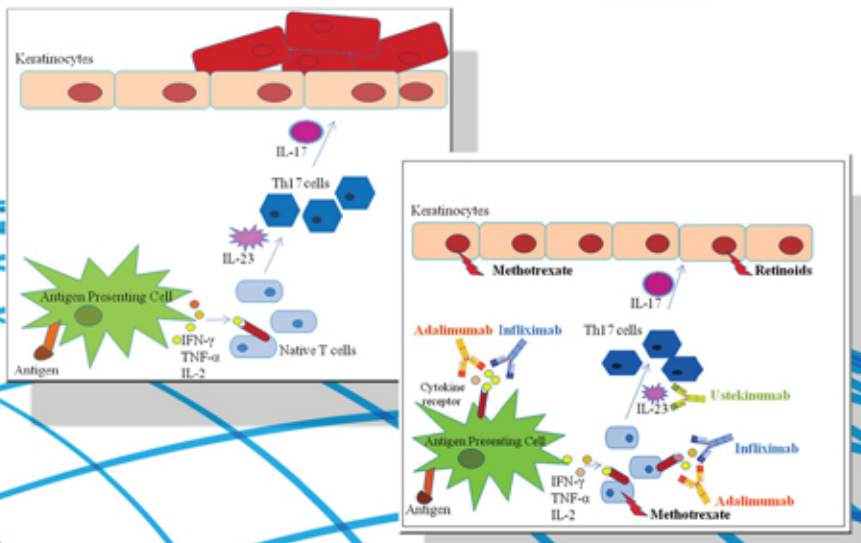
DERMATOLOGY - LABORATORY AND CLINICAL RESEARCH

Psoriasis

Epidemiology, Diagnosis and Management Strategies

Wilma Lambert
Editor



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WILMA LAMBERT
EDITOR

New York

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PREFACE

Psoriasis is a common, non-infectious, chronic inflammatory skin disease characterized by distinctive erythematous plaques that multiply and scale over with silvery patches. Psoriasis can affect any cutaneous site and is frequently found on the extensor skin surface of elbows and knees, scalp and sacral regions. Psoriasis is also associated with systemic conditions, including psoriatic arthritis, Crohn's disease and lymphoma. This book discusses the epidemiology, diagnosis and management strategies of psoriasis. Chapter One provides an overview of the challenging medical condition. Chapter Two discusses the possible factors raised by literature as main contributors to sleep disturbances and its correlation to psoriasis. Chapter Three gives an overview of the current results where blood plasma thermal changes have been detected by Differential Scanning Calorimetry (DSC) technique on psoriatic patients with different clinical stages, and monitored patients with no symptoms to patients with serious symptoms. Chapter Four discusses psoriasis treatment that targets the IL-23/Th17 axis. Chapter Five reviews natural health products for managing psoriasis.

Chapter 1 – *Introduction:* Psoriasis is a common, non-infectious, chronic inflammatory skin disease characterized by distinctive erythematous plaques that multiply and scale over with silvery patches. Psoriasis can affect any cutaneous site and is frequently found on the extensor skin surface of elbows and knees, scalp and sacral region/s. Psoriasis is also associated with systemic conditions, including psoriatic arthritis, Crohn's disease and lymphoma.

Epidemiology: Psoriasis is a common disease and is endemic across the world. It occurs in most racial groups. It affects approximately 2–5% of the population in Western countries. The severity of psoriasis varies greatly; about two thirds of people with psoriasis have a mild form (i.e., <3% of body area is

affected), but others have more extensive involvement of the skin (>10% of body area is affected).

Diagnosis: Even 160 years after its identification, the diagnosis of psoriasis largely relies on clinical signs. In a normal clinical scenario, identification of psoriasis is straightforward, based on clinical signs such as sharp, demarcated, erythematous lesions with scaling plaques on body areas. In dubious cases, elbows and knees appear to be clear; however, careful examination of the scalp and intergluteal cleft normally show characteristic skin lesions. If the diagnosis is uncertain, typically a histologic confirmation (skin biopsy) and dermatology advice will be obtained.

Clinical management: Management of psoriasis is difficult because the distribution and severity of psoriatic plaques varies enormously. Mild psoriasis is often treated with topical preparations such as emollients, keratolytics, corticosteroids, tars, calcipotriol, dithranol and tazarotene. Moderate-to-severe psoriasis has traditionally been managed with systemic therapy such as methotrexate, acitretin and cyclosporine and phototherapy (ultraviolet B, psoralen plus ultraviolet A). Biologic agents such as adalimumab, efalizumab, etanercept and infliximab are generally reserved for systemic disease involvement. Current treatment options are only effective in reducing psoriasis symptoms temporarily. About 70% of subjects are said to prefer topical therapy for the management of psoriasis.

Chapter 2 – Sleep plays a substantial role in our physiological and psychological health. It has been widely demonstrated that sleep is impaired in patients with several chronic and acute diseases. More recently, sleep pattern has also been investigated in dermatological diseases. Among them, psoriasis seems to present a complex relationship with sleep. Individuals with psoriasis present more sleep disturbances in comparison to general population, as obstructive sleep apnea, restless legs syndrome and insomnia. This chronic inflammatory disease is associated with comorbidities as metabolic syndrome, hypertension, obesity and diabetes, which are also involved in the pathophysiology of obstructive sleep apnea. The presence of pain and pruritus has the capacity to interrupt sleep, leading to sleep fragmentation and sleep deprivation. Moreover, psychiatric disorders, such as depression and anxiety, are more prevalent among patients with psoriasis, and may contribute to changes in sleep pattern. Scientific evidences point to an explicit relationship between sleep and psoriasis; however, there is a need for more studies to understand whether this association is bidirectional and which are the mechanisms involved.

