methylbutyryloxy)]-14-oxo-4,5-*cis*-acanthospermolide	IC_{50} of 2.90 μM (K1) [142]	IC_{50} of 2.45 μM (*T. b. brusei*) [142]	IC_{50} of 0.94 μM (*L. mexicana*) [142]
			9α-acetoxy-15-hydroxy-8β-(2-methylbutyryloxy)-14-oxo-4,5-*trans*-acanthospermolide	IC_{50} of 2.33 μM (K1) [142]	IC_{50} of 6.36 μM (*T. b. brucei*) [142]	IC_{50} of 2.54 μM (*L. mexicana*) [142]
C. citratus (Poaceae)	Malaria [12,121] and mosquito repellent [143]		Citral	IC_{50} of 2.33 μM (K1) [142]	IC_{50} of 6.36 μM (*T. b. brucei*) [142]	IC_{50} of 2.54 μM (*L. mexicana*) [142] IC_{50} of 2.54 μM (*L. mexicana*) [142] IC_{50} of 2.54 μM (*L. mexicana*) [142]

L, leaves; ST, stem bark; RT, root bark; S, seeds; T, tuber; PE, petroleum ether; DCM, dichloromethane; *n*-C6H6, *n*-hexane; MeOH, methanol.

regulatory authorities. Other antimalarial phytomedicines have already been developed and approved in many African countries. These include *Cochlospermum planchonii* root decoction (Burkina Faso), *C. sanguinolenta* root infusion (Ghana), Anemed® *A. annua* leaf infusion (Democratic Republic of the Congo) [147].

17.5 The Way Forward

It is evident that African medicinal plants represent a promising source of new drugs against the targeted vector-borne protozoan diseases (Figure 17.4). These plant materials could be used as starting points for the development of either pharmaceutical compound drugs or herbal medicines. Among the plant species identified, *B. sumatrana* (Simaroubaceae), *E. kummeriae* (Annonaceae), *E. kummeriae* (Annonaceae), *N. mitis* (Papilonaceae), and *Artemisia* spp. (Asteraceae) were very attractive, because of both high activity on malaria ($IC_{50} < 1$ μg/mL) and activity against other protozoan diseases. Further investigations of products from these species are likely to yield new antiprotozoal drug candidates and/or potential phytomedicines. However, the outcome of such enterprise also depends on a number of factors, including (1) the relative abundance and widespread nature of the medicinal plant; (2) the yield of the active ingredients and the possibility of mass production of the active ingredient by synthesis; (3) the stability of the concentration of bioactive ingredients with genetic, climatic, edaphic, and ecological changes; and

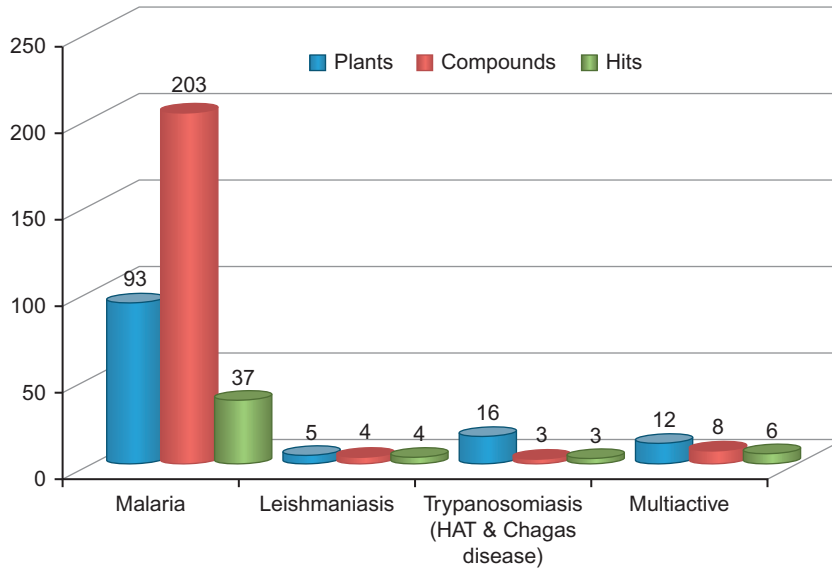

Figure 17.4 Number of significantly active antiprotozoal plants, compounds, and potential hits identified from African medicinal plants. (Note: The selective criteria used are presented in Table 17.1.)

(4) adequate analytical and production methods. Assurance of safety, quality, efficacy, and affordability of medicinal plants and herbal products is thus a critical issue [150]. As defined by the American Herbal Products Association (AHPA), standardization (applying to herbal preparations) refers to a body of information and control tools necessary to ensure product material of reasonable consistency [150,151]. Protocols for standardization of herbal extracts include a proper identification of the plant species; physical parameters (organoleptic, viscosity, moisture, pH, hardness, etc.); chromatographic and spectroscopic evaluation of chemotypes (using UV, FTIR, HPTLC, HPLC, GCMS, LCMS, NMR); microbiological parameters (*Escherichia coli* and molds, aflatoxin); pesticide residue (DDT, BHC, toxaphene, aldrin); and heavy metal analysis (mercury, lead, cadmium, arsenic, copper, iron, zinc). In addition to containing no or only sublethal toxic elements, a good source of herbal medicine should be a widespread medicinal plant growing in different edaphic and climatic environments. The phytochemical composition, especially the content of active ingredients, should remain in a very narrow range despite the diversity of habitats.

With regard to medicinal plants as a source of lead compounds, priority will be given to those with the highest extraction yield, and shorter life spans, as with herbs and shrubs which can easily be cultivated. Lead compounds that can be synthesized cost effectively are preferable.

17.6 Conclusion

From the above review, it is clear that a wide variety of plant species and families employed in the treatment of protozoan diseases contain bioactive ingredients. A total of 226 plant species belonging to 75 different families identified from African folk medicine have been shown to possess significant antiprotozoal activity. Over 200 pure compounds with significant activity have been isolated from some of these plants.

Among the active compounds, 50 potential hits were described, of which 37 are active against malaria, 4 against leishmaniasis, 3 against both African and American trypanosomiasis, and the remaining 6 showing significant activity against more than one disease. However, only a few toxicity, preclinical, and clinical studies have been conducted on these plant products. The reverse pharmacology approach looks quite attractive, fast, and cost-effective, showing promise of developing cheap and affordable products from the abundantly available biodiversity of Africa.

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18 Antiproliferative Potential of African Medicinal Plants

Victor Kuete[a], *Katrin Viertel*[b] *and Thomas Efferth*[b]

[a]Department of Biochemistry, University of Dschang, Dschang, Cameroon, [b]Department of Pharmaceutical Biology, University of Mainz, Mainz, Germany

18.1 Introduction

Cancer is increasingly recognized as a critical public health problem in Africa [1]. The number of new cancer cases will reach 15 million every year by 2020 worldwide, 70% of which will be in developing countries, where governments are less prepared to address the growing burden of cancer and where survival rates are often less than half of those in more developed countries [2]. It has been observed throughout the continent that, though communicable diseases continue to burden the population, noncommunicable diseases also require the attention of those whose goal is to ensure the health of Africans [1]. Currently, limited funding is available to tackle cancer in African countries. Awareness of this impending epidemic in Africa should be a priority today, and all possible resources should be mobilized to both prevent and to face the upcoming tragedy. Medicinal plants constitute a good alternative, considering the rich biodiversity of the continent. Nevertheless, reports on plants traditionally used for the treatment of cancer are rare in many parts of the world, as well as in Africa [3–5]. This is due to the fact that cancer involves a complex set of signs and symptoms, not easy to diagnose by unqualified personnel. During the last two decades, investigations of natural products have been particularly successful in the field of antiproliferative drug research in other parts of the world. In Africa, scientific evidence of the cytotoxicity of plants is being published more and more often. The study of the mode of action of some active samples is also being done continuously. In the present chapter, we present information on those African plants or their constituents having good antiproliferative activities against cancer cell lines.

18.2 Cancer Concern in Africa

According to the International Agency for Research on Cancer (IARC), about 715,000 new cancer cases and 542,000 cancer deaths occurred in 2008 in Africa

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[6]. In the IARC projections, there will be about 1.28 million new cancer cases and 970,000 cancer deaths by 2030 in Africa alone, mainly due to the growth and aging of the population [6], with the potential to be even higher because of the adoption of behaviors and lifestyles associated with economic development, such as smoking, unhealthy diet, and physical inactivity [7]. The most common cancer types in Africa are those related to infectious agents (cervix, liver, Kaposi's sarcoma, urinary bladder) [1]. In 2008, cervical cancer accounted for 21% of the total newly diagnosed cancers in females and liver cancer for 11% of the total cancer cases in males [1]. There is a lower survival rate after a diagnosis in Africa than in the developed world for most cancer types [1]. For example, the 5-year survival rate for breast cancer is less than 50% in Gambia, Uganda, and Algeria, compared to nearly 90% in the United States [1]. According to the World Health Organization (WHO) survey of national capacity for cancer control programs in 2001, anticancer drugs were only available in 22% and affordable in 11% of the 39 African countries that participated in the survey [8]. In parallel, efforts are being made by African scientists to search for new drugs from their most affordable resources, namely medicinal plants. Several plants from the flora of Africa have been found to be active against various types of cancer cells. Even when not reported for their antiproliferative potential, several medicinal plants of the African continent have been found to contain known antineoplastic compounds. Using a pharmacogenomics approach with Cameroonian flora as an example [9], it was demonstrated that African plants have an enormous, unstudied anticancer potential, as they contain an impressive arsenal of bioactive agents. In this chapter, we will therefore discuss the plants showing cytotoxic effects as well as those having bioactive constituents with inhibitory activity against human cancer cells.

18.3 Cytotoxicity of African Medicinal Plants

African plants from many families have been reported either to exhibit antiproliferative activity or to have bioactive constituents against malignant cells. In the U.S. National Cancer Institute (NCI) plant screening program, a crude extract is generally considered to have *in vitro* cytotoxic activity if the concentration inhibiting the growth of half the cell population (IC_{50}) following incubation between 48 and 72 h is less than 20 μg/mL [10]. This cut-off point was fixed at or below 4 μg/mL [10], or 10 μM [11] for compounds. Herein, we will refer to such threshold bars to discuss, family by family, the activity of extracts and compounds isolated from African plants.

18.3.1 Anacardiaceae

The extract of leaves of the cashew plant, *Anacardium occidentale* L., a medicinal plant used in folk medicine in South America as well as in West Africa, was found to be cytotoxic and to induce apoptosis in Jurkat (acute lymphoblastic leukemia)

cells [12]. Though the activity of the extract was rather low (IC_{50} of 62.6 μg/mL), good activity (IC_{50} of 2.04 μg/mL) was recorded for the biflavonoid agasthisflavone (Figure 18.1 (**1**)), isolated as the major active compound [12]. However, this compound exhibited only moderate activity on another leukemia cell line, HL-60 (IC_{50} of 11.03 μg/mL) [12].

18.3.2 Annonaceae

Xylopia aethiopica (Dunal) A. Rich., harvested in Cameroon, was reported for its cytotoxicity to several cancer cells. The documented IC_{50} values obtained with seed extracts were 6.68 μg/mL against the human pancreatic carcinoma cell line MiaPaCa-2, 3.91 and 7.4 μg/mL, respectively, against leukemia CCRF-CEM and CEM/ADR5000 cells [13], 12 μg/mL against the colorectal carcinoma cell line HCT116, and 7.5 μg/mL against the human promonocytic cell line U937 [14]. The diterpenoid 15-oxokaur-16-en-19-oic acid (**2**) was identified as one of the major cytotoxic compounds of the plant, with an IC_{50} of 3.7 μg/mL against the human prostate carcinoma epithelial cell line PC-3 [14,15].

18.3.3 Asteraceae

The methanol extract of the roots of *Acanthospermum hispidum* DC, collected in Nigeria, was found to be active against the human Caucasian lung-large carcinoma cell line COR-L23, with an IC_{50} of 8.87 μg/mL [16]. Though this plant has been the source of several bioactive sesquiterpenes, such as hispidunolides A and B, guaianolides, melampolides [17], and acanthospermal B [18], the cytotoxicity of the constituents of the samples has not been reported.

18.3.4 Bignoniaceae

The role of the constituents of many plants of the family Bignoniaceae as cytotoxic agents has been demonstrated [19–22]. In African plants, the naphthoquinone 2-acetylfuro-1,4-naphthoquinone (**3**), from the Cameroonian plant *Newbouldia laevis* Seem., showed good cytotoxic effects against cancer cell lines such as PF-382 (IC_{50} of 0.57 μg/mL), Colo-38 (IC_{50} of 0.67 μg/mL), HeLa (IC_{50} of 0.40 μg/mL), and Caski (IC_{50} of 0.17 μg/mL) [23].

18.3.5 Celastraceae

A plant from this family, *Elaeodendron alluaudianum* H. Perrier, collected in Madagascar, was found to be active against the human ovarian cancer cell line A2780, with an IC_{50} value of 3.3 μg/mL recorded for the ethanol extract [24]. Two new cardenolide glycosides, elaeodendrosides V (**4**) and W (**5**), were identified as the active constituents of the plant [24].

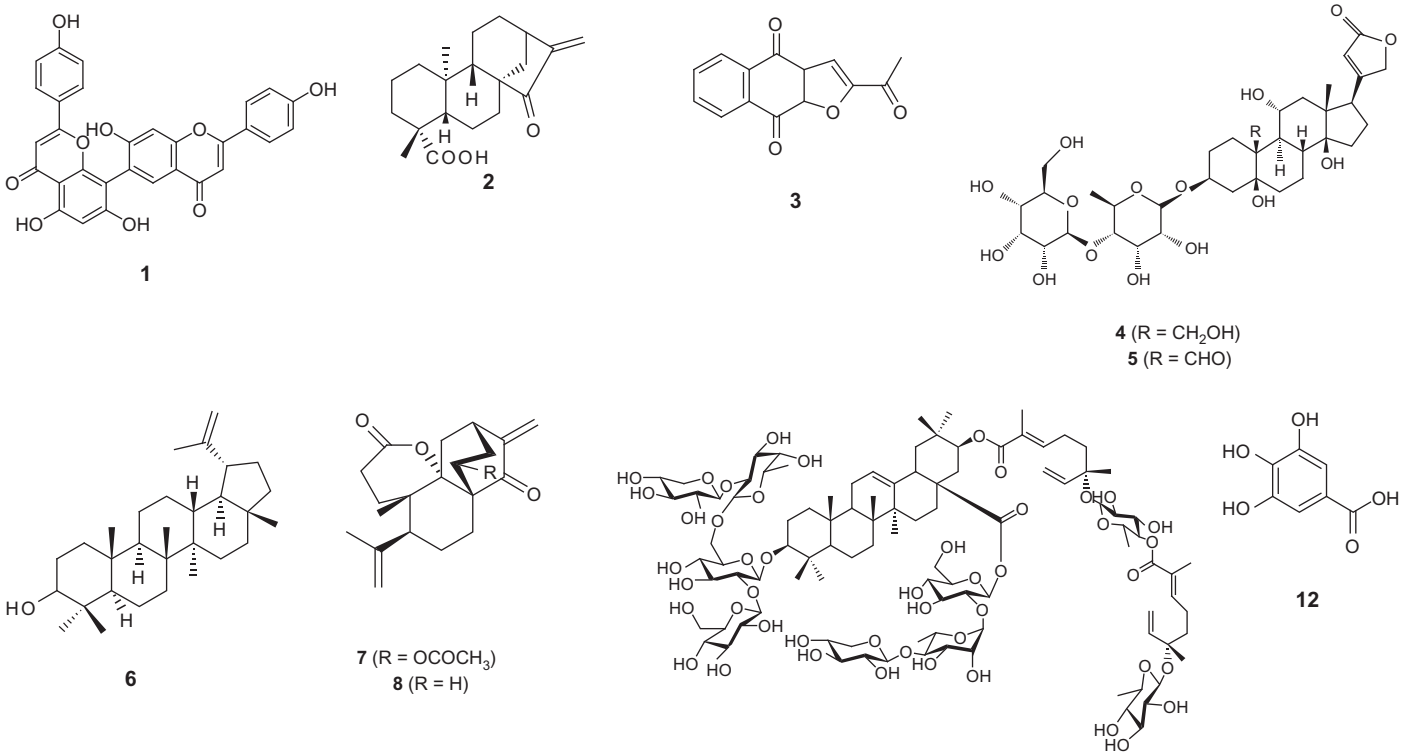
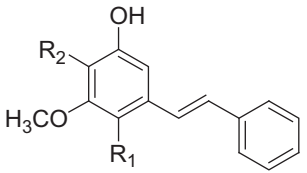
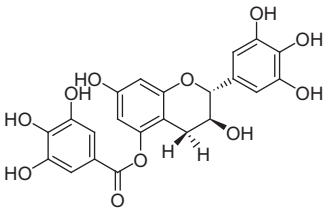


Figure 18.1 Cytotoxic compounds from African medicinal plants: agasthisflavone (**1**), 15-oxokaur-16-en-19-oic acid (**2**), 2-acetylfuro-1,4-naphthoquinone (**3**), elaeodendroside V (**4**), elaeodendroside W (**5**), lupeol (**6**), crotobarin (**7**), crotogoudin (**8**), gummiferaoside A (**9**), longistylin A (**10**), longistylin C (**11**), gallic acid (**12**), gallocatechin 5-*O*-gallate (**13**), epigallocatechin 3-*O*-gallate (**14**), xanthone V_1 (**15**), butyraxanthone A (**16**), butyraxanthone B (**17**), butyraxanthone D (**18**), mangostanin (**19**), 1,3,6-trihydroxy-7-methoxy-2,8-diprenylxanthone (**20**), and rubraxanthone (**21**).



10: R_1: H R_2 = $CH_2CHC(CH_3)$
11: R_1 = $CH_2CHC(CH_3)_2$ R_2 = H



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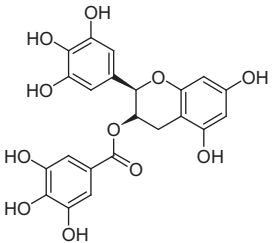

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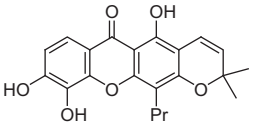

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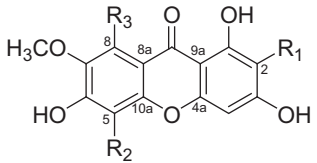
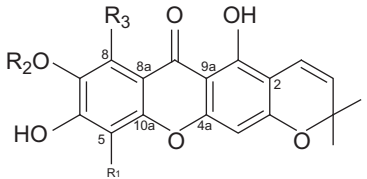


16: R_1 = Ge, R_2 = H, R_3 = Pr
18: R_1 = R_2 = H, R_3 = 8-OH-Ge
20: R_1 = R_3 = Pr, R_2 = H
21: R_1 = R_2 = H, R_3 = Ge



17: R_1 = Pr, R_2 = H, R_3 = Pr
19: R_1 = H, R_2 = CH_3, R_3 = Pr

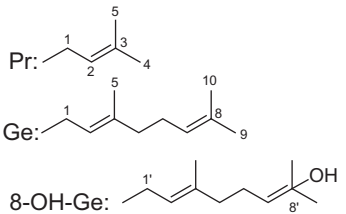


Figure 18.1 (Continued).

18.3.6 Compositae

The methanol extract of the seeds of *Echinops giganteus* var. *lelyi* (C. D. Adams) A. Rich., from Cameroon, was reported for its antiproliferative activity against leukemia CCRF-CEM (IC_{50} of 6.68 μg/mL) and CEM/ADR5000 (IC_{50} of 7.96 μg/mL), as well as against MiaPaCa-2 (IC_{50} of 9.84 μg/mL) [13]. The common triterpenoid lupeol (**6**) has been reported as one of the constituents of the plant; its cytotoxicity effect has been well known and documented in the NCI database [9].

18.3.7 Cupressaceae

The Cupressaceae or cypress family is a conifer family with worldwide distribution. Many plants of this family or their derived products have been reported for their cytotoxicity, and they have been found to induce apoptosis in cancer cells [25–28]. However, African plants of this family reported for the good cytotoxicity are rather rare. Nevertheless, significant activity, with an IC_{50} of 13.1 μg/mL, was reported for the bark methanol extract of *Cupressus lusitanica* Mill., collected in Cameroon, against the human breast adenocarcinoma cell line MCF-7 [29].

18.3.8 Euphorbiaceae

A total inhibition at 10 μg/mL was reported for two Madagascarian plants of the genus *Croton*, namely *C. barorum* Leandri and *C. goudotii* Baill., against the P388 murine lymphocytic leukemia cell line [30]. Two terpenoids, crotobarin (**7**) and crotogoudin (**8**), were identified as the active constituents of *C. barorum* and *C. goudotii*, respectively [30].

18.3.9 Fabaceae/Leguminosae

The Fabaceae or Leguminosae, commonly known as the legume, pea, or bean family, is a large, economically and medicinally important family of flowering plants. Products of plants of this family were reported for their cytotoxicity against human cancer cells [31,32]. In Africa, the ethanol extract of the roots of *Albizia gummifera* (J. F. Gmel.) C. A. Sm. var. *gummifera* (Madagascar) exhibited significant growth inhibition against the A2780 cell line, with an IC_{50} value of 7.2 μg/mL [33]. The active compound isolated from this plant was a triterpenoid saponin named gummiferaoside A (**9**) [33]. The bark methanol extract from *Guibourtia tessmannii* Harms Leonard, harvested in Cameroon, also showed antiproliferative activity, with an IC_{50} of 13.1 μg/mL against MCF-7 and 8.8 μg/mL against the human cervical cancer cells HeLa [29]. Two stilbenes isolated from the Nigerian plant *Cajanus cajan*, longistylins A (**10**) and C (**11**), showed high antiproliferative activity, with IC_{50} values ranging from 0.7 to 14.7 μM, against many different cancer cell lines including MCF-7 human breast adenocarcinoma, COR-L23 human large-cell lung carcinoma, and C32 human amelanotic melanoma [16]. Gallic acid (**12**) and its derivatives were identified as the cytotoxic constituents of the Egyptian plant *Acacia nilotica*[34]. IC_{50} values of 1.6 and

3.3 μg/mL against the two human uveal melanoma 92.1 and OCM3 cell lines, respectively, were obtained for compound **12**, 4.8 and 5.1 μg/mL toward 92.1 cells, and 11 and 8.2 μg/mL toward OCM3 cells, respectively, for gallocatechin 5-*O*-gallate (**3**) and epigallocatechin 3-*O*-gallate (**14**) [34].

18.3.10 Gramineae/Poaceae

Though some plants of this family are known to exhibit antineoplastic effects [35], there have been few data regarding the activity of those from African samples. Nevertheless, the root extracts of *Imperata cylindrica* Beauv. var. *koenigii* Durand et Schinz, harvested in Cameroon, was found to be active on some cancer cell lines, with IC_{50} values of 12.11 μg/mL against MiaPaCa-2, 8.4 μg/mL against CCRF-CEM, and 7.18 μg/mL against CEM/ADR5000 cell lines [13].

18.3.11 Guttiferae/Clusiaceae

Family Clusiaceae or Guttiferae formerly includes about 37 genera [36] and 1610 species of trees and shrubs, often plants with milky sap and fruits or capsules for seeds [36]. Plants of this family are sources of a variety of biologically active compounds. The cytotoxicities of several compounds isolated in Guttiferae plants worldwide have been reported [37–40]. In Africa, xanthone V_1 (**15**), isolated from the Cameroonian plant *Vismia laurentii*, significantly reduced the proliferation of a panel of cancer cell lines, with IC_{50} values below or around 4 μg/mL reported against CCRF-CEM (4.9 μg/mL), leukemia HL-60 (4.56 μg/mL), 786-0 renal carcinoma cells (3.79 μg/mL), U87 MG (3.80 μg/mL), A549 lung adenocarcinoma cells (3.99 μg/mL), Colo-38 skin melanoma cells (1.19 μg/mL), and Caski cervical carcinoma cells (0.24 μg/mL) [41]. Xanthones from *Pentadesma butyracea* Sabine (collected in Cameroon), among which there were three new compounds, namely butyraxanthones A (**16**), B (**17**), and D (**18**), and six known compounds, mangostanin (**19**), 1,3,6-trihydroxy-7-methoxy-2,8-diprenylxanthone (**20**), rubraxanthone (**21**), garcinone E (Figure 18.2 (**22**)), gartanin (**23**), and tovophyllin (**24**), exhibited significant antiproliferative activity against the breast cancer cell line MCF-7, with all IC_{50} values below 4 μg/mL [42]. In addition, globulixanthones A (**25**) and B (**26**), isolated from the Cameroonian plant *Symphonia globulifera* Linn. f., significantly inhibited the proliferation of the human oropharyngeal epidermoid carcinoma KB cancer cell line, with IC_{50} values of 2.15 and 1.78 μg/mL, respectively [43].

18.3.12 Melianthaceae

Plants of the family Melianthaceae, *Bersama engleriana* Engl. (Cameroon), showed IC_{50} values of 8.6 μg/mL against MCF-7 and 15.7 μg/mL against human prostate cancer (DU-145) cell lines for leaf methanol extract, 8.6 μg/mL against MCF-7, 10.9 μg/mL against HeLa cells, and 19.5 μg/mL against the liver hepatocellular carcinoma cells (HepG2) for the root methanol extract and 18.7 μg/mL against MCF-7 for the bark methanol extract [29].

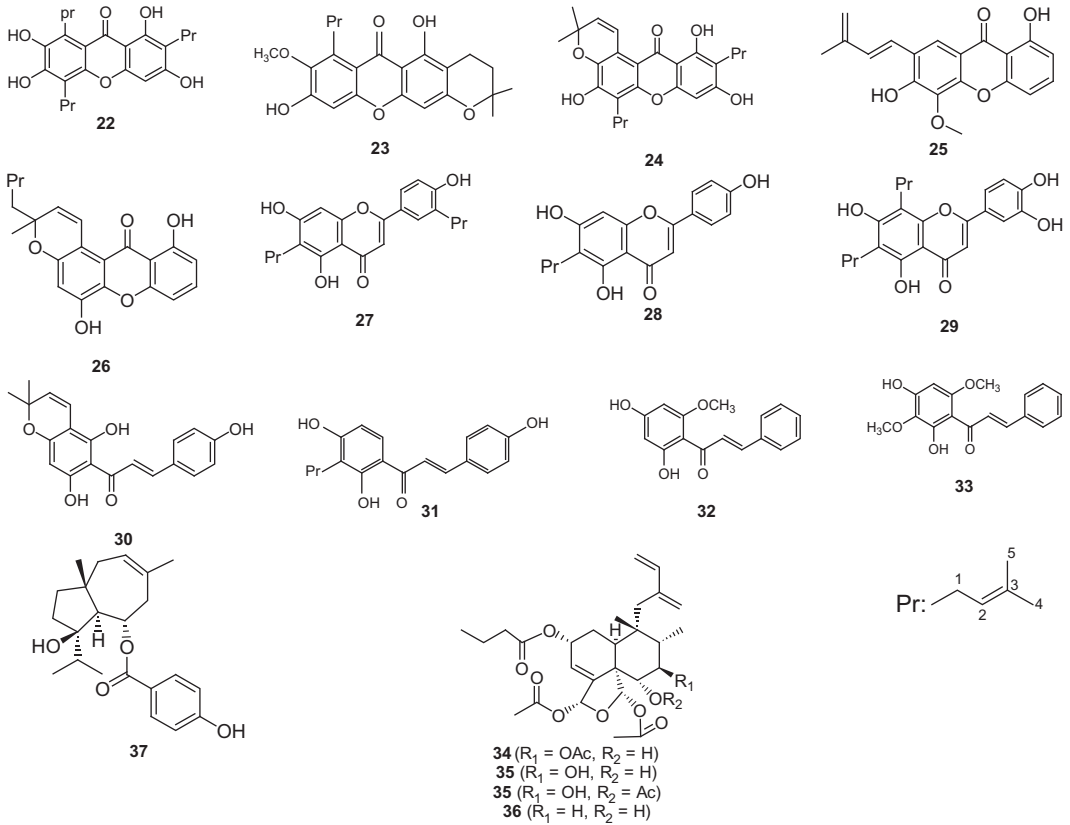


Figure 18.2 Cytotoxic compounds from African medicinal plants: garcinone E (**22**), gartanin (**23**), tovophyllin (**24**), globulixanthone A (**25**), globulixanthone B (**26**), gancaonin Q (**27**), 6-prenylapigenin (**28**), 6,8-diprenyleriodictyol (**29**), 4-hydroxylonchocarpin (**30**), isobavachalcone (**31**), cardamomin (**32**), 2′,4′-dihydroxy-3′,6′-dimethoxychalcone (**33**), caseanigrescen A (**34**), caseanigrescen B (**35**), caseanigrescen C (**36**), and caseanigrescen D (**37**).

18.3.13 Lamiaceae

Some medicinal plants of the family Lamiaceae, specifically the aerial parts of plants of the genus *Salvia*, collected in South Africa, were screened for antiproliferative activity [44]. Among them, the methanol-chloroform extract from *Salvia africana* L. showed a significant inhibitory effect against glioblastoma cell line SF-268, with an IC_{50} of 8.72 μg/mL [44]. The extract of *Salvia stenophylla* Burch. ex Benth. (IC_{50} of 17.41 μg/mL) was also active against leukemia HT-29, while that of *Salvia radula* Benth (IC_{50} of 9.69 μg/mL) was active against MCF-7 cells [44].

18.3.14 Moraceae

Within the family Moraceae, many plants and compounds of the genus *Dorstenia* were reported for their antiproliferative effects on malignant cells [13]. The methanol extract from the roots of *Dorstenia psilirus* Welwitch, collected in Cameroon, showed good cytotoxic effects, with IC_{50} values of 9.17 μg/mL against MiaPaCa-2 cells, 7.18 μg/mL against leukemia CCRF-CEM, and 7.79 μg/mL against the CEM/ADR5000 cell line [13]. Flavonoids from the genus *Dorstenia*, gancaonin Q (**27**), 6-prenylapigenin (**28**), 6,8-diprenyleriodictyol (**29**), and 4-hydroxylonchocarpin (**30**), inhibited the proliferation of a panel of 14 cancer cell lines including CCRF-CEM leukemia cells and their multidrug-resistant subline, CEM/ADR5000, PF-382 leukemia T-cells, HL-60 promyelocytic leukemia, MiaPaCa-2, Capan-1 pancreatic adenocarcinoma, MCF-7, SW-680 colon carcinoma cells, 786-0 cells, U87MG glioblastoma-astrocytoma cells, A549, Caski, HeLa, and Colo-38 cervical adenocarcinoma cells [23]. IC_{50} values below or around 4 μg/mL were reported for compound **27** on PF-382, HL-60 (4.8 μg/mL), MiaPaCa-2 (1.1 μg/mL), and MCF-7 (0.8 μg/mL); compound **28** on PF-382 (3.8 μg/mL) and MCF-7 (0.6 μg/mL); compound **29** on CCRF-CEM (4.9 μg/mL), MiaPaCa-2 (4.4 μg/mL), and MCF-7 (0.6 μg/mL); and compound **30** against CCRF-CEM (1.6 μg/mL), CEM/ADR5000 (3.7 μg/mL), MiaPaCa-2 (3.8 μg/mL), and MCF-7 (1.4 μg/mL) [23]. The chalcone flavonoid isobavachalcone (**31**), isolated from *Dorstenia barteri*[45] and *Dorstenia turbinata*[46], exhibited good cytotoxic effects against many tumor cell lines, including ovarian carcinoma OVCAR-8 cells, prostate carcinoma PC-3 cells, MCF-7, and A549 cells [47].

18.3.15 Polygonaceae

The methanol extract from the aerial parts of the Cameroonian plant *Polygonum limbatum* Meisn. showed good antiproliferative activity against leukemia THP-1 (IC_{50} of 10 μg/mL) and MCF-7 (IC_{50} of 20 μg/mL) cell lines [48]. The active constituents of the plant were flavonoids identified as cardamomin (**32**), (±)-polygohomoisoflavanone, (*S*)-(−)-pinostrobin, 2′,4′-dihydroxy-3′,6′-dimethoxychalcone (**33**), (2*S*)-(−)-5-hydroxy-6,7-dimethoxyflavanone, and (2*S*)-(−)-5,7-dimethoxyflavanone. Compounds **32** and **33** also induced significant inhibition of the proliferation of the leukemia THP-1 cells (IC_{50} below 4 μg/mL) [48].

18.3.16 Piperaceae

Piperaceae, also known as the pepper family, is a large family of flowering plants that may be small trees, shrubs, or herbs. The most well-known species is *Piper nigrum*, which yields most peppercorns that are used as spices, including black pepper, although its relatives in the family include many other spices [49]. *P. nigrum* is native to southern India and is extensively cultivated there as well as elsewhere in tropical regions, including Africa. The plant is believed to cure illnesses such as constipation, diarrhea, earache, gangrene, heart disease, hernia, hoarseness, indigestion, insect bites, insomnia, joint pain, liver problems, lung disease, oral abscesses, sunburn, tooth decay, and toothaches [50]. The alkaloid piperine has been reported to be the major cytotoxic constituent of *P. nigrum*[51,52]. The methanol extract from the seeds of another plant of the genus *Piper*, *P. capense* L.f., collected in Cameroon, inhibited the growth of some cancer cell lines, with IC_{50} values of 8.92 μg/mL (MiaPaCa-2), 7.03 μg/mL (CCRF-CEM), and 6.56 μg/mL (CEM/ADR5000) [13].

18.3.17 Salicaceae

Few medicinal plants of this family were reported for the cytotoxicity against human cancer cells. Nevertheless, *Laetia suaveolens*, harvested in Brazil, was found to be active against the squamous cell carcinoma KB-ADL#12 [53]. In addition, four new clerodane diterpenoids, caseanigrescens A (**34**), B (**35**), C (**36**), and D (**37**), isolated from Casearia nigrescens, a plant of the family Salicaceae collected in Madagascar, were found to be active against the human ovarian cancer cells A2780, with the respective IC_{50} values of 1.4, 0.83, 1.0, and 1.0 μM [54].

18.3.18 Umbelliferae/Apiaceae

Although the crude methanol extract of the Egyptian plant *Ferula hermonis* showed moderate activity, with an IC_{50} above 20 μg/mL, jaeshkeanadiol *p*-hydroxybenzoate (**37**), isolated from this plant, showed good antiproliferative activity against MCF-7 breast cancer cells (IC_{50} of 2.47 μg/mL) [55].

18.3.19 Zinziberaceae

Zinziber officinalis Roscoe, harvested in Cameroon, exhibited good cytotoxicity, with IC_{50} values of 16.33 μg/mL against MiaPaCa-2, 8.82 μg/mL against CCRF-CEM, and 6.83 μg/mL against CEM/ADR5000 for the rhizome methanol extract [13].

18.4 Mechanistic Studies with Cytotoxic Natural Products of African Medicinal Plants

Emphasis is continually put on the study of the cytotoxic mode of action of African plants and derived products, and there are some published data concerning the mechanism of induction of apoptosis and angiogenesis. With the collaboration of more

research partners worldwide, African scientists have made considerable progress in this field. For instance, the active fraction from *X. aethiopica* was shown to induce DNA damage, cell cycle arrest in the G1 phase, and apoptotic cell death in the U2OS osteosarcoma cell line [14]. The antiangiogenic properties of some Cameroonian plant extracts, such as *E. giganteus*, *P. capense*, *X. aethiopica*, and *I. cylindrica*, were reported [13]. Compounds isolated from African plants, such as **7** and **8**, were reported to induce growth arrest at the G2/M phase in the cell cycle of the K562 human leukemia cell line at 4 μM [30]. The *Dorstenia* flavonoids **27**−**30**, as well as the xanthone (**15**) from *V. laurentii* De wild, collected in Cameroon, were of low cytotoxicity on normal AML12 hepatocyte cells [23] and were found to induce apoptotic effects on leukemia CCRF-CEM cells via caspase-3 and -7 activation [23,41]. They also showed antiangiogenic properties [23,41]. The naphthoquinone (**3**), isolated from *N. laevis*, showed 59.6% inhibition of blood capillary growth on the chorioallantoic membrane of quail eggs in the antiangiogenic assay [41]. Furthermore, compound (**3**) induced cell cycle arrest in the S-phase, with significant apoptotic effects in CCRF-CEM leukemia cells [41]. Compound **31** significantly ablated Akt phosphorylation at Ser-473 and serine/threonine protein kinase (Akt) activity in cells, which subsequently led to inhibition of Akt downstream substrates and caused significant levels of the mitochondrial pathway of apoptosis [47]. Nishimura et al. [56] demonstrated that compound **31** induced apoptotic cell death with caspase-3 and -9 activation and Bax upregulation in neuroblastoma cell lines. Compound **31** also inhibited matrix metalloproteinase-2 (MMP-2) secretion from U87 glioblastoma cells [45]. In addition, compound **1**, from *A. occidentale*, was found to induce apoptosis in Jurkat cells, and this was proposed as the likely mechanism of specific cytotoxicity of compound **1**[12].

18.5 Conclusions

The present chapter obviously gives some insight into the state of the art of the antiproliferative drug research involving African medicinal plants as well as their derived natural products. It shows the effort under way throughout the continent to tackle malignancies with natural products. However, it also points out that the study of the mechanism of action is still in its early stages, and this gap should be taken as a challenge for the near future. In addition, clinical evidence is mostly nonexistent in general and should finally be taken as a priority, taking into account the large number of prominent results published to date.

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19 Anti-Inflammatory and Analgesic Activities of African Medicinal Plants

Christian Agyare[a], *David Darko Obiri*[b], *Yaw Duah Boakye*[a] *and Newman Osafo*[b]

[a]Department of Pharmaceutics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, [b]Department of Pharmacology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

19.1 Introduction

Ancient African healers had extensive plant materials; of more than 5000 plant species, most have been used as food and for the treatment of various diseases for centuries. There is no clear distinction between traditional African religions and herbal medicine, as in both practices, herbs are used as medicines. African traditional medicine has not been documented in detail, as have those of the Chinese and Indians. This leaves African medicinal plant species underrepresented in modern herbal and ethnomedicine. Some valuable medicinal plant species have been lost to deforestation over the years, and some have become endangered species because of the high demand for herbal preparations or products in Africa, and even in some developed countries such as Japan, the United States, the United Kingdom, Canada, and Germany, though the use of herbal medicines in the United States is less widespread than in the majority of developed nations. Wide distribution through pharmacies is difficult because no medical claims may be made and consumers are dependent on advice from pharmacists who, in a majority of cases, have little knowledge about medicinal herbs [1]. Medicinal plants are used in pharmaceutical preparations in pure or extracted forms as pain relievers or as anti-inflammatory agents. Many bioactive compounds have been isolated and characterized from plants. Research into medicinal plants having pain-relieving action and anti-inflammatory properties is a logical research strategy in the search for new analgesic and anti-inflammatory drugs [2].

The term inflammation is derived from the Latin word *Inflammare*, meaning burn. Any form of injury to the human body can elicit a series of chemical changes in the tissues in response to an invading pathogen (disease-causing organism) or

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the presence of noxious substances. Inflammation is a healthy process resulting from some disturbances or disease. It usually consists of immunologically specific reactions as well as various innate reactions with no immunological basis. These reactions are protective, but if inappropriately developed they may be deleterious, and if the pathogen or noxious substance persists, chronic inflammation can develop [3]. The clinical signs of inflammation are heat, redness, swelling, pain, and loss of function. Inflammation usually involves a sequence of events which can be categorized under three phases: acute transient phase, delayed subacute phase, and chronic proliferate phase. In the first phase, inflammatory exudates develop due to enhanced vascular permeability, leading to local edema. This is followed by the migration of leukocytes and phagocytes from blood to vascular tissues, which constitutes the second phase. In the third phase, tissue degradation is followed by fibrosis [2].

There are different types of inflammatory diseases and rheumatic, including ankylosing spondylitis, rheumatic fever, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, and polyarthritis nodosa [4].

Central to the inflammatory response is the role played by mast cells. At the molecular level, antigen (Ag)-induced ligation of the high-affinity immunoglobulin E (IgE) receptor (FcεRI) on mast cells triggers a cascade of signaling events that ultimately leads to a wide variety of effector functions: degranulation (release of histamine, 5-hydoxytryptamine, etc.), release of arachidonic acid and its subsequent metabolism into prostaglandins and leukotrienes respectively via the cyclo-oxygenase (COX) and lipo-oxygenase (LOX) pathways, and finally the transcription of cytokine and chemokine genes (Figure 19.1) [5]. All of these contribute to the inflammatory response. Modulation of mast cell activation may therefore provide ways to control inflammatory diseases.

Various drugs are used to treat these disorders, but they come with several adverse side effects. A typical example is the gastrointestinal disturbances associated with the use of the nonsteroidal anti-inflammatory drugs (NSAIDs) and development of Cushing's syndrome with the glucocorticoids. It is very important that ethnobotanical plants found to possess anti-inflammatory and analgesic properties. Bioactive compounds from plants can serve as a template for the synthesis of new anti-inflammatory drugs with minimal side effects but having more potent pharmacological effects. This chapter reviews some African medicinal plants and their extracts, fractions, and isolates with anti-inflammatory and analgesic properties.