Chapter 3 – Psoriasis is a long-lasting skin disorder, which is appearing in different form (plaque, nail, scalp, guttate, inverse, pustular, erythrodermic psoriasis) and in some cases can affects the joints (psoriatic arthritis). Generally the diagnosis is based on full skin physical examination rarely skin biopsy is useful to determine the exact type of psoriasis, while in the cases of psoriatic arthritis radiological examinations (X-ray, ultrasound, MRI) are necessary to differential diagnosis. Unfortunately, there are often has not specific laboratory and radiographic findings that reliably confirmed this challenging diagnosis. Recently, there are continuous research efforts to find new methods to detect and to monitor this dermatological syndrome at any stage. Differential Scanning Calorimetry (DSC) is a thermoanalytical method which monitors small heat changes between a sample and reference material. The DSC thermogram, is the unique signature for bio-molecules reflecting the normal or pathomorphological changes under given solution conditions. Moreover, DSC is useful method to evaluate local and global conformation changes in the structure of different biological samples (blood plasma and serum, tissue samples) in several previous orthopaedical and traumatological, surgical, oncological and dermatological clinical studies. Recently, numerous articles confirmed that DSC is widely used as a new diagnostic method for detection of different diseases' seriousness, and as an applicable technique during monitoring of patients. The following chapter should give an overview of the current results where blood plasma thermal changes have been detected by DSC technique on psoriatic patients with different clinical stages, and monitored patients from symptomless and till the effect of various drug therapies (Cytostatics, Retinoids, and Biologic response modifier agents) on patients with serious symptoms. The studies demonstrated that thermal changes (transition temperature, calorimetric enthalpy) of blood plasma showed strong correlation with psoriasis severity and effectivity of medical treatment, and these measurements increased our knowledge about blood plasma structural changes in one of the most common inflammatory skin disease. In case of proper validation and further investigations of this method should promise for routine clinical use.

Chapter 4 – Psoriasis is a T helper (Th)1/Th17 induced immuno-inflammatory disease and the interleukin (IL)-23/Th17 axis is believed to be crucial in the pathogenesis of this disease. A chronic, unpredictable course of the disease, and the need for periodical alternation of drugs, makes psoriasis a disease difficult to treat. A variety of therapeutic approaches are available, ranging from topical agents for milder and limited forms, to phototherapy,

photochemotherapy, systemic or biological agents for moderate and severe psoriasis.

Increased levels of IL-17 and Th17-related cytokines in psoriasis led to the proposal of therapeutic agents targeting IL-23/Th17 axis. Ustekinumab is a monoclonal antibody directed against the p40 subunit of IL-12 and IL-23. Secukinumab and ixekizumab are human monoclonal antibodies against IL-17A, while brodalumab is a fully human monoclonal antibody that targets IL-17 receptor A. Ustekinumab and most biologic agents targeting IL-17 were efficacious and safe in the treatment of moderate-to-severe psoriasis in adults, although, long-term data is still required. In the present chapter the authors will debate published data concerning the current knowledge about the importance in psoriasis of the IL-23/Th17 axis and the present and future biological agents that target this pathway, as well as their use in treatment and adverse effects.

Chapter 5 – Psoriasis is an incurable skin disorder characterized by the presence of inflammatory plaques on the skin. Although there are multiple therapeutic options to treat this disease, patients worldwide are dissatisfied. Consequently, they frequently use natural products to overcome undesirable effects and ineffectiveness of treatments. These alternative remedies are used together with conventional medications, so it can account for synergism, lack of adherence or adverse events of antipsoriatic therapies. In this chapter, the psoriasis physiopathology is analyzed on the basis on current etiopathogenic concepts. Additionally, the prevalence of natural health product use in psoriatic patients is examined. A complete review of most important extracts and isolated compounds from natural origin is also considered taking into account preclinical and clinical studies recently published (2000-2016). Moreover, the strengths and weaknesses of investigations with natural products for psoriasis will be discussed to a better understanding of their importance in holistic treatment of this disease.

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Chapter 1

PSORIASIS: A CHALLENGING MEDICAL CONDITION

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ABSTRACT

Introduction: Psoriasis is a common, non-infectious, chronic inflammatory skin disease characterized by distinctive erythematous plaques that multiply and scale over with silvery patches. Psoriasis can affect any cutaneous site and is frequently found on the extensor skin surface of elbows and knees, scalp and sacral region/s. Psoriasis is also

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associated with systemic conditions, including psoriatic arthritis, Crohn's disease and lymphoma.

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Diagnosis: Even 160 years after its identification, the diagnosis of psoriasis largely relies on clinical signs. In a normal clinical scenario, identification of psoriasis is straightforward, based on clinical signs such as sharp, demarcated, erythematous lesions with scaling plaques on body areas. In dubious cases, elbows and knees appear to be clear; however, careful examination of the scalp and intergluteal cleft normally show characteristic skin lesions. If the diagnosis is uncertain, typically a histologic confirmation (skin biopsy) and dermatology advice will be obtained.

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INTRODUCTION

Psoriasis (OMIM 177900, ICD10 – L40) is a common inflammatory, non-infectious, chronic hyper-proliferative, autoimmune skin disorder (Koks et al., 2004, Henseler, 1997, Ryan, 2008). Current research shows a link between psoriasis and major medical comorbidities such as diabetes, chronic pulmonary disease and peptic ulcer (Yeung, et al., 2013). Even though the term 'psoriasis' was not used in classical times to describe the presentation of the condition, the actual condition of psoriasis was first mentioned by the Greek physician Hippocrates (460-375 BC). However, this clinical condition was first described by the Roman scholar Cornelius Celsus (25 BC-50 AD) who referred it as 'impeto' (a variant of impetigo) (Shai et al., 2002, Freilich,

1982). The biblical Hebrew word 'Tsaraat' was used to represented psoriasis along with a range of other skin ailments, including eczema, and leprosy. The term 'psoriasis' is derived from the Greek word 'psora' meaning itch and 'iasis' meaning action, and was first thought to be named by Galen (133-200 AD) (Smith and Barker, 2006). Before this time, for centuries, psoriasis was described as a variant of leprosy, was confused with syphilis and tuberculosis and moreover was considered a contagious skin ailment (Farber and McClintock, 1968, de Jong, 1997). Robert Willan, a British physician, is accredited with the first accurate clinical description of psoriasis in his article 'On Cutaneous Diseases' published in 1808 (Willan, 1808).

Psoriasis (Figure 1) is a lifelong condition, is characterised by exacerbations and remissions, and has no known cure (Farber et al., 1968, Thomas, et al., 2015. In most patients psoriasis presents before the age of 35, although it can appear at any age (de Jong, 1997, Winterfield et al., 2005). There are several clinical patterns of psoriasis, which demonstrate well defined skin lesions, flaky indurated plaques (red or pink) with white or silvery scales, which may hurt, itch, burn or bleed (Winterfield et al., 2005). In 1910, von Zumbusch reported the pustular pattern of psoriasis. Since then, rarer clinical phenotypes of psoriasis have been identified and reported (Zumbusch, 1910, Rotstein, 1996). Physical manifestations of psoriasis such as unsightly, scaly, pruritic plaques or lesions and inflamed joints (in psoriatic arthritis patients) can result in a considerable, quantifiable reduction in the quality of life (Shelling et al., 2008). Generally, patients with affected skin areas of <5% of the total body surface area are reported as having mild psoriasis, whereas in moderate psoriasis 5-10% of the total body area is affected. In severe psoriasis >10% of the total body area is affected (Menter and Griffiths, 2007).

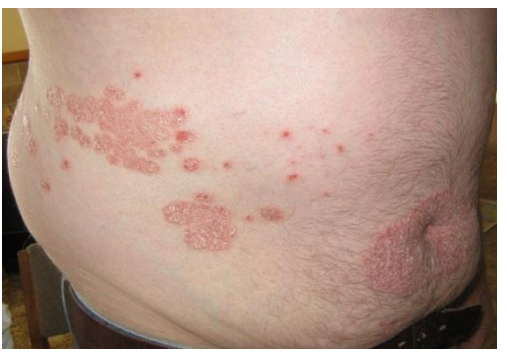

Figure 1. Active plaque psoriasis on patient's trunk (J Thomas, case material).

GENETIC FACTORS

Psoriasis is characterised by phenotypic diversity and genetic heterogeneity (Koks et al., 2004, Henseler, 1997, Ryan, 2008, Jordan, et al., 2012). Epidemiological studies have demonstrated hereditary transmission of psoriasis. The prevalence of disease is generally higher in first and second degree relatives of probands with psoriasis, when compared to the general population (Ortonne, 1996). Approximately 30% of psoriatic individuals have an affected first-degree relative. If both parents and a sibling have psoriasis, a further child has a 50% chance of developing the disease. However, if only a sibling is affected, the risk of psoriasis drops to 8%. Twin studies suggest that the risk of developing psoriasis is three-times higher in monozygotic than dizygotic twins (Griffiths and Barker, 2007).

Scientists have now identified about 25 genetic variants that make a person more likely to develop psoriatic disease. Several molecular genetic studies have reported at least nine chromosomal loci (PSORS1-9), which have been identified to have significant association with psoriasis aetiology. Of these, PSORS2, a replicated locus, binds on chromosome 17q25, at which a polymorphism associated with psoriasis has been previously described (Griffiths and Barker, 2007). The key genetic determinant of psoriasis is PSORS1, which accounts for about 35-50% of the hereditability of psoriasis. Furthermore, HLA-Cw6 (human leukocyte antigen-gene) has been reported as the susceptibility factor at PSORS1 (Ortonne 1996). Previous studies have suggested HLA-Cw6 as a strong marker for early onset psoriasis, with 85% of infected individuals with at least one HLA-Cw6 allele, compared with 15% of patients who have disease onset after 40 years of age (Griffiths and Barker, 2007). Moreover, studies have shown that guttate psoriasis is strongly linked with PSORS1, while palmoplantar pustular psoriasis and late onset of psoriasis vulgaris (>50 years of age) have not shown a significant association (Griffiths and Barker, 2007, Henseler, 1997). It has been previously observed that the frequent clustering of psoriasis and the autoimmune disorder, Crohn's disease, is attributed to genetic kinship. Both have been associated with the same gene transporter halotype, and psoriasis locus PSORS8 overlaps with Crohn's disease locus (CARD15) on chromosome 16q (Griffiths and Barker, 2007, Kourosh et al., 2008; Jordan, et al., 2012).

Epidemiology

Psoriasis is a common disease and is endemic across the world and occurs in most racial groups (Farber and Nall, 1998). Globally, psoriasis affects about 6.5% of the population in Germany, 5.5% in Ireland, 4.8% in Scotland, 3.7% in Spain, 2.3% in Sweden, 4.8% in Norway, 2.0% in the former USSR, 2.2-4.6% in the USA and 4.7% in Canada. It affects approximately 2–5% of the population in Western countries, with an estimated prevalence of 2.3–6.6% in Australia. Moreover, figures from Australia revealed that the prevalence of psoriasis in men was almost 2-fold higher than in women (8.9% vs. 4.5%), which is opposite to the majority of other countries (Farber and Nall, 1998, Parisi et al., 2013).

In general, the prevalence of psoriasis has been found to be more common in colder northern climates than in the tropical regions (Raychaudhuri and Farber, 2001). The prevalence of psoriasis in Asia is found to be 4-5.5% in Malaysia, 0-1.5% in India, 0.29-1.18% in Japan and 0.2-1.5% in China (including Hong Kong). In the Middle Eastern countries the prevalence of psoriasis is 3.1% in Kuwait and 3% in Egypt. The prevalence of psoriasis in South America is 1.3% in Brazil, 3% in Mexico, 2% in Venezuela and 4.2% in Paraguay. Typically, the prevalence of psoriasis is found to be higher in dry, rainless countries of Eastern Africa (Kenya [3.5%]; Uganda [2.8%] and Tanzania [3%]) compared to hot, humid and rainy climates of Western Africa (Nigeria [0.08-0.4%]; Mali [0.05%]; Angola [0.3%]). The rate of psoriasis in white Australians resembles that of the Western countries (approximately 2.6%); however, no psoriasis has been reported among Aboriginal Australians (Farber and Nall, 1998, Raychaudhuri and Farber, 2001, Heyes et al, 2014).