19.2 Medicinal Plants with Anti-Inflammatory and Analgesic Activities

19.2.1 Alliaceae

Agapanthus campanulatus Leighton is a deciduous plant, growing in spring and summer and dormant during winter in southern Africa. The bell agapanthus is

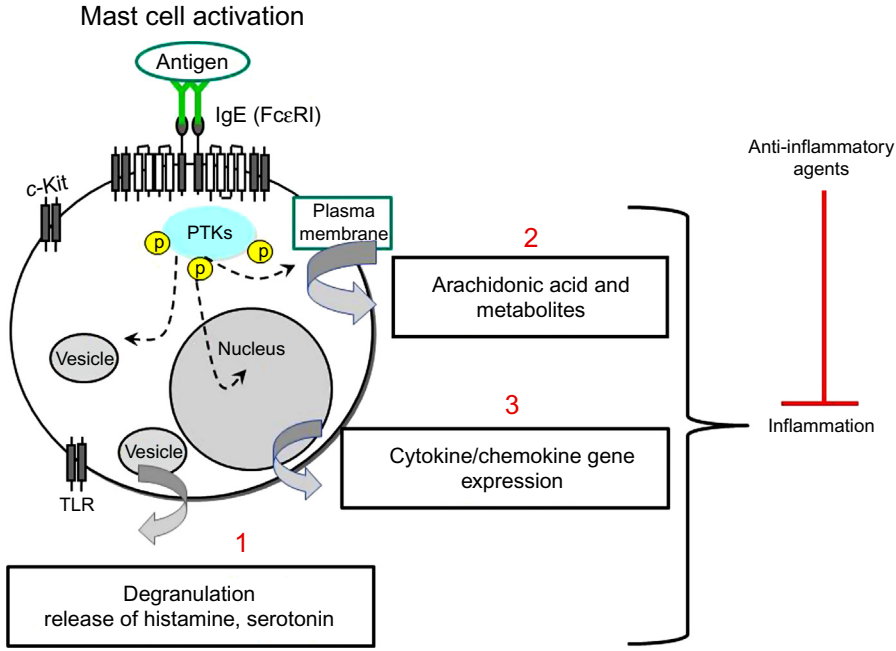

Figure 19.1 Mode of action of anti-inflammatory agents. Mast cells express on their surface a number of receptors including the Toll-like receptor, c-kit receptor, and the high-affinity immunoglobulin E (IgE) receptor (FcεRI). Antigen (Ag)-induced ligation of the FcεRI triggers a cascade of signaling events, including phosphorylation of protein tyrosine kinases (PTKs) that ultimately lead to a wide variety of effector functions: degranulation (release of histamine, 5-hydoxytryptamine, etc.), release of arachidonic acid and its metabolites, and finally the transcription of cytokine and chemokine genes. These proinflammatory compounds mediate the inflammatory response, which can be attenuated by anti-inflammatory agents.
Source: Authors (2013).

found growing in colonies in moist grassland, moist slopes, valley bottoms, drainage lines, damp cliffs, and on rocky slopes up to 2400 m in the Eastern Cape, Lesotho, KwaZulu-Natal, Gauteng, and Mpumalanga [6]. The roots are crushed and made into a lotion that is used to bathe newborn babies to make them strong, and the leaves are used to wash young babies. It is also used to treat "cradle cap" and as a protective charm against lightning [7]. The dichloromethane (DCM) root extract of *A. campanulatus* has a high COX-2 inhibitory activity (83.7%), confirming its anti-inflammatory activity [8].

19.2.2 Aloaceae or Liliaceae

Aqueous leaf extract of *Aloe ferox* Mill has been shown to exhibit anti-inflammatory and analgesic activities at the highest dose used (400 mg/kg) in rats.

This dose level exerted the highest anti-inflammatory activity for carrageenan and formaldehyde-induced rat paw edema. The analgesic activity was 57.1% and 67.3% for the 400 mg/kg dose in phase 1 and 2, respectively, of the formalin test and 88.2% in the acetic acid test. *A. ferox* reduced inflammation and relieved pain in rats at the highest dose level studied. This pharmacological property supports the extensive use of the plant as an anthelmintic in reducing the inflammation and pain that might have been caused by gastrointestinal parasite infections [9].

19.2.3 Amaryllidaceae

Crinum moorei Hook. f. is one of the larger members of the worldwide tropical to temperate ornamental lily family, Amaryllidaceae. The family includes the European narcissi and daffodils but also gardeners' favorites from southern Africa such as *Amaryllis*, *Haemanthus*, *Scadoxus*, *Clivia*, *Brunsvigia*, *Boophone*, and *Cyrtanthus. C. moorei* is used in traditional medicine for urinary tract infections and to treat cattle. The bulbs are also used by traditional healers to cleanse the blood and to treat infected sores and acne [10]. *C. moorei* (bulbs) extracts (methanol, ethanol, petroleum ether, and DCM) have been found to show good inhibitory activity against both COX-1 and COX-2 enzymes [11].

19.2.4 Apiaceae

Kundmannia sicula (L.) DC is an herbaceous and perennial plant presenting robust and ramified stems of 40−120 cm. Inferior leaves are glabrous and gleaming. They are disposed in rosettes applied on the ground. Flowers are yellow. Fruits are cylindrical, glabrous, and 7–10 mm in length. In traditional medicine, the roots and rhizomes are used as infusions or plasters in the treatment of inflammatory pathologies. In Algeria, *K. sicula* is commonly known as "ziyata," meaning "the plant that gives a lot of oil." The major components isolated from *K. sicula* include spathulenol (14.8%), caryophyllene oxide (12.2%), salvial-4(14)en-1-one (10.1%), 1,5-epoxysalvial-4(14)ene (5.2%), and germacrene D (3.2%), while samples from El Kala were found to contain salvial-4(14)en-1-one (16.4%), 1,5-epoxysalvial-4 (14)ene (6.5%), chrysanthenyl acetate (5.2%), and α-amorphene (2.9%) [12]. Aqueous, ethanol, and chloroform extracts of *K. sicula* have been found to inhibit inflammation in both topical and acute systemic studies [13].

19.2.5 Apocynaceae

Funtumia elastica (Preuss) Stapf. (Apocynaceae), known commonly as silkrubber, is traditionally used to treat whooping cough [14], inflammatory diseases such as asthma, blennorhea, and painful mensturation [15], cutaneous fungal infections, hemorrhoids, syphilis, gonorrhea [14,16], and wounds [17]. Preliminary phytochemical screening has revealed that *F. elastica* bark contains hydrolyzable tannins, sapogenetic glycosides, steroids, and saponins, while the leaves contain hydrolyzable tannins, flavonoids, starch, and alkaloids. Tannin content of the leaves and

stem bark was 2.4% and 1.3% w/w (related to the dried material), respectively [18]. Some steroidal alkaloids (holarrhetine, conessine, holarrhesine, and isoconessimine) have been isolated from the stem bark, and the conanine group, namely irehdiamines A and D, irehamine, conkuchine, and irehine, from the leaves of *F. elastica*[19]. The ethanol from leaf and bark extracts of *F. elastica* showed significant anti-inflammatory activity at 30, 100, and 300 mg/kg in carrageenan-induced inflammatory model in 7-day-old chicks [18].

Landolphia owariensis is a climbing herb of 12 m or more; young twigs are ferruginous-pubescent indumentums, later becoming grayish and rather persistent; bark on young branches is dark reddish brown with tiny circular white lenticels. Leaves are thinly coriaceous; the petiole is 5 mm long, pubescent all around; lamina are 7.5−11.6 × 3−4.4 cm, oblong, with the apex shortly acuminate, acumen rounded, and base rounded. The leaves are used traditionally as antimalarial agents, and various extracts of the plant have been found to possess anti-inflammatory and analgesic activities. Phytochemical screening of the methanolic extract of *L. owariensis* revealed the presence of alkaloids and some polyphenolic compounds. In addition, this extract exhibited some antioxidative properties. The aqueous, methanol, and chloroform leaf extracts of *L. owariensis* extracts, at 100 mg/kg each, are known to significantly inhibit paw edema induced by carrageenan in rats and the nociception induced by tail immersion in hot water (50.0°C) and acetic acid. The methanol extract produced the highest paw edema inhibition, while in thermally induced nociception, both the methanol and the chloroform extracts exhibited high and comparable analgesic activity compared to acetylsalicylic acid (150 mg/kg). However in chemically induced pain (acetic acid), methanol extract showed the highest and comparable analgesic activity to acetylsalicylic acid (150 mg/kg) [20].

Picralima nitida (Stapf) T. Durand & H. Durand is found growing in Côte d'Ivoire, Ghana, Uganda, the Democratic Republic of the Congo, and Angola. Extracts from the various parts of *P. nitida* are used in West African traditional medicine for many diseases [21,22]. The dried powdered seeds of *P. nitida* are used for the treatment of diarrhea and various types of pain. Analgesic actions comparable to morphine have been demonstrated for the aqueous extract of *P. nitida* seeds in rats [23]. Dose-dependent anti-inflammatory action has been reported for the aqueous ethanolic extract in Wistar rats over a dose range of 100−400 mg/kg body weight (bw) (*per os* or orally or p.o.) [24,25].

The stem bark, fruits, and seeds of *P. nitida* contain major indole alkaloids such as akuammine, akuammicine (strychnan class), akuammidine and akuammiline (both corynanthean class), akuammigine and the very similar alstonine, pseudo-akuammigine (ψ-akuammigine), and picraline. The seeds are particularly rich in alkaloids (3.5−4.8%); akuammine is the principal alkaloid of the mature seeds, while minor alkaloids are pseudo-akuammicine, picranitine, picratidine (*N*-methylpicraline), eburnamine (desacetylpicraline), and desacetylakuammiline (rhazimol). The root bark contains akuammigine, akuammicine, picracine, and desacetylpicraline, and the leaves contain akuammine, akuammigine, picraphylline, and melinonine A. The stem bark also contains picracine. The specific indole alkaloids from *P. nitida* have very interesting properties, which have only partly been evaluated in

tests, including some clinical trials. Akuammidine, akuammine, pseudo-akuammigine, and akuammicine are opioid compounds, having significant analgesic activities [26,27].

Pseudo-akuammigine (**1**), an alkaloid isolated from *P. nitida* seed extract, exhibits anti-inflammatory and analgesic actions. The analgesic actions are mediated via interaction with opioid receptors. The alkaloid, at 1.0, 5.0, and 50 mg/kg, dose-dependently inhibited the mean maximal paw swelling attained over 6 h to 78.21%, 74.7%, and 59.5% of the mean control value, respectively, when administered p.o. 1 h before induction of edema with carrageenan. At the same dose levels, the total paw swelling over the 6 h period was also significantly reduced to 83.2%, 73.0%, and 55.8% of the mean control response, respectively. When administered after induction of edema, ψ-akuammigine (5.0 mg/kg) significantly reduced established rat paw swelling to 82.8% of the control response after 5 h. As an analgesic, ψ-akuammigine was 3.5 and 1.6 times less potent than morphine and indomethacin, respectively. The ED_{50} values were morphine (2.9 μM), ψ-akuammigine (10 μM), and indomethacin (6.3 μM). Naloxone (1.0 mg/kg) significantly antagonized the analgesic action of the alkaloid by 35.8% [28].

19.2.6 Araceae

Colocasia antiquorum Schott. is an annual herbaceous plant with a long history of usage in traditional medicine in several countries across the world, especially in the tropical and subtropical regions. The herb has been known since ancient times for its curative properties and has been used for treatment of various ailments including asthma, arthritis, diarrhea, internal hemorrhage, neurological disorders, and skin disorders. The juice of the *C. antiquorum* corm is widely used for treatment of body ache and baldness. A wide range of chemical compounds including flavonoids, β-sitosterol, and steroids have been isolated from this species. Extracts from this plant have been found to possess various pharmacological activities. *C. antiquorum* tuber petroleum ether extract exhibited the highest (92.7%) percentage inhibition against COX-2, while the highest COX-1 percentage inhibition (100%) was exhibited by *C. antiquorum* tuber DCM extracts [11].

19.2.7 Araliaceae

Cussonia paniculata Eckl. & Zeyh. is a short tree that grows up to 5 m in height. It is sparsely branched with gray, longitudinally fissured, thick, and corky bark. The stem is thick and squat. It is a pachycaul succulent on the basis of its swollen stem base or tuber. Roots are swollen and thick. The leaves are cabbage-like, blue, and are the most distinctive feature. The leaves are made up of 7−9 and up to 13 leaflets. The leaflets are up to 30 cm in length, and the overall leaf can grow up to 60 cm [29].

The aqueous stem bark extract of *C. paniculata*, at doses of 50, 100, and 200 mg/kg body weight, has been found to significantly reduce the formation of edema induced by carrageenan and histamine. In the acetic acid-induced writhing

model, the extract showed good analgesic effect characterized by reduction in the number of writhes when compared to the control. The extract caused a dose-dependent decrease in licking time and licking frequency in rats injected with 2.5% formalin, indicating a significant analgesic effect. These results were comparable to those of indomethacin and cyproheptadine, the reference drugs used in the study. An acute toxicity test showed that the plant caused 80% mortality in rats, indicating that the plant may be toxic. These findings may justify the folkloric uses of the plant such as stomach ache, pain, and inflammation [29].

19.2.8 Asparagaceae

Asparagus africanus Lam. is an erect armed herb that grows up to 5 ft high. The plant is widely distributed in tropical Africa. In Nigeria, the plants are known as "shekan bera" in Hausa and "aluki" in Yoruba [30]. In traditional medicine, the plant is used for the treatment of headache, backache, stomach pain, and as an aid in childbirth [31]. The plant is also used for hematuria, hemorrhoids [32], malaria, leishmaniasis, bilharziasis, syphilis, and gonorrhea [33]. The root extract is applied externally for the relief of pain, rheumatism, and chronic gout [34]. It is also used as a diuretic and for sore throat and otitis [35]. Three steroidal saponins have been isolated from the roots of *A. africanus*[36]. The anti-inflammatory activity of the crude saponin extract of rhizomes of *A. africanus* against carrageenan-induced paw edema in the rat model has been reported. It is known to cause a significant reduction in rat hind paw edema compared to the control group [36].

19.2.9 Asteraceae

Echinops spinosus Turra. is common throughout the Sahara, including the Red Sea region and Sinai. The plant thrives in desert conditions with an annual rainfall of 20−100 mm and has a wide ecological range in terms of soil. It is found on coastal calcareous dunes, sandy wadi beds, and gravelly to rocky surfaces, where the plant shows an ecological optimum. A perennial herb growing to 1 m and more, with erect brownish to reddish stems, few long leaves from 10 to 15 cm, hairy, arachnoid, and with very long spines [37,38]. The inflorescence is often a single hemispherical globe up to 5 cm in diameter during the flowering period. It is surrounded with numerous long spines. The small hermaphroditic flowers that compose the dense head are tubular, turning from green to white and yellowish when in full bloom. The fruits are small achenes topped by membranous scales to ease dispersion [38].

Their phytochemical constituents are mainly sesquiterpene lactones, acetylenic elements belonging to the thiophen type. Pharmacologically, it has an efficient action on muscular fibers, as well as anti-inflammatory and hypoglycemic properties [39]. Traditionally, it is used as an abortifacient, diuretic, and for blood circulation, diabetes, dysmenorrhea, gastric pain, hemorrhoids, indigestion, and spasmolytic and varicose problems. In Egypt, the plant is taken to cure diseases related to the circulatory system (a hemostat, a vasoconstrictor for hypertension,

varices, and varicocele). In Morocco, it is mainly used to ease childbirth. A decoction of the roots in either water or olive oil is given to help pregnant women evacuate the placenta. It is also given before the birth to stimulate contractions. In Marrakech and Salé, a decoction of the roots is used for stomach pain, indigestion, and lack of appetite, as well as diabetes. In Casablanca, the entire plant, in a powder or decoction, is used as a diuretic or depurative and to cure liver diseases [40]. *E. spinosus* extracts (aqueous, ethanol, and chloroform) are known to inhibit inflammation in both topical and acute systemic studies well above 50% [13].

Microtrichia perotitii DC is a diffused, much branched pubescent annual plant, 30 cm or more in height [41]. The leaves are obovate, cuneately narrowed into the petiole, coarsely toothed, and 2.5 cm broad, the flowers are florate, and the fruits are drupes [42]. Bioactive compounds isolated from this plant include sesquiterpenes, saponins, and alkaloids [43,44]. Traditionally, the fresh or dried leaves and flowers are used for the treatment of toothache. The leaves are used for the treatment of rashes in children. However, classical Yoruba spiritualists use the herb to dispel evil spirit [45]. The *n*-butanol phase of the methanol leaf extract of *M. perotitii* has been found to possess analgesic and anti-inflammatory properties [46].

19.2.10 Bignoniaceae

Kigelia africana (Lam.) Benth. (syn. *Kigelia pinnata* Jacq. DC) is a small, spreading tree with pendulous racemes of dull liver-colored flowers and a long, stalked gourd-like fruit. It is widely grown in the tropics and was introduced from India to tropical Africa. The roots, wood, and leaves have been found to contain naphthoquinones, dihydroisocoumarines, flavonoids, and aldehydic iridoids. Among the naphthoquinones, kigelinole, isokigelinole, pinnatal, and isopinnatal have been isolated [47]. From the root and its bark the usual plant substances stigmasterol, β-sitosterol, ferulic acid, the naphthoquinones lapachol, 6-methoxymellein, and two new phenolic compounds have been isolated. Kigelin is the main component of the plant (mp 144°C, molecular formula $C_{12}H_{14}$). A minor component, 6-methoxymellein (mp 76−77°C, molecular formula $C_{11}H_{12}O_4$), has been elucidated [48]. In African folk medicine, *K. africana* is used for the treatment of dysentery, venereal diseases, and as a topical application on wounds and abscesses. In the area around Nsukka, Nigeria, the bark is used for the treatment of venereal diseases [47]. Verminoside has also been isolated from the fruit. Aqueous extract of *K. Africana* has been shown to exhibit significant analgesic and anti-inflammatory effects, inhibiting both iNOS expression and NO release [49] and prostaglandins *in vitro*[50].

Newbouldia laevis P. Beauv. is a medium-sized angiosperm of the Bignoniaceae family. *N. laevis* is native to tropical Africa and grows from the Guinea savanna to dense forests [51]. In Nigeria, the plant is used for the treatment of elephantiasis, dysentery, rheumatic swellings, syphilis, constipation, piles, and as a vermifuge [52]. The roots, leaves, stems, and fruits have been used as febrifuge, wound dressing, and for treatment of stomach ache [53], including inflamed sores, ulcers, and abscesses [54]. Phytochemical studies on the roots, root bark, and stems of this

plant have revealed the presence of alkaloids, quinoid, and phenylpropanoid [55–57]. The stem bark has been found to exhibit anti-inflammatory activity in acute inflammation and the polyarthritic phase of chronic inflammation [58]. Also, ethanolic flower extract showed anti-inflammatory activity comparable with ketoprofen [59].

19.2.11 Caryophyllaceae

Corrigiola telephiifolia Pourr. is a Moroccan medicinal plant. It is an herb, widely branched from the base, with slender prostrate branches and tiny compact inflorescences. The root, which is used for medicinal and cosmetic purposes, is a perennial taproot. This species is found in southern Europe and North Africa. In Morocco, it grows in cultivated beds on rocky and sandy soils. It is widespread in the Atlas and Rif mountains [60]. Morocco annually exports a quantity of about 370 tons [61]. When burned, the root of this plant releases an aromatic fume. The root is also used to treat flu, dermatological diseases, inflammation, ulcers, cough, and jaundice. It is also used as an anesthetic and a diuretic [60]. *C. telephiifolia* root is part of a traditional remedy given to parturient women. The powdered root is traditionally consumed plain, mixed with honey, or simply sprinkled on food [62]. The aqueous, ethanol, and chloroform extracts of *C. telephiifolia* have been reported to inhibit inflammation in both topical and acute systemic studies well above 50% [13].

19.2.12 Celastraceae

Maytenus senegalensis (Lam.) Exell is an African shrub or tree that goes under the common name of spike thorn. *M. senegalensis* has a wider distribution, including tropical African regions, Arabia, Afghanistan, and India [63]. The Celastraceae family is a source of important bioactive secondary metabolites. Alkaloid amines such as cathine often occur in this botanical family, as also, rarely, benzylisoquinolide alkaloids [64]. Celastraceae members are commonly tanniferous, containing anthocyanins, sometimes saponiferous, only rarely cyanogenic, and without iridoid compounds [64]. Different plant parts of this species are largely used in traditional medicine for treatment of infectious and inflammatory diseases. Anti-inflammatory activity of *M. senegalensis* ethanol extracts (70%) was determined in Wistar albino rats by the carrageenan-induced paw edema method. The extract exhibited significant anti-inflammatory activity (120 mg/kg, p.o.), reducing edema by 35% [65]. The highest anti-inflammatory activity is detected in the chloroform extract, which reduced the edematous response with a potency similar to that of the NSAID reference drug, indomethacin, with 50% inhibition dose (ID_{50}) of 84 and 93 $\mu g/cm^2$, respectively) [66].

19.2.13 Crassulaceae

Cotyledon orbiculata L. is a small shrub with fleshy leaves; it is widely distributed in southern Africa. It is known locally as “seredile” in Sotho and Tswana,

"plakkie" in Afrikaans, and "imphewula" in Xhosa. *C. orbiculata* is used in the treatment of various ailments in different parts of South Africa. The fleshy leaves have been used to treat corns and warts. The juice of the leaves is used as drops for earache and toothache and as a hot poultice for boils and inflammation [67,68]. *C. orbiculata* [100−400 mg/kg body weight, intraperitoneal (i.p.)] has been reported to significantly inhibit acetic acid-induced writhing and also delays the reaction time of mice to hot-plate-induced thermal stimulation. The methanol leaf extract of *C. orbiculata* (50−400 mg/kg, i.p.) also significantly attenuates the carrageenan-induced paw edema in rats. The relatively high LD_{50} (lethal dose for half the population) (400 mg/kg, p.o) shows that *C. orbiculata* may be safe in mice. *C. orbiculata* has both antinociceptive and anti-inflammatory activities, which may be produced by inhibiting various chemical mediators including prostaglandins and bradykinin, which may justify its use by traditional medicine practitioners for the treatment of painful conditions such as headache, earache, toothache, and inflammation [22].

19.2.14 Euphorbiaceae

Mallotus oppositifolius (Giesel) Mull. Arg. is a shrub or small tree up to 13 m high, common in drier types of forest and in secondary regrowth; it grows widespread across tropical Africa to Madagascar. A decoction is a vermifuge in the Côte d'Ivoire−Burkina Faso area [69]. Crushed or chewed leaves are used in Ghana as a hemostatic on wounds and sores [70] and burns [30]. This quickly arrests bleeding. In Côte d'Ivoire and Burkina Faso, the leaves are compounded into an ointment with karite butter for application to sores and ulcers [30]. The plant is believed to have anodynal properties. In Nigeria, patients with headache are treated by inhalation of the steam from boiling leaves [69]. The acute and chronic anti-inflammatory properties of the petroleum ether, DCM, and 80% ethanol extracts have been established using murine models [71].

Margaritaria discoidea (Baill.) Webster (syn. *Phyllanthus discoideus* (Baill.) Mull-Arg.) is a tree reaching a height of 30 m. It is common in Senegal, western Cameroon, and the rest of tropical Africa [72]. Many alkaloids have been isolated from this plant, of which phylochrysine and securinine are the most important. Phylochrysine is a central nervous stimulant, which may account for its stimulatory properties [69,72,73]. Traditionally, the bark is used for treatment of toothache in Sierra Leone, while in the Central African Republic, the decoction is used for relief of postpartum pains. In Congo (Brazzaville), the bark decoction is also used to relieve stomach and kidney complaints and to facilitate parturition. In Malawi, powdered bark extract is applied to swellings and inflammations for quick relief [70]. Murine models have been used to establish the anti-inflammatory and analgesic activities of the aqueous stem bark extract [74].

Phyllanthus amarus Schum. et. Thonn. is an herb found growing in some tropical African countries such as Ghana, Nigeria, and Cameroon, and some Asian countries such as India, China, and the Phillipines [75]; it can grow to 30−60 cm in height. All parts of the plant are used therapeutically. Phytochemical studies of

extracts have revealed the presence of gallic acid, terpenes, and flavonoids [58]. *P. amarus* has been found to possess anti-inflammatory properties through its inhibition of iNOS, COX-2, and cytokines via the NF-κB pathway [76].

19.2.15 Fabaceae

Dichrostachys cinerea L. is a semideciduous to deciduous tree up to 7 m tall, with an open crown. Young branches are green and hairy but dark gray-brown and longitudinally fissured on older branches and stems; smooth spines are formed from modified side shoots [77]. *D. cinerea* penetrates clear-cut areas far into the rainforest zone. In Malaysia, it occurs in areas with strong seasonal climate, usually on poor, occasionally clayey soils, in brushwood, thickets, hedges, teak forest, and grassland. It forms dense hammocks on lateritic soils in Senegal and Sudan, while in India it occurs in dry deciduous forest [77]. The bark is used to treat dysentery, headaches, toothaches, elephantiasis and is also used as a vermifuge. Root infusions are taken for leprosy, syphilis, cough, as an anthelmintic, purgative, and strong diuretic. Pounded roots and leaves are used to treat epilepsy. The roots are chewed and placed on the site of snakebites and scorpion stings, and the leaves, which are believed to produce a local anesthesia, are used for the same purpose, as well as a remedy for sore eyes and toothache. Leaves are taken as a diuretic and laxative and are used for treatment of gonorrhea and boils; the powder from leaves is used in the massaging of fractures [78]. The anti-inflammatory activity of the crude saponin extract from stem bark of *D. cinerea* has been shown to exhibit significant anti-inflammatory activity, with 72% in edema inhibition in a murine model [79].

Elephantorrhiza elephantina (Burch.) Skeels is a perennial suffrutex producing unbranched, unarmed, aerial stems up to 90 cm high. These stems represent the canopy of the much larger tree which is below ground. The bark and young branchlets are dark reddish brown. The leaves are dull green, bipinnately compound, with 2−17 opposite or subopposite pairs of pinnae. Flowers are arranged in axillary, solitary, or clustered racemes that are golden yellow to pale yellowish white and near to or protruding from ground level [80]. It is widespread and most commonly encountered from the southern parts of Angola, Namibia, Botswana, Zimbabwe, Mozambique, and the South African provinces of Limpopo, Northwest, Gauteng, Mpumalanga, Free State, KwaZulu-Natal, Northern Cape, and Eastern Cape, as well as Swaziland and Lesotho [81]. The most common folkloric use for *E. elephantina* is for the tanning of leather. In Xhosa and Zulu traditional medicinal practice, it is used for treatment of dysentery, diarrhea, stopping bleeding, intestinal disorders, hemorrhoids, heart ailments, and syphilis. It has also been used as an aphrodisiac, and a decoction from it has been used as a remedy for bovine and equine diarrhea. An extract of the fleshy underground parts of the plant is used to treat sunburn. Roasted seeds of the plant are used as a coffee substitute, although reportedly it is an acquired taste [81]. The anti-inflammatory and antinociceptive properties of the aqueous extract of *E. elephantina* has been established using murine models [82].

Indigofera pulchra Willd is an annual nonclimbing herb or shrub that can grow up to 1 m tall. It is widely distributed throughout tropical and subtropical regions of Nigeria, Niger, Togo, Benin, Ghana, and Chad [83]. In ethnomedicine, the leaves are used to treat infected wounds [72,83], while the decoction of the aerial parts is used as prophylactic against snakebite [84], as an analgesic and anti-inflammatory [85], and to treat gastrointestinal pain. The decoction is also used to counteract various poisons [72] and is effective against malaria and dysentery [86,87]. The anti-inflammatory activity of the crude saponin extract of *I. pulchra* leaves has been shown to be significant, with 40% reduction in edema compared to the control group in a murine model [79].

Tamarindus indica L. is a large, evergreen tree, with linear stipules, leaves 3.5−15 cm long, paripinnate, leaflets 10−20 cm, opposite, 1.2−1.8 cm long, 3.75 cm wide, oblong, obtuse. Racemic inflorescences with 10−15 cm pale yellow flowers, pedicels 8−10 mm, calyx circa 1.2 cm long, tube turbinate, teeth lanceolate, the lowest two connate. There are 1−3 petals 1−1.5 cm in length, pale yellow, with red veins. Pods are 7.5−20 cm long, 2−2.5 cm wide, slightly compressed, indehiscent. It contains tartaric (3−10%), acetic, citric, formic, malic, and succinic acids, as well as amino acids (alanine, leucine, phenylalanine, proline, serine), invert sugar (25−30%), pectin, protein (87.9 g/kg), fat (19.1 g/kg), some pyrazines, trans-2-hexenal, and some thiazoles (2-ethylthiazole, 2-methylthiazole) as fragrances [88]. Two triterpenes, lupanone and lupeol, have been isolated from the leaves [89]. The seeds also contain polysaccharides, with a main chain consisting of β-1,4- connected glucose molecules together with xylose (α-1,6) and galactose (β-1,2), total protein (15%), lipids with fatty oils, and some keto acids [88]. The purified pulp is used treat constipation and liver and bile problems. In Nigeria, *T. indica* is used treat various worms, including guinea worm infections and trypanosomiasis in domestic animals in Nigeria [88]. Aqueous, ethanol, and chloroform extracts from *T. indica* have been found to inhibit inflammation in both topical and acute systemic conditions [13].

19.2.16 Lamiaceae

Leonotis nepetifolia (L.) W.T. Aiton is known to be native to tropical Africa and southern India. In South Africa and the West Indies it is known as klip dagga, lion's ear, Christmas, and candlesticks. Roots of the plant have been used in the treatment of asthma and bronchitis, fever, and poisoning. Seeds are also used in treating burns, and the whole plant is used for menstrual pains. Phytochemical screening of this plant has revealed the presence of iridoid glycosides, phenylethanoid glycoside, labdanoid diterpenoids, and coumarins in the stem, and diterpenoids from leaves; seed oil contains laballenic acid, a new allenic acid. Several extracts of aerial parts of *L. nepetaefolia* have been found to possess anti-inflammatory activity on the TPA-induced edema model. Chromatography of the extracts led to the isolation of leonotinin (**2**) (Figure 19.2) and stigmasterol. The anti-inflammatory activity has been attributed to the leonotinin [90].

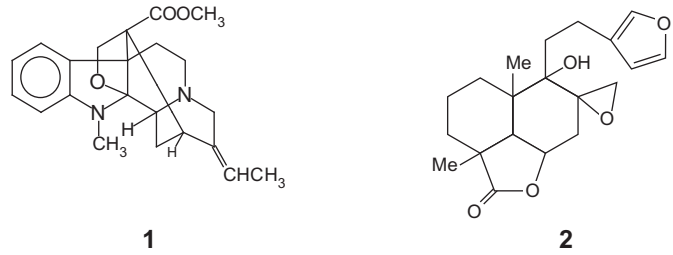

Figure 19.2 Chemical structure of two anti-inflammatory agents identified in African plants, pseudo-akuammigine (**1**) and leonotinin (**2**).

Leonotis leonurus (L.) R. BR. is an herb or shrub, annual or perennial, usually aromatic in nature. Stems and branches are usually four-angled. Leaves are opposite, rarely whorled or alternate, simple to pinnately dissected or compound, without stipules. Inflorescences are generally compound, flowers sometimes solitary and axillary, verticillasters two- to many flowered, subtended by leaves or bracts. Flowers are bisexual, zygomorphic, rarely subactinomorphic, bracteolate or not.

It is extensively used for the treatment of various ailments in the Eastern Cape province of South Africa. It is used for the treatment of gastrointestinal parasites in animals. The aqueous extract from the leaf of *L. leonurus*, at 100 and 200 mg/kg body weight, significantly reduces the formation of carrageenan-induced paw edema in rats, though with histamine-induced edema the difference is insignificant. In the acetic acid-induced writhing model, the plant extract exhibited significant reduction in the number of writhes at doses of 100 and 200 mg/kg body weight, activity similar to indomethacin [91]. This study revealed the potential of *L. leonurus* leaf aqueous extract in reducing pain and inflammation. The acute toxicity test showed that the plant is relatively safe to use [91].

19.2.17 Malvaceae

Malva parviflora L. is an annual or perennial herb with decumbent or erect habit, growing to 50 cm in height in tropical regions of Africa. It is commonly known as cheeseweed. The broad leaves have 5−7 lobes and are 8−10 cm in diameter. It has small white or pink flowers with 4−6 mm long petals. It is used for the treatment of wounds and other related ailments by the Xhosa people of South Africa. It is also known to be used in the treatment of inflamed purulent wounds, swellings, bruises, and broken limbs. Methanol extract of the plant at 100 and 200 mg/kg body weight significantly reduces the formation of edema induced by carrageenan and histamine [92]. There are reports that the methanol extract has good analgesic effect, characterized by reduction in the number of writhes and decrease in licking time and licking frequency when

compared to the control and indomethacin [92]. The above pharmacological activity may justify the use of *M. parviflora* for the treatment of inflamed purulent wounds, swellings, bruises, and broken limbs.

19.2.18 Meliaceae

Trichilia monadelpha (Thonn) JJ De Willd (syn. *Trichilia heudelotii*) is a medium-sized tree that grows 12−20 m high and up to 0.4 m in girth. The plant is distributed in deciduous and semideciduous secondary forests, often in wet places in Côte d'Ivoire, Sierra Leone, Nigeria, Benin, Congo, and Ghana [21,22]. It is commonly called "tanduru/tanduro" by the Akans in Ghana. The bark is used to treat gastrointestinal complaints, cough, gonorrhea, syphilis, and skin ulcer [22,93−95]. The bark is also used as an anthelmintic, aphrodisiac, abortifacient, antiplasmodial [93,95], and as an anti-inflammatory and analgesic agent in the management of inflammatory conditions including arthritis [94,95]. The aqueous (TWE) and petroleum ether extract (TPEE) significantly inhibited the chick-carrageenan footpad edema, with maximal inhibitions of 57.79% and 63.83%, respectively, but the alcoholic extract (TAE) did not. Furthermore, the extracts inhibited the inflammatory edema associated with adjuvant arthritis, with maximal inhibitions of 64.41%, 57.04%, and 62.18%, for TWE, TAE, and TPEE, respectively. Phytochemical screening of the plant bark confirmed the presence of a large array of plant constituents such as alkaloids, glycosides, flavonoids, saponins, steroids, tannins, and terpenoids, all of which may be potential sources of phyto-anti-inflammatory agents. In conclusion, the work suggests that *T. monadelpha* is a potential source of anti-inflammatory agents [96].

19.2.19 Molluginaceae

Glinus oppositifolius (L.) Aug. DC is a slender spreading or ascending annual herb with stems up to 40 cm long, the leaves being opposed two by two, and with white-green flowers located axially. The plant grows on damp sandy sites, occurring across West Africa from Senegal to southern Nigeria and is widely distributed in the tropics and subtropics [72]. The species is commonly found in Angola, Democratic Republic of the Congo, Malawi, Mozambique, Zambia, and Zimbabwe. Dried stems with leaves are ground into a fine powder, added to food, and used to treat abdominal pain and jaundice. A decoction of a fine powder of the aerial parts is used in the treatment of malaria [97]. A maceration of pounded plant material with oil or water is used as a wound-healing preparation [98]. *G. oppositifolius* is used by traditional healers for treatment of joint pain, inflammation, diarrhea, intestinal parasites, fever, boils, and skin disorders [98,99]. The methanolic extract of *G. oppositifolius* whole plant has found to reduce paw inflammation in mice induced by carrageenan. This result suggests that the methanolic extract of *G. oppositifolius* possesses anti-inflammatory activity and hence may justify the folkloric uses as a pain-relieving agent [100]. Significant peripheral and

central analgesic properties have been exhibited by the methanolic extract using the acetic acid-induced writhing and tail immersion tests [100].

19.2.20 Moraceae

Ficus iteophylla Miq. is a tree, sometimes initially epiphytic, up to 12 m high, its trunk up to 4 m girth, usually tortuous, rarely regular, of the Sudanian Savanna forest and into the Sahel, where it is appreciably smaller, extending across the northern part of the region from Senegal. The bark is used to treat dysentery and rheumatic pain [101]. The root has been widely used for treatment of paralysis, tuberculosis, epilepsy, convulsion, spasm, and pulmonary troubles [101]. The leaves are reported to have analgesic, anti-inflammatory [102], and antibacterial activities [103]. It is also reported to contain two furanocoumarines [104] and two flavonoid glycosides. The anti-inflammatory activity of *F. iteophylla* extracts is attributed to crude saponin content of the stem bark [102].

19.2.21 Myrtaceae

The components of the essential oil of *Eugenia caryophyllata* L. Baill are β-caryophyllen (44.7%), eugenol (44.2%), α-humulen (3.5%), eugenyl acetate (1.3%), and α-copaen (1.0%) [105]. Methanol extract of *E. caryophylla* inhibited cyclooxygenase by 80% in mouse macrophage culture [106] without affecting the COX-1 enzyme [107]. The essential oil of *E. caryophyllata* has been confirmed to have anti-inflammatory effects matching those of etodolac at 0.025 and 0.1 mL/kg and to those of indomethacin at 0.05 and 0.2 mL/kg doses [105].

19.2.22 Olacaceae

Olax viridis Oliv. is a shrub commonly found in the tropics. The plant grows well in tropical forest and in savanna regions. The morphological features have been described [108,109]. It has a wide range of applications in ethnomedicine. In West Africa, the pulverized bark and root are used as dressing for ulcers and treatment of venereal diseases, craw-craw, and ringworm infections [110]. In the northern part of Nigeria, the root is used in treatment of sleeping sickness, as a febrifuge, antidiarrhea, and in treatment of febrile headache. The leaf is used as a remedy for cough, fever, and wounds. A decoction of the leaf twigs is also used as a mouthwash and for toothache. The oil is usually placed in a hollow tooth prior to extraction. The crushed bark is applied to sores on domestic animals and is also used in the form of palm wine infusion as a remedy for typhoid fever [35]. Some of these ethnomedicinal uses could be attributed to the antimicrobial, analgesic, and anti-inflammatory properties of the plant. The anti-inflammatory and antimicrobial activities of *O. viridis* root bark extracts and fractions have been investigated. The hexane and methanol fraction at doses of 200, 400, and 800 mg/kg (i.p.) exhibited significant anti-inflammatory activity [111].

19.2.23 Orchidaceae

Spiranthes mauritianum contains water-soluble phyto-inhibitors in its leaves, which can have severe impacts on the growth of seedlings of native tropical rainforest species under controlled environmental conditions [112]. Aqueous, hexane, and methanol extracts of *S. mauritianum* have shown anti-inflammatory activity using the COX-1 assay [113].

19.2.24 Poaceae

Panicum maximum Jacq. is a tufted perennial grass, usually in large bunches from short stout rhizomes, 1−3 m tall; culms erect, stout; nodes usually densely hirsute; sheaths papillose-hirsute to glabrous, usually densely pubescent at the collar; ligule 4−6 mm long; leaves flat, bright green, 15−76 cm long, 1−3.5 cm wide, glabrous on margins. Anti-inflammatory and antipyretic activities of leaf extract of *P. maximum* have been evaluated to ascertain the folkloric uses. The crude ethanol leaf extract has been found to exhibit a significant ($p < 0.001$) dose-dependent reduction of inflammation and fever induced by different agents used. The anti-inflammatory and antipyretic effects of this plant may in part be mediated through the chemical constituents of the plant [114].

19.2.25 Phytolaccaceae

Hilleria latifolia (Lam.) H. Walt. is a perennial herb that is common on cultivated grounds and along forest paths in Ghana. It also occurs in other parts of tropical Africa. It is commonly known as "anafranaku" by the Akans in Ghana. Different parts of the plant have been used in a variety of diseases including otalgia, rheumatism [94], and boils [115]. The flowers are used for asthma [94]. *H. latifolia* is also used in Côte d'Ivoire for feverish pains and violent headache, whereas the leaves are used to treat some skin diseases in Congo [115].

In several models of chemical and thermal pain, HLE produces dose-related antinociception without tolerance induction, through mechanisms that involve an interaction with the adenosinergic, muscarinic, cholinergic, and opioid pathways. The antinociceptive effect exhibited by *H. latifolia* extract (HLE) in the formalin test was partly or wholly reversed by the systemic administration of naloxone, theophylline, and atropine. Notably, HLE, unlike morphine, did not induce tolerance to its antinociceptive effect in the formalin test after chronic administration; morphine tolerance also did not cross-generalize to HLE. Interestingly, as well, the chronic concomitant administration of HLE and morphine significantly suppressed the development of morphine tolerance [116]. The extract exerts *in vivo* anti-inflammatory activity after oral administration [117]. HLE (10−300 mg/kg^{-1}, p.o.), either preemptively or curatively, significantly inhibited carrageenan-induced foot edema in 7-day-old chicks. In the Freund's adjuvant induced-arthritis model in rats, HLE showed significant anti-arthritic properties when applied to established

adjuvant arthritis. HLE (10−300 mg/kg^{-1}, p.o.) significantly reduced edema in the ipsilateral paw of rats but failed to prevent systemic arthritic spread.

19.2.26 Rubiaceae

Morinda lucida Benth. is commonly found from Senegal to Sudan and southward to Angola and Zambia. It is sometimes planted around villages, e.g., in Benin [72]. An evergreen shrub or small- to medium-sized tree up to 18−25 m tall, with bole and branches often crooked or gnarled; bark smooth to roughly scaly, gray to brown, often with some distinct purple layers. The bitter-tasting roots are used as flavoring for food and alcoholic beverages, and in Nigeria they are popular as chewing sticks. Decoctions and infusions or plasters of the root, bark, and leaves are used as remedies against different types of fever, including yellow fever, malaria, trypanosomiasis, and feverish condition during childbirth. The plant is also employed in cases of diabetes, hypertension, cerebral congestion, dysentery, stomach ache, ulcers, leprosy, and gonorrhea [93]. The major constituents of *M. lucida* extracts are various types of alkaloids, anthraquinones, and anthraquinols. Adewunmi and Adesogan also isolated and characterized two compounds (oruwalol and oruwal) and 10 anthraquinones from the stem of the plant [114]. Petroleum ether and DCM extracts of *M. lucida* have shown anti-inflammatory activity in COX-1 and COX-2 assays [118].

Canthium subcordatum DC. is a tree, 5−15 m tall, with a palm-like habit, associated with ants, the branches are often hollow and swollen with access pores; young branches distinctly square in cross section, often slightly winged on the angles, glabrous to pubescent. Leaf blades are 9.5−22(30) × 4.5−16.5 cm, oblong to ovate or sometimes broadly ovate, shortly acuminate at apex, obtuse to rounded or truncate to subcordate at base and glabrous.

The main constituent of the stem bark of *C. subcordatum* has been found to be shanzhiside methyl ester, an iridoid recently described for two *Mussaenda* species; it is accompanied by the new iridoid shanzhisin methyl ester gentiobioside [114]. Petroleum ether and DCM extracts of *C. subcordatum* have shown anti-inflammatory activity in COX-1 and COX-2 assays [119].

19.2.27 Rutaceae

Zanthoxylum chalybeum Engl. is a deciduous spiny shrub or tree up to 12 m, crown rounded but open. *Z. chalybeum* is a tree of medium to low altitudes in dry woodland or grassland, often on termite mounds. It is very common in Sub-Saharan Africa [78]. Decoctions of this plant are traditionally used in the treatment of malaria, sickle cell disease, measles, skin infections, and coughs [120]. The aqueous, hexane, and methanol extracts of *Z. chalybeum* have demonstrated anti-inflammatory activity using the COX-1 assay [113].