Diagnosis of Psoriasis

Even 160 years after its identification, the diagnosis of psoriasis still largely relies on clinical signs. Although histological assessment of skin biopsy is used occasionally, no haematological, biochemical or serological tests are presently available as diagnostic tools for disease confirmation. In the everyday clinical scenario, identification of psoriasis is straightforward, based on clinical signs (Smith and Barker, 2006, Khachemoune and Guillen, 2006; Raychaudhuri et al., 2014). The presence of sharp, demarcated, erythematous

lesions with scaling plaques on body areas should raise 'serious suspicion' of psoriasis. In dubious cases, elbows and knees appear to be clear; however, careful examination of the scalp and intergluteal cleft normally show characteristic skin lesions (Pardasani et al., 2000, Griffiths et al., 2000). When typical clinical features are absent, pitted fingernails, subungual hyperkeratosis or other nail changes can assist in the diagnosis. When patients present with atypical skin lesions (Table 1), these should be differentiated from tinea, mycosis fungoides, discoid lupus or seborrhoeic dermatitis, ptyriasis rubra, Sezary syndrome or non-specific skin signs, such as minimal scaling of the scalp, isolated flexural erythema, or genital lesions (Khachemoune and Guillen, 2006). If the diagnosis is uncertain (e.g., pustular forms), a histologic confirmation (skin biopsy) can be obtained and specialist dermatology advice can be sought (Pardasani et al., 2000).

Table 1. Differential diagnosis of psoriasis

Disease entity	Differentiating signs/ symptoms	Differentiating tests
Lupus erythematosus, subacute (SLE)	Sub-acute SLE may have clinical signs that mimic psoriasis; however, plaques are less scaly and not lamellar	Skin biopsy, including direct and indirect immunofluorescent tests, is normally employed to confirm SLE.
Ptyriasis rosea	Lesions normally show features of guttate psoriasis but are in a characteristic Christmas tree-shaped distribution. Lesions normally subside within 8 weeks.	Clinical diagnosis is usually adequate.
Seborrhoeic dermatitis	Scaly eruptions normally limited to scalp eyebrows, paranasal region, ears and chest. Scales normally appear as fine and not lamellar in shape.	Skin biopsy shows dermatitis instead of psoriasis.
Mycosis fungoides	Lesions are highly itchy and scaly; mostly seen on scalp or ears. Lesions are not found on nails/joints.	Skin biopsy shows atypical lymphocytes and Pautrier abscess.

Disease entity	Differentiating signs/ symptoms	Differentiating tests
Diaper dermatitis	Lesions are oozy, weepy and itchy in nature. Only seen in diaper regions.	Clinical diagnosis is usually sufficient.
Onychomycosis	This condition only involves nails.	Culture of the nail shows fungal growth.
Squamous cell carcinoma/actinic keratosis	Often not very scaly or fine scales may be present in case of actinic keratosis. Squamous cell cancer is limited to few lesions only.	Skin biopsy shows atypical squamous cells.
Eczema	Lesions are normally very itchy, mostly oozy, crusted with numerous scratch marks.	Skin biopsy shows dermatitis instead of psoriasis.
Lichen planus	Limited to wrists and limbs. Compared with psoriasis oral mucosa is more likely to be involved. Lesions are thick and without a scaly or desquamated appearance	Skin biopsy shows lichenoid lymphocyte infiltrates under epidermis.
Lichen simplex chronicus	Usually limited to a few areas easily reached by hands. Lesions are normally thick without scaly or desquamated appearance.	Skin biopsy reveals chronic dermatitis with epidermal acanthosis.
Subcorneal pustular dermatosis	Pustular lesions are subcorneal and in annular or serpiginous forms. Lesions normally present on stomach axillae and groin regions.	Skin biopsy reveals no bacteria. It shows predominantly neutrophilic perivascular infiltration with minimal spongiosis.

Adopted from (British Medical Journal, Best Practice, 2009; Raychaudhuri et al., 2014).

Psoriasis Treatments

On the basis of several factors, such as diverse clinical presentations, anatomical locations affected, nature and severity of the psoriasis, quality of life considerations, *coexisting co-morbidities* (psoriatic arthritis, Crohn's disease, metabolic syndrome, coronary heart disease), predisposing factors (stress, medications, infections) and patient commitment towards the treatment regimen, a tailored approach is indicated for the management of psoriasis (Milavec-Puretić et al., 2011; Keratoacanthoma et al., 2010). Generally, three therapeutic interventions (topical therapy, phototherapy, and systemic/biological agents) are suggested. Figure 2 provides a general approach to psoriasis management for adults.

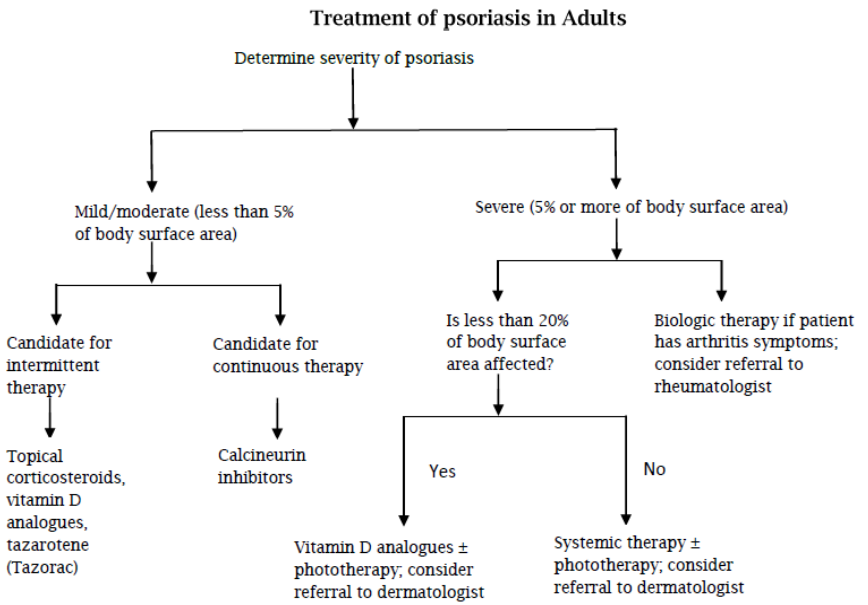

Figure 2. A suggested treatment algorithm for the management of psoriasis in adults, modified from Weigle & Mcbane (2013).

Conventional antipsoriatic treatment involves a stepwise, systematic approach based on disease severity in which topical therapy is first indicated followed by phototherapy, systemic and/or biological agents (Table 2).

Table 2. Categories of current treatment modalities for psoriasis

Topical Therapies
Emollients
Corticosteroids
Vitamin D3 analogues
Calcipotriol
Calcipotriol + combinations with topical corticosteroids (e.g., betamethasone dipropionate)
Calcitriol
Tacalcitol
Topical tar preparations (e.g., crude coal tar preparations and LCD [liquor carbonis detergens, a tar distillate])
Retinoid: Tazarotene
Calcineurin inhibitors —tacrolimus 0.1% and pimecrolimus 1%
Anthralin —dithranol
Ultraviolet (UV) therapy
Ultraviolet B (UVB) radiation (290 to 320 nm)
Narrow band UVB (311 nm)
Photochemotherapy (PUVA) - oral or bath psoralen followed by ultraviolet A (UVA) radiation (320 to 400 nm)
Systemic therapies
Immunosuppressive or immunomodulatory drugs
methotrexate
cyclosporine
Retinoids – acitretin
Systemic calcineurin inhibitors — cyclosporine
Biologic agents
Etanercept
Infliximab
Adalimumab
Ustekinumab
Secukinumab
Alefacept
Other
Hydroxyurea
6-thioguanine
Azathioprine
Apremilast
Fumaric acid esters (fumarates)
Hydroxyurea

Adopted from (eTG, 2015; Menter and Griffiths, 2007).

Table 3. A partial summary of undesirable side effects listed to various antipsoriatic treatments

Psoriasis Treatments		Reported Side Effects
Topical		
	Vitamin D analogues	Irritation
	Retinoids	Pruritus, erythema and burning sensation
	Corticosteroids	Tachyphylaxis, cutaneous atrophy
	Anthralin	Erythema
	Tar-based preparations	Photosensitivity
	Urea	Irritation
	Salicylic acid	Irritation
Phototherapy		
	Broadband UVB	Burns, erythema, photoaging
	Narrowband UVB	Burns, photoaging
	Excimer Laser	Erythema, hyperpigmentation, blister, erosion and pain
	Psoralen + UVA	Nausea, phototoxicity, malignant skin cancer
Systemic		
	Methotrexate	Nausea, mucosal ulceration, erectile dysfunction, stomatitis, hepatotoxicity
	Acitretin	Teratogenesis
	Cyclosporin A	Nephrotoxicity, hypertension
	Fumaric acid esters	Abdominal pain and diarrhoea
	Sulfasalazine	Headache, gastrointestinal symptoms or rash
	Hydroxyurea	Bone marrow toxicity with leucopenia or thrombocytopenia
Biologics		
	Alefacept	Headache, pruritus, infection, pharyngitis and rhinitis
	Efalizumab	Psoriasis rebound, erythroderma, demyelinating disease
	Ustekinumab	Respiratory tract infection, chest pain, gastric ulcer haemorrhage
	Infliximab	Infusion reactions, infections, increased risk for malignancies, headache, vertigo/dizziness, abdominal pain, diarrhoea, nausea and dyspepsia
	Etanercept	Injection-site reactions, rash, pneumonia, interstitial lung disease
	Adalimumab	Injection-site reactions, increased risk of opportunistic infections such as histoplasmosis, coccidioidomycosis, listeriosis and pneumocystis, risk of lymphoproliferative diseases and malignancies

Adopted from Garcia-Perez et al., 2012.

Table 4. Recommended treatment options for the management of different types of psoriasis

Clinical variant of psoriasis	Treatment options
Scalp psoriasis	
Scalp psoriasis if starting with steroid	methylprednisolone aceponate 0.1% lotion topically, once daily until skin is clear (usually 2 to 6 weeks) OR mometasone furoate 0.1% hydrogel or lotion topically, once daily until skin is clear (usually 2 to 6 weeks).
If the response to treatment of the scalp is inadequate after 2 weeks, change to:	betamethasone dipropionate 0.05% lotion topically, twice daily for 6 weeks OR clobetasol propionate 0.05% shampoo topically, once daily for 6 weeks.
if psoriasis is still not controlled after a topical corticosteroid	calcipotriol+betamethasone dipropionate 50+500 micrograms/g gel topically, once daily until skin is clear (expect some response within 2 weeks).
Once symptoms are controlled	use a coal-tar–based shampoo (available over-the-counter)—this can aid withdrawal of the topical corticosteroid preparation
If the scalp develops thickened psoriatic scale	LPC 6% + salicylic acid 3% in aqueous cream topically, twice daily
Chronic stable psoriasis on the trunk and limbs	
Preferred treatment	coal tar prepared 1% emulsion or gel topically, once daily at night or twice daily for 1 month OR LPC 6% + salicylic acid 3% cream or ointment topically, twice daily for 1 month
If a tar preparation alone is not sufficient, or for acute flares	methylprednisolone aceponate 0.1% cream, ointment or fatty ointment topically, once daily until skin is clear (usually 2 to 6 weeks) OR mometasone furoate 0.1% cream, hydrogel or ointment topically, once daily until skin is clear (usually 2 to 6 weeks).
If the response to treatment is inadequate after 3 weeks	betamethasone dipropionate 0.05% cream or ointment topically, once daily until skin is clear (usually 2 to 6 weeks).
Once symptoms are controlled	reduce the potency of the topical corticosteroid gradually, and withdraw if possible. Continue using the tar as maintenance therapy.
If patients with only a few scattered plaques of psoriasis do not respond to a tar, or need longer-term control with a topical corticosteroid	calcipotriol + betamethasone dipropionate 50 + 500 micrograms/g ointment topically, once daily until skin is clear (usually about 6 weeks).
When treating widespread psoriasis	do not use more than 100 g ointment or cream (5 mg calcipotriol) per week, as theoretically it can cause hypercalcaemia.
Palmoplantar psoriasis	
Treatment starts with a tar, combined with a topical keratolytic	LPC 6% + salicylic acid 6% cream or ointment topically, twice daily for 1 month