Zanthoxylum usambarense (Engl.) Kokwaro is found in highland areas, especially in dry forest, especially in Nairobi, Narok, Kiambu, Kericho, and Samburu in Kenya. A decoction made from its stem bark is taken for the treatment of malaria

and for relief from malarial fevers. It is also used in upper respiratory tract infections, cough, rheumatism, tooth decay, and sore gums in Kenya and other African countries. Both its roots and its leaves are taken for relief from severe colds and for treatment of pneumonia. A decoction made from its bark is drunk for relief from rheumatism [121]. Some isolated constituents of *Z. usambarense* include canthin-6-one 1 (fungicide) and pellitorine 4 (insecticide), together with oxychelerythrine 2, norchelerythrine 3, (+)-sesamin 5, and (+)-piperitol-3,3-dimethylallyl ether [122]. A mixture made from its bark and its roots is taken for relief from coughs. The aqueous, hexane, and methanol extracts of *Z. usambarense* are established as possessing anti-inflammatory activity using the COX-1 assay [113].

19.2.28 Solanaceae

Nicotiana tabacum L. is a perennial herbaceous plant. It is found only in cultivation, where it is the most commonly grown of all plants in the *Nicotiana* genus, and its leaves are commercially grown in many countries to be processed into tobacco. It grows to heights between 1 and 2 m. The plant galls are widely distributed, and their extracts are used in traditional medicine worldwide. Traditional remedies containing extracts of plant galls in China, India, and some African countries are effective in the treatment of various pathologies. The leaves are applied externally in the treatment of rheumatic swelling, skin diseases, painful piles, and stings.

Aqueous, methanol, chloroform, and hexane extracts of *N. tabacum* leafy galls induced by *Rhodococcus fascians* were used to evaluate phenolic and flavonoid contents, and anti-inflammatory activity was determined by the lipoxygenase inhibition assay. Infection by *R. fascians* modifies significantly the phytochemical profile of *N. tabacum*, as well as its biological properties. The total polyphenolic content was increased (120−307%), and that of flavonoids was reduced (20−42.5%). The anti-inflammatory activity of noninfected tobacco extracts is significantly modified compared to plants treated with leafy gall extracts. Infection by *R. fascians* enhanced the production of anti-inflammatory compounds in *N. tabacum*[123].

Schwenkia americana L. is an annual or short-living perennial herb, erect and spreading, up to 100 cm tall. The stem is grooved and glaborous. The leaves are arranged spirally, simple, and entire. It is found growing in tropical Africa, including West, Central, and East Africa, as a weed. The plant sap and decoction is used to treat headache, sinusitis, and conjunctivitis. It is also used to relieve pains and to manage inflammatory diseases caused by swellings, hernia, rheumatism, arthritis, gout, hemorrhoids, and stomach problems. Crude saponin extract of whole *S. americana* has been shown to significantly decrease carrageenan-induced paw edema in the rat model. It has activity similar to ketoprofen [79].

19.2.29 Zygophyllaceae

Zygophyllum gaetulum is a perennial shrub of intermediate size, 50 cm, woody at the base, with intense ramifications of the branches. The young shoots are thin and

are covered with white hairs. The leaves are small, with two fleshy folioles (stipules) at the base, also covered with white hairs [62]. The flowers, borne on a small hairy peduncle, are tiny (5 mm), ovoid, with five white petals. The fruit has a tubular base which widens toward the top, with five lobes, and is approximately 2 cm long. It usually flowers in spring but has been observed to flower in the autumn [62]. Its principal constituents include flavonoids, mono- and diglycoside of three flavonols: kaempférol, quercetine, isorhamnetine, and saponoside [124]. Pharmacologically, the hypoglycemic effect of its leaves makes the plant known for its anti-diabetes properties [125]. Traditionally, it is used for diabetes, eczema, and liver and stomach pain and is a hemostat. The dried flower heads are used to make a refreshing drink or added to tea. Forming extensive pastures, it is appreciated by herds of goats and camels. In the Dra and Tarfaya regions (Western Sahara), the dried leaves in a decoction used to be drunk for stomach pain or for the liver swollen due to excess of bile. The finely powdered leaves are applied externally to wounds to act as a hemostat and as a maturing plaster on furuncles and abscesses [62]. The ethanol extract of *Z. gaetulum* reduced the increase of the paw volume, with a significant percentage of inhibition of 46% and aqueous extract was 47.48%, confirming its anti-inflammatory property [126].

19.2.30 Sterculiaceae

Pterygota macrocarpa (K. Schum.) is a large tree that grows in dense semideciduous forests, usually distributed in West Africa from Sierra Leone to Cameroon. It is known in the local Asante-Twi language as "kyereye" in Ghana. The soaked leaves are used to treat stomach ache, pains, and disorders of digestion. Leaf decoctions are used for the treatment of gonorrhea and other urinary tract infections [22,127,128]. Traditionally, the bark is used in the management of hemorrhoids, dropsy, swelling, edema, gout, leprosy, and pain [129]. The seeds of *P. macrocarpa* have been found to contain phytate, oxalate, and tannins [130]. Both the ethanol leaf and stem bark extracts of *P. macrocarpa*, at 30, 100, and 300 mg/kg body weight, exhibited significant anti-inflammatory activity. These biological activities may confirm the ethnobotanical uses of the plant as an anti-inflammatory agent [130].

Cola gigantea A. Chev. is a large tree in dry semideciduous forests in West Africa and the West Indies. It is commonly known as giant cola; the Asante-Twi name is "watapuo" in Ghana. The nuts (mostly called kola) are often used to treat whooping cough, asthma, malaria, and fever. Other traditional uses include increasing the capacity for physical exertion and for enduring fatigue without food, stimulating a weak heart, and treating nervous debility, weakness, lack of emotion, nervous diarrhea, depression, despondency, brooding, anxiety, and seasickness [22,127,129,131]. Kola nut is the name of the mature fruits of the *Cola* species [132]; it has a bitter flavor and high caffeine content [133,134], and when the fruit is ingested, it acts as a stimulant and thus creates an ecstatic and euphoric state [134]. The caffeine acts as a bronchodilator, expanding the bronchial air passages [135]. These fruits are also chewed in communities during traditional ceremonies

and also are known to reduce hunger pangs. The ethanol leaf extract of *C. gigantea* has been shown to be active against *Candida albicans*, and phytochemical screening of the leaf extract indicated the presence of alkaloids, saponins, tannins, anthraquinones, and cardenolides [136]. The ethanol stem bark extract, but not the ethanol leaf extract, of *C. gigantean*, at 30, 100, and 300 mg/kg, exhibits significant anti-inflammatory activity [136].

19.2.31 Tiliaceae

Glyphaea brevis (Spreng) Monachino is a tree, mainly present in forest regrowth, swampy places, rocky savanna, forest galleries, and fallow land. In addition to enhancing childbirth and hastening delayed labor, the leaves are used for dyspepsia and ulcers. The root decoction is used as an aphrodisiac, appetizer, laxative, and as a remedy for chest pain, diarrhea, dysentery, and sleeping sickness [93,94]. In doses of 30, 100, and 300 mg/kg body weight, the leaf and stem bark extracts significantly suppressed carrageenan-induced edema in 7-day-old cockerels [137].

19.2.32 Vitaceae

Cyphostemma natalitium (Szyszyl) J. J.M, van der Merwe, *Rhoicissus digitata* (L.F.) Gilg et Brandt, *Rhoicissus rhomboidea* (E. Mey. ex Harv.) Planch., *Rhoicissus tomentosa* (Lam.) Willd & R.B. Drumm, and *Rhoicissus tridentata* (L.f.) Willd & R.B. Drumm.

Rhoicissus is a small genus of evergreen climbers native to tropical and southern Africa. In South Africa, the family Vitaceae is represented by 5 genera and 53 species, and the genus *Rhoicissus* is represented by 10 species, which occur in all the provinces except for Northern Cape. Methanolic extracts of *Cyphostemma natalitium* root, *R. digitata* leaf, *R. rhomboidea* root, *R. tomentosa* leaf and stem, and *R. tridentata* root from KwaZulu-Natal, South Africa, significantly inhibited COX-1, with the highest inhibition of prostaglandins observed in *R. digitata* leaf and *R. rhomboidea* root extracts [138].

19.3 Conclusion

Most of the medicinal plants with demonstrated *in vivo* and *in vitro* anti-inflammatory and analgesic properties have had their activities attributed to their crude extracts and fractions. A few compounds, including pseudo-akuammigine from the seeds of *P. nitida* and leonotinin from the aerial parts of *L. nepetaefolia*, have been isolated from these medicinal plants used traditionally as pain-relieving agents in herbal medicine practice in different parts of Africa. There is a need for scientists, including phytochemists and pharmacologists, and especially in the Africa, to concentrate much in the identification of bioactive compounds from these plants and even possibly to engage in structural modifications to improve

their anti-inflammatory or analgesic property. Different protocols and experimental models should be used to determine the anti-inflammatory and analgesic activities of the various principles from medicinal plants. Effort should also be made by pharmacologists to determine the mechanisms of action of these bioactive agents and the effects or influence of some of these isolated compounds and plant extracts in humans after thorough toxicological studies have been conducted on these agents. There is also a need to increase investigations of claims of plants in Africa traditionally used for the management of various forms of pain and inflammation.

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20 Antidiabetes Activity of African Medicinal Plants

Roland N. Ndip[a,b], *Nicoline F. Tanih*[a] *and Victor Kuete*[c]

[a]Department of Biochemistry and Microbiology, University of Fort Hare, Alice, South Africa, [b]Department of Microbiology and Parasitology, University of Buea, Buea, Cameroon, [c]Department of Biochemistry, University of Dschang, Dschang, Cameroon

20.1 Introduction

Diabetes is gaining recognition as the world's leading and most common endocrine metabolic disorder. Due to associated high morbidity and mortality, diabetes is becoming the third greatest "killer" of mankind, after cancer and cardiovascular and cerebrovascular diseases [1]. The disease has now become an epidemic, with a worldwide incidence of about 5% of the population and now kills more than AIDS [2,3]. It is a major health problem of this century, with high prevalence rates reported worldwide [4]. According to the World Health Organization (WHO), more than 171 million people (>2.8%) are suffering from the disease worldwide [5]. The International Diabetic Federation has predicted that the number of individuals with the disease will increase from approximately 240 million in 2007 to 380 million in 2025 [2,3,6]. About 80% of the disease burden occurs in low- and middle-income countries. Diabetes is commonly mellitus and less often, insipidus [3,4]. However, when the term diabetes is used without qualification, it usually refers to diabetes mellitus. This disease was previously associated with the developed or Western world, but recently, high prevalence rates have been reported in Africa and other developing nations [7]. Interestingly, Africa and Asia are the two continents where diabetes is expected to rise the most [8].

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia, resulting in defects in insulin secretion, insulin action, or both [3,9]. It is a major cause of disability and hospitalization, which results in a significant financial burden [10]. Complications that result from the disease could be acute, subacute, or chronic, resulting from defects in metabolism of carbohydrates, fats, proteins, and electrolytes in the body [2]. Characteristically, the symptoms include polyuria, polydipsia, polyphagia, pruritus, and unexpected weight loss. Hypoglycemia,

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diabetic ketoacidosis, hyperosmolar, and hyperglycemic nonketotic syndromes embody acute complications, while subacute complications include thirst, polyuria, lack of energy, visual blurriness, and weight loss [11]. Chronic hyperglycemia causes glycation of body proteins, which in turn leads to complications that may affect the eyes, kidneys, nerves, and arteries [12].

There are two main types of diabetes mellitus [3]. Type 1, known as insulin-dependent diabetes mellitus (IDDM), is caused by immunological destruction of pancreatic β-cells, resulting in insulin deficiency [2]. Many of the acute effects of this disease can be controlled by insulin replacement therapy; however, it has long-term adverse effects on blood vessels, nerves, and other organs of the body [2,13]. Although both children and adults can be affected by type 1 diabetes, it was traditionally called "juvenile diabetes" because it represents a majority of the diabetes cases among children [5].

Noninsulin-dependent diabetes mellitus (NIDDM), also known as type 2, is characterized by either impaired insulin secretion or peripheral resistance to the action of insulin, which is often associated with obesity and hereditary disposition [2,3,14]. It is associated with elevated postprandial hyperglycemia. NIDDM diabetes can lead to cardiovascular damage [15]. Some type 2 patients have abnormal insulin receptors and/or defective insulin signaling, though no defects have been identified in others. Type 2 (NIDDM) is the most prevalent form globally, with about 97% of diabetics suffering from it [16]; it is generally contracted over the age of 40 years [5,15]. This type is due primarily to lifestyle factors and genetics. Generally, NIDDM is controlled through dietary therapy, exercise, and hypoglycemic agents [14,17].

Diabetes insipidus (DI) is characterized by excessive thirst and excretion of large amounts of severely diluted urine, with reduction of fluid intake having no effect on the concentration of the urine [9]. Different types of DI exist, each with a different cause. The most common type in humans is central DI, caused by a deficiency of arginine vasopressin, also known as antidiuretic hormone. This is followed by nephrogenic DI, which is caused by an insensitivity of the kidneys to antidiuretic hormone. It can also be an iatrogenic artifact of drug use. Diagnosis and treatment are not the same for the two types of diabetes (mellitus and insipidus), though they share some common symptoms such as frequent urination and excessive thirst [9].

Diabetes exerts a significant health challenge, especially with its high and increasing global prevalence [3]. Apart from being a metabolic disease, communicable and noncommunicable diseases could influence the high prevalence of diabetes worldwide [7]. In developed countries, diabetes is ranked as the third cause of death after heart diseases and cancer, affecting about 6% of the population [5]. Diabetics are likely to have increased risk of various significant infections, including tuberculosis, pneumonia, and sepsis [7]; they are prone to complications such as hyperglycemia, hyperosmolar state, diabetic ketoacidosis, oxidative stress resulting from elevated glucose concentration, microvascular pathologies (retinopathy, albuminuria, and neuropathy), and impaired immune response (making diabetics prone to respiratory infections); foot ulcers and trauma to the hand have been

associated with the disease, which can terminate in death [2,3]. Also, some infections such as urinary tract infections, gangrene, and sepsis have been implicated in diabetes [7]. These no doubt rank the condition as one of the worst metabolic diseases. In a Tanzanian survey, infection accounted for 48% of deaths in indeterminate diabetes cases, with 32% of type 1 and 23% of type 2 [18].

A comparatively higher prevalence of type 2 diabetes has been recorded in urban areas; this was associated with obesity and lack of regular physical exercise [7]. Statistics indicate that by 2025, 70% of Africans will live in cities, with a regional annual urban growth rate of 4.5%, suggesting that type 2 diabetes will follow. Hence, reducing the onset of type 2 diabetes could focus on increasing the level of physical activity and prevention of obesity [7].

Diabetes remains a chronic metabolic disease of the human race. Management of the disease has been daunting, coupled with the absence of appropriate treatment. Drugs such as insulin and oral hypoglycemics have been used for management of the disease [2]. However, no cure exists to date. A rich resource of nature's plant wealth seems promising.

The field of herbal medicine has expanded significantly in the last few years, and these drugs are gaining popularity both in developing and developed countries because of their natural origin [9]. Side effects associated with the use of orthodox drugs such as insulin and oral hypoglycemic agents may have promoted the use of herbal therapy [19]. In the developing countries, with poverty-stricken populations and where people cannot afford or access modern treatments, herbal therapy has been useful. The use of herbal remedies for the treatment of diabetes has been authorized by WHO [20]. Africa alone is endowed with a rich biodiversity; a significant number of plants from this continent have been used by traditional healers for the treatment of various illnesses, including diabetes [19,21]. Myriad plants and some potentially active compounds such as saponins, tannins, alkaloids, flavonoids, and glycosides isolated from some of these plants have been reported to play an important role in diabetic therapy [22–24]. This chapter expands on others, highlighting potential African medicinal plants in the management of diabetes on the continent, as well as exploring further lead plants which could be employed in the discovery of drugs against diabetes.

20.2 Diabetes Worldwide and in Africa

Diabetes was previously thought of as a disease of the developed world, but today inhabitants of both the developing and the developed world are frequently diagnosed with it. According to the WHO report of 2000, the disease was estimated at 173 million in adults, two-thirds of whom live in developing countries [4]. In 2007, approximately 241 million people in the world were diabetic, and this number is projected to increase to 380 million by 2025 [2,3,6,25]. Different studies have projected an increase in diabetes rates in the years to come [25]. Alongside the metabolic disorders which are the main causal factors of diabetes, diseases, inclination

to Western diet, and sedentary lifestyle may all be responsible for the very high statistics being reported [7,25]. Recently, Shaw et al. [25] reported interesting diabetic prevalence rates in both the developed and developing countries, revealing very high rates across the globe. Prevalence greater than 10.1% but less than 13.6% was observed for the following countries: Malaysia, Sri Lanka, Canada, Germany, Portugal, the United States, Cuba, Mexico, Egypt, and Saudi Arabia. The highest prevalence of 13.6% was reported in Saudi Arabia, while the lowest (10.1%) was reported in Malaysia [25]. Asia and Africa are regions presenting the greatest risks, where diabetes could rise to two- or threefold above the present level [25].

Africa is located within the tropical and subtropical climate zones, and because of its tropical conditions, Africa has an unfair share of strong ultraviolet rays of the tropical sunlight, and myriad pathogenic microbes, including several species of bacteria, fungi, and viruses to which diabetics may be susceptible [26]. Diabetes rates have spiraled globally in the last two decades, usually resulting in serious complications and culminating in death in some cases. In addition, the prevalence of the disease is expected to increase in Africa, where most patients are likely to be found by 2030 [5].

In Africa, diabetes has increased rapidly in the population and is currently regarded as a public health problem [7,27]. A study conducted in Sub-Saharan Africa by Hall et al. [7] indicated that patient mortality related to diabetes ranged from 4% to 57%. Moreover, 41% of individuals with IDDM died within 5 years in a study in Tanzania, and half of the deaths were as a result of ketoacidosis [18]. The prevalence of people living with diabetes in Africa was estimated to be 12.1 million in 2010, and this is projected to increase to 23.9 million by 2030. The trend is emerging in countries and regions reported with high rates of communicable diseases, including HIV, tuberculosis [28], and malaria. The prevalence has been expected to get worse for noncommunicable lethal diseases such as cardiovascular and renal diseases, which impacts seriously on morbidity and mortality [29].

Nonetheless, type 2 NIDDM accounts for over 90% of diabetes cases in Sub-Saharan Africa, while type 1 diabetes and other types of the disease including gestational diabetes, "ketosis-prone" diabetes, and malnutrition-related diabetes constitute the remainder [7]. Generally, data on diabetes in African countries are lacking, and the situation is even more absurd concerning information on type 1 diabetes cases in most African countries [7]. Prevalence surveys in the last decade have shown that type 2 diabetes ranged from 0.6% in rural Uganda [30] to 12% in urban Kenya [31]. In Cameroon, Ghana, Guinea, Kenya, Nigeria, and South Africa, the prevalence was between 0.7% while in Zimbabwe it was $>10\%$. This variation in prevalence between countries and even between regions on the same country is frequently observed, with higher prevalence rates recorded in urban and city dwellers. For example, a study conducted in Kenya reported a prevalence of 2% in rural areas and 12% in urban areas [31]. Reports from a recent cohort study of type 2 diabetes in Kinshasa revealed an incidence rate of 29 (95% CI 15−43) per 1000 person-years [32].

Only a few studies estimating the prevalence and/or incidence of type 1 diabetes in Africa have been available in the literature since 1990—a paucity of data [7]. Prevalence ranged from 12 per 100,000 persons in Zambia [33] to 4 per 100,000 persons in Mozambique. Recorded incidence ranged from 1.5 per 100,000 persons per year in Tanzania [34] to 2.1 per 100,000 persons per year in Ethiopia [35].

A number of risk factors, including increased obesity, diet, and reduced physical activity, have been reported to influence the increased rates of diabetes in both the developed and developing nations [7]. Obesity is becoming an epidemic worldwide and has been associated with a number of pathologies. The most-used measure for obesity is body mass index.

Diabetes has long been associated with obesity and overweight [16]. In developed nations like the United States, obesity and diabetes are both epidemic. Specific risk factors could be linked to either type 1 or type 2 diabetes [16]. Over 90% of type 2 diabetes cases result from overweight [2,16]. It is important to note that obesity is a major risk factor for type 2 diabetes; with millions of people throughout the world and most especially in the Western world being obese, the probability of an increased prevalence of this disease is very high. Almost a quarter of adults in the United Kingdom are recorded as being obese [36]. This number has been reported to increase in both adult and children. Also, sedentary lifestyle without sufficient exercise is seriously damaging to health. Overweight, which results from consumption of high-carbohydrate foods and lack of exercise, can lead to prediabetes and type 2 diabetes [2,16]. Activity decreases insulin resistance and helps in the efficiency of the body [16]. Furthermore, the "Western diet," mostly processed foods with poor-quality fats and little fiber content, is thought to be a major contributor to diabetes and metabolic syndrome [16].

Cross-sectional studies conducted by different investigators in Sub-Saharan Africa have identified some chronic complications of diabetes, including neuropathy, retinopathy, microalbuminuria, coronary heart disease, and foot ulcers [7]. Diabetic nephropathy is one of the most serious chronic complications of diabetes mellitus [37]. Neuropathy was delineated in Cameroon, Nigeria, and Sudan, with prevalence rates of 27.3%, 34.2%, and 40%, respectively. Foot ulcers have also been reported in several African countries, notably in Cameroon, Nigeria, and Tanzania, with Nigeria having the highest prevalence. Retinopathy and microalbuminuria have also been reported in many more countries. Retinopathy was observed in Botswana, Cameroon, Ethiopia, Ghana, Nigeria, Kenya, South Africa, and Tanzania, while microalbuminuria was found in Cameroon, Ghana, Kenya, Nigeria, and Tanzania [7].

Estimating the current and future burden of diabetes is important in order to allocate community and health resources, to emphasize the role of lifestyle, and to encourage measures such as the use of medicinal plants, with particular reference to the antioxidant components of the plants found on the continent, which could be of immense benefit to the poor, who lack the technological and economic resources to counteract the increasing prevalence of the disease.

20.3 Pharmacological Activities of Medicinal Plants

Africa is blessed with enormous biodiversity of resources, but plagued with several diseases, including those of metabolic disorders such as diabetes. Diabetes is a major health problem, with its frequency increasing every day in most countries.

All forms of diabetes have been treatable since insulin became medically available, but a cure is difficult. Generally, the disease is believed to be incurable [9]. Currently, diabetes therapy is based on the use of oral hypoglycemic agents (sulfonylureas and biguanides), insulin, plant supplements, controlled diet, and physical exercise [38]. Other current medications include vitamins and minerals. Mineral supplements can benefit patients with mineral deficiencies, as demonstrated with magnesium and zinc, some of which may not be suitable for usage during pregnancy [3]. Diet is also known to be the foundation of diabetic control, and the dietary recommendations for diabetic patients are entirely consistent with a normal healthy balanced diet. Salt, refined sugars, and foods rich in cholesterol have to be minimized while ensuring adequate vitamins and minerals are added to the diet [38]. Generally, treatment and management of the disorder entails huge sums of resources for medicines, diets, and physical training [27]. Before the advent of insulin therapy, starvation diets and traditional plant treatments were the cornerstone of antidiabetic therapies. Insulin administration is required in type 1 diabetics, while type 2 diabetics require administration of oral hypoglycemic drugs or insulin.

The legacy of plants in the treatment of several diseases has been established [39−45]. Herbal product usage in medicine has played an important role in nearly every culture on earth [3,39,46]. Herbal medicines have been long used for the treatment of diabetic patients, and they are currently accepted as an alternative therapy [21,23,39,47,48].

With the increasing incidence of diabetes in rural populations throughout the world, coupled with the inability of current therapies to control the metabolic defects of the disease and their pathological consequences, as well as the great expense of modern therapy, the demand by patients to use natural products with antidiabetic activity is increasing, since access to traditional medicines is less constraining and more affordable [9,10,27]. Furthermore, plant drugs are frequently considered to be less toxic and freer from side effects than synthetic ones.

Ethnobotanical surveys have provided preliminary information on the use of these plants, and, according to WHO, more than 1200 plant species are currently used as traditional remedies in the treatment of diabetes mellitus, with a substantial number of the plants demonstrating effective hypoglycemic activity after laboratory testing [3,16,20]. WHO estimates that 80% of the world's population presently uses herbal medicine for some aspect of primary health care with proven efficacy, hence the recommendation by WHO on the use of medicinal plants for treatment of diabetes mellitus, which has enhanced both usage and investigation of medicinal plants in the development of novel therapeutic agents in the management of diabetes [20,49,50].

Based on the historical success of natural products as antidiabetic agents and the ever-increasing need for new antidiabetics, a number of African medicinal plants have been evaluated and credited for their hypoglycemic activity [21,23,47]. Although an orally active botanical substitute for insulin is unlikely, phytochemicals may stimulate insulin biosynthesis and promote insulin action. Many plants with antidiabetic properties probably act in part through their content of fiber, vitamins, or mineral content. To this end, plants rich in minerals have been shown to enhance glycemic control in diabetic patients [38]. Evaluation of their antidiabetic potential has been either through *in vitro* or *in vivo* analysis [20,51].

In vivo studies using these plants have been based largely on the use of animal models involving rats or mice weighing on average 19−300 mg/kg body weight, divided into groups (conventionally four groups) [21,23,52], with each group administered different treatment options including a control (untreated normal), treated normal animal, and diabetic treated animals [23]. Typically, diabetes is induced using alloxan or streptozotocin (STZ) at different concentrations [37,51].

Interestingly, in some findings, glibenclamide, a standard drug used for the treatment of diabetes, was not able to lower blood glucose in STZ-diabetic rats, while it significantly lowered the blood sugar in normoglycemic rats [2,53]. Evaluation of antidiabetic potential is usually executed at different time intervals, usually from 1 h to 21 days. Several other factors including body weight index, toxicity assay, and effect on proteins have also been monitored along with blood sugar [21,53].

Some of these plants have been found to lower the blood sugar levels in experimental animals. *Viburnum dilatatum* Thunb. (Gamazumi) has been demonstrated to exhibit hypoglycemic activity in STZ-induced diabetic rats [54]. Similarly, other plant materials such as *Urtica dioica*, green tea, and *Ceiba pentandra* have been reported to have antidiabetic activity [50], while others showed little or no activity. Toxicity remains an important concept in phytomedicines. Astoundingly, some traditionally prescribed plants have been found to be toxic, either acutely or severely. Symptoms could be overt or may even result in death. Some mild symptoms include increased somatomotor activity, tachypnea, bilateral narrowing of the eyelids, tremor, piloerection, and increased feeding pattern [21].

Reports exist of plants with tremendous effect on body weight. *Clerodendrum capitatum*, for example, upon administration to rats, did not alter the feeding pattern of the treated rats or weight gain in the treated groups [21]. However, in another study by Adewoye et al. [47], severe progressive weight loss was noted in the untreated diabetic rats, while the rats in all *Musa sapientum* root extract-treated diabetic groups gained weight. Treatments employed using some of these plants have been shown to have an impact on fasting plasma lipids, including serum creatinine, urea, total cholesterol, triglycerides, total protein, and level of lipid peroxidation [21].

In the search for hypoglycemic potential, administration of aqueous fresh leaf extract of *C. capitatum* induced a significant ($p < 0.05$) dose-related decrease in the plasma total cholesterol, very low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, but significant ($p < 0.05$) dose-related elevation in plasma triglycerides and high-density lipoprotein cholesterol [21].

Plants with tremendous antidiabetic activity might possess a hidden wealth of potentially useful natural products for the control of diabetes. Phytochemical analyses of plants studied have revealed the presence of phytoconstituents that could be responsible for the activity observed in most plants. Such analysis revealed the presence of new phytochemicals, adding to the existing ones in the literature. These include flavonoids, alkaloids, saponins, tannins, cardiac glycosides, hexose sugars, pentose sugars, and phlobatannins [19,46,55]. Flavonoids, for instance, are known to exhibit a wide spectrum of biological action, including hypoazotemic, hypotensive, hypoglycemic, estrogenous, spasmolytic, cholagogue, anti-inflammatory, antilipidemic, and antioxidant activities. Worthy of note is the fact that the higher the concentration of flavonoid in an extract, the more likely its hypoglycemic effects [21].

In most developing countries, plant-based traditional medicines have been used for hundreds to thousands of years to treat diabetes and related complications. A number of indigenous plants are traditionally used for the treatment of diabetes across Africa (Table 20.1). However, studies on antidiabetic properties of plants (which may appear unique) are prominent in some countries in Sub-Saharan Africa (South Africa, Nigeria, Cameroon; Table 20.2) and North Africa (Morocco, Egypt, Tunisia; Table 20.3). In South Africa, several species have been identified for the treatment of diabetes based on major ethnobotanical surveys. Similar ethnobotanical surveys have been conducted in Nigeria and some other countries in Africa. Studies relating to some of these plants are reviewed in the following section with a view to highlighting the potential of African medicinal plants in antidiabetic drug discovery and the need for further investigations of antidiabetic plants.

20.3.1 Sclerocarya birrea *(A. Rich.) Hochst. (Anacardiaceae)*

S. birrea is also known as marula. In Africa, the tree is commonly found in savanna regions, and its geographical distribution stretches from the Gambia in the west across to Nigeria and Cameroon, in Central Africa, and to Ethiopia, Sudan, and East and South Africa. This plant is highly valued in Southern Africa, and numerous studies have delineated its antidiabetic potential. A number of studies have reported the hypoglycemic effect of aqueous stem bark extract of the plant in normal and STZ-treated diabetic rats [9,105]. Methanol/methylene chloride (1:1) extract of the plant reduced blood glucose and increased plasma insulin levels in diabetic rats [22]. The extract also prevented body weight loss and reduced plasma cholesterol, while the triglyceride and urea levels tended toward normal. The diabetic rats also showed significant improvement in glucose tolerance following administration of the extract. Gondwe et al. [57] also investigated the hypoglycemic effect of the stem bark extract of the herb in normal and diabetic rats along with the major complications of diabetes. Although the extract exhibited a dose-dependent reduction in blood glucose level, the same extract did not significantly alter kidney function; blood pressure was reduced in all the animals.

Table 20.1 Antidiabetes Medicinal Plants Occurring in More than One Country in Africa

Plant and Family	Plant Part Used	Traditional Use	Countries of the Studies	Potentially Active Compounds	Activities
Ageratum conyzoides L. (Asteraceae)	Leaves	Constipation, hepatitis, eczema, epilepsy, wounds, dizziness, diarrhea, vomiting, fever, headaches, intestinal worms, filariasis, painful menstruation, itching eye, and against lice	Cameroon Nigeria	Mono- and sesquiterpenes, flavonoids, triterpenoids, sterols, alkaloids, coumarins, essential oils, and tannins [1,38]	Antidiabetic antidiarrheal, antiparasitic, anti-inflammatory, anticoagulant, antifungal, antipyretic, and antirheumatic [1,38]
Catha edulis (Celastraceae)	Leaves	To attain a state of euphoria and stimulation	South Africa Kenya	Terpenoids, saponins, flavonols, flavones, flavonoids, chalcones, tannins, free anthraquinones, and bound anthraquinones [23]	Antidiabetic [23]
Catharanthus roseus (Apocynaceae)	Leaves	Diabetes, cancer chemotherapy, and diarrhea	South Africa Nigeria Congo	Saponins, tannins, alkaloids, phlobatannins, flavonoids, triterpenoids, reducing sugars, anthraquinones, and glycosides [55]	Antimicrobial and antidiabetic [23,53,55]

(*Continued*)

Table 20.1 (Continued)

Plant and Family	Plant Part Used	Traditional Use	Countries of the Studies	Potentially Active Compounds	Activities
Hypoxis hemerocallidea (Hypoxidaceae)	Whole plant	HIV/AIDS, arthritis, yuppie flu, hypertension, diabetes, cancer, psoriasis, ulcers, tuberculosis, urinary tract infections, asthma, and some central nervous system disorders, especially epilepsy and childhood convulsions	South Africa Lesotho Mozambique Zimbabwe North and East Africa	Phytosterols and/or sterolin [19]	Antidiabetic [9]
Momordica charantia (Cucurbitaceae)	Roots, aerial parts, and whole plants	Diabetes mellitus and hypertension	South Africa Botswana	Cucurbitacins, charantin, saponins, diosgenin, β-sitosterol and stigmasterol glucosides, momordicoside, alkaloids, oleic, and other organic acids [56]	Hypoglycemic, depression of key gluconeogenic enzymes, and hypertension [9]
Vernonia amygdalina (Asteraceae)	Leaves	Diabetes, parasitic infection, cancer, helminthic, and	Nigeria South Africa	Saponins and alkaloids, terpenes, steroids, coumarins,	Schistosomicidal, antiplasmodial, leishmaniacidal,

		protozoal and bacterial infections		flavonoids, phenolic acids, lignans, xanthones, anthraquinones, edotides, and sesquiterpenes [46]	anticancer effects, and antidiabetic [5,7]
Sclerocarya birrea (Anacardiaceae)	Stem bark	Diabetes mellitus, snakebite, pruritis, pharyngitis, splenomegaly, goiter, diarrhea, dysentery, proctitis, stomach ailments, ulcers, inflammation, arthritis, hypertension, skin diseases, fever, malaria, diabetes mellitus, fungal infections, snake poison, and sore eye	Cameroon Ghana South Africa Tanzania Zimbabwe	Flavonoids, alkaloids, triterpenoids, coumarins, ascorbic acid, and amino acids [57]	Antihypertensive [57], antimicrobial, and antidiabetic [22,24,57]
Psidium guajava (Myrtaceae)	Seeds	Antispasmodic, antidiabetic, diarrhea, and dysentery	South Africa Nigeria	Tannins, flavonoids, pentacyclic triterpenoids, guiajaverin, quercetin, and other chemical compounds present in the plant [58]	Antidiabetic [58,59], antimicrobial, and antispasmodic [59]

(*Continued*)

Table 20.1 (Continued)

Plant and Family	Plant Part Used	Traditional Use	Countries of the Studies	Potentially Active Compounds	Activities
Sutherlandia frutescens (Fabaceae)	Leaves	Cancer, diabetes, stress, and HIV/AIDS	South Africa Namibia Botswana	L-Canavanine, L-arginine, cyclitol pinitol, flavonols, and triterpenes including SU1, a cycloartane-type triterpene saponin [60]	Antiproliferative, anti-HIV, antidiabetic, anti-inflammatory, analgesic, antibacterial, antistress, anticonvulsant, and antithrombotic [26,60]
Mangifera indica Linn. (Anacardiaceae)	Leaves	Bronchitis, catarrh, internal hemorrhage, skin diseases, antihelminthic, and toothache	Nigeria South Africa	NA	Antihyperglycemic and antihypertensive [61]
Persea americana Mill. (Lauraceae)	Leaves Seeds	Hypertension and diabetes mellitus	Nigeria South Africa	NA	Antidiabetic [58]

NA, not available.

Table 20.2 Documented Antidiabetic Plants Used in Sub-Saharan Africa Herbal Medicine

Country and Species	Parts Used	Reference
Nigeria		
Commelina africana (Commelinaceae)	Leaves	[39]
Bryophyllum pinnatum (Crassulaceae)	Leaves	[62]
Zingiber officinale (Roscoe) (Zingiberaceae)	Rhizomes	[63]
Azadirachta indica (Meliacae)	Leaves	[64]
African mistletoe (Loranthaceae)	Whole plant	[65]
Diaphananthe bidens (Orchidaceae)	Leaves	[3]
Axonopus compressus (Poaceae)	Leaves	[66]
Bauhinia thoningii (Caesalpiniaceae)	Leaves	[2]
Mucuna pruriens (Leguminosae)	Seeds	[67]
Parquetina nigrescens (Asclepiadaceae)	Leaves	[68]
Ficus exasperata (Moraceae)	Leaves	[69]
Cnidoscolus aconitifolius (Euphorbiaceae)	Whole plant	[70]
Buchholzia coriacea (Capparaceae)	Seeds	[37]
Telfaria occidentalis (Cucurbitaceae)	Leaves	[61]
Spondias mombin Linn. (Anacardiaceae)	Leaves	[71]
Combretum micranthum (Combretaceae)	Leaves	[72]
M. sapientum (Musaceae)	Roots	[47]
Cnestis ferruginea DC (Connaracea)	Leaves	[50]
Hunteria umbellata (Apocynaceae)	Seeds	[73]
Murraya koenigii (Rutaceae)	Leaves	[74]
Citrus paradisi Macfad. (Rutaceae)	Seeds	[75]
Heinsia crinata (Rubiaceae)	Leaves	[76]
Morinda citrifolia (Rubiaceae)	Fruit juice	[77]
Viscum album (mistletoe) (Viscaceae)	Leaves	[78]
C. capitatum (Verbenaceae)	Whole plant	[21]
Cymbopogon citratus Stapf. (Graminaceae)	Leaves	[79]
Globimetula cupulata (DC) (Loranthaceae)	Leaves	[80]
Picralima nitida (Apocynaceae)	Seeds	[81]
Stachytarpheta angustifolia (Verbanaceae)	Whole plant	[82]
Ocimum gratissimum L. (Lamiaceae)	Leaves	[83]
Parkia biglobosa (Mimosaceae)	Seeds	[84]
Phyllanthus amarus (Euphorbiaceae)	Leaves and seeds	[85]
Garcinia kola (Guttiferae)	Seeds (fractions)	[86]
Bryophyllum pinnatum (Crassulaceae)	Leaves	[62]
Tetrapleura tetraptera (Fabaceae)	Fruit	[87]
Loranthus micranthus (Linn.) (Loranthaceae)	Leaves	[88]
Musa paradisiaca (Musaceae)	Fruits	[89]
Anacardium occidentale (Anacardiaceae)	Stem bark	[90]
C. pentandra L. Gaertn (Bombacaceae)	Bark	[91]
Arachis hypogaea (Fabaceae)	Whole plant	[92]
Morinda lucida Benth. (Rubiaceae)	Leaves	[93]
Dioscorea dumetorum (Dioscoreaceae)	Tubers	[94]

(*Continued*)

Table 20.2 (Continued)

Country and Species	Parts Used	Reference
South Africa		
Artemisia afra Jacq. Ex Willd. (Asteraceae)	Leaves, roots	[52]
Brachylaena elliptica Thunb. (Asteraceae)	Leaves	[95]
Brachylaena discolor (Asteraceae)	Leaves, roots, and stem	[23,52]
Bulbine natalensis Mill. (Asphodelaceae)	Roots	[52]
Bulbine frutescens L. (Asphodelaceae)	Roots	[52]
Camellia sinensis (Theaceae)	Intact white tea and pure green tea	[96]
Cannabis sativa L. (Cannabaceae)	Leaves	[23]
Chilianthus olearaceus Burch. (Buddlejaceae)	Leaves and twigs	[52]
Chironia baccifera L. (Gentianaceae)	Whole plant	[23]
Clausena anisata (Willd.) Hook (Rutaceae)	Roots	[97]
Cissampelos capensis L.f. (Menispermaceae)	Leaves	[23]
Combretum molle R. Br. ex G. Don (Combretaceae)	Leaves	[98]
Conyza scabrida DC (Asteraceae)	Leaves	[99]
Elytropappus rhinocerotis (L.f.) (Asteraceae)	Leaves	[99]
Euclea undulata Thunb. var. *myrtina* (Ebenaceae)	Roots	[100]
Galium tomentosum Thunb. (Rubiaceae)	Roots	[101]
Globimetula cupulata (DC) Van Tieghem (Loranthaceae)	Leaves	[86]
Harpephyllum caffrum Bernh. ex CF Krauss (Anacardiaceae)	Stem bark	[102]
Herichrysum nudifolium L. (Asteraceae)	Leaves and roots	[52]
Herichrysum odoratissimum L. (Asteraceae)	Whole plant	[52]
Herichrysum petiolare H & B.L. (Asteraceae)	Whole plant	[52]
Heteromorphica arborescens H. (Asteraceae)	Leaves and roots	[52]
Hypoxis colchicifolia Bak. (Hypoxidaceae)	Corms	[52]
Leonotis leonurus L. (Lamiaceae)	Leaves and flowers	[99]
Momordica balsamina L. (Cucurbitaceae)	Stem and flowers	[23]
Momordica foetida Schumach. (Cucurbitaceae)	Whole plant	[23]
Petroselenium crispum (Mill.) (Apiaceae)	Leaves	[99]
Prosopis glandulosa (Fabaceae)	Whole plant	[103]
Rhus chirindensis (Baker F.) (Anacardiaceae)	Stem bark	[104]
Ricinus communis L. (Euphorbiaceae)	Leaves	[99]
Ruta graveolens L. (Rutaceae)	Leaves	[23,99]
Securidaca longepedunculata (Fresen.) (Polygalaceae)	Roots	[105]
Vinca major L. (Apocynaceae)	Leaves, roots, and stem	[23]
Vernonia oligocephala Sch. Bip. (Asteraceae)	Leaves, twigs, and roots	[52,99]

(*Continued*)

Table 20.2 (Continued)

Country and Species	Parts Used	Reference
Cameroon		
Mammea africana (Guttiferae)	Stem bark	[106]
Kalanchoe crenata (*Crassulaceae*)	Whole plant	[10]
Ipomoea aquatica (Convolvulaceae)	Leafy stem	[107]
Vernonia colorata (Willd.) Drake (Asteraceae)	Leaves	[108]
Laportea ovalifolia (*Urticaceae*)	Aerial parts	[109]
Terminalia superba (Combretaceae)	Stem bark	[110]
Canarium schweinfurthii (Burseraceae)	Stem bark	[110]
Trema orientalis (Linn.) (Urticaceae)	Stem bark	[54]

20.3.2 Vernonia amygdalina *Del. (Asteraceae)*

V. amygdalina, commonly known as "bitter leaf," occurs wild in most countries of tropical Africa. It appears to be the most-used plant in the genus *Vernonia*. The leaves are consumed either as a vegetable or as aqueous extracts used as tonics for the treatment of various illnesses [9]. A number of investigators have reported the hypoglycemic potential of this plant [46,136–138]. Gyang et al. [137] reported that chloroform extract of the plant has hypoglycemic activity in both normoglycemic and alloxan-induced hyperglycemic rats. Ebong et al. [139] also reported the antidiabetic efficacy of combined ethanolic extracts of *A. indica* (neem) and *V. amygdalina* in rats. Activity of the combined extracts compared well with chlorpropamide and the nondiabetic control. Hence, the authors recommended consumption of the vegetable by diabetic patients for therapeutic purposes.

20.3.3 Hypoxis hemerocallidea *Fisch. (Hypoxidaceae)*

H. hemerocallidea is used worldwide, but particularly in Africa and has got its common name African potato. The plant is widespread in South Africa, Lesotho, Mozambique, Zimbabwe, and north into East Africa [140]. Studies by Ojewole [141], which evaluated the antidiabetic activity of aqueous extracts of the plant on STZ-induced diabetic rats, revealed significant reductions in the blood glucose concentration of the animals. Mahomed and Ojewole [19] also found that aqueous extract of the plant caused 30.20% and 48.54% reductions in the blood glucose concentrations of fasted normal and STZ-treated diabetic rats, respectively. This indicates that African potato exhibits hypoglycemic activity, and thus lends credence to the folkloric use of the herb in the control and/or management of diabetes mellitus [9].

20.3.4 Catha edulis *Forrsk. ex Endl. (Celastraceae)*

C. edulis is popularly called khat. In East Africa the plant is chewed to attain a state of euphoria and stimulation. *C. edulis* has spread in several African countries

Table 20.3 Documented Antidiabetic Plants Used in North African Herbal Medicine

Country and Species	Parts Used	Reference
Morocco		
Coriandrum sativum (Apiaceae, Umbelliferae)	Seeds	[16]
Argania spinosa (Sapotaceae)	Virgin argan oil	[111]
Chamaerops humilis (dwarf fan palm) (Arecaceae)	Leaves	[112]
Nigella sativa L. (Ranunculaceae)	Seeds	[113]
Ajuga iva (L.) Schreber (Labiatae)	Whole plant	[114]
Triticum repens (Graminae)	Leaves	[115]
Retama raetam (Fabaceae)	Whole plant	[20]
Chamaemelum nobile (Asteraceae)	Aerial parts	[52]
Lepidium sativum L. (Brassicaceae)	Seeds	[40]
Carum carvi (Apiaceae), *Capparis spinosa* (Capparidaceae)	Fruits	[116]
Calamintha officinalis Moench.	Aerial parts	[117]
Origanum vulgare (OV) (Lamiaceae)	Leaves	[118]
Fraxinus excelsior	Seed	[119]
Silybum marianum	Aerial parts	
U. dioica (Urticaceae)	Aerial parts	[120]
Rubus fructicosis (Rosaceae)	Leaves	
Globularia alypum (Globulariaceae)		[121]
Suaeda fruticosa (Chenopodiaceae)	Whole plant	[122]
Spergularia purpurea (Caryophyllaceae)	Whole plant	[123]
Zygophyllum gaetulum (Zygophyllaceae)	Aerial parts	[124]
Tunisia		
Artemisia campestris (Asteraceae)	Leaves	[125]
Centaurium erythrea (Gentianaceae)	Leaves	[126]
Linum usitatissimum (Linaceae) and *Cucurbita maxima* (Cucurbitaceae)	Seeds	[127]
Olea europaea (Oleaceae)	Leaves	[128,129]
Egypt		
Cleome droserifolia (Forssk.) (Cleomaceae)	Aerial parts	[130]
Artocarpus heterophyllus Lam. (jack fruit) (Moraceae)	Leaves	[131]
Zizyphus spina-christi (L.) Willd. (Rhamnaceae)	Leaves	[132]
Cynanchum acutum L. (Asclepiadaceae)	Aerial parts	[133]
Morus alba (Moraceae)	Root bark	[134]
Eruca sativa (Cruciferae)	Seeds	[135]

including South Africa. Studies conducted by van de Venter et al. [23] reported moderate *in vitro* antidiabetic properties for *C. edulis*; however, there is no published scientific article substantiating this claim in animal models. On the other hand, an insignificant increase in blood glucose concentration in type 2 diabetic khat chewers was observed by Saif-Ali et al. [142] in a study involving human subjects. This action was likely to be due to indirect sympathomimetic action [9].

20.3.5 Sutherlandia frutescens *Linn.* *(Fabaceae)*

S. frutescens is indigenous to South Africa, Lesotho, southern Namibia, and south-eastern Botswana and is widely used in traditional medicine. This plant is generally reputed as the most beneficial of the medicinal plants in Southern Africa [9]. Ojewole [143] reported the hypoglycemic effect of aqueous shoot extract of the plant in STZ-induced diabetic rats. Similar findings were reported by Chadwick et al. [26] in rats fed with a diabetogenic diet. The extract demonstrated an ability to normalize insulin levels and glucose uptake in peripheral tissues and suppressed intestinal glucose uptake [26].

20.3.6 Catharanthus roseus *(Apocynaceae)*

C. roseus (L.) G. Don (Apocynaceae), also known as *Vinca rosea* and originating from Madagascar, has now spread throughout Africa as a result of human activities. Studies on animal models have shown that ethanolic extracts of the leaves and flowers of *C. roseus* lower blood glucose levels [55]. Aqueous leaf extract of the herb could lower blood glucose by about 20% in diabetic rats, while dichloromethane and methanol extracts lowered blood glucose by 49–58% [55]. Glucokinase activity is reported to be responsible for increased glucose utilization [9]. Hypoglycemic effects of this plant seem to relate to increased glucose utilization in the liver. As active as it could be, adverse effects are not common with the use of this extract, except that serum acid and alkaline phosphatase levels were elevated in both untreated and treated diabetic rats [9].

20.3.7 Psidium guajava *Linn.* *(Myrtaceae)*

P. guajava is considered native to Mexico, but has extended to other continents including Africa [9]. Bark and leaves of *P. guajava* have been widely studied for their antidiabetic property. Mukhtar et al. [59] and Ojewole [58] studied the effect of aqueous extract in alloxan-induced and STZ-induced diabetic rats, respectively. The observed hypoglycemic activity was attributed to potentially active compounds such as tannins, flavonoids, pentacyclic triterpenoids, guiajaverin, quercetin, and other chemical compounds present in the plant. In another study, Mukhtar et al. [59] examined the antihyperglycemic activity of the ethanol extract of the stem bark of the plant on blood glucose levels of normal, alloxan-induced hyperglycemic, and normal glucose-loaded rats. The results showed that the extract exhibited significant hypoglycemic activity but was devoid of hypoglycemic effects in normal and glucose-loaded rats. Another study by Wang et al. [144] revealed significant inhibition of α-glucosidase activity in the small intestine of diabetic mice that were administered leaf extract of the herb.

20.3.8 Ageratum conyzoides *L.* *(Asteraceae)*

A. conyzoides is commonly known in Cameroon as "nyada elog." It is found in Cameroon, Nigeria, and other parts of Africa [145]. The hypoglycemic and antihyperglycemic properties of the aqueous extracts of the leaves of the plant were evaluated in normoglycemic and in STZ-induced diabetic rats. The aqueous extracts at 200 and 300 mg/kg showed statistically significant hypoglycemic and antihyperglycemic activity. The maximum reduction (27.15%; $p < 0.01$) was observed 8 h after administration of the extract at 300 mg/kg. Glibenclamide at 10 mg/kg appeared to be less efficient than the extract of *A. conyzoides* at 200 and 300 mg/kg, respectively. Consequently, the results confirmed the hypoglycemic properties of the leaves of the plant [1].

20.3.9 Momordica charantia *(Cucurbitaceae)*

M. charantia Linn. (Cucurbitaceae) is commonly known as African cucumber or bitter gourd. Various morphological parts (roots, stems, leaves, and fruits) have been used in the management of a plethora of human ailments, including diabetes mellitus and hypertension [146,147]. This plant has been studied in Botswana and South Africa. Acute administration of *M. charantia* whole-plant extract in STZ-induced diabetic rats produced dose-related, significant reductions ($p < 0.05-0.001$) in the blood glucose levels of normal and diabetic rats [146,147].

20.3.10 Mangifera indica *Linn.* *(Anacardiaceae)*

M. indica is used traditionally for the treatment of bronchitis, catarrh, internal hemorrhage, skin diseases, and toothache in Nigeria [148]. Leaf tea derived from the plant is used for the treatment of fever, diarrhea, and insomnia; an infusion of the bark is used for hypertension. The antidiabetic potential of the plant was investigated in a study conducted by Aderibigbe et al. [148]. Using aqueous extract and glucose administered simultaneously, and with the extract administered independently to rats 60 min before oral (1 g/kg) administration of glucose, they observed that it did not alter the blood glucose level. The stem bark aqueous extract of *M. indica* has also been reported to possess antidiabetic activity in South Africa by Ojewole [149]. The results lend pharmacological credence to the folkloric uses of the plant in the management and control of diabetes.

20.3.11 Persea americana *Mill.* *(Lauraceae)*

P. americana, commonly known as avocado, is found in many countries on the African continent and is used traditionally for the treatment of hypertension and diabetes mellitus. The antidiabetic potential of the plant has been validated in Nigeria and South Africa [150,151]. Gondwe et al. [150] studied the hypoglycemic and renal function effects of *P. americana* leaf ethanolic extract in STZ-induced diabetic rats and observed that *P. americana* induced a dose-dependent hypoglycemic response

in STZ-induced diabetic rats. Also, the effects of aqueous extract of alligator pear seed on normal and alloxan-induced diabetic rats were investigated [151]. Blood glucose levels were significantly reduced ($p < 0.05$) by 73.26−78.24% in diabetic rats on consumption of the extract, with greater effect exhibited by the 600 mg/kg dose. In normal rats, blood glucose levels were significantly reduced ($p < 0.05$) by 34.68−38.9% on consumption of the seed extract [151].

However, other plants, including *P. nigrescens* (Asclepiadaceae), *M. pruriens* (Leguminosae), *A. compressus* (Poaceae), *K. crenata* (Crassulaceae), *M. africana* (Guttiferae), *C. ferruginea* (Connaracea), and *C. micranthum*, *B. coriacea* (Capparaceae), which have been used in the treatment of diabetes traditionally, still present with scanty data in the literature, although they have been used in a number of countries on the continent.

20.3.12 Potential Antidiabetes Compounds Identified in African Medicinal Plants

In the last two decades, there has been an increase in the popularity among researchers in Sub-Saharan Africa of the search for antidiabetic drugs from medicinal plants. A good number of plant extracts have successfully undergone *in vitro* screening, and the hit samples involved both crude drugs and compounds. Investigation for new antidiabetes compounds in Africa has also involved the search for new α-glucosidase inhibitors. In effect, α-glucosidase inhibitors are oral antidiabetic drugs used for diabetes mellitus type 2 that work by preventing the digestion of carbohydrates, reducing the impact of carbohydrates on blood sugar. Hit antidiabetes products of Africa therefore include plant extracts as well as compounds with direct effect *in vivo* on the decrease of blood glucose levels, and samples acting *in vitro* as α-glucosidase inhibitors.

Several medicinal plants of Africa displayed significant antidiabetes activity, through either their organic extracts or their isolated constituents. Such plants include *Pteronia divaricata*, *Garcinia brevipedicellata*, *G. kola*, *Elaeodendron transvaalense*, *T. superba*, *E. undulata*, *Harungana madagascariensis*, *Dorstenia psilurus*, *Fagara tessmannii*, *Oriciopsis glaberrima*, and *Stachytarpheta cayennensis* (Table 20.4). Some compounds isolated in African plants with good α-glucosidase inhibitory activity include brevipsidone D [Figure 20.1 (**1**); IC_{50} of 7.04 μM], isolated from a threatened species, *G. brevipedicellata* [154]; gallic acid (**2**; IC_{50} of 5.2 μM) and its methylated derivative, methyl gallate (**3**; IC_{50} of 11.5 μM) [160]; 3,4′-di-*O*-methylellagic acid 3′-*O*-β-D-xylopyranoside (**4**; IC_{50} of 7.95 μM) [161], isolated from *T. superba*; kenganthranol B (**5**; IC_{50} of 6.3 μM); harunganol B (**6**; IC_{50} of 12 μM); harunganin (**7**; IC_{50} of 6.0 μM), isolated from *H. madagascariensis* [175]; 3β-acetoxy-16β-hydroxybetulinic acid (**8**; IC_{50} of 7.6 μM), isolated from *F. tessmannii*[171]; dorsilurin C (**9**; IC_{50} of 11.17 μM); dorsilurin F (**10**; IC_{50} of 4.13 μM); dorsilurin G (**11**; IC_{50} of 7.51 μM); and dorsilurin J (**12**; IC_{50} of 16.91 μM), isolated from *D. psilurus* [161].

Table 20.4 Hit Investigated Antidiabetes Plants of Africa

Family	Species	Traditional Uses	Area of Plant Collection	Potentially Active Compounds	Screened Activity
Asteraceae	*P. divaricata* (P.J. Bergius) Less.	Diabetes [152]	South Africa	Volatile oils [153]	Good inhibition of α-glucosidase activity for bark acetone extract (IC_{50} of 32.95 μg/mL) [152]
Clusiaceae	*G. brevipedicellata* (Baker f.) Hutch. & Dalziel	Not reported (threatened species)	Cameroon	Brevipsidones A, B, C, and D (**1**), damnacanthal, scopoletin, stigmasterol, and β-sitosterol [154]	Significant inhibition of α-glucosidase activity for compound **1** (IC_{50} of 7.04 μM) [154]
	G. kola Heckel	Catarrh, abdominal colicky pain, laryngitis, diabetes, and liver disorders [155]	Nigeria	Kolaviron, a biflavonoid complex that contains *Garcinia* biflavanones 1 and 2 and kolaflavanone in 2:2:1 ratio [156,157]	Kolaviron significantly reduced fasting blood glucose in both normoglycemic and STZ-diabetic rats [157]
Celastraceae	*E. transvaalense* (Burtt Davy) R.H. Archer	Diabetes [152]	South Africa	Lup-20(30)-ene-3α,29-diol; lup-20(29)-ene-30-hydroxy-3-one; Ψ−taraxastanonol; β-sitosterol; 4′-*O*-methylepigallocatechin [158]	Good inhibition of α-glucosidase activity for bark acetone extract (IC_{50} of 50.62 μg/mL) [152]
Combretaceae	*T. superba* Engl. and Diels	Diabetes mellitus, gastroenteritis, female infertility, and abdominal pains [159]	Cameroon	Gallic acid (**2**); ellagic acid, methyl gallate (**3**), ellagic acid 3,3′-dimethyl ether, ellagic acid-4-*O*-β-D-xylopyranoside-3,3′-dimethyl ether, 3,4′-di-*O*-methylellagic acid 3′-*O*-β-D-xylopyranoside (**4**),	Significant inhibition of α-glucosidase activity for compounds **2** (IC_{50} of 5.2 μM), **3** (IC_{50} of 11.5 μM) [160], and **4** (IC_{50} of 7.95 μM) [161]

				4′-*O*-galloy-3,3′-di-*O*-methylellagic acid-4-*O*-β-D-xylopyranoside [160,161]	
Ebenaceae	*E. undulata* var. *myrtina* Thunb.	Diabetes [152]	South Africa	α-Amyrin-3-*O*-β-(5-hyroxy) ferulic acid, betulin, lupeol, and epicatechin [162]	Good inhibition of α-glucosidase activity for bark acetone extract (IC_{50} of 49.95 μg/mL) [152], α-amyrin-3-*O*-β-(5-hyroxy) ferulic acid (IC_{50} of 4.79 μg/mL), lupeol (IC_{50} of 6.27 μg/mL), and epicatechin (IC_{50} of 5.86 μg/mL) [162]
Hypericaceae	*H. madagascariensis* Lam.	Diarrhea, dysentery, indigestion, and poor pancreatic function [163,164]	Cameroon	Harunmadagascarins A and B, harunganol B (**6**), harungin (**7**), anthrone, kengaquinone, kenganthranols A, B (**5**), and C [165]	Significant inhibition of α-glucosidase activity for compounds **5** (IC_{50} of 6.3 μM), **6** (IC_{50} of 12.0 μM), and **7** (IC_{50} of 6.0 μM) [165]
Moraceae	*D. psilurus* Linn.	Arthralgia, cardiovascular disorders, rheumatism, snakebites, headache, stomach disorders, diuretic, tonic, stimulant, and analgesic [159,166−168]	Cameroon	Dorsilurins A, B, C (**9**), D, E, F (**10**), G (**11**), H, I, J (**12**), and K [169]	Significant inhibition of α-glucosidase activity for compounds **9** (IC_{50} of 11.17 μM), **10** (IC_{50} of 4.13 μM), **11** (IC_{50} of 7.51 μM), and **12** (IC_{50} of 16.91 μM) [169]
Rutaceae	*F. tessmannii* Engl.	Tumors, swelling, inflammation, and gonorrhea [170]	Cameroon	β-Sitosterol, stigmasterol, campesterol, stigmastanol, lupeol, arctigenin methyl ether, sesamin, vanillic acid, 2,6-dimethoxy-1,4-	Significant inhibition of α-glucosidase activity for compound **8** (IC_{50} of 7.6 μM) [171]

(*Continued*)

Table 20.4 (Continued)

Family	Species	Traditional Uses	Area of Plant Collection	Potentially Active Compounds	Screened Activity
				benzoquinone, betulinic acid, 3β-acetoxy-16β-hydroxybetulinic acid (**8**) and 3β,16β-diacetoxybetulinic acid [171]	
	O. glaberrima Engl.	Hypotension, mycoses, and dermatitis infection [172]	Cameroon	Oriciacridone C, D, E, and F, 1,3,5-trihydroxyl-4-prenylacridone, atalaphyllidine, atalaphyllidine, oleanolic acid, butulinic acid, β-sitosterol, stigmasterol, and glucoside of stigmasterol [173]	Good inhibition of α-glucosidase activity for 1,3,5-trihydroxyl-4-prenylacridone (IC_{50} of 17 μM) [173]
Verbenaceae	*S. cayennensis* (LC Rich.) Vahl.	Fever, rheumatism, antidiabetes, worms, ulcers, insecticidal, and larvicidal [174]	Nigeria	6β-Hydroxyipolamide, ipolamide, and isoverbascoside [174]	Aqueous (125 mg/kg, p.o.) and methanol (2000 mg/kg) extracts of the leaves to alloxan-diabetic rats showed significant blood glucose reductions of 43% and 53%, respectively (at the end of 4 h), similar to the strong effect of glibenclamide (at 5 mg/kg, p.o.) [174]

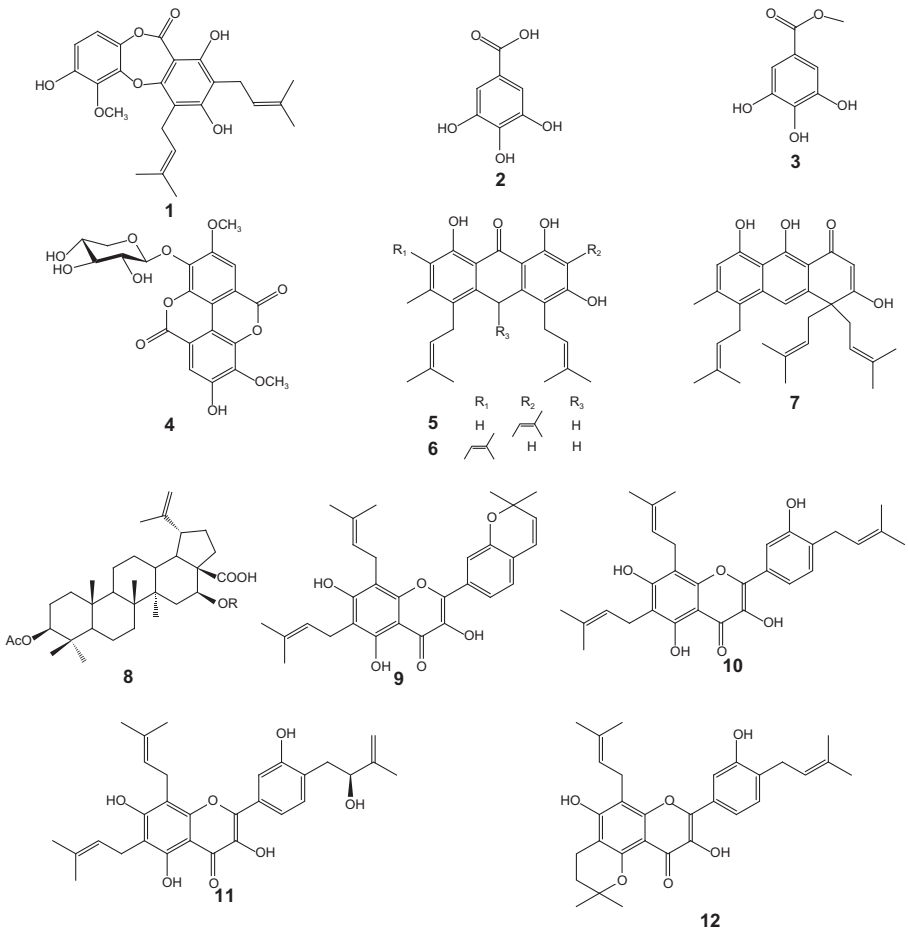

Figure 20.1 Chemical structures of some potential antidiabetes compounds identified in African plants: brevipsidone D (**1**); gallic acid (**2**); methyl gallate (**3**); 3,4′-di-*O*-methylellagic acid 3′-*O*-β-D-xylopyranoside (**4**); kenganthranol B (**5**); harunganol B (**6**); harunganin (**7**); 3β-acetoxy-16β-hydroxybetulinic acid (**8**); dorsilurins C (**9**), F (**10**), G (**11**), and J (**12**).

20.4 Conclusion

Diabetes exerts a significant health challenge with its high and increasing global prevalence, especially in rural populations lacking access to health facilities and that have only limited financial power. In Africa, the demand by patients to use natural products with antidiabetic activity is increasing since access to traditional medicines is less constraining and more affordable. With Africa being blessed with enormous plant biodiversity, investigations of medicinal plants in the development of novel therapeutic agents for the management of diabetes should be pursued more vigorously.

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21 Antioxidant Activity of African Medicinal Plants

Mikhail Olugbemiro Nafiu[a], *Musa Oyewole Salawu*[a] *and Mutiu Idowu Kazeem*[b]

[a]Department of Biochemistry, University of Ilorin, Ilorin, Nigeria,
[b]Department of Biochemistry, Lagos State University, Ojo, Nigeria

21.1 Introduction

Antioxidants are powerful free radical scavengers in the body, while free radicals are highly reactive chemical substances such as superoxide, hydroxyl radical, or singlet oxygen [1] that travel around in the body and cause damage to body cells. Free radical damage is one of the most prominent causes of devastating diseases that are responsible for killing many people in the world, such as cardiovascular disease, which can manifest as heart attacks, and cancer [2]. The aging process has been linked by some researchers to free radical damage in the body [3]. Free radicals naturally occur in the body as a result of chemical reactions during normal cellular processes. They can also be formed in response to environmental factors such as excess pollution, excessive UV rays, and exposure to cigarette smoke, automobile exhaust, and pesticides. Inadequate rest or sleep, inability to manage stress responses, and unhealthy eating habits can also cause free radical damage [3–5].

In chronic infections and inflammation, as well as in other disorders, release of leukocytes and other phagocytic cells readily defends the organism from further injury. The cells do this by releasing free oxidant radicals, and these by-products are generally reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical, nitric oxide, and hydrogen peroxide, which result from cellular redox processes [6,7]. At low or moderate concentrations, ROS exert beneficial effects on cellular responses and immune function [7,8]. At high levels, however, free radicals and oxidants generate oxidative stress, a deleterious process that can damage cell structures, including lipids, proteins, and DNA [9]. Oxidative stress plays a major role in the development of chronic and degenerative ailments such as cancer, autoimmune disorders, rheumatoid arthritis, cataracts, aging, cardiovascular, and neurodegenerative diseases [9,10].

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21.2 Sources of Antioxidants

An array of intracellular and extracellular antioxidant mechanisms are essential to scavenge any oxidant "reactive intermediates," which are continuously generated in almost all aerobic cells; otherwise, tissue damage occurs [11,12]. An antioxidant is any substance which, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of substrate. The term "oxidizable substrate" includes almost everything found in living cells, including proteins, lipids, DNA, and carbohydrates [13]. Antioxidants are compounds that protect biological systems against the potentially harmful effects of processes or reactions that can cause excessive oxidation [14,15]. They act as free radical scavengers by preventing and repairing damage caused by ROS and, therefore, can enhance the immune defense and lower the risk of cancer and degenerative diseases [6,12]. The human body is equipped with an antioxidant defense system that deactivates these highly reactive free radicals [16]. Antioxidant enzymes (made in the body) and antioxidant molecules (found in plants) soak up all the excess energy that these free radicals have, turning them into harmless particles or waste products that we can then get rid of [3].

The adverse effects of oxidative stress on human health have become a serious issue. One solution to the problem is to supplement the diet with antioxidant compounds that are contained in natural plant sources [17]. The World Health Organization (WHO) has estimated that 80% of earth's inhabitants rely on traditional medicine for their primary health care needs, and most of this therapy involves the use of plant extracts and their active components [18]. These natural plant antioxidants can therefore serve as a type of preventive medicine. Recent reports indicate that there is an inverse relationship between the dietary intake of antioxidant-rich foods and the incidence of human disease [19]. However, synthetic antioxidants, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), have been widely used as antioxidants in the food industry and may be responsible for liver damage and carcinogenesis [20,21]. For this reason, interest in the use of natural antioxidants has increased. Plants have been the basis of traditional medicines throughout the world for thousands of years and continue to provide new remedies to humankind; a great deal of effort has therefore focused on using available experimental techniques to identify natural antioxidants from plants.

21.3 African Medicinal Plants with Antioxidant Potential

21.3.1 Diospyros abyssinica *Hiern*

Diospyros abyssinica (also known as kôforonto and baforonto) is a species of trees in the Ebenaceae family that grows in the southern part of Africa, particularly in Mali. It can also be found in Angola, Guinea, Eritrea, and Ethiopia [22].

The trees have been used in many traditional medical systems around the world, including traditional Ayurvedic, African, and Chinese medicine. Nearly every part of these plants has been used as a medicine in some way, for example, as an astringent and to cure biliousness [22].

In Zimbabwe, a juice made from the bark and leaves of *D. abyssinica* combined with the root juice of *Albizia lebbeck* is used as a remedy for snakebites. The most frequently isolated compounds from *D. abyssinica* are the triterpenoids betulin, betulinic acid (**1**), and lupeol [23]. All of these compounds are well-known anti-inflammatory compounds. This species has a significant medicinal value, as demonstrated by its use in traditional medicine (Figure 21.1).

The root bark from *D. abyssinica* has been tested for antioxidant activity [24]. It was extracted with a series of solvents, including petroleum ether, dichloromethane, chloroform, 80% aqueous ethanol, and water (at 50°C and 100°C). It was determined that the root bark of *D. abyssinica* is the richest source of extracted

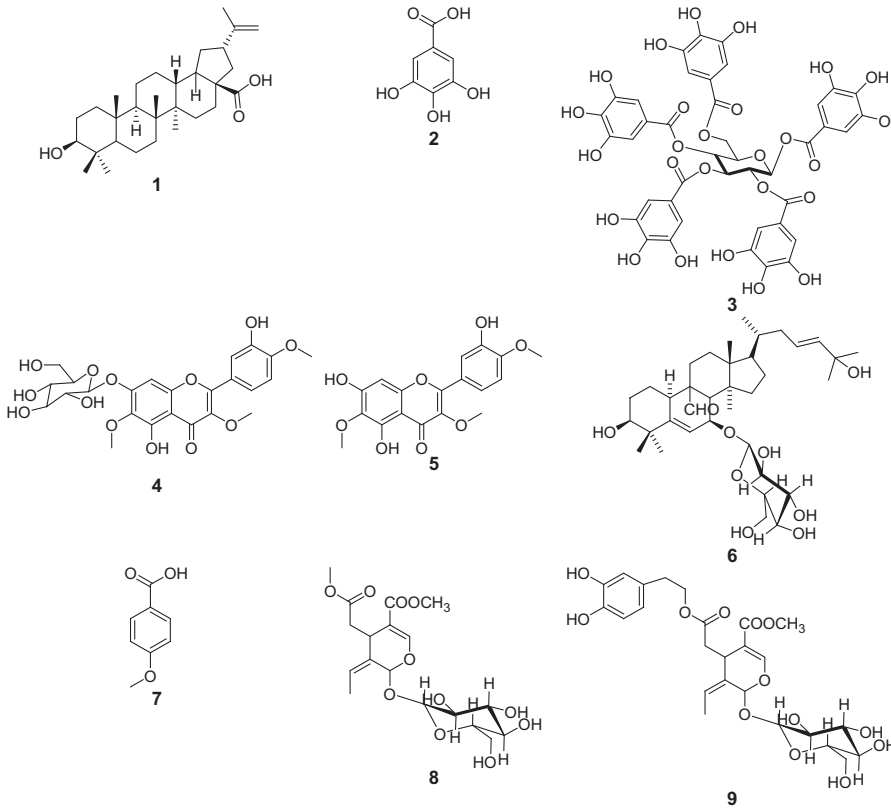

Figure 21.1 Chemical structures of selected antioxidant compounds identified in African plants: betulinic acid (**1**); gallic acid (**2**); 1,2,3,4,6-pentagalloyl glucose (**3**); centaurin (**4**); centaureidin (**5**); momordicoside (**6**); *p*-methoxybenzoic acid (**7**); oleoside (**8**); oleuropein (**9**).

compounds—36.7% of the weight of the plant material is composed of antioxidants. *D. abyssinica* exhibited the greatest radical scavenging activity with the 80% ethanol and methanol extracts. Thus, this plant appears to be an excellent source of antioxidants (Table 21.1) [24].

21.3.2 Pistacia lentiscus *L.*

P. lentiscus is extensively used in folk medicine by rural populations in Algeria, Morocco, and Egypt. *P. lentiscus* is important because of its medicinal value. The aerial parts have traditionally been used as a stimulant, for their diuretic properties, and to treat hypertension, coughs, sore throats, eczema, stomach aches, kidney stones, and jaundice [25,26]. The reducing power and radical scavenging activity of the extracts from the leaves of *P. lentiscus* in solvents such as ethanol, ethyl acetate, aqueous/ethyl acetate, hexane, aqueous/hexane, chloroform, and aqueous/chloroform have been studied *in vitro* [28].

Using the diphenylpicryhydrazyl (DPPH) scavenging activity assay, it was found that all of the *P. lentiscus* extracts, except for the chloroform extract, have a high radical scavenging activity (90%), equivalent to that of the standard, BHA (89%). The ethanolic and aqueous fractions from the ethyl acetate extract have high scavenging activities, with values of 78% and 90.29%, respectively. Overall, *P. lentiscus* exhibited outstanding reducing power, good radical scavenging activity against DPPH and H_2O_2, slow inhibition of lipid peroxidation, and richness in tannins; however, it also showed a lack of flavonoids [28].

In vitro antioxidant and antimutagenic activities of two polyphenols isolated from the fruits of *P. lentiscus* have been investigated. These polyphenols are gallic acid (**2**) and 1,2,3,4,6-pentagalloyl glucose (**3**) [27].

21.3.3 Urtica dioica *L.*

Stinging nettle or common nettle, *U. dioica*, is a herbaceous perennial flowering plant native to Europe, Asia, northern Africa, and North America, and is the best-known member of the nettle genus *Urtica*. *U. dioica* L. (Urticaceae) leaves have been used in Libya in the form of a medicinal tea or decoction as diuretic and antidiabetic therapies and to treat stomach disorders [29].

The antioxidant capacity of this plant was evaluated using several *in vitro* methods such as superoxide anion scavenging (SAS) and 2,2-diphenylpicryhydrazyl methods. The SAS method determined that the antioxidant activity of *U. dioica* at an acidic pH was 0.013 μg/mL resorcinol equivalents (Re eq.); the DPPH method in methanolic solution determined that the antioxidant activity was 419 μg/mL. The total phenolic content was found to be 0.35 mg/l gallic acid equivalent (GAE) [64].

Concentrations of *U. dioica* L. extract of 50, 100, and 250 μg/mL showed 39%, 66%, and 98% inhibition, respectively, of the peroxidation of a linoleic acid emulsion. By contrast, α-tocopherol, the positive control, at 60 μg/mL, exhibited only 30% inhibition [30]. It can be concluded that *U. dioica* L. has powerful antioxidant activities.

Table 21.1 Hit African Medicinal Plants with Antioxidant Potential

Plant and Family	Traditional Uses	Countries of the Studies	Potentially Active Compounds	Reported Activities
D. abyssinica (Ebenaceae)	Snake bite [23], astringent [22]	Mali, Guinea	Betulinic acid [23], lupeol [24]	Anti-inflammatory [22]
Pistacia lentiscus (Anacardiaceae)	Stimulant, diuretic, hypertension [25], cough, kidney stones, jaundice [26]	Algeria, Morocco, Egypt	Gallic acid, 1,2,3,4,6-pentagalloyl glucose [27]	Antioxidant, antimutagenic [27,28]
Urtica dioica (Urticaceae)	Diuretic, antidiabetic [29]	Libya	Not identified	Antioxidant [30]
Bidens pilosa (Asteraceae)	Anti-inflammatory, antiseptic, antidiabetic [24], anticancer [31,32]	Nigeria	Centaurin, centaureidin [33]	Antihypertensive [34]
Momordica charantia (Cucurbitaceae)	Antidiabetic [35]	Morocco, Egypt	Momordicoside, methoxy benzoic acid [36]	Antioxidant [37]
Dorstenia picta (Moraceae)	Antidiabetic, hypertension [38], cough, headache analgesic [34]	Cameroon	Quercitrin, 6,8-dipreny leridictyol [39]	Antihypertensive, antioxidant, anti-inflammatory, antinociceptive [40]
Eucalyptus camaldulensis (Myrtaceae)	Antibacterial, expectorant [41], antidiarrhea [42]	Ghana, Togo	1,8-cineole [43]	Antimicrobial, analgesic, inflammation, antioxidant [44]
Olea europaea (Oleaceae)	Dysentery, fever, piles, and fistula [45], anti-inflammatory, antibacterial, antihypertensive, antidiabetics [46]	Tunisia	Oleuropein, oleside, ligstroside [47]	Antimicrobial [48,49], gastroprotective [50], antioxidant [51,52], antiatherosclerotic [53], antiviral [54], antitumor [55,56]
Pelargonium reniforme (Geraniaceae)	Gastroenteritis, hemorrhage, kidney disorder [57]	South Africa	Not identified	Antioxidant [58]
Sacoglottis gabonensis (Humiriaceae)	Vaginal infection, abdominal pain [59], diarrhea, diabetes [60]	Gambia, Angola, Senegal	Bergenin [60]	Antioxidants [60]
Mallotus oppositifolius (Euphorbiaceae)	Anemia, pneumonia, aphrodisiac, antimalarial [61], inflammation [62]	Nigeria	Not identified	Anti-inflammatory [62], antimicrobial effects [63]

21.3.4 Bidens pilosa *Linn.*

B. pilosa Linn. (*Asteraceae*) is widely distributed in subtropical and tropical regions. It is 30−100 cm in height with yellow flowers and is commonly known as "hairy beggar ticks," "sticks tights," and "Spanish needles." The plant is used in various folk medicines for its anti-inflammatory, antiseptic, liver-protective, blood-pressure lowering, and hypoglycemic effects [34]. The plant has been widely used in Nigeria as a traditional medicine and as a major ingredient of an herbal tea that is believed to prevent inflammation and cancer [31,32].

Phenylpropanoid glucosides, polyacetylenes, diterpenes, flavonoids, and flavone glycosides have been identified as the bioactive components of this plant and are thought to be involved in its antioxidant activity [33]. The methanol extract of *B. pilosa* was shown to prevent the onset of hypertension and to reduce blood pressure in rats [34]. In addition, the fresh leaves and flowers of *B. pilosa* were subjected to steam distillation, and colorless and yellowish essential oils were obtained in amounts of 0.08% and 0.06% (w/w), respectively. Gas chromatography−mass spectrometry analysis of these essential oils resulted in the identification of 44 compounds. Chang et al. [65] also isolated two compounds, centaurin (**4**) and centaureidin (**5**), from the butanol fraction of the plant.

21.3.5 Momordica charantia *L.*

The bitter gourd (*Momordica charantia* L.) belongs to the family Cucurbitaceae and has long been used in foods and medicines [66]. The bitter gourd is known by different names, such as balsam pear and karela, and it grows in tropical and subtropical regions of India, Malaysia, China, Africa, the Middle East, the United States, and Thailand [66]. It is common in the North African countries such as Morocco and Egypt. The bitter gourd can be used to treat diabetes mellitus and appears to be a safe alternative to reduce blood glucose [35].

In the DPPH radical scavenging assay, the activity of the positive control, ascorbic acid, was the highest (200 mg/mL), followed by the leaf, the green fruit, the stem, and the ripe fruit fractions of the bitter gourd. The IC_{50} values were lowest in the leaf fraction (9.72 mg/mL), followed by the green fruit fraction (11.00 mg/mL), the stem fraction (17.8 mg/mL), and the ripe fruit fraction (27.6 mg/mL). In the hydroxyl radical scavenging assay, the activity of the leaf fraction was greater than that of the other fractions but lower than that of ascorbic acid. The green fruit had the highest IC_{50} value (119 mg/mL), followed by the leaf (167 mg/mL), the stem (267 mg/mL), and the ripe fruit (173 mg/mL) [37].

Bio-guided fractionation of the methanol extract of *M. charantia* dried gourds led to the isolation of 11 compounds. These include momordicoside (**6**) and *p*-methoxybenzoic acid (**7**) [36].

21.3.6 Dorstenia picta *L.*

D. picta (Moraceae) is an herbaceous plant used in southern Cameroon as an antidiabetic and antihypertensive drug. Other traditional uses of the genus *Dorstenia* are

against headaches and abdominal pain [38]. It has been reported that *Dorstenia psilurus*, *Dorstenia cilianta*, and *Dorstenia barteri* have antihypertensive, antioxidant, anti-inflammatory, and antinociceptive activity, respectively [40]. Many antioxidant compounds have been isolated from this plant. They include quercitrin, 6,8-diprenyleridictyol, bartericin A, and 6-prenylapigenin [39].

A decoction from the leaves of the *D. psilurus* is used to treat cough, headache, and stomach pain in Cameroon. In Panama and Mexico, *D. contrajerva* leaves are used to fight against fever and snake venom [34]. Aside from their medicinal uses, *Dorstenia* plants are also used in the preparation of food, as in the case of *D. foetida*, whose tubers are cooked and eaten in Oman, and *D. psilurus*, whose rhizomes are used as spices for the preparation of *na'a poh* in Cameroon [67].

21.3.7 Eucalyptus camaldulensis *Dehnh.*

E. camaldulensis is an important ethnomedicinal plant belonging to the family Myrtaceae. It is used as a remedy for sore throat and other bacterial infections of the respiratory and urinary tracts. Essential oils of the leaves are used in the treatment of lung diseases, while the volatile oils are used as expectorants [41]. Topical ointments containing eucalyptus oil have also been used in traditional Aboriginal medicines to heal wounds and fungal infections. Eucalyptus oil obtained by steam distillation and rectification of the fresh leaves has eucalyptol (1,8-cineole) as its active ingredient, and this is responsible for its various pharmacological actions [43]. Antimicrobial activity of the methanolic extracts of *E. camaldulensis* has also been reported [68,69].

The tree is widely used in traditional medicine to treat a variety of disease conditions including cold, asthma, cough, diarrhea and dysentery, hemorrhage, laryngalgia, laryngitis, sore throat, spasm, trachea, and vermifuge [42]. Some studies have demonstrated that leaf extract and essential oil of *Eucalyptus* sp. have antifungal, repellent, antibacterial, analgesic, and anti-inflammatory activities [44]. It has been determined that essential oil of eucalyptus possesses hydroxyl radical scavenging activity greater than BHT and curcumin, which were used as positive controls in the study, and also possessed the greatest capacity to scavenge superoxide radicals [44]. Abd El-Mageed et al. [70] also determined and published the chemical composition of the essential oil from *E. camaldulensis*.

21.3.8 Olea europaea *L.*

O. europaea L., belonging to the family Oleaceae, is a small evergreen tree, from 12 to 20 ft high, with hoary, rigid branches and a grayish bark. In many countries, extract of *O. europaea* is used in the treatment of migraines, insomnia, diarrhea, dysentery, fever, piles, and fistula [45].

O. europaea is abundantly found in Tunisia, with more than 50 different cultivars. There has been increasing interest in olive products and by-products of the olive tree, and especially the olive leaves, due to their various bioactivities. Historically, olive leaves have been used as a remedy for fever and other diseases

such as malaria [71]. According to Tunisian folk medicine, olive leaves are recommended in a wide range of ailments, including inflammatory disorders, bacterial infections, hypertension, and diabetes, but modes of preparation and administration vary: earache is cured by using olive leaves in hot olive oil with salt [46]. Olive leaf juice, despite its irritation, is recommended for curing trachoma. When chewed, this plant organ is used to relieve tooth pain and to treat lip irritation. A decoction of the leaves, used as a liquid mouthwash, is used for treating aphthous, gingivitis, and glossitis [72,73].

Previous studies have demonstrated that olive leaves are used for their antimicrobial [48,49], gastroprotective [50], antioxidant [51,52], hypotensive [74], hypoglycemic [75], antiatherosclerotic [53], antiviral [54], antitumor [55,56], and anti-inflammatory properties [76].

The pharmacological properties of olive oil, the olive fruit, and its leaves have been recognized as important components of medicine and a healthy diet because of their phenolic content [77]. Phenolic compounds are found in all parts of the olive plant, but their nature and concentration varies greatly among the various tissues. In *O. europaea*, oleuropein, demethyl-oleuropein, ligstroside, and oleoside (**8**) represent the predominant phenolic oleosides [47], whereas verbascoside [78] is the main hydroxycinnamic derivative of the olive fruit. [79] Oleuropein (**9**) is generally the most prominent phenolic compound in olive cultivars.