Table 4. (Continued)

Clinical variant of psoriasis	Treatment options
If the skin does not improve significantly over a month	calcipotriol + betamethasone dipropionate 50 + 500 micrograms/g ointment topically, once daily until skin is clear (usually about 6 weeks).
Initial treatment for palmoplantar pustular psoriasis is a tar	LPC 6% + salicylic acid 3% cream or ointment topically, twice daily
If the tar is not tolerated or has no effect after 2 weeks	betamethasone dipropionate 0.05% ointment topically, once daily until skin is clear (usually 2 to 6 weeks) OR mometasone furoate 0.1% ointment topically, once daily until skin is clear (usually 2 to 6 weeks).
If the response to treatment is inadequate after 3 weeks	betamethasone dipropionate 0.05% ointment in optimised vehicle topically, once daily until skin is clear (usually 2 to 6 weeks).
For a patient who needs a topical corticosteroid for more than 2 months	calcipotriol + betamethasone dipropionate 50 + 500 micrograms/g ointment topically, once daily until skin is clear (usually about 6 weeks).
Nail psoriasis	
Starting therapy	calcipotriol + betamethasone dipropionate 50 + 500 micrograms/g ointment topically, in proximal nail fold and under nail, once daily at night for up to 3 months.
For psoriasis presenting as onycholysis or subungual hyperkeratosis	betamethasone dipropionate 0.05% lotion topically, twice daily under nail for up to 3 months.
Flexural and genital psoriasis	
The first step in topical therapy for flexural psoriasis is	methylprednisolone aceponate 0.1% ointment or fatty ointment topically, once daily until skin is clear (this may take several weeks), but for no longer than 2 weeks in a child wearing nappies.
When the initial flare has settled but some rash remains	LPC 2% in emulsifying ointment topically, once daily
If LPC is not tolerated	ichthammol 1% cream or ointment topically, once daily.
If topical therapy for flexural psoriasis is unsuccessful	refer the patient for expert advice—phototherapy works well.
Psoriasis of the face	
For an adult with psoriasis in the centre of the face	methylprednisolone aceponate 0.1% cream, ointment or fatty ointment topically, once daily until skin is clear (usually 2 to 6 weeks).
For an adult with psoriasis around the ears and along the hairline	mometasone furoate 0.1% cream or ointment topically, once daily until skin is clear (usually 2 to 6 weeks).
For a child	hydrocortisone 1% cream or ointment topically, once daily until the skin is clear (usually 2 to 6 weeks).
Once symptoms are controlled	LPC 2% + salicylic acid 2% in aqueous cream topically, once daily at night
Guttate psoriasis	
In the presence of active infection	oral antibiotics
Widespread lesions with plaques	treat as for psoriasis on the trunk and limbs.

Adopted from (eTG, 2015).

Given the need to individualize therapy, it is not surprising that considerable variability has been reported in the therapeutic management of psoriasis (Ashcroft et al., 2000, Menter and Griffiths, 2007; Garcia-Perez et al., 2012). However, treatment should be customized to meet patient requirements and taking into consideration the potential benefits and adverse effects of therapies (Table 3) (Menter and Griffiths, 2007; Garcia-Perez et al., 2012).

A summary of various treatment modalities recommended in Australia for the management of psoriasis is listed in Table 4. Current standard therapies (Table 4) can control psoriasis in the majority of cases; however, potential therapy-related toxicities (Table 3) can limit the dose and duration of the treatment regimen. If topical therapy fails or when treatment with phototherapy or systemic agents is required, the patient should be referred to a dermatologist. Patients with psoriasis have an increased cardiovascular disease risk and should be advised to manage cardiovascular risk factors, including but not limited to smoking. Before commencing treatment with immune-suppressants baseline and periodic monitoring are necessary because of the risk of serious infection (e.g., hepatitis B, tuberculosis, human immunodeficiency virus [HIV]) (AMH 2015).

Topical Therapy

Topical interventions play a mainstay role in the management of mild psoriasis (Lebwohl, et al., 2005, Menter and Griffiths, 2007, eTG, 2015). Generally, in patients with psoriatic lesions the treatment regimen starts with topical therapy. Phototherapy may be commenced if topical treatment is not practical or adequately effective, and systemic treatment is indicated in nonresponsive cases (Feldman et al., 2008).

Topical Corticosteroids

Globally, topical corticosteroid medications are the most widely prescribed treatment for the management of psoriasis. These vary from over-the-counter weak agents (hydrocortisone 1%) to highly potent corticosteroid preparations (e.g., clobetasol propionate, halobetasol propionate, and betamethasone dipropionate) (Lebwohl et al., 2005). Topical corticosteroids are available in various dosage forms (powders, sprays, lotions, foams,

solutions, creams, emollient creams, ointments, gels, tape) and they provide cosmetic acceptability, rapid efficacy and versatility of administration (Lebwohl et al., 2005, Menter and Griffiths, 2007). The availability of formulations in different vehicles is useful in treating different body sites (e.g. use of foams, solutions and gels for hair-bearing areas) and ensuring enhanced patient compliance (Lebwohl et al., 2005).