Oleuropein possesses good antioxidant properties. It potently and dose dependently inhibits copper sulfate-induced oxidation of low-density lipoproteins (LDL) [80,81]. Oleuropein has the ability both to scavenge nitric oxide and to cause an increase in inducible nitric oxide synthase (iNOS) expression in the cell. A scavenging effect of oleuropein was also demonstrated with respect to hypochlorous acid (HOCl) [80].

21.3.9 Pelargonium reniforme *Curt.*

*P. reniforme*A, belonging to the family Geraniaceae, is native to the coastal regions of South Africa [82]. The plant is notable for its narrow, deep-red flowers and its large, heart-shaped leaves. Along with other closely related species, the root has been used for centuries as a traditional herbal remedy in South Africa [83].

Pelargonium species are widely used by traditional healers in areas of southern Africa by Sotho, Xhosa, Khoi-San, and Zulus for its curative and palliative effects in the treatment of diarrhea, dysentery, fever, respiratory tract infections, liver complaints, wounds, gastroenteritis, hemorrhage, and kidney and bladder disorders [57,84,85].

Both the rhizome and the herb have been used for different purposes since ancient times to treat malaria, inflammation, and abdominal and uterine disorders. The root extracts have been shown to have antibacterial, antifungal, and antitubercular activities; this may justify its use by the people of South Africa in the treatment of cough and tuberculosis [86].

The leaves were used to treat wounds and abscesses and were used externally to treat neuralgia, throat infections, and a wide range of skin diseases such as

ringworm, ulcers, and rashes [87]. In folk medicine, *Pelargonium* was used internally as a styptic for metrorrhagia, menorrhagia, hematuria, hemorrhoids, syphilis, and peptic and duodenal ulcers. Paracelsus described it as having cardiotonic and antidepressive activity and suggested it for leucorrhea as a mouthwash. It is commonly used for childhood ailments such as chicken pox, measles, and mumps [88].

Methanol and water extracts assessed by three established *in vitro* methods, namely, 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and ferric ion reducing power, showed that *P. reniforme* extract possessed strong scavenging and antioxidant activities and moderate reducing power, thus validating its traditional use in the treatment of liver diseases. Flavonoids and hydrolyzable tannins of *P. reniforme* showed marked antioxidant effects using a DPPH radical generating system and a luminol-dependent chemiluminescence assay [58].

21.3.10 Sacoglottis gabonensis *Baill.*

S. gabonensis Baill. is a perennial tree that grows across Africa, from Senegal and Gambia east to the Central African Republic and south to Angola. Decoctions of *S. gabonensis* stem bark are used to treat illnesses such as abdominal pains, fever, gonorrhea, and diarrhea, and are sometimes used to treat hypertension and diabetes in various parts of Africa. In Senegal and Congo, a stem bark decoction is mixed with other plants and added to bath water to treat ovarian troubles, vaginal infections, and children with fever. The stem bark of this plant is also used as a palm wine additive, as it is claimed to prolong the shelf life of the wine, add potency, reduce foaming, and impart a bitter taste [89,90]. It is also reported to have aphrodisiac properties.

The main active ingredient in the stem bark decoction of *S. gabonensis* is bergenin, an isocoumarin. The stem bark extract has been reported to have hepatoprotective properties and antilipid peroxidation activity *in vivo* in rats [91]. Bergenin has been reported to protect against 2,4-dinitrophenylhydrazine (DNPH)-induced hepatotoxicity and toxicity to red blood cells in rats. The stem bark extract of *S. gabonensis* and its main isolated compound bergenin have been reported to have antioxidant properties [59]. However, more research is needed to evaluate its potential as a lead drug. The effect of the bark extract on 2,4-DNPH experimental lipid peroxidation and the side effects of 2,4-DNPH and ethanol on natural antioxidant enzymes and vitamins were studied. The bark extract, like bergenin, exerted a protective action on brain tissue, though to a lesser extent, as against oxidant 2,4-DNPH. The inhibitory effect is dependent on dose and on activity per unit weight basis. The extract appears a more powerful inhibitor than vitamins E and C [60,92]. This suggests that the pharmacologic action of the bark extract as an anticancer agent may possibly be due to the antioxidant potentials of the extract and bergenin, which is believed to be the active substance in the *S. gabonensis* stem bark extract.

21.3.11 Mallotus oppositifolius *Lour.*

M. oppositifolius is a shrub of the family Euphorbiaceae that grows in many parts of Africa. It is used in folk medicine and herbal preparations for the treatment of dysentery, worms, and malaria. It is also used traditionally for the treatment of convulsion, epilepsy, parasitic eye and kidney infections, as a diuretic and painkiller, and in treatment of paralysis, spasm, headache, and swelling. A decoction of the root is used for anemia, pneumonia, and as an aphrodisiac, and the stick is chewed for oral hygiene and teeth cleaning [61]. Anti-inflammatory [62] and antimicrobial effects [63,93] of the plant have also been reported.

M. oppositifolius extracts were found to contain alkaloids, cardiac glycosides, and phenolic compounds, with higher concentrations residing in the leaves than in the roots [62,63]. Antioxidant and anti-inflammatory activities of the crude extracts in hexane and methanol were evaluated by the β-carotene linoleate model system and the carrageenan-induced rat paw edema animal model [62]. The root methanolic and ethanolic extracts showed antioxidant activity. Thin-layer chromatographic analyses of the extracts showed the presence of phenolic compounds in the crude extracts, two of which were flavonoids. The anti-inflammatory activity of the crude extracts therefore could be due to those compounds.

In a recent study, the antioxidant properties of the methanolic extract of the leaves of *M. oppositifolius*, in comparison with BHA as a standard antioxidant, using three free radical generators, namely, hydrophilic radical generator 2,2-azobis (2-amidino propane) dihydrochloride (AAPH), hydrophobic radical generator 2,2-azobis(2,4-dimethylvaleronitrile) (AMVN), and hydroxyl radical and nonspecific radical generator Fe^{2+}/ascorbate system in an *in vitro*, *in vivo*, and *ex vivo* model systems, were performed. *In vitro* study indicated that the methanolic extract of *M. oppositifolius* (MEMO) leaves failed to inhibit lipid peroxidation induced by AAPH, while BHA offered 55.5% inhibition [62]. In addition, while AMVN-induced lipid peroxidation was inhibited by 17.7% and 29.4% by MEMO and BHA, respectively, Fe^{2+}/ascorbate system-induced lipid peroxidation was inhibited by 57.9% and 78.9% by MEMO and BHA, respectively. *Ex vivo* studies showed that MEMO at 100 mg/kg body weight reduced malondialdehyde and protein carbonyl levels by 34.5% and 12.0%, respectively, compared with the control. *In vivo*, MEMO increased ($p < 0.05$) superoxide dismutase and catalase activities by 408.0% and 295.0%, respectively. Therefore, this study demonstrates that MEMO exhibits antioxidant and radical scavenging activity, as well as enhancement of enzymatic antioxidant capacity, and as such could intervene in toxicological processes mediated by free radical mechanisms [62].

21.3.12 Thonningia sanguinea *Vahl.*

Thonningia sanguinea Vahl. (Balanophoraceae), also called "kulla" by the Hausa of Nigeria, is a plant devoid of chlorophylls with bright red-colored flowers that grows as parasite on *Hevea brasiliensis* (rubber tree), *Phoenix dactylifera* (oil palm), and *Theobroma cacao* (cocoa trees) [94,95]. The flowers and rhizomes of

the plant are used in herbal medicine as vermifuge, astringent, and treatment for dysentery, diarrhea, leprosy, cutaneous infections, abscesses, dental caries, gingivitis, hemorrhoids, and fever [96]. *T. sanguinea* extracts have also been reported to possess antibacterial activity, including against multidrug-resistant strains [97].

The flowers of *T. sanguinea* are widely used in Ivory Coast in the treatment of microbial diseases, mainly the salmonellae diseases [98]. In Africa, multidrug-resistant nontyphoidal salmonellae (NTS) are one of the leading causes of morbidity and high mortality in children under 5 years of age [99]. *T. sanguinea* is also known to possess antioxidant activity [100,101]. N'Guessan et al. [102] successfully isolated two phenolic antioxidant compounds from this plant. These are brevifolin carboxylic acid and gallic acid.

21.4 Conclusions

This review discussed medicinally significant plant species selected from Africa with high antioxidant activities when compared to synthetic antioxidants. It focuses on plants belonging to several different families from around Africa to understand their therapeutic uses and their potential antioxidant activities. Different antioxidant chemical compounds isolated from some of these plants were also discussed in order to know the active constituents responsible for the antioxidant potential of the plants.

However, it is worthy of note that most scientific studies on the antioxidant potential of these medicinal plants were conducted *in vitro* using different methods such as DPPH radical scavenging activity and SAS assay. The results obtained from these *in vitro* assays may not necessarily imply that the same effect will be produced when performed in the living organism. Therefore, there is need for *in vivo* studies before these plants can be validated for use in medicine.

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22 African Medicinal Plants Acting on the Reproductive, Cardiovascular, and Central Nervous Systems

Emmanuel Mouafo Tekwu[a], *Veronique Penlap Beng*[a] *and Victor Kuete*[b]

[a]Laboratory for Tuberculosis Research, Biotechnology Centre, University of Yaoundé I, Yaoundé, Cameroon, [b]Department of Biochemistry, University of Dschang, Dschang, Cameroon

22.1 Introduction

Through the ages, humans have relied on nature for their basic needs for the production of foodstuffs, shelter, clothing, means of transportation, fertilizers, flavors and fragrances, and, not least, medicines [1]. Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years and continue to provide humankind with new remedies [1]. People worldwide have long applied poultices and imbibed infusions of thousands of indigenous plants, dating back to prehistory [2]. The existence of traditional medicine depends on plant species diversity and related knowledge of their use as herbal medicines [3,4]. Traditional medicine occupies a central place among rural communities of developing countries for the provision of health care in the absence of an efficient primary health care system [4–7]. According to WHO, 80% of the world's population, primarily those of developing countries, rely on plant-derived medicines for their health care [8,9]. Although some of the therapeutic properties attributed to plants have proven to be erroneous, medicinal plant therapy is based on the empirical findings of hundreds or thousands of years [1]. Apart from their cultural significance, herbal medicines are generally more accessible and affordable [10]. Moreover, the widespread use of medicinal plants is partly due to the low toxicity attributed to these natural products [11]. As a consequence, the interest in nature as a source of potential chemotherapeutic agents continues. Furthermore, there is an increasing trend worldwide to integrate traditional medicine with primary health care [12]. Natural products and their derivatives represent more than 50% of all the drugs in clinical use in the

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world [1]. Higher plants contribute no less than 25% of the total pharmacopoeia [1]. Already an estimated 122 drugs from 94 plant species have been discovered through ethnobotanical leads [13]. Renewed interest in traditional pharmacopoeias has meant that researchers are concerned not only with determining the scientific rationale for a plant's usage but also with the discovery of novel compounds of pharmaceutical value. Instead of relying on trial and error, as in random screening procedures, traditional knowledge helps scientists to target plants that may be medicinally useful [14]. Various assays can be used to test for biological activity, first *in vitro* and later, for promising natural products, *in vivo* [12]. One of the most challenging pursuits in the realm of pharmaceutical and medical sciences is the search for newer and more potent drugs with few toxic effects and that are self-administrable, less expensive, and completely reversible. Many of these properties are observed in the drugs of plant origin [15]. During the latter part of this century, the practice of herbalism has become mainstream throughout the world. This is due in part to the recognition of the value of traditional medical systems and the identification of medicinal plants from indigenous pharmacopoeias [15].

Crude or fractionated extracts, and sometimes individual compounds, reported here were screened for their activity on the reproductive, cardiovascular, and central nervous systems. In testing for biological activity *in vitro*, a standard drug is always included in the test system to ensure that the assay is working effectively. The prescription and use of traditional medicine in many African countries is currently not regulated, with the result that there is always the danger of misadministration, especially of toxic plants [12].

22.2 African Traditional Medicine

African traditional medicine is the oldest and perhaps the most diverse of all medicine systems [1]. Africa is considered to be the cradle or humankind, with a rich biological and cultural diversity and marked regional differences in healing practices [1]. Unfortunately, the systems of medicines are poorly recorded and remain so to date. Yet the documentation of medicinal uses of African plants is becoming increasingly urgent because of the rapid loss of the natural habitats of some of these plants because of anthropogenic activity [1]. The African continent is reported to have one of the highest rates of deforestation in the world [1]. The paradox is that it is also a continent with a high rate of endemism [1].

African traditional medicine, in its varied forms, is holistic, involving both the body and the mind. The healer typically diagnoses and treats the psychological basis of an illness before prescribing medicines to treat the symptoms [1]. Famous African medicinal plants include *Acacia senegal* (gum arabic), *Agathosma betulina* (buchu), *Aloe ferox* (Cape aloe), *Aloe vera* (North African origin), *Artemisia afra* (African wormwood), *Aspalathus linearis* (rooibos tea), *Boswellia sacra* (frankincense), *Catha edulis* (khat), *Commiphora myrrha* (myrrh), *Harpagophytum procumbens* (devil's claw), *Hibiscus sabdariffa* (hibiscus, roselle), *Hypoxis hemerocallidea* (African potato), and *Prunus africana* (African cherry) [1].

Though several studies have been carried out on medicinal plant resources in Africa [1,4,16–21], a large number of plants and associated indigenous uses are still waiting for proper documentation.

22.3 Pharmacological Activities of Medicinal Plants

22.3.1 Reproductive System

Reproductive health care addresses the reproductive processes, functions, and systems at all stages of life [22]. It encompasses the sexual health of both men and women, as well as maternal and child health [23]. Ethnomedical literature contains thousands of references to the use of plants for a variety of reproduction-related purposes [24]. Plants have been used globally across varied cultures as a safe, natural source of medicines [25]. A large majority of herbal plants possess pharmacological principles, which has rendered them useful as curatives for numerous diseases, and several plants have been reported to enhance reproductive processes [25].

Male reproduction is a complex process that involves the testes, epididymis, accessory sex glands, and associated hormones. The testes perform two highly organized and intricate functions, called spermatogenesis and steroidogenesis, which are crucial for the perpetuation of human life [25]. Spermatogenesis, a highly dynamic and synchronized process, takes place within the seminiferous tubules of the testis with the support of somatic sertoli cells, leading to the formation of mature spermatozoa from undifferentiated stem cells [26]. The interstitial compartment, which consists of Leydig cells, is the site of steroidogenesis in the testes [25].

The female reproductive system is complex as compared to the male reproductive system. Females have to bear the fetus during the fetal period of development within their bodies. Modifications and adaptations to bear the fetus make female reproductive systems more complex. The main role of the female reproductive system is to produce eggs and allow the process of fertilization and development to take place within the body. The organs of the female reproductive system consist of internal (uterus and ovaries) and external parts (vulva, labia, and clitoris).

22.3.2 Medicinal Plants as the Source of Contraceptive Compounds

The population explosion raises many problems, including lack of food, water, energy and raw material supply, and decline in mortality [15]. Among the three ways of controlling population, i.e., abortion, sterilization, or contraception, currently, the contraceptive method of birth control is one of the most popular way [15]. The term contraceptive refers to those chemical substances that either inhibit sperm production and sperm motility in males or prevent the formation of ova and produce some changes in the endometrium, rendering it nonreceptive to a fertilized ovum in females [27–29]. Different types of contraceptive devices are being used in the world: mechanical devices [diaphragm, cervical cap, intrauterine devices (IUD)], physiological devices

(oral pills), and surgical procedures (tubectomy/vasectomy) [15]. In females these devices act upon any of the reproductive organs or physiological aspects: Anti-ovulatory means inhibition of the union of ova and sperm, and abortifacients exert anti-implantation activity and have effects on the uterus [15]. Male contraceptives are mainly directed toward development of antispermatogenic agents to suppress sperm production and to prevent sperm maturation, sperm transport through the vas deferens, and sperm deposition [15,30]. Conventional drugs used as contraceptives are often inadequate [31]. The adverse effects caused by oral and injectable contraceptives are increased blood transaminase, cholesterol levels, indigestion, weight gain, headache, depression, fatigue, hypermenorrhea, and intermenorrheal bleeding [32–34]. They also disturb the metabolism of lipids, proteins, carbohydrates, enzymes, and vitamins [35–37].

In view of above discussion, scientists have started to tackle this serious problem by developing effective contraceptives from natural sources [15]. Various reviews have been published on medicinal plants and their active principles for fertility regulation [38–50]. Several studies affirm the indisputable role of plant products in impairing testicular steroidogenesis [51–54]. In males, luteinizing hormone (LH, also known as lutropin and sometimes lutrophin) plays a role in the reproductive function by modulating testicular Leydig cell differentiation and steroidogenesis [25]. Testosterone secreted by Leydig cells, in turn, promotes male sexual differentiation, pubertal androgenization, and fertility [25]. In the testes, functional LH receptors are expressed in Leydig cells during fetal development, transiently in early postnatal life, and from puberty to adult life [55]. The hormonal regulation of spermatogenesis is well organized, with a feedback mechanism involving the hypothalamus, pituitary gland, and testes [56]. The neurons of the hypothalamus synthesize and secrete gonadotropin-releasing hormone, which induces the production and release of LH and follicle-stimulating hormone (FSH) from the pituitary gland [25]. LH causes the synthesis of testosterone in the Leydig cells of the testes, which exerts a negative feedback on hormone release from the hypothalamus and pituitary [57]. FSH acts on sertoli cells, resulting in the production of androgen-binding protein, which helps in the passage of testosterone through sertoli–sertoli junctional complexes [25]. Any factor that could perturb the LH-stimulated Leydig cell steroidogenesis could have an enormous impact on endocrine regulation of spermatogenesis and could lead to infertility [25]. Numerous plant products are known to target Leydig cells and hinder their functions [25].

22.3.3 Use of Medicinal Plants for Fertility Regulation

Infertility can be defined as a couple's inability to become pregnant after one year of regular and unprotected intercourse [58]. For most couples, the inability to have a child is a tragedy, and most of them use either traditional medicine and modern therapies, or both, as treatment [58].

A large number of plants or their extracts have been used as antifertility agents in traditional medicine in indigenous systems of medicine in different countries throughout the world [59]. Throughout history, human beings have tried to control

their fertility with various levels of societal support, and the information has been passed from mother to daughter and generation to generation [59]. Many herbal remedies are traditionally used as contraceptives, abortifacients (to prevent implantation), emmenagogue (to stimulate uterine flow), or oxytocic (to stimulate uterine contractions, particularly to promote labor) agents [60]. Several countries have used and continue to use traditional plants for fertility regulation, e.g., South Africa [61], Brazil [62,63], Cameroon [64], California [65], Haiti [66], Korea [50], Russia [67], and India [68], as evident from the available literature.

In this section, we review the current status of African medicinal plants in the treatment of infertility (Tables 22.1 and 22.2).

The leaves and roots of *A. precatorius* Linn. (Fabaceae) are sweetish and traditionally used to cure fever, stomatitis, asthma, and bronchititis [69,70]. Various African tribes use *A. precatorius* powdered seeds as oral contraceptives [71]. *A. precatorius* exhibits various pharmacological activities, including antifertility [73], anti-implantation [74], antimicrobial [75], antitumor [76], immunopotentiating [77], and sperm antimotility. Zia-ul-Haque et al. [72] reported the postcoital (days 2−5) antifertility (100% sterility) effect of abridine, a constituent isolated from *A. precatorius*, when administered p.o. at a dose of 1 mg/mL in female rats. Thus, *A. precatorius* possesses 100% antifertility activity in female rats.

A. indica is an annual erect herb found throughout various parts of the world, including tropical Africa. The plant has wide uses in the traditional medicines of various countries as a diuretic, purgative, and anthelmintic. It is also used for bronchitis, asthma, pneumonia, rheumatism, scabies, and other cutaneous diseases [78,79]. *A. indica* is traditionally used for emmenagogue and contraceptive purposes [79,80]. The postcoital antifertility [81], antivenom [82], wound healing [83], anti-inflammatory [84], and antibacterial activities [85] of *A. indica* have been reported. At a dose of 600 mg/kg body weight p.o. (5−6 days postcotium), the petroleum ether and ethanol extracts of the whole plant showed significant anti-implantation activity. It was suspected that the loss of implantation caused by *A. indica* extracts may be due to antizygotic, blastocytotoxic, or anti-implantation activity [59]. The petroleum ether and ethanol extracts also exhibited estrogenic activity, as shown by the significant increase in uterine weight, diameter of the uterus, thickness of the endometrium, height of the endometrial epithelium, and vaginal epithelial cornification in immature rats [59].

A. comosus has long been one of the most popular of tropical and subtropical fruits. It is grown extensively in many parts in the world, including Cameroon, Kenya, and South Africa. *A. comosus* is traditionally used for treatment as an antidyspepsial, antidiarrheal [87], and antidiabetic agents [88]. The juices of the unripe fruits and leaves of *A. comosus* possess abortifacient properties in Indian medicine [89]. The antifertility effect of the rhizome [91] and green fruits [92,93] have been reported. β-Sitosterol, isolated from *A. comosus* leaves, showed a significant abortifacient effect after day 1 in mice when administered orally before and after implantation at a dose of 30 mg/kg body weight [90]. Ergosterol peroxide showed the maximum abortifacient effect at both stages of pregnancy. The 250 and 500 mg/kg body weight doses increased ($p < 0.05$) the serum concentrations of progesterone and estrogen in

Table 22.1 Traditional Use and Potentially Active Compounds from Plants with Antifertility Potential

Plant and Family	Traditional Use	Countries of the Studies	Potentially Active Compounds	Documented Activities
Abrus precatorius Linn. (Fabaceae)	Leaves and roots are sweetish and used to cure fever, stomatitis, asthma, and bronchititis [69,70]; oral contraceptive [71]	Nigeria, India	Abridine [72]	Antifertility [73], anti-implantation [74], antimicrobial [75], antitumor [76], immunopotentiating [77], and sperm antimotility; 100% antifertility [72]
Acalypha indica L. (Euphorbiaceae)	Diuretic, purgative, and anthelmintic properties; bronchitis, asthma, pneumonia, rheumatism scabies, and other cutaneous diseases [78,79]; emmenagogue and contraceptive [79,80]	India, Bangladesh, Sri Lanka, Philippines, and tropical Africa	Sterols and flavonoids [59]	Postcoital antifertility [81], antivenom [82], wound healing [83], anti-inflammatory [84], and antibacterial activities [85]
Ananas comosus Linn. (Bromeliaceae)	Dysuria [86], antidyspepsial or antidiarrheal [87]; antidiabetic agent [88]; abortifacient properties of juices of the unripe fruits and leaves [89]	Hawaii, Philippines, Caribbean area, Malaysia, Taiwan, Thailand, Australia, Mexico, Kenya, South Africa, Hainan province of China	β-Sitosterol; ergosterol peroxide [90]	Antifertility effect of the rhizome [91] and green fruits [92,93]
Aristolochia bracteolata Lam. (Aristolochiaceae)	Gastric stimulant, treatment of cancer, lung inflammation, dysentery, and snakebites [94]; antifertility and abortifacient effects [95]	Sudan, India	Aristolochic acid A (isolated from the root in Sudan), aristolic acid [96]	Antifertility (anti-implantation) [97], anthelmintic and trypanocidal effects [98], antiallergic [99], antibacterial, and antifungal [100]

Bambusa vulgaris Linn. (Poaceae)	Emmenagogue, abortifacient, appetizer, respiratory diseases, and gonorrhea [101]	Nigeria	Alkaloids, tannins, phenolics, glycosides, saponins, flavonoids, and anthraquinones [102]	Abortifacient potential [102]
Bulbine natalensis Baker (Asphodelaceae)	Wounds, burns, rashes, itches, ringworm, and cracked lips [103]; vomiting, diarrhea, convulsion, venereal diseases, diabetes, and rheumatism [104]; aphrodisiac and sexual invigorator [103]	South Africa	Alkaloids, tannins, saponins, cardiac glycosides, and anthraquinones [105]	Increased libido, levels of reproductive hormones [103], significantly increased penile erection indices, frequencies of mount, intromission, and ejaculation, as well as postejaculatory interval [105]
Citrus medica Linn. (Rutaceae)	Fertility regulation [39]	Africa, India	Citronellal, citronellol, limonene, citronellyl acetate, isopulegol, and linalool [106]	Anthelmintic [107], antidiabetic [108], fungitoxic [109], estrogenic [110], and anti-implantation [111]
Dalbergia saxatilis Linn. (Fabaceae)	Accelerate birth, expel the placenta in human subjects [112]	Nigeria	Triterpenoid glycoside [113]	Anticonceptive [113] and antispermatogenic [114]
Gloriosa superba (Liliaceae)	Preparation for impotence, also used as abortifacient [115,116]; thermogenic, abortifacient, antipyretic, rheumatic fever [79,117]; treatment of inflammations, leprosy, piles, ulcers [118]; intestinal worm infestations, thirst, bruises, skin problems, snakebites [119]	Tropical Africa, Zambia	Colchicine [120,121], superbine, gloriosine, gloriosol, phytosterols, and stigmasterol [121]	Analgesic, anti-inflammatory [117], anthelmintic [122], antifungal [123], and antispermatogenic [124] activities; abortifacient, anti-implantation, and uterotonic activities [125]

(*Continued*)

Table 22.1 (Continued)

Plant and Family	Traditional Use	Countries of the Studies	Potentially Active Compounds	Documented Activities
Heliotropium indicum (Boraginaceae)	Skin diseases and expectorant [126]; diarrhea, malaise, or vomiting [127]; treat ulcers and fever [128]; treatment of ophthalmic disorders, erysipelas, pharyngodynia, inflammation; astringent, expectorant, and febrifuge [129]	Nigeria, India, Belgium	Pyrrolizidine alkaloids [130,131]	Antiseptic, febrifuge, secretagogue, menstruation activator [132]; anti-inflammatory [133], antitumor [134], wound healing [83] properties; abortifacient, moderate anti-implantation [135,136]
Hibiscus rosa-sinensis Linn. (Malvaceae)	Abortifacient [137,138] and aphrodisiac [139]	Cameroon, Nigeria, India	Cyanidin, quercetin, entriacontane, calcium oxalate, thiamine, riboflavin, niacin, and ascorbic acid [140]	Hepatoprotective [141], anti-implantation, antispermatogenic [142,143], and uterotropic [144]
Pausinystalia johimbe (K. Schum) Pierre ex Beille (Rubiaceae)	Aphrodisiac [145,146]; improve reproductive success, performance enhancer for athletes [147,148]; treat cardiac disease and male impotence [149]	Gulf of Guinea (Nigeria, Congo, Cameroon, etc.)	Alkaloid yohimbine [150]	Safe treatment for psychogenic impotence (restoring satisfactory sexual functioning) [151]

Table 22.2 African Plants with Traditional Use in Fertility Regulation

Plant and Family	Parts Used	Countries	Traditional Uses
Acacia farnesiana (L.) Willd. (Fabaceae)	Fruits, flowers	Egypt	Contraceptive [152]
Adenia cissampeloides Harms (Passifloraceae)	Roots, stems	Cameroon	Abortifacient [64]
Ageratum conyzoides Linn. (Asteraceae)	Flowers	Cameroon	Abortifacient [138]
Albizia ferruginea (Guill. et Perr.) Benth. (Mimosaceae)	Leaves	Cameroon	Abortifacient [64]
Albizia lebbek Linn. Benth (Fabaceae)	Stem bark	Cameroon	Abortifacient [138]
Basella alba Linn. (Basellaceae)	Roots, Leaves	Cameroon	Oxytocic, abortifacient [64,138]
Bidens pilosa L. (Asteraceae)	Leaves	Cameroon	Oxytocic [64]
Capsella bursa-pastoris Moench. (Brassicaceae)	Whole plant	Ethiopia	Abortifacient, emmenagogue [153]
Cassia alata L. Roxb. (Fabaceae)	Leaves	Cameroon	Abortifacient [138]
Ceiba pentandra (L.) Gaertn. (Bombacaceae)	Leaves, stem bark	Cameroon	Abortifacient [64]
Citrus aurantifolia (Christm.) Swingle (Rutaceae)	Fruits (juice)	Cameroon	Abortifacient [64]
Cordia quarensis Gürke (Boraginaceae)	Roots	Africa	Contraceptive [43,154]
Crassocephalum montuossum (Asteraceae)	Leaves	Uganda	Abortifacient [4]
Croton lobatus HBK. Hutch. (Euphorbiaceae)	Whole plant	Ivory Coast	Sterilizer [155]
Croton penduliflorus Hutch. (Euphorbiaceae)	Fruits	Nigeria	Abortifacient [156]
Croton tiglium Linn. (Euphorbiaceae)	Roots, seeds	Africa	Abortifacient [130]
Cuminum cyminum Linn. (Apiaceae)	Fruits	Tunisia	Abortifacient [157]
Cyperus esculentus (Cyperaceae)	Peduncles	Cameroon	Abortifacient [138]
Desmodium ramosissimum G. Don (Fabaceae)	Leaves	Cameroon	Abortifacient [64]
Diospyros mespiliformis Hochst. (Ebenaceae)	Roots	Cameroon	Abortifacient [138]

(*Continued*)

Table 22.2 (Continued)

Plant and Family	Parts Used	Countries	Traditional Uses
Drymaria cordata Will. ex Roem. et Schult. (Caryophyllaceae)	Leaves	Cameroon	Abortifacient [64]
Ehretia cymosa Thonn. (Boraginaceae)	Leaves, bark	Nigeria	Contraceptive [158]
Erythrophleum guineensis G. Don (Caesalpiniaceae)	Stem bark	Cameroon	Abortifacient [64]
Fleura aestuans Linn. (Urticaceae)	Roots	Cameroon	Abortifacient [138]
Flueggea virosa (Willd.) Voigt (Phyllanthaceae)	Roots	Uganda	Abortifacient [4]
Hibiscus rosa-sinensis Linn. (Malvaceae)	Stem bark	Cameroon	Abortifacient [138]
Maesopsis eminii Engl. (Rhamnaceae)	Stem bark	Cameroon	Abortifacient [64]
Manihot esculenta Crantz (Euphorbiaceae)	Leaves	Cameroon	Abortifacient [64]
Mareya micrantha (Benth.) Müll.Arg. (Euphorbiaceae)	Bark, leaves	Nigeria	Abortifacient [159]
Mariscus cylindristachyus Steud. (Cyperaceae)	Peduncles	Cameroon	Abortifacient [138]
Microglossa pyrifolia Lam. Kuntze (Asteraceae)	Leaves, roots	Nigeria	Abortifacient [158]
Momordica charantia Linn. (Cucurbitaceae)	Seeds, leaves	Cameroon	Abortifacient [64,138]
Momordica foetida Schum. (Cucurbitaceae)	Leaves	Cameroon	Abortifacient [59]
Musa sapientum L. Syn. *M. paradisiaca* Auct. (Musaceae)	Roots, young plant	Ethiopia, Cameroon	Oxytocic, abortifacient [64,160]
Musanga cecropioides R. Br. (Cecropiaceae)	Leaves	Cameroon	Oxytocic [64]
Nicotiana tabacum L. (Solanaceae)	Leaves	Cameroon	Abortifacient [64]
Ocimum gratissimum L. (Lamiaceae)	Leaves	Cameroon	Oxytocic [64]
Oxytenanthera abyssinica Munero (Poaceae)	Leaves	Cameroon	Abortifacient [138]
Pentaclethra macrophylla Benth. (Mimosaceae)	Fruits, stem bark	Cameroon	Abortifacient [64]
Persea americana Mill. (Lauraceae)	Leaves	Cameroon	Abortifacient [64]

(*Continued*)

Table 22.2 (Continued)

Plant and Family	Parts Used	Countries	Traditional Uses
Physalis angulata Linn. (Solanaceae)	Seeds	Cameroon	Abortifacient [138]
Piliostigma thonningii (Schum.) Milne-Redh. (Fabaceae)	Roots	East Africa	Contraceptive [42]
Piptadeniastrum africanum (Hook. f.) Brenan (Mimosaceae)	Stem bark	Cameroon	Oxytocic [64]
Pleioceras barteri Baill. (Apocynaceae)	Leaves, roots	Nigeria	Abortifacient, emmenagogue [156]
Pouzolzia hypoleuca Wedd. (Urticaceae)	Roots	Zimbabwe	Contraceptive [161]
Pterocarpus angolensis DC (Fabaceae)	Seeds	Tanzania	Abortifacient [162]
Pterocarpus erinaceous Poir. (Fabaceae)	Leaves, stems	Nigeria	Abortifacient [163]
Rauwolfia vomitoria afz. (Apocynaceae)	Roots	Cameroon	Abortifacient [138]
Saccharum officinarum L. (Poaceae)	Stems	Cameroon	Abortifacient [64,138]
Sida acuta Burm.f. (Malvaceae)	Leaves	Cameroon	Abortifacient [138]
Solanum sanctum L. (Solanaceae)	Fruits	Nigeria	Contraceptive [164]
Vernonia amygdalina Delile (Asteraceae)	Leaves	Cameroon	Abortifacient [138]
Vigna phaseoloides Baker (Fabaceae)	Roots	East Africa	Contraceptive [42]
Waltheria americana Linn. (Sterculaceae)	–	Africa	Abortifacient [145,165]
Wedelia trilobata (L.) Hitchc. (Asteraceae)	–	Africa	Abortifacient [166]
Withania somnifera Dunal (Solanaceae)	Roots	Cameroon	Abortifacient [138]
Xylopia aethiopica (Dunal) A. Rich (Annonaceae)	Fruits	Africa	Abortifacient [164]

pregnant rats. Finally, the petroleum ether extract of green fruits and rhizomes of *A. comosus* exhibit antifertility activity [90].

A. bracteolata Lam. (Aristolochiaceae) is a climbing perennial plant known as "worm killer" due to its anthelmintic activity and trypanocidal effects [98]. It possesses potent antiallergic [99], antibacterial, and antifungal properties [100]. *A. bracteolata* is used in traditional medicine as a gastric stimulant and in the

treatment of cancer, lung inflammation, dysentery, and snakebites [94]. This plant is used for antifertility and abortifacient effects [95]. The ethyl acetate-soluble fraction of the ethanolic extract of *A. bracteolate*, at doses of 20 and 40 mg/kg body weight by the oral route (5−6 days postcotium), exhibited 28.86% and 58.65% anti-implantation effectiveness, respectively. These treatments also caused 18.61% ($p < 0.01$) and 37.22% ($p < 0.001$) abortifacient activity, respectively. Total antifertility activity in the precoital studies was found to be 47.47% and 95.87% for the two doses tested, respectively [97]. *A. bracteolata* exhibits significant antifertility activity in female rats; the main active constituent responsible for antifertility activity is identified as aristolic acid [96].

B. vulgaris Linn. (Poaceae) is found especially in the wet tropics. The presence of alkaloids (4.10%), tannins (0.93%), phenolics (2.27%), glycosides (0.63%), saponins (1.14%), flavonoids (0.05%), and anthraquinones (0.06%) have been reported in the leaves of *B. vulgaris* [102]. *B. vulgaris* leaves have long been used as an astringent, ophthalmic solution, and febrifuge. In Nigerian traditional medicine, it is used as an emmenagogue, abortifacient, appetizer, and for managing respiratory diseases, as well as for gonorrhea [101]. The extract, at 250 and 500 mg/kg body weight doses, reduced the survival rate of the fetus to 29% and 0%, whereas the same doses produced abortion at rates of 60% and 100%, respectively. The extract also decreased the concentrations of serum progesterone and FSH and LH. *B. vulgaris* possesses abortifacient potential [102].

B. natalensis Baker (Asphodelaceae) is widely distributed in the eastern and northern parts of South Africa. The leaf sap is widely used in the management of wounds, burns, rashes, itches, ringworm, and cracked lips [103]. The infusion of the roots is taken orally to quell vomiting, diarrhea, convulsions, venereal diseases, diabetes, and rheumatism [104]. The aqueous extract of the stem contains alkaloids (0.200%), tannins (0.481%), saponins (1.970%), cardiac glycosides (0.887%), and anthraquinones (0.152%) [105]. It has been reported that the administration of aqueous extract of *B. natalensis* stem to male Wistar rats significantly increased penile erection indices, frequencies of mount, intromission, and ejaculation, as well as postejaculatory interval [105]. This justified the acclaimed folkloric use of the stem as an aphrodisiac and sexual invigorator. Yakubu and Afolayan [103] reported that the aqueous extract of *B. natalensis* stem, at doses of 25 and 50 mg/kg body weight, enhanced the success rate of mating and fertility due to increased libido as well as levels of reproductive hormones in male rats. The absence of alterations in the reproductive parameters of female rats at doses of 25 and 50 mg/kg body weight of *B. natalensis* stem extract suggest that the extract is "safe" for use at these doses by females during the organogenic period of pregnancy, whereas the extract dose of 100 mg/kg body weight portends a negative effect on some reproductive functions of male and female rats [103].

C. medica Linn. (Rutaceae), commonly known as citron, is found in almost all parts of Africa and has been used in traditional medicine for centuries. The major constituents in leaf oil are citronellal, citronellol, limonene, citronellyl acetate, isopulegol, and linalool [106]. Fruit decoction of *C. medica* is used in Indian traditional medicine for fertility regulation [39]. *C. medica* is reported to have anthelmintic

[107], antidiabetic [108], and fungitoxic activity [109]. The petroleum ether extract of *C. medica* seeds exhibited estrogenic activity [110], while alcoholic extract (2.5 mg/kg) and chloroform extract (1.0 g/kg) in female Wistar rats (1−7 days post-coital) exhibited significant anti-implantation activity, respectively. The ethanol and chloroform extracts of *C. medica* peel showed 71.96% and 77.19% anti-implantation activity, respectively [111].

D. saxatilis Linn. (Fabaceae) is a local African shrub used as a remedy for diverse forms of ailment in southern Nigeria [112], where aqueous root extract is used to accelerate birth and to expel the placenta in human subjects. The antifertility activity of a triterpenoid glycoside, isolated from the root, was investigated in female Wistar rats of breeding age. When administered by gastric intubation at a dose rate of 200 mg/kg body weight at the premating period, conception was inhibited in 71.4% of the treated animals [113]. Vasudeva and Vats [114] have reported the antispermatogenic potential of *D. saxatilis* stem bark.

G. superba (Liliaceae) is a semiwoody herbaceous climber native to tropical Africa [167]. *G. superba* contains alkaloids in all parts, mainly colchicine, an amino alkaloid derived from the amino acids phenylalanine and tyrosine [120]. This composition could be responsible for its medicinal effect. The active principles were found to be superbine, colchicine, gloriosine, gloriosol, phytosterol, and stigmasterol [121]. In Zambia, the tuber of *G. superba* is part of a preparation for impotence and also used as abortifacient [115,116]. *G. superba* is an important corm-bearing genus that provides commercial colchicines and colchicoside [168]. Corms are thermogenic, abortifacient, and antipyretic, and the powder of the root tuber is given for rheumatic fever [79,117]. It is also used for the treatment of inflammation, leprosy, piles, ulcers [118], intestinal worm infestations, thirst, bruises, skin problems, and snake-bites [119]. *G. superba* also possess analgesic, anti-inflammatory [117], anthelmintic [122], antifungal [123], and antispermatogenic [124] activity. Aqueous extract of *G. superba* at 50, 100, and 200 mg/kg body weight by oral route shows significant abortifacient, anti-implantation, and uterotonic activities in female Wistar rats [125]. The early abortifacient activity of the plant is owing to its oxytocic potential, which may be due to the presence of alkaloids such as colchicines.

H. indicum (Boraginaceae) is distributed in the tropical and temperate regions of the world. The plant is reported to be highly valued in folkloric medicine and is believed to be useful in skin diseases and as a powerful expectorant [126] for diarrhea, malaise, or vomiting in infants in Belgium [127], and to treat ulcers and fever in Nigeria [128]. Its leaves are used in the treatment of ophthalmic disorders, erysipelas, pharyngodynia, inflammation, and tumor; the roots are used as an astringent, expectorant, and febrifuge [129]. Phytochemical screening of *H. indicum* has reported various compounds including pyrrolizidine alkaloids, tannins, and saponins [130,131]. Its antiseptic, febrifuge, secretagogue stimulation, menstruation activation [132], anti-inflammatory [133], antitumor [134], and wound healing [83] properties are conferred by its alkaloidal components. Andhiwal et al. [135] have reported 40% anti-implantation effectiveness for *H. indicum*. Extract from *H. indicum* leaves, administered orally at 200 and 400 mg/kg body weight in albino rats, has shown better abortifacient (30−50%) and moderate anti-implantation activity (30−60%).

The effect on percentage of preimplantation loss in pregnant rats was 30−60% in extract at a dose of 200 and 400 mg/kg body weight [136a]. *H. indicum* possesses better abortifacient activity and moderate anti-implantation effect.

H. rosa-sinensis Linn. (Malvaceae) is widely distributed in tropical and subtropical regions of the world and possesses various medicinal properties. *H. rosa-sinensis* has a protective effect against the tumor promotion stage of cancer development [136b]. Some of the chemical constituents isolated from this plant include cyanidin, quercetin, entriacontane, calcium oxalate, thiamine, riboflavin, niacin, and ascorbic acid [140]. The anthocyanidins isolated from the plant were found to be hepatoprotective [141]. The plant has been used traditionally as an abortifacient in India and Cameroon [137,138] and as an aphrodisiac in Nigeria [139]. The flowers have been reported to possess anti-implantation and antispermatogenic properties [142,143]. *H. rosa-sinensis* ethanolic root extract, at 400 mg/kg body weight orally, from days 1 to 7 of gestation, prevented pregnancy in colony-bred female albino rats and showed strong anti-implantation (inhibition 100%) and uterotropic activity [144]. In another study on mice, oral administration of the benzene extract of *H. rosa-sinensis* flowers, at a dose level of 1 g/kg body weight/day from days 5 to 8 of gestation, led to termination of pregnancy in about 92% of the animals, where the effect was associated with a significant fall in the peripheral level of progesterone and an increase in uterine acid phosphatase activity, as measured on day 10. Olagbende-Dada et al. [139] reported the anabolic effect of the leaf extract of this plant in immature albino male rats. Finally, *H. rosa-sinensis* possesses anti-implantation activity, which might be due, at least partly, to the estrogenic property of the extract. Some African medicinal plants, along with their chemical substances and their pharmacological activities and effects on the reproductive system, are being summarized in Table 22.1.

22.3.4 Cardiovascular System

For a very long time, cardiovascular diseases (CVD) were considered negligible in African countries, especially compared with other public health issues [169]. Recent data have demonstrated an epidemiological transition from a predominant burden of infectious diseases to one with chronic diseases, particularly CVD related to atherosclerosis [169]. The rate of CVD mortality is increasing in Africa [170]. CVD is already the leading cause of death not only in developed countries but, as of the mid-1990s, in developing countries as well [171]. This situation might result from a complex combination of population, lifestyle, and genetic characteristics [169]. There is growing evidence of increasing rates of CVD mortality in African countries [170]. Cardiovascular pathologies such as arterial hypertension, atherosclerosis, and thrombosis lead to many complications, including blood coagulation and platelet aggregation disorders. Blood platelets are directly involved, by their aggregation, in many physiological events such as homeostasis. Indeed, it has been reported that patients with hypertension or coronary heart disease tend to have increased platelet reactivity [172]. Several studies in hypertensive patients have showed that platelets were more sensitive to thrombin [173] and exhibited an elevation in their intracellular free calcium [174,175]. This latter may potentiate

the platelet activity and increase the risk of thrombosis. Therefore, many investigations have been carried out in order to prevent this abnormal hyperactivity of platelets by using different therapies, including the use of medicinal plants.

Oxidative modification of LDL is believed to play a crucial role in atherogenesis. Atherosclerosis is an inflammatory disorder that may be initiated by several factors including LDLs. LDLs usually enter the artery wall from plasma and may also return to the plasma. However, if the plasma level of LDL exceeds a threshold, they enter the artery faster than they can be removed, and thus they can accumulate [176]. As they accumulate, they become oxidized. Oxidized LDLs are a potent inducer of developing atherosclerotic plaque. High-density lipoproteins (HDLs) contain an enzyme, paraoxonase, which is believed to confer protection against oxidation of LDL cholesterol in the artery wall and thus protect against the disease [176]. It is supposed that carotenoids help prevent LDL oxidation and reduce oxidative stress and plaque formation [177]. Epidemiological studies also show that a high intake of vitamin E could reduce the risk of coronary heart disease. In addition, the protective effects of phenolic compounds (flavonoids) against cardiovascular diseases have been confirmed [178–180]. Thus, the consumption of certain medicinal plants containing antioxidants such as phenols can reduce cardiovascular diseases incidence [181]. Several studies have mentioned the role of some medicinal plants as significantly antithrombotic both *in vitro* and *in vivo* [182]. Constituents such as flavonoids and carvone with strong antioxidant activity might be involved in hypolipidemia. The terpenoid and flavonoid metabolites can act in a complementary manner to protect against myocardial ischemia–reperfusion injury [176].

There is evidence concerning the participation of reactive oxygen species (ROS) in the etiology and physiopathology of human diseases, such as neurodegenerative disorders, inflammation, viral infections, and autoimmune pathologies, and digestive system disorders such as gastrointestinal inflammation and gastric ulcer [183]. In living systems, free radicals are generated as part of the body's normal metabolic process, and free radical chain reactions are usually produced in the mitochondrial respiratory chain, liver mixed function oxidases, by bacterial leukocytes, through xanthine oxidase activity, by atmospheric pollutants, and from transitional metal catalysts, drugs, and xenobiotics [184]. In addition, chemical mobilization of fat stores under various conditions, such as lactation, exercise, fever, infection, and even fasting, can result in increased radical activity and damage, particularly to the immune and nervous systems, while the stress hormones adrenalin and noradrenalin, secreted by the adrenal glands under conditions of continuing and excessive emotional stress, are metabolized into simpler, albeit free radical molecules [184]. Free radicals are atoms or molecules with unpaired electrons in their outer orbits, making them highly reactive with macromolecular structures, leading to cellular injury and homeostatic disruption [185]. Free radicals are produced as a by-product of normal metabolism and endogenous mechanisms exist to reduce their formation or enhance their inactivation [186,187]. Disruption of the prooxidant and antioxidant balance in favor of the former may be a potential fundamental mechanism of human disease [185]. Free radicals or oxidative injury now appears to be the fundamental mechanism underlying a number of human neurologic and other disorders [185]. For instance, in diabetes, increased

oxidative stress in coexistence with reduction in antioxidant status has been postulated: Oxygen-free radicals can initiate peroxidation of lipids, which in turn stimulates glycation of protein, inactivation of enzymes, and alteration in the structure and function of collagen basement and other membranes, and thus play a role in the long-term complication of diabetes [188–190]. The antioxidants vitamins C and E have been shown to reduce oxidative stress in experimental diabetes [191]. Supplementation of antioxidant vitamin C has also been shown to lower glycosylated hemoglobin in diabetic patients [192]. Many plant extracts and plant products have been shown to exhibit significant antioxidant activity [193–195]. In the case of carcinogenesis, ROS are responsible for initiating the multistage carcinogenesis process, starting with DNA damage and accumulation of genetic events in one or a few cell lines, which leads to progressively dysplastic cellular appearance, deregulated cell growth, and finally carcinoma [196]. Therapy using free radical scavengers (antioxidants) has the potential to prevent, delay, or ameliorate many neurologic disorders [185], since the antioxidants are endogenous or exogenous compounds that either reduce the formation of free radicals or react with and neutralize them, thus potentially protecting the cell from oxidative injury [185]. Because the biochemistry of free radical injury is complex, many substances may act as potential antioxidants and thus provide protection against disease or limit its consequences [185]. Over the past three decades, evidence from laboratory studies has demonstrated that some edible plants as a whole, or their identified ingredients with antioxidant properties have substantial protective effects on human carcinogenesis [197–203]. Similar evidence also exists to demonstrate the chemopreventive capacities of ethnobotanicals and components of vegetable diets with free radical scavenging potential on ulcers [204], diabetes [190], memory and cognitive function [205], Alzheimer's disease [206,207], age-related neurological dysfunction [185,208], cardiovascular and renal disorders [209,210], and several other human ailments. Moreover, some medicinal plants have been shown to have both chemopreventive and/or therapeutic effects on breast cancer [211] and skin cancer [212]. Spices and herbs are recognized as sources of natural antioxidants that can protect from oxidative stress and thus play an important role in the chemoprevention of diseases that have their etiology and pathophysiology in ROS [184].

Africa has the advantage to be located within the tropical and subtropical climate zones. It is known that plants accumulate antioxidant chemicals as secondary metabolites as a natural means of surviving in a hostile environment [213]. Because of its tropical conditions, Africa gets an unfair share of strong ultraviolet rays from tropical sunlight and myriad pathogenic microbes, including species of bacteria, fungi, and viruses, suggesting that African plants could accumulate chemopreventive substances more than plants from the northern hemisphere [184]. Abegaz et al. [214] have indeed observed that of all species of *Dorstenia* (Moraceae) analyzed, only the African species, *Dorstenia mannii* Hook. f., a perennial herb growing in the tropical rainforest of Central Africa, contained the antioxidants mono-, di-, and triprenylated and also mono- and digeranylated flavonoids. Some traditional uses and potentially active compounds from African plants with potential activity on the cardiovascular system are summarized in Table 22.3.

Table 22.3 Traditional Use and Potentially Active Compounds from Plants with Potential Activity on Cardiovascular System

Plant and Family	Traditional Uses	Countries of the Studies	Potentially Active Compounds	Documented Activities
Pausinystalia johimbe (K. Schum) Pierre ex Beille	Cardiac disease and male impotence [149]; aphrodisiac [145,146]; performance enhancer for athletes [147,148]	Gulf of Guinea (southern Nigeria to Congolese Mayombe)	Alkaloid [215]	Cardiac disease and male impotence [149]
Arbutus unedo (Ericaceae)	Arterial hypertension [216]; astringent, diuretic, and urinary antiseptic [217]	Morocco	Flavonoids and tannins [218]	Endothelium-dependent vasodilatation on isolated rat aorta [219]; inhibitory activity on platelet aggregation [220]; IC_{50} about 6 mg/mL
Urtica dioïca (Urticaceae)	Arterial hypertension [216]; stimulation of human lymphocyte proliferation [221]; anti-inflammatory action [222]; antihyperglycemic activity [223]; hypotensive and diuretic effect [224]; treatment of prostatic hyperplasia [225]	Oriental Morocco	Flavonoids and tannins [226,227]	Hypotensive effect of aerial parts on anesthetized rats [224]; aerial parts on vasoconstriction [228]; roots on vasodilatation [229]; inhibitory activity on platelet aggregation [220]; IC_{50}: 15.5 ± 0.3 mg/mL for thrombin and 12.8 ± 0.7 mg/mL for ADP [220]
Petroselinum crispum (Apiaceae)	Arterial hypertension [216], hypnotic [226], diuretic [230], antidiabetic [231]	Oriental Morocco	Flavonoids and tannins [232]	Inhibitory activity on platelet aggregation [220]; $IC_{50} \approx 6$ mg/mL
Equisetum arvense (Equisetaceae)	Vasorelaxant [233]; highly recommended as hemostatic [220]	–	Flavonoids and tannins [234]	Inhibitory activity on platelet aggregation [220]; $IC_{50} \approx 6$ mg/mL

(*Continued*)

Table 22.3 (Continued)

Plant and Family	Traditional Uses	Countries of the Studies	Potentially Active Compounds	Documented Activities
Allium cepa (onion)	–	–	–	Inhibitory activity on platelet aggregation [235]; $IC_{50} \approx 6$ mg/mL
Allium sativum (garlic)	–	–	–	Inhibitory activity on platelet aggregation [236]; $IC_{50} \approx 6$ mg/mL
Lycopersicum esculentum (tomato)	–	–	–	Inhibitory activity on platelet aggregation [237]; $IC_{50} \approx 6$ mg/mL
Citrus ladaniferus	–	–	Flavonoids and tannins [227,232]	Inhibitory activity on platelet aggregation [220]
Siphonochilus aethiopicus (Schweinf.) B.L. Burtt (Zingiberaceae)	Pain and inflammation [238–240]	South Africa	Furanoterpenoid [241]	Inhibitory action against prostaglandin synthesis [239,240,242]
Ocotea bullata (Burch.) Baill. (Lauraceae)	Pain and inflammation [238–240]; stem bark is used to cure headaches, urinary disorders, and stomach ailments	South Africa	Sibyllenone extracts [242]	Good prostaglandin synthesis inhibitory activity [238]
Eucomis autumnalis (Mill.) Chitt. (Hyacinthaceae)	Pain and inflammation [238–240]	South Africa	–	Anti-inflammatory activity: high activity (70–100%) for ethanolic bulb extracts; moderate activity (40–70%) for aqueous extracts [12]

22.3.5 Central Nervous System

The central nervous system (CNS) consists of the brain (encephalon) and the spinal cord (medulla spinalis). The brain is located in the cranial cavity and is protected by the skull. The spinal cord lies in the vertebral canal and is protected by the vertebrae. The CNS is distinguished from the peripheral nervous system, which is composed of the remaining network of neurons throughout the body [243]. The CNS is the processing center for the nervous system. It receives information from and sends information to the peripheral nervous system. The brain processes and interprets sensory information sent from the spinal cord. Both the brain and the spinal cord are protected by three layers of connective tissue called the meninges. There are numerous diseases and disorders of the CNS, and these can affect either the spinal cord or the brain. These include:

1. Infections by bacteria or viruses: Meningitis (acute inflammation of the meninges of the brain or the spinal cord), encephalitis (inflammation of the brain due to a direct invasion by a virus), or poliomyelitis, which involves inflammation of the gray matter of the spinal cord and which may not have any symptoms or may cause paralysis of the lower limbs.
2. Degenerative disorders include Huntington's chorea, which leads to progressive deterioration of the nervous system and is thought to be due to GABA abnormalities; dementia, which involves loss of memory with age; Alzheimer's disease, which is a severe form of senility marked by advanced memory loss and may be due to the formation of protein plaques in the brain with brain cell destruction; Parkinson's disease, which involves tremors of the limbs and difficulty in maintaining balance along with muscle rigidity and could be due to lack of dopamine; amyotrophic lateral sclerosis (ALS), which affects motor neurons, leading to muscle degeneration and loss of function; and multiple sclerosis, which is a chronic, progressive disease that leads to loss of the myelin sheath over the nerves.
3. Epilepsy caused by derangements of normal connections in the brain.
4. Cerebral palsy, a disorder of childhood occurring from birth in many. It is caused by lack of oxygen during birth, which damages motor areas of the cerebral cortex and leads to weakness of the arms and legs.
5. Mental disorders include depression caused by a lack of serotonin and/or norepinephrine in the brain; schizophrenia, which is a severe mental illness probably linked, in part, to a surplus of dopamine; and phobias, which are excessive and abnormal fears.
6. Stroke or cerebrovascular accident is caused by rupture of a blood vessel within the brain, leading to pressure over vital areas of the brain, which may cause paralysis and weakness of the limbs.
7. Other problems with the CNS include headaches, migraines, and head injuries.

Several studies have described the use of herbal products in patient populations with varying chronic conditions. In a systematic analysis published during 1997, it was assessed that 157 of 520 drugs (30%) approved by Food and Drug Administration (FDA) in the United States during 1983–1994 were natural products or their derivatives [244]. During the same period, 61% of anticancer agents approved were natural products or their derivatives. There were no analgesics, antidepressants, anxiolytics, or other CNS-active drugs derived from natural products which were approved during the 11-year time period analyzed [245]. Although identification of leads from secondary plant metabolites continue to be a major goal of many drug discovery projects,

most such efforts do not concentrate on the search for agents potentially useful for the treatment of CNS disorders [245]. In addition, the comparatively few reports on neuronal function modulating activities of herbal extracts and their active constituents that do appear regularly are, in general, not subsequently evaluated adequately in terms of their potential for identifying structurally or functionally novel CNS-active drugs [245]. The main goals of such reports have been the evaluation of traditionally known CNS-active herbal remedies in terms of our current understanding of brain functions or to identify their active constituents [245]. In general, the main goal of these reports has been to generate more evidence-based knowledge justifying their traditionally known therapeutic uses [245]. A few studies published to date, however, have investigated the prevalence of herbal product use among specific psychiatric patient populations [246]. Despite the lack of formal surveys, health care practitioners have become increasingly aware of the growing number of patients using botanical products [246]. The increasing use of these products has created a need for health care practitioners to expand their knowledge about herb efficacy and safety. The goal of this section is to provide an evidence-based review of some herbs with CNS activity.

A variety of indigenous plants are used by African traditional healers to treat mental illnesses and disorders of the CNS, including anxiety, fits, convulsions, epilepsy, hysteria, nightmares, and mental disturbances [247–250]. A preliminary inventory of plants used for psychoactive purposes in South African traditional healing has been compiled [251]. Many authors have also documented the effectiveness of traditional medicines in treating such disorders [252–255].

Hypericum perforatum L. (Hypericaceae), popularly called St. John's wort, is a yellow flowering plant naturally found in various locations around the world including western Asia, Europe, and North Africa. *H. perforatum* has been studied for its effects in treating depression and attention deficit hyperactivity disorder [256]. It became apparent that *H. perforatum* extracts could be as useful for the treatment of mildly to moderately depressed patients as imipramine and that *H. perforatum* extracts were better tolerated by the patients than many synthetic antidepressants [245]. The Milestones in Drug Therapy series by Muller [257] and the Medicinal and Aromatic Plants – Industrial Profiles series by Ernst [258] have nicely summarized our current knowledge on CNS function modulating effects of *H. perforatum* extracts [245]. Many studies have focused on hyperforin, a prenylated phloroglucinol present in this plant, as being primarily responsible for the antidepressant activity of *H. perforatum* [259–261], and many of the experimental and clinical studies have confirmed the antidepressant activity [262–266] and neuroprotective effects [267,268] of this compound. Species related to *H. perforatum* have yet to be screened for similar activity and chemical composition.

The mood-elevating properties of *Sceletium tortuosum* (L.) N.E. Br. (Mesembryanthemaceae) have been attributed to mesembrine, an alkaloid with potent selective serotonin reuptake activity [249]. Selective serotonin reuptake inhibitors such as mesembrine have become important treatments in the therapeutic management of depression [269,270]. The standard selective serotonin reuptake inhibitor drugs currently in use are citalopram, fluoxetine, fluvoxamine, paroxitine, and sertraline. In southern Africa, 102 species are used in traditional healing

practices for the treatment of convulsive conditions [251], although the efficacy of most of these plants has yet to be confirmed. *Leonotis leonurus* (L.) R. Br. (Lamiaceae) exerts an anticonvulsant effect via nonspecific mechanisms, delaying the latency of seizures produced by agents affecting both GABAergic and glutaminergic systems in animal studies [271]. Aqueous extracts of *L. leonurus* protected 37% and 50% of mice subjected to pentylenetetrazole (90 mg/kg) induced seizures at doses of 200 and 400 mg/kg, respectively [271]. The standard antiepileptic drugs, phenobarbitone (10 mg/kg) and diazepam (0.5 mg/kg), profoundly antagonized (100% protection) the seizures produced by pentylenetetrazole [12]. *Synaptolepis kirkii* Oliv. (Thymelaeaceae) is a traditional medicinal plant endemic to southeastern Kenya and northeastern Tanzania. In Kenya, *S. kirkii* is locally known as lama (Boni), mgirambira (Giriama), or mkatu (Swahili), and the roots of the plant are used against snakebite and for the management of epilepsy [272]. It contains kirkinine, which showed powerful neurotrophic activity, promoting neuronal survival in a concentration-dependent fashion [273]. At doses of 7000, 700, and 70 μM, kirkinine exhibited 142%, 103%, and 57% nerve growth factor-like activity [273], respectively.

Neurotrophic factors (NTFs) are endogenous proteins that regulate the development, maintenance, and survival of neurons. Recent evidence suggests that NTFs may play a role in processes of neuronal plasticity. Therefore, NTFs, or compounds acting as NTFs, can protect and rescue certain neuronal populations from various neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [272]. Synaptolepis factor and kirkinine have shown exceptional potential activity in this test, with EC_{50} values of 8.8×10^{-9} and 4.5×10^{-8} M, respectively [272].

Amaryllidaceae alkaloid galanthamine is used in a number of European countries for the treatment of Alzheimer's disease [274]. Galanthamine is also found in several traditionally used African Amaryllidaceae [275]. Galanthamine and other acetylcholinesterase enzyme (AChE) inhibitors alleviate the symptoms of Alzheimer's disease by inhibiting the activity of AChE and hence maintaining or elevating the levels of acetylcholine in the brain [276]. Amaryllidaceae alkaloids of various ring types from *Crinum moorei* Hook. f. (Amaryllidaceae), *Crinum macowanii* Bak. (Amaryllidaceae), *Crinum bulbispermum* (Burm.) Milne-Redhead and Schweickerdt (Amaryllidaceae), and *Cyrtanthus falcatus* R.A. Dyer (Amaryllidaceae) were screened for AChE inhibition activity [277]. The alkaloid 1-*O*-acetyllycorine (IC_{50} of 0.96 μM) was twice as potent as galanthamine (IC_{50} of 1.9 μM) in its AChE inhibitory activity. Various studies have shown that adaptogenic plants affect the nervous system, improving cognitive functions by slowing the deterioration of cognitive processes observed in elderly people [12]. The southern African Amaryllidaceae *Brunsvigia grandiflora* Lindl. and members of the genus *Crinum* are used traditionally as such "tonics" [247]. Both contain galanthamine [275]. *Clausena anisata* and *Catha edulis* (Vahl) Endl. (Celastraceae), traditionally used as tonics, are recognized scientifically for their psychotropic activity [12]. *C. edulis* stimulates the CNS [278] and causes other autonomic and toxic responses [116,279,280]. The most abundant alkaloid in fresh *C. edulis* leaves is cathinone [281]. As the most important ingredient in *C. edulis*, cathinone, has a close structural similarity to amphetamine as well as common

Table 22.4 Traditional Use and Potentially Active Compounds from Plants with Potential Activity on the CNS

Plant and Family	Traditional Use	Countries of the Studies	Potentially Active Compounds	Documented Activities
Hypericum perforatum L. (Hypericaceae)	Treatment of mental health conditions	Western Asia, Europe, and North Africa	Hypericin and hyperforin (quinones) [267,268]	Antidepressant activity [262–266], neuroprotective effects [267,268]
Leonotis leonurus (L.) R. Br. (Lamiaceae)	Treatment of cough, cold, influenza, chest infections, diabetes, hypertension, eczema, epilepsy, delayed menstruation, intestinal worms, constipation, spider bites, scorpion stings, antidote for snakebite, hemorrhoids, skin rashes, boils [289]	South Africa	Premarrubiin, marrubiin [289]	Anticonvulsant activity [271]
Synaptolepis kirkii Oliv. (Thymelaeaceae)	Used against snakebite and for management of epilepsy [272]	Kenya, Tanzania	Synaptolepis factor K7, kirkinine [272,273]	Neurotrophic and antileukemic activity [273]
Diospyros mespiliformis Hochst. (Ebenaceae)	Leaves: sleeping sickness, malaria, headache, and anthelmintic [286] Bark: cough [285]	Nigeria	Alkaloids, quinones, saponins, sterol and/or triterpenes, and tannins [287]	Neuropharmacological activity [288]

pharmacodynamic features, it was suggested that this alkaloid is responsible for the major pharmacological effects of this plant [282]. For addictive drug abuse, ibogaine, one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga* Baill. (Acanthaceae), is claimed to be an effective treatment [283]. One of a number of *Lobelia* species (Lobeliaceae), lobeline is found to possess many nicotine-like effects including tachycardia, hypertension, anxiolytic activity, and improvement of learning and memory [284].

Diospyros mespiliformis Hochst. (Ebenaceae) is a plant that grows wild in tropical Africa. This plant was reported to be of medicinal value [285,286]. Its stem bark was reported to contain alkaloids, quinones, saponins, sterol and/or triterpenes, and tannins [287]. Adzu et al. [288] screened the neuropharmacological activity of the aqueous extract of *D. mespiliformis* stem bark in mice (Table 22.4). The extract (at 100 and 200 mg/kg, p.o.) produced a significant prolongation of pentobarbital-induced sleeping time and reduced spontaneous motor activity and exploratory behavior.

22.4 Conclusion

Current interest in traditional medicine has led to the rapid development and study of many herbal remedies employed for health care. Novel information gathered from the current data is important in preserving indigenous folk knowledge as well as in the discovery of novel potential compounds with promising activity on the reproductive, cardiovascular, and central nervous systems. Thus, this chapter clearly indicates that it is time to increase the number of experimental studies to find novel potential chemical entities from the vast array of unexploited plants having traditional roles.

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23 Legislation on Medicinal Plants in Africa

Mainen Julius Moshi[a] *and Paulo Peter Mhame*[b]

[a]Department of Biological and Pre-Clinical Studies, Institute of Traditional Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania, [b]The Traditional Medicine Section, Ministry of Health and Social Welfare, Dar es Salaam, Tanzania

23.1 Introduction

Medicinal plants include plants that are used as traditional medicines: plants used as sources of pure-molecule pharmaceuticals such as quinine and quinidine (from *Cinchona* species), reserpine (from *Rauvolfia* species), vincristine and vinblastine (from *Catharanthus roseus*), and artemisinin (from *Artemisia annua*); plants used as sources of nutraceuticals such as ginseng, *Ginger officinalis*, *Moringa oleifera*, and so on; and plants used as sources of essential oils that are used for cosmetics, food additives/flavors, and carminatives. It is estimated that between 40,000 and 50,000 plant species are used as traditional medicines and as sources of modern medicines [1]. According to the World Health Organization (WHO), 70−95% of the population in developing countries rely on traditional medicines, especially herbal medicines, for the provision of their daily health care needs [2]. In African countries south of Sahara (with the exception of South Africa and Egypt, which have some herbal pharmaceutical industries), medicinal plants are used mainly as traditional medicines or modified traditional medicines. It is notable that the use of herbal medicines worldwide is expanding at an estimated rate of 5−18% [2], sparking an enormous upsurge of international trade in herbal medicines. The retail sales volume is estimated to be US$6 billion in Europe, $2.1 billion in Japan, and $33.9 billion in the United States [2]. The upsurge of public interest in natural therapies in industrialized countries in recent years has significantly increased international demand for medicinal plants and herbal medicines [3]. The trade in herbal medicines ranges from the sale of raw unprocessed medicinal plant material in open marketplaces, to the sale of packaged semiprocessed herbal medicines, to highly refined herbal medicines processed in sophisticated modern pharmaceutical industries.

The medicinal plants used locally and those being exported from African countries are mostly harvested from nature (wild forests, conserved areas, game reserves,

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and national parks); only a small fraction is from cultivated sources (see Chapter 24). Cultivation of medicinal plants in Africa is still in its infancy, and only a few countries (Egypt, Libya, Madagascar, Morocco, Tunisia, Sudan, and South Africa) have taken the initiative toward commercial cultivation of medicinal plants. Scattered efforts toward cultivation exist in other countries—*A. annua* in Uganda, Kenya, and Tanzania; some cultivation initiatives in the Democratic Republic of Congo; and possibly others—but none at a significantly large commercial scale. Thus, African countries continue to depend on harvested medicinal plants from the wild, at the risk of species extinction, environmental degradation, and imminent threat of desertification. The supply of medicinal plant materials is further threatened by the expansion of cultivated land, cutting of trees for fuel (charcoal) and timber, expanding human settlements, and urbanization, leading to encroachment into forests and other naturally conserved areas, as well as forest fires and settlement of refugees as a result of frequent political conflicts. The threat of depletion of African medicinal plant resources is compounded by weaknesses in legislation, ranging from lack of legislation, to weak legislation, to failure to enforce existing laws and regulations [4].

Collection of plants from the wild for medicinal use and for other purposes constitutes a large source of income for rural households in developing countries, in Africa in particular [5], but in many of these countries, direct and coherent efforts to conserve plant species have not received adequate policy attention and research support [6]. Given that very few plants are cultivated, harvesting from the wild has become of particular concern to environmentalists, since a number of plant species are now threatened. *Prunus africana*, *Ocotea bullata*, *Stephania* spp., *Holarrhena floribunda*, West African *Garcinia* spp., *Dalbergia odorifera*, *Siphonochilus aethiopicus*, *Afzelia* spp., *Stangeria eriopus*, *Warburgia elongata*, *Warburgia salutaris*, and others are among the overharvested plants that have been included in the International Union for Conservation of Nature (IUCN) red list [7]. There are many international foundations, development agencies, and agricultural research centers that are making considerable effort at conservation, and through these initiatives, many countries have initiated activities directed at conservation of plants and in some cases cultivation, especially of commercially viable plants. The Global Strategy for Plant Conservation (GSPC) 2002 has been the key strategy guiding countries to formulate policies for plant conservation. Some of the targets are being achieved through establishment of botanic gardens, facilitated by the Botanic Gardens Conservation International (BGCI), which supports a network of botanic gardens around the world [8]. Ethiopia is among the African countries that have followed through on the implementation of the 16 targets of the Global Strategy with notable success [8].

Areas of the African continent that require cooperative action among stakeholders in conserving medicinal plants include the rapidly urbanizing regions with a high level of endemic taxa: in West Africa (Guineo-Congolian region), specifically Ivory Coast, Ghana, and Nigeria; in East Africa, Ethiopia, Kenya, and Tanzania; in southeastern Africa, South Africa, Swaziland, and the Afromontane forest and the coastal forests of the Zanzibar-Inhambane regional mosaic [9].

23.2 The Status of Medicinal Plants in Some African Countries

The Association for African Medicinal Plants Standards (AAMPS) was initiated in 2005; it consists of experts in the area of herbal medicines and seeks to promote the industrial production of African medicinal plants. The AAMPS has its headquarters in Mauritius and is developing an African Herbal Pharmacopoeia. The Pharmacopoeia provides detailed and current botanical, phytochemical, and commercial information on 51 important African medicinal plants. Information covered also includes microscopic features of the plant material, high performance liquid chromatography (HPLC) profiles, thin layer chromatography (TLC) chromatograms of adulterants, and distribution maps. The medicinal plants being promoted include *Catharanthus roseus*, *Cryptolepis sanguinolenta*, *Hoodia gordonii*, *Prunus africana*, *Harpagophytum procumbens*, *Pelargonium sidoides*, and *Sutherlandia frutescens* [10]. This initiative is expected to promote research, support plant material collectors, and foster industrial production of herbal medicines and consequently commercial cultivation of medicinal plants.

According to the WHO African Region, by the year 2010, 12 countries had issued authorization to market traditional medicines, ranging from three in Cameroon and Congo to over 1000 in Ghana and Nigeria. The countries involved include Burkina Faso, Cameroon, Congo, Democratic Republic of the Congo, Ghana, Ivory Coast, Madagascar, Mozambique, Niger, Nigeria, Tanzania, and Zambia. Countries producing traditional medicines locally include Burkina Faso, Cameroon, Democratic Republic of the Congo, Ghana, Madagascar, Mali, Mauritania, Niger, Nigeria, Rwanda, São Tome Principe, Senegal, Seychelles, South Africa, and Zimbabwe. So far, six countries have developed guidelines for the protection of intellectual property rights (IPRs) and traditional medicine. By 2010, six countries (Botswana, Cameroon, Chad, Ghana, Nigeria, and South Africa) had national tools for protection of IPRs and traditional medicine knowledge (TMK). Eight countries have established databases on traditional medicine practitioners, TMK, and access to biological resources. The Democratic Republic of the Congo, Ghana, and Nigeria have developed National Herbal Pharmacopoeias. Cameroon, Chad, Ivory Coast, and Seychelles have carried out national inventories of medicinal plants [11].

23.3 Legislation in the Areas of Medicinal Plants

The area of medicinal plants is closely linked to other sectors, and as such several legal and legislative frameworks are involved, including conservation of biodiversity, environmental laws, forest laws, food and agriculture, traditional medicine, intellectual property rights, access and benefit sharing, and others. At the international level, applicable laws and conventions include the Global Strategy for Plant Conservation (GSPC), the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), the Convention on Biological Diversity

(CBD), and the Kyoto Protocol 2010. These international conventions are the overall guiding documents to the formulation of national policies and legislation, and many African countries are signatories, except for the Kyoto Protocol 2010, which is currently at the stage of national-level discussions around signing and implementation strategies.

Historically, a number of influential documents have been published to inform and influence conservation initiatives, including documents developed by the Centre for Our Common Future [12], a document by Abramovitz for the World Resources Institute [13], and the Consultative Group on International Agricultural Research [14]. Others include the World Bank document written by Hawkes [15], the joint International Union for Conservation of Nature (IUCN)/United Nations Environmental Programme (UNEP)/World Wide Fund for Nature (WWF) document [16], McNeely et al. [17] for the International Union for Conservation of Nature and Natural Resources, Warren [18] for the U.S. National Research Council, Britain's Overseas Development Administration, Sohmer and Knutsen for the U.S. Agency for International Development [19], the Global Biodiversity Strategy: Policymakers' Guide produced by the World Resources Institute, the World Conservation Union, and the United Nations Environment Programme [20], and the CITES. The main international legal framework for biodiversity conservation is the CBD, established during the Earth Summit of 1992. These international documents and initiatives have fostered participation by various governments, including African countries. The International Convention on Biological Diversity has three objectives: conservation of biological diversity, sustainable utilization of biological resources, and fair and equitable sharing of biological genetic resources. Many African countries are signatory to the International Convention on Biological Diversity, CITES, and regional treaties related to conservation of flora and fauna. The Kyoto Protocol 2010 is an improvement on the CBD Objective 3, which further elaborates how to achieve equitable sharing of the benefits of biological resources, thus empowering countries to develop their own legislation to govern access and benefit sharing and shifting responsibility to local communities to be the guardians and direct beneficiaries of the biological resources, associated indigenous knowledge, and TMK. At the same time, it empowers them to develop mechanisms to ensure infusion of technological and research inputs to develop the resources for commercial exploitation, while plowing back to the local communities the accrued benefits to foster sustainable exploitation.

23.3.1 Environmental Protection Legislation

Sustainable harvesting of medicinal plants in Africa is an environmental issue. Urbanization, population growth, and unrestricted collection of medicinal plants from the wild is resulting in overharvesting of medicinal plants in several countries. Plants that are slow to grow and reproduce are particularly vulnerable to excessive collection and are therefore threatened and in danger of extinction [21]. South Africa is one country that is already experiencing overharvesting of medicinal plants [21]. Measures being adopted by individual countries include establishing

conservation areas and restricting bark harvesting [21]. In South Africa, a number of laws have been enacted, such as the Limpopo Environmental Management Act (LEMA), the National Environmental Management: Biodiversity Act 2004 (NEM:BA) and its 2007 Amendment, the National Environmental Management: Protected Area Act (NEM:PAA), and the National Forest Act 1998 (Act No. 84 of 1998). Other countries have similar laws that are directed toward protection against overharvesting of medicinal plant species. African countries with environmental laws and policies include Algeria, Burkina Faso, Cape Verde, Comoros, Congo, Egypt, Gabon, The Gambia, Ghana, Guinea, Libya, Mali, Madagascar, Malawi, Nigeria, Senegal, Seychelles, South Africa, Tanzania, Togo, Tunisia, Uganda, Zambia, Lesotho, Morocco, Niger, Guinea-Bissau, Kenya, Zimbabwe, Burundi, Cameroon, Mauritania, and Mozambique [22]. The Declaration for Global Partnership on the Environment Initiative of the New Partnership for Africa's Development (NEPAD) was adopted at the Partnership Conference on the Environment Initiative of NEPAD, December 16, 2003 [23].

The enacting of laws on environment is of great significance due to the fact that most of the plants are harvested from the wild. Contamination by industrial waste, the mining industry, sewage sludge, and pesticides that are poorly disposed of [24] are of considerable importance in the area of medicinal plants in Africa, affecting the quality and safety of herbal medicinal products.

23.3.2 Legislation on Threatened Species

The protection of endangered medicinal plant species can be furthered under the provisions of the CITES. A total of 42 African countries are party to CITES, although compliance and reinforcement are a major bottleneck. Countries which have signed CITES include Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Democratic Republic of the Congo, Congo, Ivory Coast, Egypt, Equatorial Guinea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Morocco, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Africa, Swaziland, Tanzania, Togo, Tunisia, Uganda, Zambia, and Zimbabwe. Implementation of the he GSPC 2002 has been another avenue through which initiatives for the protection of endangered species can be furthered by African countries, especially through the establishment of botanical gardens.

23.3.3 Forest Legislation and Medicinal Plants Protection in Africa

Medicinal plants in African countries are harvested almost entirely from natural forests, forest reserves, national parks, and other natural habitats because commercial cultivation is still in its infancy. Under these circumstances, forest laws are of considerable importance in the area of medicinal plants and have a role in ensuring sustainable availability of medicinal plants. There is a huge volume of illegal international timber trade all over the world, which represents a serious threat to sustainable development in most African countries [25]. Statistics from the World

Bank estimate that the volume of illegal timber trade is worth $10 billion and that the loss of government revenue stands at $5 billion [26]. Forest degradation resulting from illegal logging exacts a high cost in terms of climate change and species loss, directly affecting the availability of medicinal plant species. Under these circumstances, forest laws are of great importance in the area of medicinal plants and have a role in ensuring sustainable availability of medicinal plants.

A number of African countries have enacted forest laws, but like other existing laws, they have deficiencies, e.g., failure to link forest sector development with economic and social development objectives, weak forest administrative structures, low or poor compensation being given to the local communities that are custodians of the forest resources [4], poor definition of legal and institutional frameworks regarding forest management and use, and land tenure problems [25]. Forest laws in the region are also described as prescriptive rather than people centered [25].

The Southern African Development Cooperation (SADC) region is used here as an example to illustrate the state of forest legislation in Africa. The SADC region manages forestry issues under the Protocol on Forestry of 2002, under which member states commit to assist and support each other to address important issues about forestry, including deforestation, climate change, forest fires, genetic erosion, diseases, pests, invasive alien species, building capacity for law enforcement, trade promotion, and implementation of harmonized approaches [26]. Through the SADC Protocol on Forestry 2002, common initiatives and mechanisms for legal frameworks have been developed, but not all countries have fully developed their forest laws. For example, Angola, Botswana, and the Democratic Republic of the Congo have not fully developed their forestry legislation, though they have made significant progress toward this goal. Other countries already have forest laws, including the Lesotho Forest Act of 1978, the Tanzania Forest Act of 2002, the Namibia Forest Act of 2001, the Mozambique Wild Life and Forestry Law of 1999, the South Africa Forest Act No. 84 of 1998, the Zambia Forest Act of 1999, and the Zimbabwe Forest Act of 1999. The newly enacted laws have incorporated community participatory approaches and incentives in the management of forest resources [27]. Thus, through community empowerment, many medicinal plants will be conserved and sustainably harvested for both provision of health care and poverty reduction.

23.3.4 Ethics Committees for Plant Toxicity Testing Using Animal Species

In the African region, reference to medicinal plants has almost an implied reference to traditional medicine due to the fact that the herbal medicine industry is still in its infancy. Therefore, ethical, safety, and efficacy issues surround the administration, use, and biological and clinical evaluation of traditionally used medicinal plants. The Alma-Ata Declaration of 1978 recognized traditional health practitioners and recommended they be included among health workers who are called upon to respond to the expressed health needs of the community, along with physicians, nurses, midwives, auxiliaries, and community workers on the

basis of suitable training [28]. It is imperative, therefore, that initiatives should be put in place in all countries using traditional medicines, including African countries, to provide capabilities for safety, efficacy, and quality evaluation of these products.

All African countries have some form of capacity to conduct research on medicinal plants, but only a few have sophisticated research laboratories that use animal models to ascertain the safety of medicinal products. South Africa's Medical Research Council (MRC) has developed a research center in Cape Town that undertakes toxicity studies on medicinal plants, among other research. Other African countries with facilities for safety and efficacy testing are Ghana, Nigeria, Mali, Ethiopia, Tanzania, Kenya, Uganda, and others. These countries have facilities that are at different stages of advancement, for example, the MRC laboratory can do full-scale quality, safety, and efficacy evaluation following internationally accepted ethical and quality standards. In Ghana, the Noguchi Memorial Institute has a state-of-the-art animal house facility that can support conduct of full-scale animal toxicity studies using Good Laboratory Practice (GLP) standards. The Kenya Medical Research Institute laboratory for traditional medicine collaborates with the Kenya Primate Institute, which gives them the capability to do full-scale animal toxicity studies, and both institutions have experts who are GLP trained. The WHO, under the WHO/TDR capacity strengthening for tropical diseases research, has been building capacity for GLP since 1999; in this period, researchers from Ghana, Nigeria, Mali, Sierra Leone, Mali, Kenya, Uganda, Tanzania, and South Africa have been trained, and some of these countries now have GLP compliant facilities that can do internationally acceptable preclinical safety studies. Similarly, WHO Afro, in collaboration with WHO Geneva, has conducted training of African researchers in the area of traditional medicine to build capacity for preclinical safety studies and has developed a booklet with guidelines for safety evaluation of traditional/herbal medicines [29]. The Institute of Traditional Medicine in Tanzania is running a master of science program in Traditional Medicines Development, and the graduates from this program are being exposed to both the International Conference on Harmonization (ICH) and Organization for Economic Cooperation and Development (OECD) guidelines for nonclinical safety testing.

23.3.5 Regulation and Registration of Herbal Medicines

The increase in the use and industrial processing of herbal medicines has meant that many countries are importing them. These countries are supposed to have in place some formalities for registering herbal medicines. However, the legal situation regarding registration procedures differs from one country to another. In some African countries, such as South Africa, Ghana, Mali, Nigeria, and Egypt, herbal medicines are well established, but in others they are considered food supplements, and therapeutic claims are not allowed [3]. African countries have a large number of traditionally used herbal medicines, and a lot of ethnomedical information about these plants, but the majority of them have hardly any legislative criteria to establish these traditionally used herbal therapies as part of national drug legislation [3]. Factors that are used for

regulatory categorization of herbal or traditional medicinal products include description in a pharmacopoeia monograph, prescription status, claim of therapeutic effect, scheduled or regulated ingredients or substances, and periods of use [3]. The WHO African Region has been interested in supporting African countries to develop policy and a legislative framework for the regulation of traditional medicines. In response, many countries have already developed either policy alone or both policy and legislation. The following countries have a traditional medicine policy: Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Ivory Coast, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Niger, Nigeria, Rwanda, Sierra Leone, South Africa, Togo, Uganda, Tanzania, Zambia, and Zimbabwe.

23.3.5.1 Categories of Traditional Medicines Used for Registration

In order to facilitate registration of traditional medicines, the WHO has defined four categories of traditional medicines:

Category 1: These are traditional medicines that have been prepared by traditional health practitioners for treatment of their patients. These are medicines that are prepared extemporaneously using traditional methods.
Category 2: These are traditional medicines widely available in the community and that have commercial value. They are traditionally used in a given locality and well known in that setting in terms of composition and treatment; the formulation is well known, preparation is according to traditional methods, and safety and efficacy are justified by a long history of use.
Category 3: These are traditional medicines developed through scientific research based on ethnomedical use; their formulation, dosage, and therapeutic use are based on research data, and their safety and efficacy information is based on standard scientific and clinical investigation.
Category 4: This category belongs to imported traditional medicines that originate from other countries, including WHO African countries. These are required to meet the definition of traditional medicines, should be registered in the source country, and should meet the regulatory requirements of the country into which they are being imported. In some countries, such as Tanzania, this category has fairly stringent regulatory requirements, similar to conventional medicines.

23.3.5.2 Overview of Regulatory Guidelines in Some African Countries

23.3.5.2.1 Benin

A policy on traditional medicines has existed since 2002; there is a traditional medicine Program in the Ministry of Public Health, with a director. They have 14 Medicinal Plant Gardens located in different ecological zones in Benin, which are managed by traditional health practitioners under the supervision of the Ministry of Public Health [30]. They have well-established commercial production of herbal medicines [3,30].

23.3.5.2.2 Congo

Congo has about 10,000 plant species, of which 3000 are endemic [31]. To date, Congo does not have legislation on traditional medicine, but the government recognizes traditional medicine health practitioners. A unit of traditional medicine in the Ministry of Health and Social Affairs was created in 1974 to develop a national herbarium and to register traditional health practitioners in the country. In 1982, the unit was elevated to a Traditional Medicine Service to do research, enrich the National Herbarium, gather medicinal plant formulae, promote traditional medicine, and establish modalities for integration in the health care system. In 1987, the National Centre of Traditional Medicine was established and charged with the responsibility to promote research, manufacture traditional medicinal products, and train allopathic health practitioners and students in traditional medicine.