The major limitations of topical steroid therapy include: tachyphylaxis (loss of efficacy with prolonged application), skin atrophy, telangiectasia (dilated blood vessels appearing on the surface of the skin), development of striae (appearance of dermal scars, accompanied by epidermal atrophy), and perioral dermatitis (acneiform eruptions). The systemic side-effects include iatrogenic Cushing's syndrome and hypothalamic-pituitary-adrenal axis suppression, which are rarely reported (Menter and Griffiths, 2007, Ellison et al., 2000, Menter and Griffiths, 2007). Potent steroid preparations should be avoided on the face and also on intertriginous body areas, such skin areas that are more liable to develop steroid-related adverse effects. Treatment guidelines limit the use of steroids to a maximum of 50 to 60 g per week; occlusive dressings should be avoided in body areas except the scalp, palms and soles; and in children potent steroids must be avoided or used minimally (Lebwohl et al., 2005, Menter and Griffiths, 2007).

Coal Tar

Coal tar has been used in the therapeutic management of various skin diseases since ancient times (Downing and Bauer, 1948). Becker and Serle (1681) first described coal tar; nevertheless, its application in dermatological ailments was first reported much later by Fishel in 1894 (Everett et al., 1961). However, Goeckerman (1925) demonstrated the scientific use of coal tar with ultraviolet radiation in the management of psoriasis.

Coal tar is obtained as a secondary product during the distillation and destructive carbonisation of coal as it presents in the crude form. Further distillation of crude coal tar (CCT) at temperatures 200-1300°C generates various coal tar distillates (Thami and Sarkar, 2002). The chemical composition of coal tar depends heavily on

- The nature of the coal used
- The type of the distillation apparatus
- Distillation temperatures

Due to these factors, it is difficult to make accurate comparisons between different production batches (Thami and Sarkar, 2002). Coal tar contains approximately 10,000 constituents, comprising 48% hydrocarbons, 42% carbon components and 10% water (Thami and Sarkar, 2002). Coal tar is extemporaneously dispensed in various pharmaceutical dosage forms, including ointment, cream, lotion, shampoo, solution and foam. Emulsifying ointment (containing soft paraffin and lanolin) and an emulsifying agent (e.g., Tween 80) are typically used for the preparation of tar ointment. Liquor carbonis detergens (LCD) is generally used for the management of scalp psoriasis, as 20% CCT in alcohol with Tween 80 (Thami and Sarkar, 2002, Lebwohl, 2005). Efforts were undertaken to prepare white tar (tar alba, LCD decoloratus) by decolourising LCD with lead acetate and other compounds. Although several coal tar preparations have been introduced (including Exorex®, a synthetic analogue resembling the complex essential fatty acids found in banana skin), these products have not been shown to be superior to CCT (Smith and Lebwohl, 2000, Sarkar et al., 2001).

Vitamin D Analogues

Vitamin D derivatives are the second most common group of medications used in the management of psoriasis. At present, three vitamin D_3 analogues (calcitriol, tacalcitol and calcipotriol) are available, mostly as creams, ointments, or solutions (Lebwohl et al., 2005, Lebwohl, 2005, Menter and Griffiths, 2007, Ashcroft et al., 2000). Calcitriol is reported to be an effective and tolerable treatment option in easily irritated skin areas (face, hairline, flexural areas). Vitamin D_3 derivatives are commonly used in conjunction with topical steroid preparations. Frequently reported side-effects include pruritus, burning, oedema, erythema, and dryness. Application of larger quantities can result in higher absorption, consequently leading to hypercalcaemia. Therefore, the recommended dose is <120 g/week of cream or ointment (Scott et al., 2001, Lebwohl et al., 2005). Some vitamin D analogues are unstable, and phototherapy may inactivate vitamin D analogues and, conversely, vitamin D analogues may block the therapeutic component of ultraviolet light. Therefore, phototherapy and vitamin D_3 analogues should not be used in combination (Lebwohl et al., 2003).

Topical Retinoids

A topical retinoid therapy, tazarotene (Tazorac), has been reported to have therapeutic efficacy in the management of chronic plaque psoriasis (Weinstein et al., 2003). Previous clinical studies demonstrated its effectiveness alone and in combination with topical steroids, in the treatment of psoriasis (Lebwohl, 1998, Lebwohl et al., 1998). Bruner et al. (2003) reported a higher percentage of treatment-related adverse effects in patients being treated with tazarotene compared to corticosteroids. These mainly include perilesional irritation and teratogenic effects (Bruner et al., 2003, Luba and Stulberg, 2006).

Topical Immuno-Suppressants

Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are not approved by the FDA for the management of psoriasis (Luba and Stulberg, 2006). Some authors have reported their efficacy in the management of intertriginous psoriasis (Lebwohl et al., 2004, Gribetz et al., 2004). These drugs are expensive and the main adverse drug reactions include itching and burning. Skin cancer and lymphoma have been reported after the use of these medications; however, its close causative association remains to be investigated (Wooltorton, 2005, Luba and Stulberg, 2006).

Miscellaneous Agents

Anthralin (Dithranol®)

This product is often recommended when psoriatic plaques are large or few, and is used in combination with ultraviolet B (UVB) light therapy (Luba and Stulberg, 2006). Dithranol acts by restoring the normal rate of epidermal cell proliferation and by keratinization, leading to a reduction in mitotic activity of the hyperplastic epidermis (AMH, 2015). However, this treatment has been poorly accepted for the management of psoriasis due to its adverse effects, including but not limited to burning sensation and temporary staining of the skin and/or hair (AMH, 2015).

Other

Other topical modalities include keratolytics (e.g., salicylic acid) and moisturizers. Keratolytics (normally prescribed between 2-10%) aid in the

removal of accumulated scales and facilitate the penetration of other topical agents (e.g., coal tar, dithranol, corticosteroids) through the epidermis (Federman et al., 1999, Luba and Stulberg, 2006). Moisturizers hydrate and soften the scaly, hyperkeratotic surface of psoriasis and are often useful in the management of mild psoriasis or in patients who prefer treatment with minimal adverse effects (AMH, 2015, Luba and Stulberg, 2006).