23.3.5.2.3 Egypt

Herbal medicines are officially recognized, and there are published national registration requirements for herbal medicines [31]. Four pharmaceutical companies, MEPACO, SEKEM, ROYAL, and NERHADOU, are engaged in the production of herbal medicines in accordance with good manufacturing practice (GMP) standards, and they all have large farms for the cultivation of medicinal and aromatic plants. Manufactured herbal medicines are exported to Arab countries, Europe, and the United States [30].

23.3.5.2.4 The Gambia

The Gambia has a forest cover of 46%, and so far it is able to meet domestic needs for traditional medicines resources, but it does not have any legislation dealing with protection of biodiversity, with the exception of Forest Policy of 1995, which emphasizes biodiversity conservation and sustainable use. However, The Gambia is signatory to international conventions on biological diversity, CITES, and other international conventions that offer protection to the forest ecosystems that serve as habitats for the various flora and fauna species. The Ministry of Health and Social Welfare has a functional Traditional Medicines Unit and a Traditional Medicines Policy. Traditional medicine practice is regulated under the Code of Ethics for Traditional Medicine Practice.

23.3.5.2.5 Ghana

Traditional medicine activities are regulated under the Traditional Medicine Practice Act 595 of 2000, overseen by the Directorate of Traditional and Alternative Medicine of the Ministry of Health. The Directorate has organized all traditional healers under the Ghana Federation of Traditional Medicine Associations (GHAFTRAM). The Ghana Food and Drugs Board is responsible for registration of herbal medicines for sale in Ghana; it monitors advertisements for traditional medicine, issues manufacturing and export licenses for herbal medicines, and conducts GMP inspections of manufacturing premises [30]. The Ghana Standards Board (GSB) sets standards for all locally manufactured goods, including herbal medicines [30].

Safety, efficacy, and quality evaluation of herbal medicines is undertaken by the Centre for Scientific Research into Plant Medicine (CSRPM), the Noguchi

Memorial Institute of Medical Research; in addition, the National Centre of Pharmacovigilance routinely conducts safety monitoring of all medicines, including herbal medicines [29]. Herbal medicines are produced mainly from plant materials harvested from the wild and are marketed by traditional health practitioners, private entrepreneurs, government institutions, and NGOs. Ghana also consumes imported herbal medicines from India, the United States, China, Korea, and Egypt [30].

23.3.5.2.6 Guinea

Guinea has legislative and regulatory guidelines for the practice of traditional medicine, a licensing process, and a registry of traditional health practitioners. They have local and national intersectoral councils for traditional medicine [3]. Local authorities have a mandate to register traditional health practitioners in their administrative and/or health subdivisions, and some traditional health practitioners are involved in Guinea's primary health care program [3,31].

23.3.5.2.7 Kenya

Kenya, with only 2% closed-canopy forest cover, is one of countries of Africa with very little land that is under forest cover [32]. The Kenya Forest Act of 2005 aims to provide for the establishment, development and sustainable management, conservation, and rational utilization of forest resources for the socioeconomic development of the country [32]. Kenya ratified the CBD and has made significant progress in putting in place measures for biodiversity use and conservation. The Kenya Environmental Management and Coordination Act (EMCA) of 1993 coordinates the management of biodiversity resources in Kenya, including agricultural biodiversity, forest biodiversity, and mountain, marine, and coastal biodiversity. The Forest Act has protected and made reserves in forests, including national parks, reserved areas, and the coastal areas where mangrove grows. Concerns around medicinal plant species are dealt with by the Kenya Forest Research Institute (KEFRI), the Museums of Kenya, and the Kenya Medical Research Institute (KEMRI), which are responsible for documentation of medicinal plant species; in addition, KEMRI deals with evaluation for safety and efficacy of the plants under the umbrella of traditional medicines.

Kenya does not have a national policy or any legislation to govern the practice of traditional medicine and has no regulatory authority or expert committee on traditional medicine. Research on safety and efficacy of traditional medicines is being undertaken by the KEMRI, and so far there are no industries producing herbal medicines. The Kenya Pharmacy and Poisons Board has guidelines for registration of herbal medicines, and herbal, complementary, and alternative medicines are being imported from other countries such as India and China. The Government of Kenya, although it still lacks general consensus on traditional medicines, under the Development Plan of 1989–1993, recognized traditional medicine and made a commitment to promote the welfare of traditional health practitioners [3,33].

23.3.5.2.8 Madagascar

Madagascar is one of the biodiversity hot spots of the world, being home to a diversity of plants. An ongoing floristic inventory already lists well over 12,000 vascular

plant species that show a high degree of endemism, about 90% [34]. Madagascar is involved in the trade of medicinal plants, and in 2010 over 900 tons, valued at nearly €2.85 million, were exported. This export trade involved 50 plant species, of which 33 are from the forest [34]. The exported plants include *Cinnamomum camphora*, *C. roseus*, *Centella asiatica*, *Aphloia theiformis*, *Drosera madagascariensis*, and *P. africana* [34].

The Ministry of Health of Madagascar has created a Service of Pharmacopoeia and Traditional Medicine (*Service de la Pharmacopée et de la médecine Traditionnelle*, SPMT) currently in four volumes, listing hundreds of plant species; the first volume was completed in 2012 [34].

23.3.5.2.9 Mali

Traditional medicines in Mali have a high level of support from the government, and research and development in this area are managed under the Department for Traditional Medicine within the National Institute for Research on Public Health, which is part of the Ministry of Health. The main policy emphasis is on the use of improved traditional medicines, also referred to as Material Transfer Agreements (MTAs) [35], and for regulatory purposes, traditional medicines have been classified into four categories:

Category 1: Traditional medicines that are prepared by a traditional health practitioner for an individual patient with fresh or dried raw materials, with a short shelf life.
Category 2: Traditional medicines currently used in the community that are prepared in advance and composed of crude raw plant materials.
Category 3: Standardized plant extracts prepared in advance and supported by scientific research.
Category 4: Isolated pure compound molecules from traditional medicines following scientific research.

The improved traditional medicines are recognized on the basis of having pharmacological evidence of safety and efficacy, development of standardized dosage forms, and quality control [30]. Marketing authorization is given after a dossier of information on a remedy's safety and efficacy has been submitted to the *Commission Nationale d'Autorisation de Mise sur le Marché* of the Ministry of Health. The information needed for dossier submission in order to get regulatory approval varies depending on the category of traditional medicines.

Currently, there are seven improved traditional medicines, and these are included in the Malian Essential Drugs List and the Malian National Formulary alongside conventional medicines, and they are distributed in pharmacies [35,36].

23.3.5.2.10 Nigeria

Nigeria is one of the countries with a high preponderance of the use of traditional medicines, but it has not made significant progress in the manufacture of herbal medicines. Nigeria has documented 7895 plant species in 338 families and 2215 genera [37]. However, economic hardships have led to excessive harvesting of nontimber forest products for various uses, leading to threats to the populations of medicinal plant species [37]. According to the National Biodiversity Report,

349 plant species are threatened, including nine medicinal plant species: *Masilania accuminata*, *Garcinia mannii*, *Oucunbaca aubrevillei*, *Erythrina senegalensis*, *Cassia nigricans*, *Nigella sativa*, *Hymenocardia acida*, and *Kigelia africana* are endangered, and *O. aubrevillei* is almost extinct [1].

23.3.5.2.11 Tanzania

Tanzania, with over 12,000 plant species, is another international biodiversity hotspot; the Eastern Arc mountains are home to a number of plants that are endemic, and a number of them are used as traditional medicines. As in many other African countries, Tanzania loses extensive areas of forests due to expansion of human settlements and agricultural activity, forest fires, tree felling for timber and international trade, and refugees activities.

Tanzania is party to CITES and the CBD. It is party to the regional Lusaka Agreement on cooperative enforcement operations directed at illegal trade in wild fauna and flora, and which supports CITES, and has initiated a number of programs and projects that support biodiversity. However, there is weak enforcement, and as a result, Tanzania continues to lose plant biodiversity through illegal timber and medicinal plant trade. Harvesting of medicinal plants by traditional health practitioners has a significant impact on medicinal plants as they do not practice sustainable harvesting.

In addition to CITES and CBD, the Forest Act of 2002 is another law that is available for safeguarding biodiversity; it covers the creation and declaration of forest resources. It is largely an administrative instrument for enabling the establishment of forest reserves. The Act has been extended to cover the establishment of institutions beyond state forest reserves, including village forest reserves, controlled areas, and silvipastoral areas for pastoralists. Some of the forests are now being managed by various agencies. Despite the provision in the Act for payable fees in the form of royalties and penalties, such fees do not reflect the value of the forest products to the society or even the resource replacement cost. Illegal lumbering and artificially low wood prices hamper farmers from making investments in growing trees because of the projected low earnings.

Despite research being conducted by the Tanzania Forestry Institute (TAFORI) and the Sokoine University of Agriculture on various aspects of forest conservation modalities, there are no specific initiatives that are devoted to cultivation of medicinal plants. Commercial cultivation of medicinal plants has never been a priority in government-led initiatives; the only efforts that can be found in the country (e.g., the cultivation of *A. annua*, *M. oleifera*, *Hibiscus sabdariffa*, and a few others) are initiatives of private enterprises. There are some entrepreneurs who export essential oils, including sandalwood oil, rosemary oil, eucalyptus oil, tea tree oil, thymus oil, myrrh oil, lemon grass oil, ocimum oil, geranium oil, sandalwood stick, and wood. All these products are being sourced from the wild, and in some cases, such as sandalwood, there are already indications of likely extinction of the species resources, especially in the Shengena forest of the Southern Pare.

Tanzania has both policy and legislation on traditional medicine and has an established Section for Traditional Medicine in the Ministry of Health and

Social Welfare, with a deputy director responsible for traditional medicine, and a Council for Traditional, Complementary, and Alternative Medicine. Each regional and district council has a coordinator responsible for traditional medicine development in their areas. A mandate to conduct research into traditional medicines is vested in the Institute of Traditional Medicine of the Muhimbili University of Health and Allied Sciences, but other institutions, including the National Institute for Medical Research, the Departments of Chemistry and Botany of the University of Dar es Salaam, and recently, the Faculty of Veterinary Medicine of Sokoine University of Agriculture, are also doing research in traditional medicines, looking into aspects of safety, efficacy, and also phytochemical studies and herbal product formulation. However, so far, there are no officially commercialized herbal medicines, and almost all herbal products registered by the Tanzania Food and Drugs Authority are imported (TFDA). The TFDA has developed guidelines for registration of herbal/traditional medicines and has created categories which make it easy to recognize and register traditional medicines.

23.3.5.2.12 South Africa

South Africa is regarded as a hotspot for global biodiversity, with more than 22,000 plant species, which is about 10% of the plant species of the world, and it is one of the countries involved in the medicinal plant trade at the local and international level. Over 3000 species of South African plants are used regularly in traditional medicine, and around 38 species are being exploited commercially [38]. A number of these species have been developed to varying stages, including *Agathosma betulina*, *Aloe ferox*, *Aspalathus linearis*, *H. procumbens*, *Hypoxis hemerocallidea*, *Lippia javanica*, *P. sidoides*, *Xysmalobium undulatum*, *Artemisia afra*, *H. gordonii*, *Mesembryanthemum tortuosum*, *S. aethiopicus*, *S. frutescens*, and *W. salutaris* [38].

Large urban markets in areas such as Durban and Johannesburg have shifted the harvesting of medicinal plants from subsistence to commercial trade, thus increasing the intensity of harvesting from wild habitats. South Africa has enacted protective laws such as the KwaZulu Natal Nature Conservation Act of 1997 and the National Forest Act No. 84 of 1998. Under the Forest Act, there are flexible arrangements such as the participatory approach of establishing a bark harvesters' association (Sizamphilo) in the Umzimkhulu District. This is a legal entity whose conception is drawn from provisions of the Forest Act that established an element of participatory community involvement in the management of forest resources. This participatory approach has also been practiced in other countries such as Tanzania.

Over 21 plant species are traded locally in areas in the Limpopo Province [39]. The locally sold plants include *Sclerotome ilicifolius* (Acanthaceae), *Alepidea amatymbica* (Apiaceae), *A. afra* (Asteraceae), *Callilepsis laureola* (Asteraceae), *Elephantorrhiza elephantina* (Fabaceae), *Hypoxis obtusa* (Hypoxidaceae), *Pyrenacantha grandiflora* (Icacinaceae), and *S. aethiopicus* (Zingiberaceae) [39].

South Africa is a party to CITES. The National Environmental Management: Biodiversity Act (Act 10 of 2004 NEMBA) and Amendments 2007 and 2012

regulate all CITES-listed species; environmental management inspectors, operating on a national basis, ensure compliance with NEMBA. South Africa has also a developed bioprospecting, access, and benefit sharing regulatory framework [40].

23.4 Conclusions

Africa is home to abundant plant biodiversity, with a high preponderance of endemic species, and a significant number of them are used as medicinal plants and could contribute significantly to the improvement of health and socioeconomic development. These plants are mainly being harvested from nature and cannot cope with the expanding use of herbal medicines around the world. African countries will only benefit from the ever-growing international herbal trade if they put in place adequate legal structures to ensure sustainable supply of medicinal plants. Deliberate efforts are also needed to promote commercial cultivation of medicinal plants.

Review of various Acts regarding forests, the environment, IPRs, and traditional medicine should be done in line with the various international protocols such as CITES, CBD, and the Kyoto Protocol 2010. Sustainable use of medicinal plants will assist African countries to continue benefiting from traditional medicines, particularly the use of herbal medicines and the establishment of a local herbal medicine industry.

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24 Medicinal Plants Market and Industry in Africa

Jean P. Dzoyem[a], *Emmanuel Tshikalange*[b] *and Victor Kuete*[a]

[a]Department of Biochemistry, University of Dschang, Dschang, Cameroon, [b]Department of Plant Science, University of Pretoria, Pretoria, South Africa

24.1 Introduction

Africa is endowed with diverse vegetation types, including tropical rainforests, coastal and alpine forests, savannas, woodlands, and scrublands [1]. The continent has a unique diversity of geographic and climatic factors, and an exceptionally rich, varied flora, with an estimated 68,000 plant species, of which about 35,000 are known to be endemic [2]. This great biodiversity and climate variation as well as rainfall and soils are suitable environments to provide for indigenous medicinal plant growth; as a result, there is an immense diversity and variation of the vegetation in the whole continent [3]. Tropical and subtropical Africa are endowed with approximately 45,000 species of plant with potential for development, of which 5000 species are used medicinally, constituting nearly 25% of the world trade in biodiversity [4]. Probably because of this natural advantage, African people have a tremendous passion for medicinal plants and use them for a wide range of health-related applications, from common cold, to memory improvement, to enhancement of general immunity. There are many effective plant-based formulations used in folk medicine and known to rural communities [5,6]. In the oral traditions of all African countries, local communities have discovered the medical uses of thousands of plants found in the local ecosystem. Africa has one of the richest plant medical cultures in the world. There is a long history of the use of many traditional practices, experience that is passed from generation to generation, which has demonstrated the safety and efficacy of African medicinal plants [7]. According to the World Health Organization (WHO), traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement, or treatment

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of physical and mental illnesses [8]. Traditional medicine includes herbs, herbal materials, herbal preparations, and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations [9]. Traditional African medicine is a socioeconomic and sociocultural heritage, serving over 80% of the population, who rely on it for their primary health care needs, not only because natural plants are available and cheaper than modern medicines but also because natural remedies are often the only medicines available in remote rural regions. Significant quantities of medicinal plant resources are consumed in all African countries in their traditional health care practices at the household level, under the guidance of traditional healers and practitioners of African systems of medicine. The sheer numbers of Africans using plants for health care and the diversity of plant species used in these practices have created an increased demand for and supply of medicinal plants [10,11].

There has recently been a growth of interest in medicinal plants in the international pharmaceutical industry, including in Europe and America. Medicinal plants are viewed by the pharmaceutical industry as a source of "qualified leads" in the identification of bioactive agents in the production of synthetic modern drugs. It is for this reason that all the major herbal-based pharmaceutical companies are showing constant growth. There is also a growing interest in obtaining samples of plant materials or traditional knowledge about plant uses, to explore for new commercial medical products [12]. This resurgence of interest in plant-based drugs has opened enormous opportunities for Africa, given the continuous demand for raw materials. Thus, demand for medicinal plants is increasing as the population grows in both developing and developed countries [13]. In this context, there is a large-scale international trade in medicinal plants, used both for herbal medicine and manufacturing of pharmaceutical drugs. In Africa, there is a huge number of registered herbal industries engaged in production of herbal health care formulations, herbal-based cosmetic products, and herbal nutritional supplements. A multitude of unregistered cottage-level herbal enterprises depend on the continuous supply of medicinal plants for manufacturing these herbal medical formulations [14]. The international market in medicinal plants is over $60 billion per year, and it is growing at a high rate [15]. According to a 2009 study by BCC Research, the global market for botanical and plant-derived drugs is expected to increase from $19.5 billion in 2008 to $32.9 billion in 2013, an annual growth rate of 11.0% [16]. The world trade in natural products is dominated by the United States, the European Union (EU), and Japan [17]. Medicinal plant resources in Africa are a major source of income, in addition to domestic trade; medicinal plants are widely exported in large volumes to the international market. The continent comes second to Asia in export figures [18,19]. The trade in African medicinal plants involves the sale of relatively large quantities of unprocessed or semiprocessed products, but the actual scale of trade is difficult to assess because of a paucity of reliable statistics and trade secrecy. Organizationally, not much information is available on the commercialization and industrial utilization of medicinal plant products in Africa. No surveys have been carried out on this topic on a continental scale.

This chapter attempts to provide an overview of the industrial utilization and trade in African medicinal plants. It focuses mainly on broad trends or tendencies and the most common situations in the production and marketing of medicinal plants. While reading through this chapter, the reader should keep in mind that the relative opacity of the medicinal plant trade at the level of gatherers, traders, and the industry as a whole makes it very difficult to assess the global situation; furthermore, it is not possible to explore each individual plant or product, country, or situation. Nevertheless, the current situation of the local market structure in some countries is reviewed. Flow throughout the trade chain, from wholesalers to retailers and from raw material to the final product, as well as demand, supply, economic value, and implications health care are also presented.

24.2 Current Status and Trend in Medicinal Plant Resources in Africa

24.2.1 Diversity and Distribution of African Medicinal Plant Resources

Africa is the world's second largest continent after Asia, in terms of both area and population [20]. The continent has a unique diversity of geographic and climatic factors and an exceptionally rich, varied flora, with an estimated 68,000 plant species, of which about 35,000 are known to be endemic. The continent is estimated to have about 216,634 ha of closed forest area, despite a calculated annual loss of about 1% due to deforestation. Compared to other continents, most of the plants found in Africa are endemic. In the north of Africa there is a diverse ecosystem, with about 10,000 vascular plant species [21,22]. It has arid, semiarid, and a range of subclimatic zones. The Mediterranean basin is one of the 25 internationally recognized biodiversity hot spots in the world, and it has extraordinary plant diversity and species endemism. Morocco has the highest rate of species endemism in the region [23]. The habitat diversity of West Africa ranges from semidesert vegetation to savannas, tropical rainforests, and mangroves. It contains many plant species of medicinal value, especially in the rainforests. The upper Guinea forests are rich in species endemism, with nearly 2000 endemic plant species [24]. The East African region has a variety of vegetation, ranging from dense tropical forests and woodlands to dry savannas. In Tanzania, 30−40% of the floristic diversity is found in the tropical forests. The forested areas are the abode of a large number of endemic plant species. The Abyssinian highlands of Ethiopia, Somalia, and Sudan are known as the world's center of genetic diversity in cultivated plants. The biological resources of the region have great national and global economic importance. Madagascar is the world's most fascinating center of plant diversity and species endemism; it is a vast reserve of plant resources of medicinal value.

The Central African region has a wide diversity of habitats, from tropical rainforests and savannas to mangrove woods. The tropical forests are rich in floristic

diversity and species endemism. This region encompasses the Congo basin, which represents the second largest contiguous rainforest in the world after the Amazon. The Congo basin forests cover 20% of the world's tropical moist forests and 80% of the tropical moist forests of Africa. It is also one of the most biologically diverse and poorly understood ecosystems of the African continent [25]. There are about 40,850 plant species, of which about 6500 are reported to be endemic; of these, 175 are reported to be rare [26]. Southern Africa possesses a rich diversity of medicinal and aromatic plants, as well as knowledge of their use. There are about 24,000 vascular plants in the region, and 4000 of them are medicinal and aromatic. About 350 plants are widely used in traditional remedies. The Cape Floristic Province in South Africa has the greatest extratropical concentration of higher plant species in the world. This province alone has 8600 species, and 68% of them are reported to be endemic.

24.2.2 African Traditional Medicine System

Traditional medicine is defined by the WHO as the sum total of knowledge or practices, whether explicable or inexplicable, used in diagnosing, preventing, or eliminating a physical, mental, or social disease, which may rely exclusively on past experience or observations handed down from generation to generation, verbally or in writing. It also comprises therapeutic practices that have been in existence, often for hundreds of years before the development of modern scientific medicine and are still in use today without any documented evidence of adverse effects [8]. African traditional medicine is a holistic discipline that uses indigenous herbalism combined with some aspects of spirituality; it is deeply rooted in a sociocultural milieu that varies from one community to another. Practices of traditional medicine vary greatly from country to country, and from region to region, as they are influenced by factors such as culture, history, personal attitudes, and philosophy. The explicable form of traditional medicine can be described as the simplified scientific and the direct application of plant, animal, or mineral materials for healing purposes and which can be investigated, rationalized, and explained scientifically [7]. Traditional medicine includes a diversity of health practices, approaches, knowledge, and beliefs incorporating plant, animal, and/or mineral-based medicines, spiritual therapies, manual techniques, and exercises, applied singly or in combination to maintain well-being through treating, diagnosing, or preventing illnesses. The comprehensiveness of the term "traditional medicine" and the wide range of practices it encompasses make it difficult to define or describe, especially in a global context. Traditional medical knowledge may be passed on orally from generation to generation, in some cases with families specializing in specific treatments, or it may be taught in officially recognized universities. Sometimes, its practice is quite restricted geographically, and it may also be found in diverse regions of the world. However, in most cases, a medical system is called "traditional" when it is practiced within the country of origin. The term complementary or alternative medicine is used in some countries to refer to a broad set of health care practices that

are not part of the country's own tradition and are not integrated into the dominant health care system [8]. Traditional knowledge related to the health of humans and animals exists in all African countries. Every region has had, at one time in its history, a form of traditional medicine. Each African community has its own particular approach to health and disease, even at the level of ethnopathogenic perceptions of diseases and therapeutic behavior. Traditional healers and remedies made from plants play an important role in the health of millions of people [12].

24.3 Trade and Marketing

Indigenous medicinal plants have played an important role in the sociocultural, spiritual, and health care needs of rural and tribal people in Africa. In many African countries, a large portion of the population still relies on traditional systems of medicine to meet their health care needs. As a consequence, there is an enormous demand for medicinal plants for domestic use as well as commercial trading. This has led to a many-fold increase in the demand for medicinal plants and their products not only in Africa but also in many other countries around the world. The use of and trade in plants for medicine are therefore no longer confined to traditional healers but have entered both the informal and formal entrepreneurial sectors in African economies, resulting in an increase in the number of herbal gatherers and traders. The global resurgence of interest in medicinal plants provides opportunities for African countries to derive economic benefit, since a large portion of drugs produced by the pharmaceutical industry are derived from medicinal plants, and the demand for the raw materials is steadily rising. In Africa, there is a huge trade in medicinal plants on the local, regional, national, and international levels.

African countries are very rich in a plethora of natural product resources and supplies. The continent's rich botanical heritage offers an excellent opportunity to diversify away from its more traditional exports while still being able to both preserve and conserve its genetic resources. Medicinal plants are produced and offered in a wide variety of products, from crude to processed materials to packaged products including pharmaceuticals, herbal remedies, teas, spirits, cosmetics, sweets, dietary supplements, varnishes, and insecticides [27,28]. The use of medicinal plant raw materials is in many cases much cheaper than using alternative chemical substances. An estimated 70,000 plant species are used in folk medicine worldwide [29]. African medicinal plant resources are a major source of income, and the trade has a significant socioeconomic importance, as it allows millions of people to alleviate poverty by collecting and marketing plants [30–32]. In addition to the domestic trade, medicinal plants are widely exported in large volumes to the international market. The continent comes second to Asia in export figures. The global market of herbal drugs is estimated to be about $60 billion per year, growing at a rate of 7%. Most medicinal plant materials are

exported to Europe, with the rest to the United States and Asia. In 1996, about 26,500 metric tons of medicinal and aromatic plant materials were exported to Europe.

24.3.1 African Medicinal Plants and International Trade

According to the Secretariat of the Convention on Biological Diversity, cited by the WHO, global sales of herbal products totaled an estimated $60,000 million in 2002 [33]. The major part of this material is sold to plant trading companies. These plant traders hold enormous stocks, and they have the facilities to undertake the quality controls required for raw material used in the production of drugs. They play an enormously powerful role in the medicinal plant trade, partly because of the large quantities they purchase, which enables them to more or less dictate the price. This price and quality guarantee is a major incentive to the end user for whom cost, quality, reliability, and flexibility are said to be the key requirements for purchasing pharmaceutical raw materials [34]. There are also brokers who buy plant material and sell it on, adding a commission; however, they do not stock material or have any warehousing facilities. In the past, the brokers played a more important role, as they had the contacts at the purchasing level.

International trade generally has greater visibility than the domestic market because of export figures, but this is not the case for African countries. International trade in medicinal plants from African countries is very difficult to estimate because of a paucity of reliable statistics and trade secrecy. Furthermore, much of the local trade in most countries is either unrecorded or poorly classified because medicinal plants are also used in nonmedicinal end uses, which are not reported separately. Many small companies export herbal medicines, but little is known about their marketed volume or value. Domestic trade involving traditional healers and consumption at the household level is poorly recorded. It is, therefore, not possible to assess global trade in all medicinal plants on the whole continent. Therefore, this section focuses on informal local trade in raw material, unprocessed or semiprocessed, which is largely representative of the global scheme of the medicinal plant trade in most African countries, where an important bulk of indigenous medicinal plant material are traded.

24.3.2 Local Trade: Structure and Marketing Channel

24.3.2.1 Market Conditions

A global overview of the medicinal plant trade in African countries indicates that local markets have continued to be buoyant. The local market is an informal trading sector in most African countries, and the marketing channel is quite complex. The traders are organized according to type of product; thus they are found together

in the same part of the market. A wide range of wild harvested plants are traded as parts of a single species or as mixtures of plant parts from many species, in the raw form or with limited processing, and with few controls regarding quality. The conditions in the markets are generally poor.

24.3.2.2 Products Traded

Medicinal plant traders have a large assortment of products. Plants are sold in the form of roots, wood, shredded leaves, bulbs, bark, fruits, and whole plants. The products consumed are generally unrefined plant medicines with limited processing apart from grinding, chopping, and mixing. Plant products purchased are taken as medicines in the following forms: infusions, concentrates, smoke inhalants, and burnt plants.

24.3.3 Trade Structure and Marketing Channel

A wide range of wild harvested medicinal plants are traded in the local market. Trade is carried out at several levels. Plant material goes through a complex network of buyers and sellers to reach the final consumer. Plant products are collected from the wild by villagers who can be qualified as gatherers or collectors and are brought to the local markets. Traders may be either those who collect certain species in large quantities for export purposes or those who collect many assorted items in small quantities for the local market. Therefore, the first transaction is between the people who gather plant materials from the forests or nearby fields, and the village traders. After the gathering, there may be a long chain of trade, with many layers of marketing, including secondary collectors and producers, local traders, and regional wholesalers. In some countries, there are also brokers who buy plant materials and sell it on, adding a commission. Raw plant materials are bought directly by consumers, who may process it themselves following instructions provided by the healers or traders. Brokers can purchase part of these materials. The plants are traded, either in the raw form or with limited processing and with few controls regarding quality. Prices for products in the informal sectors of the medicinal plant market are highly variable; the plant materials are usually traded in units of handfuls, bowls, bags, or sacks. Products are packaged using recycled waste materials. Another category of vendors involved in the trade network is the street peddlers, who move from one market to another, depending on when each local market is open. In Sudan, for instance, brokers usually purchase on the spot large volumes of these botanicals. Their business assets are transportation means and some cash to pay in order to purchase collected plants from villagers [35]. In Ethiopia, medicinal plant products are distributed in a wide range of retail outlets, markets, and locations. Markets are frequently associated with sites of informal trading and dense clusters of small shops located near public transport nodes. Retail outlets are usually associated with concentrations of consumers, either in residential areas or in central markets [36].

Careful analysis of the medicinal plant markets in most African communities reveals a similar structure involving several levels in the supply, distribution, and consumption channel. Five major levels of medicinal plant transactions in the market can be identified: direct consumers, street traders, shop traders, traditional healers, and manufacturing companies.

24.3.4 Direct Consumers

This level of the market consists of consumers who purchase medicinal products for self-medication from street markets, shops, rural markets, or practicing healers and/or who purchase prescribed medicines from indigenous healers. They can also purchase medicinal products directly from the people harvesting or from various intermediaries, who would themselves have purchased from gatherers or other intermediaries. In urban centers in South Africa, most of the trade takes place through intermediaries, while in rural areas products are bought directly from the person who gathered the plants [37]. In rural areas of Ethiopia, self-medication is the cheapest and often the only form of health care available. Friends, relatives, and neighbors provide traditional treatment free of charge or are paid in flexible arrangements such as payment in cash, in kind, or on a credit basis [36]. Direct consumers and consumption at the household level have also contributed significantly to the buoyancy of medicinal plant products in African local markets.

24.3.5 Street Traders

The bulk of the trade in medicinal plant products is carried out by street traders. They sell a large quantity of unprocessed or semiprocessed products. In the street, plants can be sold as raw material or as partially processed (chopped or ground). In Ghana and Rwanda, street vendors' products are packaged in reused newspaper or reused liquor bottles; medicines are sold in dry powder form or in a wet mixture, most often with water being used as the liquid component. The stability and hygiene of these products is unknown, but probably varies enormously between traders and traditional healers [38]. In South Africa, the plant materials are traded in the street markets. An estimated 20% of the trade, or 220 metric tons, is reported to be traded between the street traders themselves and not to consumers, healers, or shop traders. Several traders have erected wood and tin huts for trading and storage purposes, or plastic sheets are used to cover the products at night and from rain. The street markets play both a local and a regional retailing and wholesale role, which includes supplying wholesale products to healers and shops, and retail products to end consumers. Street traders generally obtain their products from gatherers, though some traders gather plant material themselves [39].

24.3.6 Shop Traders

In this category, medicinal plants and their derivatives are locally sold in special shops. Shop owners mainly deal in whole or chopped plants and standard mixes, which they buy either in the rural areas directly from harvesters, or from street traders at the informal markets [37]. There is little standardization in terms of product quality, although recycled waste is used for packaging. In South Africa, shops are established within a shopping center, and consist of a shop with counters, extensive shelves to keep stacks of different plants, and a back area where processing takes place. They have extensive displays of plant products. Shop clients are similar to the street clients. Healers also buy from shops, but in declining volumes due to a narrow product range relative to the street trade. Some shop traders act as wholesalers to other shop owners. A wide range of medicinal products are traded, including raw materials, processed materials (such as chopped bark and standard mixes), and patent medicines. They also trade quality packaged traditional medicines supplied by manufacturers. Shop traders purchase largely from street traders and gatherers. Some of the gatherers are hawkers, while others may have direct contact with the shop trader. Shop traders may also obtain material from a local wholesaler or from other shop traders [37].

24.3.7 Traditional or Indigenous Healers

Traditional healers are present in almost every community in Africa. They are the first health care providers to be consulted in up to 80% of cases, especially in rural areas. In Ethiopia, indigenous healers commercialize the crude materials or charge together with the treatment they provide upon their diagnosis. In Sudan, traditional healers usually provide counseling to their patients in addition to dispensing herbal preparations [36]. There are also formal traditional medicine suppliers; this type of trader is widespread in almost all African countries [40], as in the South African situation, which does not differ significantly from the rest of the continent. The formal traditional medicine suppliers are made up of retail shops, health shops, pharmaceutical manufacturers, and *laissez-faire* manufacturers. In recent years, there has been a considerable growth in *laissez-faire* manufacturers of traditional medicines who make numerous claims as to the efficacy of their products. Most of these manufacturers seem not to conform to industry good manufacturing practice (GMP) standards. There are relatively few large, certified pharmaceutical manufacturers producing formalized traditional medicines.

24.4 Phytopharmaceutical Manufacturing Companies

In the context of the local plant market, there is no distinction between pharmaceutical and phytopharmaceutical companies, as both may sell products made from standardized extracts of plant material. However, phytopharmaceutical

companies use not only plant extracts but also raw plant material, for example, to make tinctures, teas, or in capsule form.

There is another category of traders in this group that has been emerging, referred to as the "ecological trade" by Lange [28]. These traders source botanical material for use generally by the smaller herbal medicine/health product companies and alternative practitioners. These trading companies tend to be more discerning and ethical in their purchasing approach, and often trade extensively in organically cultivated products. They often establish their own contacts in the source countries and have shorter sales routes involving fewer parties, partly because they purchase only raw material rather than extracts.

24.5 Supply of Medicinal Plants in Africa

The indigenous medicine market is based on indigenous plants that are generally harvested from natural vegetation [37]; a very small number of species are cultivated. Kuipers [18] reported that there are two sources of supply of medicinal plants: (1) material collected from the wild and (2) cultivated material. In some countries, harvesting is carried out with or without the consent of the landowners or local authorities. For consumption at the household level, families rely on medicinal plants from the home garden, or on weeds that grow wild around human habitation. The cultivated medicinal plants are mostly produced in home gardens, either for medicinal or other primary purposes. Globally, this remains complex to assess as it is difficult to distinguish between wild and cultivated material in the market.

24.6 Overview of Local Trade in Some Selected African Countries

Benin: In Benin, most markets exhibit an array of products including vegetables, fruits, household products, animals and livestock, fish and meat, construction materials, and medicinal and magical plants. Most plant parts are typically sold in bundles, with between 2 and 10 pieces of root or bark in a bundle. Prices are highly dependent on the species, but prices per bundle typically range between \$0.10−0.40 for green leaves or branches and \$0.40−0.80 for bark and roots [41]. Medicinal plant parts commonly sold vary according to species: roots (*Bridelia ferruginea*, *Rauvolfia vomitoria*, *Caesalpinia bonduc*, *Mondia whitei*, *Sarcocephalus latifolius*, *Zanthoxylum zanthoxyloides*), bark (*B. ferruginea* and *Nauclea xanthoxylon*), and seeds (*C. bonduc*). The major marketing channels identified from a survey carried out by Vodouhe et al. [42] included collectors, wholesalers, retailers, and consumers. Collectors, who are key actors, have the lowest gross margins compared with retailers, who have the highest margins. Collectors seeking higher profit collect more plants and thus destroy vegetation

and species diversification. Plant parts are collected in their natural habitats and brought to the market for sale. The sites where plant parts are collected are not far from the markets. Collectors bring products to the markets and sell them directly to retailers (Table 24.1) [42].

Cameroon: Medicinal plants are sold regularly on the markets of urban centers in Cameroon all the year. According to a survey carried out by Betti [43] on medicinal plants sold in Yaoundé markets, a total of 35 medicinal plants were sold by 18 sellers. The Annonaceae, Mimosaceae, Caesalpiniaceae, and Euphorbiaceae were the more frequently represented plant families. Dibong et al. [46] reported 29 genera belonging to 25 families were sold in three markets of Douala, the dominant species being of the Magnoliopsida family. Cameroon is also the major source of *P. africana* (Hook.f) Kalkman bark. Over the past 40 years, the trade in *P. africana* bark harvest from Cameroon has changed from low-volume subsistence use as a local medicine and for timber and fuel wood to a high-volume international trade predominantly driven by the European and American pharmaceutical industry and the "botanicals" health product sector. The bark is mainly sourced from the southwest and northwest provinces of Cameroon, Mount Cameroon, Mount Kupe, and the Bamenda Highlands. In 1976, about 10 metric tons of bark were exported to France. About 11,537 metric tons from 1986 to 1991 and 600 to 920 metric tons in the period 1994−1995 were processed by a local trade company in southwestern Cameroon [51]. The bark is exported both raw and as extracts. In the period between 1985 and 1994, the annual export of bark extract was 8990 kg, corresponding to 1116−3900 metric tons of bark. World trade was worth $220 million in the late 1990s [52]. The bark of *P. africana* is sold in its raw form in many markets, which exist everywhere in the regions where it is produced. The hawkers sell it in other regions of the country as well, where it is used as a traditional medicine. Another data source on the trade of *P. africana* bark revealed that 3083 metric tons were exported from Cameroon between 2005 and 2007 [53].

Egypt: According to Karan and Kumar [51], the annual export of medicinal plants is valued at more than $43.17 million. High quality added value crops such as chamomile, fennel, and peppermint have the potential to boost Egyptian exports. The country is the main supplier of German chamomile (*Matricaria recutita* L.). About 500−600 metric tons of Egyptian henbane (*Hyoscyamus muticus* L.) are exported annually to Germany. Alexandrian senna (*S. alexandrina* Mill.) is a significant export item which grows wild and can also be cultivated. Major markets for the medicinal plant trade in Egypt are Attarin in Cairo, El-Tour, Sharm El-Sheikh, and Dahab. The small-scale pharmaceutical production units in El-Tour also export some quantity of medicinal plant material [51].

Ethiopia: The average national annual output of exudates in the period between 1978 and 1991 was over 1500 metric tons. Since 1992, production has grown to over 2000 metric tons [51]. Bekele [36] reported data on the trade in medicinal plants in Ethiopian market. According to this report, most of the medicinal plants used by the herbalists in Ethiopia are collected from natural vegetation, but home-based medicinal plant use relies on plants from the home garden and weeds that

Table 24.1 Medicinal Plants Commonly Found in Some African Local Market

Plant Name	Family	Part Used	Traditional Use	Countries Involved in Trade	Average Price/kg (US$)	References
Adenia gummifera (Harv.) Harms	Passifloraceae	Roots	–	South Africa	–	–
Aframomum melegueta K. Schum.	Zingiberaceae	Fruits, leaves	Male sexual impotence, measles, ritual, aphrodisiac, spice	Nigeria, Ghana, Cameroon	1.6	[43–45]
Afrostyrax lepidophyllus	Huaceae	–	Convulsions	Ghana	–	[44]
Ageratum conyzoïdes Linn.	Asteraceae	–	–	Cameroon	–	[46]
Albizia versicolor Welw.	Fabaceae	Root bark	Anemia, anthelmintic, sterility in women	–	–	[12]
Alepidea amatymbica	Apiaceae	–	–	South Africa	0.32	[47]
Aloe vera Linn.	Liliaceae	Leaves	Malaria, baldness	Cameroon, Ethiopia	1.65	[36,46]
Alstonia boonei De Wild.	Apocynaceae	–	Convulsions, ulcers, measles	Ghana	0.630	[12]
	Apocynaceae	Stem bark	Hypertension, hemorrhoids, malaria/fever	Cameroon	3.2	[43,46]
Anonidium mannii (Oliv.) Engl. & Diels	Annonaceae	Stem bark	Male impotence, lumbago	Cameroon	4.3	[43]
Anthocleista vogelii Planch.	Loganiaceae	Bark	Anemia	Cameroon	–	[46]
Antrocaryon klaineanum Pierre	Anacardiaceae	Stem bark	Chlamydiae	Cameroon	8	[43]
Argemone mexicana L.	Papaveraceae	Leaves	Measles	Nigeria	–	[45]
Artabotrys brachypetalus Benth.	Annonaceae	Roots	–	South Africa	–	–
Artemisia herba-alba	Asteraceae	Whole plant	Antispasmodic	Egypt	3.88	[14]

Artemisia judaica Lour.	Asteraceae	Whole plant	Anthelmintic, insect repellent	Egypt	10.79	[14]
Aspalathus linearis	Fabaceae	Leaves	–	Sub-Saharan countries	–	[3]
Baillonella toxisperma Pierre	Sapotaceae	Stem bark	Diabetes, kidney disorders, anemia, lumbago	Cameroon	13.64	[43,46]
Bambusa vulgaris L.	Gramineae	Leaves	Measles	Nigeria	–	[45]
Bidens pilosa Linn.	Asteraceae	Leaves, bark	Diabetes, kidney disorders	Cameroon	–	[46]
Bosqueia angolensis Ficalho.	Moraceae	Bark	Blood supply	Nigeria	–	[45]
Brackenridgea zanguebarica	Ochnaceae	Bark	–	Mozambique	–	[48]
B. ferruginea (Benth.)	Euphorbiaceae	Roots, bark	Diarrhea, dysentery, food poisoning	Benin	0.54−6.8	[42]
Bridelia atroviridis Mull. Arg.	Phyllanthaceae	Leaves	Eczema	Nigeria	–	[45]
Cardiogyne africana Bureau	Moraceae	Roots	–	South Africa	–	–
Carica papaya Linn.	Caricaceae	Leaves	Jaundice	–	–	[46]
Carrisa spinarum	Apocynaceae	–	–	Ethiopia	0.94	[36]
Cassia alata Linn.	Cesalpiniaceae	Leaves	Yellow fever	Cameroon	–	[46]
Cassia didymobotrya L.	Caesalpinioideae	Leaves	Anemia, anthelmintic, laxative	–	–	[12]
C. bonduc (Linn.) Roxb.	Caesalpiniaceae	Roots, seeds	–	Benin	0.54−1.292	[42]
Ceiba pentandra (L.) Gaertn	Bombacaceae	Bark	Malaria, chlamydia	Cameroon	–	[46]
	Bombacaceae	Stem bark	Asthma, neuritis	Cameroon	5.7	[43]
Cissus rotundifolia (Forssk.) Vahl	Vitaceae	Roots	–	South Africa	–	–
Cleome droserifolia Delile	Capparaceae	Whole plant	Infantile convulsions	Egypt	6.46	[14]

(*Continued*)

Table 24.1 (Continued)

Plant Name	Family	Part Used	Traditional Use	Countries Involved in Trade	Average Price/kg (US$)	References
Cola gigantea A. Chev.	Sterculiaceae	Leaves	Blood supply	Nigeria	–	[45]
Corynanthe pachyceras	Rubiaceae	–	–	Ghana	–	[48]
Costus afer Ker-Gawl.	Costaceae	Leaves	Malaria, yellow fever, typhoid	Cameroon	–	[46]
Croton macrostachyus	Euphorbiaceae	–	–	Ethiopia	15.75	[36]
Cryptolepis sanguinolenta	Asclepiadaceae	Leaves, roots	–	Sub-Saharan countries	–	[3]
Cucumis prophetarum, *Cucumis ficifolius*	Cucurbitaceae	–	–	Ethiopia	0.28	[36]
Cussonia arenicola Strey.	Araliaceae	Roots	–	South Africa	–	–
Cylicodiscus gabunensis Harms	Mimosaceae	Stem bark	Gonorrhea	Cameroon	4	[43]
Cymbopogon citratus Stapf.	Poaceae	Leaves	Malaria, jaundice	Nigeria, Cameroon	–	[45,46]
Dacryodes edulis (G. Don.) H.J. Lam	Burseraceae	Leaves	Anemia	Cameroon	–	[46]
Dennettia tripetala	Annonaceae	–	–	Ghana	–	[48]
Dissotis prostrata Thon. Benth.	Melastomataceae	Leaves	Malaria, typhoid	Cameroon	–	[46]
Drimia sanguinea	Asparagaceae	–	–	South Africa	2.36	[47]
Drypetes gossweileri	Euphorbiaceae	Stem bark	Diarrhea, abdominal pain	Cameroon	10	[43]
S. Moore	Euphorbiaceae	Stem bark	Lumbago	Cameroon	–	[43]
Duparquetia orchidacea	Fabaceae	–	–	Ghana	–	–
Echinops kebericho	Asteraceae	–	–	Ethiopia	3.06	[36]
Elaeis guineensis Jacq.	Arecaceae	Sap	Lactation failure, food poisoning, diarrhea, abdominal pain	Cameroon	1.2	[43]

Embelia schimperi	Myrsinaceae	–	–	Ethiopia	3.39	[36]
Emilia coccinea (Sims) G. Don	Asteraceae	Leaves	Stomach disorders	Cameroon	–	[46]
Enantia chlorantha Oliv.	Annonaceae	Stem bark	Anemia, malaria/fever, jaundice	Cameroon	4.6	[43,46]
Enantia polycarpa	Annonaceae	–	Fever, malaria, stomach ulcers	Ghana	0.023	[12]
Entada abyssinica Steud.	Fabaceae	Roots, bark	Chronic cough, headache, stomach pain	–	–	[12]
Entandrophragma candollei Harms	Meliaceae	Bark	Malaria, yellow fever, typhoid	Cameroon	–	[46]
Entandrophragma cylindricum (Sprague)	Meliaceae	Bark	Typhoid	Cameroon	–	[46]
Eremomastax speciosa (Hochst.) Cufod.	Acanthaceae	Leaves	Anemia, cough	Cameroon	–	[46]
Erythrophleum suaveolens (Guil. & Perr.) Brenan	Caesalpiniaceae	Stem bark	Wounds	Cameroon	10	[43]
Eucalyptus saligna Smith	Myrtaceae	Leaves	Herpes	Cameroon	–	[46]
Eucomis pallidiflora	Asparagaceae	–	–	South Africa	4.2	[47]
Euphorbia quadrangularis Pax	Euphorbiaceae	Aerial parts	Body weakness	–	–	[12]
Ficus capensis Thunb.	Moraceae	Leaves	Blood supply	Nigeria	–	[45]
Ficus platyphylla Delile	Moraceae	Roots	–	South Africa	–	–
Ficus stuhlmannii Walp.	Moraceae	Stem bark	Chronic wounds	–	–	[12]
Garcinia kola Heckel.	Guttiferae	Bark, roots, seeds	Body pain reliever, diarrhea, abdominal pain, male impotence	Nigeria, Cameroon	4	[43,45,46]

(*Continued*)

Table 24.1 (Continued)

Plant Name	Family	Part Used	Traditional Use	Countries Involved in Trade	Average Price/kg (US$)	References
Glinus lotoides	Molluginaceae	–	–	Ethiopia	2.26	[36]
Gloriosa superba	Liliaceae	Seeds	–	Mozambique	–	[48]
Gnetum africanum Welw.	Gnetaceae	Leaves	Anemia	Cameroon	1.6	[43]
Gnidia kraussiana	Thymelaeaceae	Tuber	Constipation, swollen stomach	–	–	[12]
Griffonia simplicifolia	Fabaceae	Seeds	–	Ghana, Ivory Coast, Cameroon	–	[48]
Guarea thompsonii Sprague & Hutch.	Meliaceae	Stem bark	Lumbago	Cameroon	9	[43]
Guibourtia tessmannii (Harms) Léonard	Caesalpiniaceae	Stem bark	Anemia, hernia, convulsions, malaria/ fever, lumbago	Cameroon	7.2	[43]
Hagenia abyssinica	Rosaceae	–	–	Ethiopia	2.86	[36]
Harpagophytum procumbens	Pedaliaceae	Roots	–	Namibia, Mozambique, Botswana	–	[48]
Harpagophytum zeyheri	Pedaliaceae	Roots	–	Namibia, Mozambique, Botswana,	–	[48]
Helichrysum kraussii	Asteraceae	–	–	South Africa	0.29	[47]
Hexalobus crispiflorus A. Rich.	Annonaceae	Stem bark	Gonorrhea	Cameroon	6	[43]
Hunteria eburnea	Apocynaceae	Bark	–	Ghana	–	[48]
Hydnora johannis	Hydnoraceae	–	–	Ethiopia	17.95	[36]
Hypoxis hemerocallidea Fisch. & C.A. Mey	Hypoxidaceae	Roots/tubers	–	South Africa	–	–

Hypoxis obtusa	Hypoxidaceae	–	–	South Africa	2.76	[47]
Irvingia gabonensis (Aubry-Lecomte ex O'Rorke) Baill.	Irvingiaceae	Stem bark	Jaundice	Cameroon	5.5	[43]
I. gabonensis	Irvingiaceae	Stem bark	Amebic dysentery	Cameroon	–	[43]
Isolona hexaloba (Pierre) Engl. & Diels	Annonaceae	–	–	Cameroon	2.8	[43]
I. hexaloba	Annonaceae	Stem bark	Constipation	–	–	[43]
Jasminum abyssinicum	Oleaceae	–	–	Ethiopia	1.43	[36]
Jateorhiza palmata	Liliaceae	Roots	–	Tanzania, Mozambique	–	[48]
Kalanchoe crenata (Andrews) Haw.	Crassulaceae	Leaves	Malaria, yellow fever, typhoid	Cameroon	–	[46]
Khaya ivorensis A. Chev.	Meliaceae	Bark	Blood supply	Nigeria	–	[45]
Khaya senegalensis	Meliaceae	–	Blood tonic, malaria, stomach ulcers, waist pain, menstrual pain, headache, ulcers	Ghana	0.115	[44]
Kirkia wilmsii	Anacardiaceae	–	–	South Africa	2.12	[47]
Klainedoxa gabonensis Pierre	Irvingiaceae	–	–	Cameroon	19	[43]
Lantana camara Linn.	Verbenaceae	Leaves	Malaria, yellow fever	Cameroon	–	[46]
Lawsonia inermis L.	Lythraceae	Leaves	Typhoid	Nigeria	–	[45]
Lecaniodiscus cupanioides Planch. ex Benth.	Sapindaceae	Roots	Heal fractures and wounds of the leg	Nigeria	–	[45]
	Ochnaceae	Bark	Typhoid	Nigeria	–	[45]

(*Continued*)

Table 24.1 (Continued)

Plant Name	Family	Part Used	Traditional Use	Countries Involved in Trade	Average Price/kg (US$)	References
Lophira alata Banks ex F. Gaertn.f.						
Mammea africana Sabine	Clusiaceae	Stem bark	Chlamydia	Cameroon	7.9	[43]
Mentha longifolia (L.) Huds.	Lamiaceae	Leaves	Antispasmodic	Egypt	10.79	[14]
Milicia excelsa (Welw.) Berg.	Moraceae	Stem bark	Stomach pain	Cameroon	80	[43]
Mitragyna stipulosa (DC) O. Kuntze	Rubiaceae	Stem bark	Lactation failure	Cameroon	3.4	[43]
Momordica charantia	Cucurbitaceae	–	Ritual, fever, measles, abortion	Ghana	–	[44]
M. whitei (Hook.f.) Skeels	Periplocaceae	Roots	Deworming	Nigeria, Benin	0.784–7.205	[42,45]
Monodora myristica	Annonaceae	–	Spice, induce menstruation	Ghana	–	[44]
Morinda lucida	Rubiaceae	–	Aphrodisiac, puerperal fever, phlegm, malaria	Ghana	–	[44]
Mucuna sloanei	Fabaceae	–	Ritual	Ghana	–	[44]
Myrsine africana	Myrsinaceae	–	–	Ethiopia	2.13	[36]
N. xanthoxylon (A. Chev.) Aubrev.	Rubiaceae	Bark	–	Benin	0.87–7.07	[42]
Nauclea diderrichii (De Wild.) Merril	Rubiaceae	Stem bark	Lumbago	Cameroon	6.6	[43]
Nauclea latifolia Sm.	Rubiaceae	Roots	Jaundice	Nigeria	–	[45]
*Nephrolepis s*p.	Davalliaceae	Leaves	Urinary tract infections	Cameroon	–	[46]
Nesogordonia papaverifera (A. Chev.) R. Capuron	Sterculiaceae	Bark	Fibroid	Nigeria	–	[45]
Nicotiana tabacum Linn.	Solanaceae	Leaves	Baldness	Cameroon	–	[46]
Ocimum americanum	Lamiaceae	–	Ritual	Ghana	–	[44]

Ocimum basilicum Linn.	Lamiaceae	Leaves	Skin disorders	Cameroon	–	[46]
Ocimum lamiifolium	Lamiaceae	–	–	Ethiopia	5.41	[36]
Okoubaka aubrevillei	Octonemataceae	–	Ritual, convulsions, miscarriage prevention	Ghana	–	[44]
Oldfieldia africana Benth. & Hook.f.	Euphorbiaceae	Stem bark	Old wound	Cameroon	13	[43]
Olea europaea	Oleaceae	–	–	Ethiopia	0.90	[36]
Origanum syriacum L.	Verbenaceae	Seeds, roots	Urine retention, toothache	Egypt	3.88	[14]
Pachyelasma tessmannii (Harms) Harms	Caesalpiniaceae	Fruits	Diarrhea, abdominal pain, diabetes	Cameroon	6.4	[43]
Panax ginseng C.A. Meyer	Araliaceae	Roots	Typhoid	Cameroon	–	[46]
Passiflora foetida Linn.	Passifloraceae	Leaves	Yellow fever, fontanel, menstrual cramps	Cameroon	–	[46]
Paullinia pinnata	Sapindaceae	–	Bone diseases, fertility enhancer, fracture, rheumatism, joint diseases, waist and joint pains, stomach ulcer	Ghana	0.093	[12]
Pausinystalia yohimbe (K.Schum.) Pierre ex Beille	Rubiaceae	Bark	Sexual weakness	Cameroon	–	[46]
	Rubiaceae	Bark	–	Cameroon	–	–
Pentaclethra macrophylla Benth.	Mimosaceae	–	–	Cameroon	6.5	[43]
Physostigma venenosum	Fabaceae	Fruits	–	Ivory Coast, Nigeria	–	[48]
Picralima nitida (Staph) Th. & H. Dur.	Apocynaceae	Bark, leaves, roots, fruits	Malaria, yellow fever, typhoid	Cameroon	–	[46]
	Apocynaceae	Fruits	Jaundice, malaria/fever	Cameroon	8.6	[43]
Piptadeniastrum africanum (Hook.f.) Bren.	Mimosaceae	Stem bark	Meningitis, convulsions, wounds, lumbago	Cameroon	4.4	[43]

(*Continued*)

Table 24.1 (Continued)

Plant Name	Family	Part Used	Traditional Use	Countries Involved in Trade	Average Price/kg (US$)	References
P. africana	Rosaceae	Bark	–	Cameroon, Madagascar, Kenya, Uganda	–	[48]
Pteleopsis suberosa	Combretaceae	–	Clean uterus, STDs (Sexually transmitted diseases)	Ghana	–	[44]
Pycnanthus angolensis (Welw.) Exell	Myristicaceae	–	Blood tonic, constipation, menstrual pains, unstable pregnancy, stomach ulcers	Ghana	0.07	[12]
	Myristicaceae	Stem bark	Hemorrhoids, vomiting, constipation	Cameroon	18	[43]
Raphia mombuttorum Drude	Arecaceae	Stem bark, sap	Lactation failure, anemia, diabetes	Cameroon	4.58	[43]
R. vomitoria (Afzel.)	Apocynaceae	Roots	–	DRC, Rwanda, Mozambique	–	–
	Apocynaceae	Roots	–	Benin	0.42–7.04	[42]
	Apocynaceae	–	Aphrodisiac, piles, blood cleansing	Ghana	0.076	[12]
Ricinodendron heudelotii (Baill.) Pierre ex Heckel.	Euphorbiaceae	Seeds	Elasticity of the womb, increased fertility, menstrual disorder and pain	Ghana	0.121	[12]
	Euphorbiaceae	–	–	Cameroon	5	[43]
Ricinus communis	Euphorbiaceae	Seeds	–	–	–	–
Rumex abyssinicus	Polygonaceae	–	–	Ethiopia	5.63	[36]
Sacoglottis gabonensis (Baill.) Urban	Humiriaceae	Stem bark	Diabetes	Cameroon	6.6	[43]

Salvia acetabulosa L.	Lamiaceae	Leaves	Urinary tract disease	Egypt	6.47	[14]
S. latifolius (Smith) Bruce	Rubiaceae	Roots	–	Benin	1.3–3.5	[42]
Schrebera arborea A. Chev.	Oleaceae	Seeds	Skin tear on a child's head	Nigeria	–	[45]
Securidaca longepedunculata	Vitaceae	Roots	Infertility	Ethiopia, South Africa	1.12	[36,49]
Senna alexandrina Mill.	Caesalpiniaceae	Whole plant	Bronchial asthma	Egypt	2.81	[14]
Senna occidentalis, *Senna italica*	Caesalpiniaceae	–	–	Ethiopia	3.17	[36]
Senna petersiana (Bolle)	Caesalpinioideae	Roots	–	South Africa	–	–
Silene macrosalen	Caryophyllaceae	–	–	Ethiopia	2.95	[36]
Siphonochilus aethiopicus	Zingiberaceae	–	–	South Africa	0.294	[47]
Sorghum bicolor	Poaceae	–	Strengthen pregnant women, anemia	Ghana	–	[44]
Sphenocentrum jollyanum Pierre	Menispermaceae	–	Aphrodisiac	Ghana	–	[44]
	Menispermaceae	Roots	Malaria, typhoid	Nigeria	–	[45]
Staudtia kamerunensis Warb.	Myristicaceae	Stem bark	Vomiting, intestinal helminthiasis, constipation, scabies	Cameroon	3.3	[43]
Strophanthus gratus	Apocynaceae	Fruits	–	Cameroon	–	[48]
Strophanthus hispidus	Apocynaceae	–	STDs, fever during pregnancy, body pain	Ghana	–	[44]
Strophanthus kombe	Apocynaceae	Fruits	–	–	–	[50]
Strychnos heterodoxa Gilg.	Loganiaceae	Roots	Inflammation, fever	–	–	[12]
Syzygium guineense (Willd.) DC	Myrtaceae	Bark	Purgative	Nigeria	–	[45]
Tabernaemontana elegans	Apocynaceae	Seeds	–	Mozambique	–	[48]
Tabernaemontana elegans Stapf.	Apocynaceae	Roots	–	South Africa	–	–
Taverniera abyssinica	Fabaceae	–	–	Ethiopia	4.56	[36]

(*Continued*)

Table 24.1 (Continued)

Plant Name	Family	Part Used	Traditional Use	Countries Involved in Trade	Average Price/kg (US$)	References
Teucrium polium L.	Lamiaceae	Whole plant	Skin allergy	Egypt	8.63	[14]
Terminalia sericea Burch.	Combretaceae	Roots, bark	Diarrhea, vomiting, stomach problems	Ghana, Mozambique	0.094	[12,14]
Tetrapleura tetraptera (Schum. & Thonn.) Taub.	Mimosaceae	Stem bark	Vomiting	Cameroon	5	[43]
Theobroma cacao L.	Sterculiaceae	Bark	Blood supply	Nigeria	–	[45]
Thymus decussatus	Labiatae	Leaves, flowers, roots	Toothache, antispasmodic	Egypt	9.71	[14]
Tiliacora funifera (Miers) Oliv.	Menispermaceae	Roots	–	South Africa	–	–
Treculia africana Decne.	Moraceae	Roots	Skin irritation	Nigeria	–	[45]
Voacanga africana Stapf.	Apocynaceae	Seeds	–	Cameroon, Ivory Coast	–	[50]
	Apocynaceae	Leaves	Typhoid	Cameroon	–	[46]
Voacanga thouarsii	Apocynaceae	Seeds	–	Cameroon	–	[48]
Warburgia salutaris (Bertol.f.) Chiov.	Canellaceae	Bark	–	South Africa	–	–
Withania somnifera	Solanaceae	–	–	Ethiopia	3.03	[36]
Ximenia americana	Olacaceae	–	–	Ethiopia	34.92	[36]
Xylopia aethiopica	Annonaceae	–	Laxative, ritual, spice	Ghana	–	[44]
Zanthoxylum heitzii (Aubr. & Pell.)	Rutaceae	Stem bark	Male impotence	Cameroon	11	[43]
Z. zanthoxyloides (Lam.) Zepen.	Rutaceae	Roots	–	Benin	0.33–7.74	[42]
Zingiber officinale Rosc.	Zingiberaceae	Roots	Typhoid	Nigeria	–	[45]

(–), data not available.

grow wild around human habitation. The cultivated medicinal plants are mostly produced in home gardens, either for medicinal or other primary purposes. The informal trade takes the major share in rural areas, except at the level of healers who commercialize just the crude materials or together with the treatment they provide upon their diagnosis. In the countryside, people may access medicinal plant products through informal information networks in addition to market days, which take place weekly or twice a week. In rural areas of Ethiopia, medicinal plant treatments may also be given free of charge, but some token is believed to be in order for the medicine to take effect. In rural areas of Ethiopia, self-medication using indigenous medicine is the cheapest and often the only form of health care available [36].

Ghana: Tinde et al. [44] reported that the trade in herbal medicine is of considerable economic importance to Ghana. An estimated 951 metric tons of crude herbal medicines are sold annually at the herbal markets sampled in this study, with a total value of around $7.8 million. Accra has five markets where substantial amounts of medicinal plants are sold. In the same study, 244 medicinal plant products belonging to 209 species were recorded. *X. aethiopica*, *M. myristica*, and *A. melegueta* were the plants most frequently in demand, followed by the medicinal bark of *K. senegalensis* and *Pteleopsis suberosa* [44]. Market stalls are generally large ones, selling substantial amounts of herbs, bark, roots, pottery, and animal products. The species of plants most frequently requested for malaria in Ghana are *M. lucida* Benth. and *N. latifolia* Sm. [54].

Kenya: Eighty-nine plant species were found to be sold in two urban areas in Kenya (Thika and Nairobi). These species were found to belong to 42 families, most of the species being in the families Asteraceae, Solanaceae, Rutaceae, and Rubiaceae [55]. Most traders have established clinics for treatment of patients as well as dispensing herbal remedies; this category of traders, as along with retailers of herbal products, comprises the most popular form of commercial herbal traders in this study area. Rural herbalists are the main suppliers. Plant materials are collected from urban processors, but each level of the supply channel can make its own collection of materials in the rural wild areas, usually from the forests. Data from Karan and Kumar [51] revealed that Kenya exports significant quantities of *P. africana*, *W. salutaris*, and *Aloe* spp. to the international market. Since 1990, about 1100 metric tons of *P. africana* bark have been sold to the French firm Prosynthese. Kenya has exported annually about 300 metric tons of bark worth about $0.57 million. About 79 metric tons of *W. salutaris* (Bertol.f.) Chiov. bark or extract, worth $0.14 million, and about 5 metric tons of *Aloe* spp. extract, worth $5986 were exported to Germany in 1992 and 1993, respectively. Furthermore, Kenya is the major supplier of *Tanacetum cinerariifolium* to the world market and has dominated world production since 1933, when it first started commercial production of *T. cinerariifolium* [51].

Nigeria: Local markets form an integral part of the life and culture of the people of Nigeria. The markets are also important socioeconomic institutions. The traders in these markets sell large amounts of medicinal plants to the locals

and foreigners who seek their help. Most of the plant parts (barks, roots, stems, and leaves) are sold in dried form. The majority of medicinal plant traders were women (64.29%) between the ages of 40 and 60 years [45]. According to Karan and Kumar [51], Nigeria is the second largest supplier of gum arabic to the international market, with an annual production of 4000−10,000 metric tons. In northern Nigeria, gum arabic is produced by tapping *Acacia senegal* (L.) Willd. and natural exudates of *Acacia seyal* Delile. Despite large afforestation schemes involving *A. senegal*, most of the gum arabic production comes from wild trees [51].

Sudan: A study carried out by Khalid et al. [35] described the situation of medicinal trade in Sudan markets. In this country, medicinal and aromatic plants and their derivatives are sold locally in special shops called *atareen*. Brokers usually purchase on the spot large volumes of these botanicals; their business assets are means of transportation and some cash to pay in order to purchase collected plants from villagers. Collectors of wild medicinal plants may be either those who collect certain species in large quantities for export purpose or those who collect many assorted items in small quantities for the local market. The number of unknown traditional healers (herbalists, bone-setters, and spiritual practitioners) is large. Elderly religious men and women and some guardians of holy tombs and mosques usually practice traditional healing in Sudan. They usually purchase their material from collectors or collect it themselves. Karan and Kumar [51] reported that Sudan imports a variety of plant species for use in traditional medicine in their crude form or as herbal teas. Plant materials are mainly imported from Egypt, Syria, India, China, Niger, Guatemala, Saudi Arabia, Tanzania, and other African countries. The estimates of plant material imported from these countries were more than 800 metric tons between 1993 and 1996, and exceeded 1000 metric tons in 1992. This costs the country about $900,000 annually. However, these figures do not cover the smuggled materials and imports through unofficial channels. The annual export value of medicinal and aromatic plants from Sudan was worth $10 million in the period between 1995 and 1999. Sudan is one of the main gum-producing countries, exporting gum arabic as a primary product to Western European countries and the United States. The largest markets for this commodity are the EU, Switzerland, and Scandinavia (40% of the world market), the United States (25%), and Japan (10%) [51].

South Africa: The trade in traditional medicines in South Africa is estimated to be worth R2.9 billion per year, representing 5.6% of the National Health budget. With 27 million consumers, the trade is vibrant and widespread. There are at least 133,000 people employed in the trade, a large percentage of them being rural women [39]. According to Dold and Cocks [56], a minimum of 166 medicinal plant species were traded in the Eastern Cape Province, amounting to 525 metric tons of plant material valued at approximately R27 million annually. The same study reported that poorly educated black middle-aged women of low economic standing dominate the trade. In KwaZulu-Natal, an estimated 4500 metric tons of plants are traded annually, while in the Durban street

markets approximately 1200 metric tons of plants are traded annually. Over 400 species are traded in the markets, both wholesale and retail. Products are sold in both the whole form or in a semiprocessed form, where products are chopped into small pieces [57]. Mander [37] made an overview of the demand, supply, current marketing practices, potential, and limitations within the medicinal plant market in KwaZulu-Natal province in South Africa, and specifically in Durban. The study found that over 400 species of plants are marketed in large quantities within KwaZulu-Natal. While the mixing and prescription of plant products is sophisticated, the processing and development of products are extremely limited. Local trade is largely informal, with much cross-border trading taking place [37].

24.7 Medicinal Plant Products Industry and Manufacturing

24.7.1 Medicinal Plants in Industry

Medicinal and aromatic plants are botanical raw materials, also known as herbal drugs, that are primarily used for therapeutic, aromatic, and/or culinary purposes as components of cosmetics, medicinal products, health foods, and other natural health products. There is a clear industrial demand for medicinal plants, thanks to the increasing production of herbal health care formulations, herbal-based cosmetic products, and herbal nutritional supplements. Natural products made from medicinal plants are increasingly prescribed, and this has led to a growing pharmaceutical industry and small-scale processing for herbal product manufacturing [58,59]. Thus, medicinal plants are employed not only in medicine but also in the nutrition and cosmetics industries. According to De Silva [49], a wide range of products can be made from medicinal plants; for instance, herbal products can be used in conventional and traditional medicine, in food supplements/dietary supplements and foodstuffs, or in cosmetics (Figure 24.1).

24.7.2 Main Applications of Medicinal Plants in Industry

The main industrial sectors which use medicinal plants are medicine, herbal, foodstuffs, and cosmetics. Within these sectors, we find the following industries: pharmaceutical and herbal, food, conditioning, essential oil manufacture, and extraction-formulation industries. The pharmaceutical industry is the most important user of medicinal plants; this group includes all therapeutic and preventive uses of medicinal plants. The pharmaceutical and herbal industries use dried plants, extracts, or isolated active ingredients to manufacture medicines. But this sector also includes the aromatherapy industry, which is another important branch that has created a market, generating a demand for essential oils of a higher

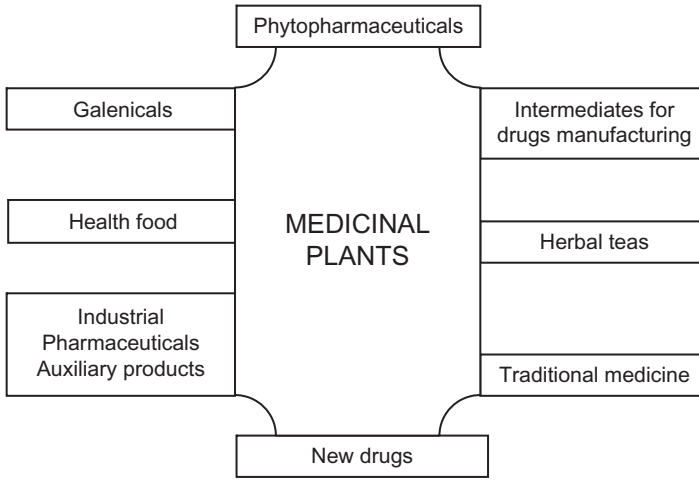

Figure 24.1 Industrial uses of medicinal plants [47].

quality than traditionally accepted. Pharmaceutical companies use medicinal plants for the isolation of single purified drugs or in advanced extract form, where the extract is highly standardized in terms of its active constituents. In many cases, these are in admixtures with other ingredients. The cosmetics and parapharmacy industries are major consumers of vegetable derivatives and medicinal plants such as oils, essential oils, and waxes for the manufacture of cosmetic products, bath gels, deodorants, mouthwashes, toothpastes, elixirs, and so on. Over the past few years, demand has increased considerably due to a rise in the use of natural products [59].

In the food sector, there are many areas in which the food industry uses medicinal plants and their derivatives, among them the enhancement of quality. Precooked meals are increasingly taking the place of home-cooked food, and their preparation requires the use of antioxidants, preservatives, flavor enhancers, and coloring agents, all of natural origin. The food-farming industry is increasingly using natural condiments rather than synthetic ones; this group encompasses the spice and condiment industry as well as food additives, preservatives, and coloring agents.

In Africa, although there are some problems limiting the development of phytomedicine such as lack of standardization, efficacy, and quality control of plants used, there are some registered herbal industries, and a multitude of unregistered cottage-level herbal enterprises are involved in the manufacturing of herbal medical formulations based on African systems of medicine. Table 24.2 gives some African industrial companies involved in the development of natural products from African medicinal plants.

Table 24.2 Some African Companies, Suppliers of Medicinal Plant Products

Product Name	Distributor	Plant Source	Part Used	Medicinal Use	Country
Aloe powder extract	Afriplex Pty. Ltd.	*Aloe ferox*	–	–	South Africa
Sutherlandia frutescens PE	Afriplex Pty. Ltd.	*Sutherlandia frutescens*	Twigs, leaves	Mental and chemical stress	South Africa
Warburgia raw material	Big Tree Neutraceuticals	*Warburgia* sp.	Bark, leaves	Antimicrobial, antifungal	South Africa
African ginger raw material	Big Tree Neutraceuticals, Holle	*Zingiber* sp.	Roots	Anti-inflammatory, pain reliever	South Africa
Sutherlandia frutescens raw material	Big Tree Neutraceuticals	*S. frutescens*	Whole plant	Daptogen, immune stimulant	South Africa
Sceletium tortuosum raw material	Big Tree Neutraceuticals	*Sceletium tortuosum*	Whole plant	Antidepressant, mood enhancer	South Africa
Warburgia 100 mg tablets	Big Tree Neutraceuticals	*Warburgia* sp.	Inner bark	Antimicrobial, antifungal	South Africa
Sceletium 50 mg tablets	Big Tree Neutraceuticals	*Sceletium tortuosum*	Whole plant	Antidepressant, mood enhancer	South Africa
Sutherlandia frutescens 300 mg tablets	Big Tree Neutraceuticals	*S. frutescens*	–	Adaptogen, immune stimulant	South Africa
Sutherlandia frutescens 350 mg vegetarian capsules	Big Tree Neutraceuticals	*S. frutescens*	–	Adaptogen, immune stimulant	South Africa
Pelargonium raw material	Big Tree Neutraceuticals	*Pelargonium sidoides*	–	Antibiotic	South Africa
Green *Rooibos* extract raw material	Big Tree Neutraceuticals	*Rooibos* sp.	Leaves	Antioxidant, youth enhancing	South Africa
Devil's claw	CAS	*H. procumbens*	Tubers	Inflammatory bowel disease	Mozambique
Aloe & Xylitol Brushing Salts	Holle	*Propolis* sp., *Ginkgo biloba*, *Echinacea purpurea*, *Cinnamon* sp.	–	Immune system stimulant	South Africa
Malaria-x	NWD CC	Plant mixture	–	Malaria	South Africa

(*Continued*)

Table 24.2 (Continued)

Product Name	Distributor	Plant Source	Part Used	Medicinal Use	Country
Kekana	NWD CC	–	–	Blood cleaner/detoxifier, diseases of the liver bile	South Africa
Femina	NWD CC	Plant mixture	–	Pain, menstrual cycle, endometriosis, fertility	South Africa
Stop drop	NWD CC	Plant mixture	–	Gonorrhea, hepatocirrhosis, hepatitis	South Africa
G-caps	NWD CC	Plant mixture	–	Liver disorders, cirrhosis, cancer of the liver	South Africa
Castor oil and seed	Tropical as a Source of Health Care Research Center (T.S.H.C.R.C.) Cameroon	*R. communis*	Seeds	Antimicrobial, immune system, lymphatic stimulant	Cameroon
Acacia nilotica pods powdered	Natural African Forest Products (NAFOP)	*Acacia nilotica*	Pods	Antioxidant	Sudan
Aloe vera extract	Masingers & Martners Pty.	*A. vera*	Leaves	Immune system enhancement, duodenum disease, arthritis, glycemia	South Africa
Sunflower oil refined	Masingers & Martners Pty	*Helianthus annuus*	Seeds	Food	South Africa
Sesame seeds	Dr Sidi Herbal Clinic	*Sesamum indicum*	Seeds	Food	Ghana, Burkina Faso
Melon seed 3 in 1	Dr Sidi Herbal Clinic	*Citrullus lanatus*	Seeds	Food	Ghana
Gonomixture medicine	Dr Sidi Herbal Clinic	Plant mixture	–	Irine retention, gonorrhea, syphilis	Ghana
Moringa seeds	Moringa Nigeria project RIVERS	*Moringa oleifera*	Seeds	Athritic pains, headaches, detoxifying	Nigeria
Harpagophytum procumbens root powder	Zamerc Investments CC	*H. procumbens*	–	Pain, fever, digestion stimulation	Namibia

(–), data not available.

24.8 Conclusions

In Africa, there is an enormous demand for medicinal plants for both domestic and commercial uses, resulting in a huge trade on the local, national, regional, and international levels. This trade represents an important opportunity to rural communities as a source of both affordable medicine and income. But there is a real opacity of the medicinal plant trade at the level of the assessment of data concerning demand and supply. As most of the plants are collected from wild sources, conservation of biodiversity and protection of threatened species is an important issue, and governments need to introduce regulations and rules to provide guidelines to control the collection, cultivation, production, certification, registration, and marketing of medicinal plants in order to promote the development of African medicines in the most appropriate manner and to protect public health and safety.

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Medicinal Plant Research in Africa

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Pharmacology and Chemistry

Edited by

Victor Kuete
Department of Biochemistry, Faculty of Science,
Univeristy of Dschang, Dschang, Cameroon

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Preface

Today there are many scientific publications demonstrating the importance of African medicinal plants. The pharmacopoeias of most African countries are available and contain an impressive number of medicinal plants used for various therapeutic purposes. Many African scholars have distinguished themselves in the fields of organic chemistry, pharmacology, pharmacognosy, and other areas related to the study of medicinal plants. However, to date, there is no global standard book on the nature and specificity of chemicals isolated in African medicinal plants; nor is there a book bringing together and discussing the main bioactive metabolites of these plants. To place African research globally, I have considered it necessary to offer students and researchers from Africa and around the world, who are beginning to turn to African medicinal flora, this book, which explores the essence of natural substances from African medicinal plants and their pharmacological potential. In light of possible academic use, this book also scans the bulk of African medicinal plants having promising pharmacological activities, even if their phytochemistry has not been described.

This book covers all aspects of phytochemistry and pharmacology related to the secondary metabolites isolated from medicinal plants from Africa, including terpenoids, phenolic compounds, and alkaloids. Emphasis has also been placed on the biosynthetic pathways of the plant metabolites discussed, taking into account the latest knowledge in the field. Hence, in the group of terpenoids, there is discussion of mono- (Chapter 1), sesqui- (Chapter 2), di- (Chapter 3), and tri-terpenoids, and steroids (Chapter 4). The chemical compositions and pharmacological potential of essential oils from African medicinal plants are discussed in Chapter 5. In the group of phenolics, we also discuss, in a similar way, the simple phenols, phenolic acids, and related esters from the medicinal plants from Africa (Chapter 6), phenylpropanoids and related compounds (Chapter 7), coumarins and related compounds (Chapter 8), flavonoids and related compounds (Chapter 9), quinones and benzophenones (Chapter 10), xanthones (Chapter 11), lignans (Chapter 12), and tannins (Chapter 13). Alkaloids isolated from African plants are reported in Chapter 14, while Chapter 15 brings out information on ceramides, fatty acids, and other related compounds from the medicinal plants from Africa. An emphasis has also been placed on the metabolites isolated for the first time from African medicinal plants, and those bioactive metabolites that have until now been isolated only in African plants. Chapters 16 through 20 are devoted to African medicinal plants having good pharmacological activity and identified hit compounds. This book finally discuss the legislation on medicinal plants in Africa (Chapter 23) and the medicinal

plant market and industry in Africa (Chapter 24), two topics that have not required great attention from scientists to date. All these topics are discussed globally and technically in the book, with a focus on illustration of the different chemical structures. This document is the first of its kind on African medicinal plants. The book also opens the door for future volumes, which will update the various aspects according to the evolution of research at the continental level in the future. The highlight of this book is an exhaustive compilation of scientific data from up to 60 top scholars from more than 15 countries, including Botswana, Cameroon, Canada, China, Egypt, Germany, Ghana, Japan, Kenya, the Netherlands, Nigeria, Saudi Arabia, the United States, South Africa, and Tanzania. Finally, I would like to thank Sarah Lay, the editorial project manager, Radhakrishnan Lakshmanan, the production manager and Unni Kannan, the technical assistant at Elsevier for their help and fruitful collaboration.

Victor Kuete

About the Editor

Dr. Victor Kuete is a scholar/scientist at the University of Dschang, Dschang, Cameroon. He has been a fellow of TWAS (2007), AUF (2008), DAAD (2009), the University of Mainz in Germany (2010), Alexander von Humboldt (2012–2014), and an International Foundation for Science Grantee (2008–2009, 2012–2013). His research program is focused on pharmacognosy, and he mainly investigates African medicinal plants and isolated compounds as potential antimicrobial, antiviral, and antiproliferative agents. This program emphasizes on multidrug-resistant phenotypes as well as the mode of action of active ingredients. Dr. Kuete is the author of more than one hundred scientific publications in the field of medicinal chemistry.

List of Contributors

Tchoukoua Abdou Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Cameroon

Berhanu M. Abegaz African Academic of Sciences, Nairobi, Kenya

Christian Agyare Department of Pharmaceutics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Pantaleon Ambassa Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Cameroon

Stephen O. Amoo Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Francis M. Awah Natural Product Research Unit, Department of Biochemistry, Madonna University, Elele Campus River State, Nigeria

Maurice D. Awouafack Department of Paraclinical Sciences, University of Pretoria, Onderstepoort, South Africa, and Laboratory of Natural Products Chemistry, Department of Chemistry, University of Dschang, Dschang, Cameroon

Veronique Penlap Beng Laboratory for Tuberculosis Research, Biotechnology Centre, University of Yaoundé 1, Yaoundé, Cameroon

Yaw Duah Boakye Department of Pharmaceutics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Krishna Prasad Devkota Molecular Targets Laboratory, Center for Cancer Research, Frederick National Laboratory for Cancer Research, Frederick, MD

Jean P. Dzoyem Department of Biochemistry, University of Dschang, Dschang, Cameroon

Thomas Efferth Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, University of Mainz, Mainz, Germany

Jacobus N. Eloff Department of Paraclinical Sciences, University of Pretoria, Onderstepoort, South Africa

Kenneth O. Eyong Department of Organic Chemistry, University of Yaounde 1, Yaounde, Cameroon

Aimé G. Fankam Department of Biochemistry, Faculty of Science, University of Dschang, Cameroon

Ghislain W. Fotso Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Cameroon

Rebecca Hamm Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, University of Mainz, Mainz, Germany

Maurice Mmaduakolam Iwu International Centre for Ethnomedicine and Drug Development, Nsukka, Nigeria

Justin Kamga Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Cameroon

Mutiu Idowu Kazeem Department of Biochemistry, Lagos State University, Ojo, Nigeria

Guy B. Kougan Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon

Victor Kuete Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon

Oladipupo A. Lawal Department of Chemistry, Lagos State University, Lagos, Nigeria

Mohamed S. Marzouk Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, and Chemistry of Natural Products Group, Center of Excellence for Advanced Sciences, National Research Center, Dokki, Cairo, Egypt

Ofentse Mazimba Department of Chemistry, University of Botswana, Gaborone, Botswana

Paulo Peter Mhame The Traditional Medicine Section, Ministry of Health and Social Welfare, Dar es Salaam, Tanzania

Mainen Julius Moshi Department of Biological and Pre-Clinical Studies, Institute of Traditional Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

Mack Moyo Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Mikhail Olugbemiro Nafiu Department of Biochemistry, University of Ilorin, Ilorin, Nigeria

Jerald J. Nair Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Frederic Nana Department of Organic Chemistry, University of Yaoundé 1, Cameroon

Bhekumthetho Ncube Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Ashwell R. Ndhlala Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Roland N. Ndip Department of Biochemistry and Microbiology, University of Fort Hare, Alice, South Africa, and Department of Microbiology and Parasitology, University of Buea, Buea, Cameroon

Bonaventure T. Ngadjui Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Cameroon

Bathelemy Ngameni Department of Pharmaceutical Sciences and Traditional Pharmacopoeia, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon

David Darko Obiri Department of Pharmacology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Isiaka A. Ogunwande Department of Chemistry, Lagos State University, Lagos, Nigeria

Christopher O. Okunji International Centre for Ethnomedicine and Drug Development, Nsukka, Nigeria, and USP Headquarter, Rockville, MD

Newman Osafo Department of Pharmacology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Hervé Martial Poumale Poumale Department of Organic Chemistry, Faculty of Science, University of Yaoundé 1, Yaoundé, Cameroon, and Department of Bioresource Engineering, Faculty of Agriculture, Yamagata University, Tsuruoka, Yamagata, Japan

Musa Oyewole Salawu Department of Biochemistry, University of Ilorin, Ilorin, Nigeria

Louis Pergaud Sandjo Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon

Abdelaaty A. Shahat Medicinal, Aromatic and Poisonous Plants Research Centre, King Saud University, Riyadh, Saudi Arabia, and Department of Phytochemistry, Center of Excellence for Advanced Sciences, National Research Center, Dokki, Cairo, Egypt

Yoshihito Shiono Department of Bioresource Engineering, Faculty of Agriculture, Yamagata University, Tsuruoka, Yamagata, Japan

Girija S. Singh Department of Chemistry, University of Botswana, Gaborone, Botswana

Turibio Tabopda Department of Organic Chemistry, University of Yaoundé 1, Yaoundé, Cameroon

Pierre Tane Laboratory of Natural Products Chemistry, Department of Chemistry, University of Dschang, Dschang, Cameroon

Nicoline F. Tanih Department of Biochemistry and Microbiology, University of Fort Hare, Alice, South Africa

Michel Kenne Tchimene International Centre for Ethnomedicine and Drug Development, Nsukka, Nigeria

Emmanuel Mouafo Tekwu Laboratory for Tuberculosis Research, Biotechnology Centre, University of Yaoundé 1, Yaoundé, Cameroon

Vincent P.K. Titanji Biotechnology Unit, University of Buea, Buea, Cameroon

Emmanuel Tshikalange Department of Plant Science, University of Pretoria, Pretoria, South Africa

Apollinaire Tsopmo Food Science and Nutrition, Department of Chemistry, Carleton University, Ottawa, ON, Canada

Johannes Van Staden Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Robert Verpoorte Institute of Biology, Leiden University, Leiden, The Netherlands

Katrin Viertel Department of Pharmaceutical Biology, University of Mainz, Mainz, Germany

Igor K. Voukeng Department of Biochemistry, Faculty of Science, University of Dschang, Cameroon

Jean Duplex Wansi Department of Chemistry, University of Douala, Douala, Cameroon

Yanqing Zang College of Food Science, Heilongjiang Bayi Agricultural University, Daqing, China

Denis Zofou Biotechnology Unit, University of Buea, Buea, Cameroon