Phototherapy

Light therapy includes UVB phototherapy and UVA photo-chemotherapy, usually administered in specialty clinics. Phototherapy is recommended for the management of moderate to severe psoriasis (Thornton et al., 2004). UVA photo-chemotherapy involves the combination of oral psoralen (a photosensitizer) followed by exposure to UVA (psoralen plus UVA [PUVA] therapy). PUVA is generally reserved for the management of severe psoriasis, which is unresponsive to other treatments (Luba and Stulberg, 2006, Thornton et al., 2004). However, patients receiving phototherapy require frequent monitoring due to the risk of developing adverse effects such as skin rash, sunburn, redness, dryness, cutaneous aging, wrinkling and skin cancer (AMH, 2015, Thornton et al., 2004).

Systemic Treatments

Systemic therapy is indicated when psoriasis is widespread, severe or causing disfigurement or disability in patients. Before prescribing a systemic medication, physicians should discuss it with the patient to weigh the risk benefit ratio (eTG, 2015). Widely used systemic treatment options for the management of psoriasis include methotrexate, cyclosporine, acitretin and fumaric acid esters (limited to some countries). With the exception of fumaric acid esters, conventional systemic drugs exhibit drug-drug interactions and cumulative organ toxicities; however; with continuous monitoring (therapeutic drug monitoring and regular blood tests) all except cyclosporine can be used for the maintenance therapy of psoriasis. Cyclosporine is usually given as a short term treatment (4-8 weeks) (Menter et al., 2009).

Table 5. A partial summary of various biologic treatments indicated for the management of psoriasis

Treatment Type	Mechanism of action	Method of delivery	Dosage and Frequency	Common side effects	Possible risks	Monitoring
Secukinumab	Inhibits Interleukin-17A (IL-17A)	Subcutaneous self-injection	Week 0, 1, 2, 3 and 4, and every four weeks thereafter	Cold symptoms, diarrhea, upper respiratory infection	Inflammatory bowel disease, reactivation of latent infections	Hypersensitivity reactions, inflammatory bowel disease, screening for latent tuberculosis infection
Etanercept	Inhibits TNF-Alpha	Subcutaneous self-injection	Once or twice per week	Injection site reaction, upper respiratory infection	Blood disorders, hepatitis B reactivation, Lupus-like syndrome nervous system problems, new or worsening heart failure	Annual blood count, liver tests, screening for latent tuberculosis infection
Adalimumab	Inhibits TNF-Alpha	Subcutaneous self-injection	Once every other week	Headache, injection site reaction, upper respiratory infection	Hepatitis B reactivation, low blood count, lupus-like syndrome, nervous system problems, new or worsening heart failure	Annual blood count, liver tests, screening for latent tuberculosis infection
Infliximab	Inhibits TNF-Alpha	Intravenous (IV) infusion by a health care provider	Three times in the first 6 weeks, and then once every 8 weeks	Abdominal pain, headache, upper respiratory infection	Hepatitis B reactivation, liver damage or hepatoxicity, low blood count Lupus-like syndrome, lymphoma and other malignancies, nervous system problems, new or worsening heart failure	Annual blood count, liver tests, screening for latent tuberculosis infection

Treatment Type	Mechanism of action	Method of delivery	Dosage and Frequency	Common side effects	Possible risks	Monitoring
Ustekinumab	Inhibits Interleukin-12 and Interleukin-23 (IL-12/23)	Subcutaneous injection by a health care provider or self-injection	Week 0 and 4, and every three months thereafter	Fatigue, headache, upper respiratory infection	Malignancies, reversible posterior leukoencephalopathy syndrome	Screening for latent tuberculosis infection
Ixekizumab	Inhibits IL-17A	Subcutaneous injection by a health care provider or self-injection	Week 0 and every 2 weeks for three months, and every 4 weeks thereafter	Fungal infections, injection site reaction, nausea, upper respiratory infection	Hepatitis B reactivation	Hypersensitivity reactions, inflammatory bowel disease, screening for latent tuberculosis infection

Adopted from National Psoriasis Foundation, treatments (online edition, 2016).

Biological Therapies

Biologic therapies have been marketed for almost fifteen years and the associated long-term safety data continues to accumulate. Several biological therapies (etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, certolozumab and golimumab) have been developed and approved by FDA for the management of psoriasis (Table 5) (National Psoriasis Foundation, 2016). Biological therapies are immune-modulators that either target T cells or block pro-inflammatory cytokines. Except etanercept (which is a fusion protein produced by recombinant DNA), other approved biologicals are monoclonal antibodies (Ehrlich et al., 2004). Ustekinumab (blocks interleukin 12 and 23), and secukinumab (blocks interleukin 17A) are marketed for the management of moderate to severe psoriasis; certizumab is recommended only for active psoriatic arthritis. TNFα inhibitors etanercept, adalimumab, and infliximab are approved for the treatment of psoriasis and psoriatic arthritis, whereas golimumab is approved by the FDA for the management of psoriatic arthritis (Menter et al., 2009). Biological therapies seem to have better clinical efficacy than conventional treatments for short-term management of psoriasis and psoriatric arthritis, and they are also indicated for long-term use (Lebwohl M., 2003). Most patients start to improve by four weeks and achieve good reductions in disease severity by 12 weeks. At present, only limited clinical trial data are available to make conclusive remarks about their safety and efficacy profile with long-term use (Girolomoni et al., 2012).

All these medications are administered by intravenous infusion, intramuscular injection or subcutaneous injection. The treatment regimen varies depending on the medication, and can be onerous for the patient. Monitoring of adverse effects requires at least an annual blood and liver tests and TB screening (Ehrlich et al., 2004, Menter et al., 2009; Boehncke & Schon., 2015, National Psoriasis Foundation, 2016). Common side effects for biologics include respiratory infections, flu-like symptoms, and injection site reactions. Rare side effects for biologics that require monitoring include serious nervous system disorders, such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes; blood disorders including certain types of cancer (e.g., lymphoma); lupus-like syndrome; and hepatitis B reactivation (Ehrlich et al., 2004, Menter et al., 2009, Boehncke & Schon., 2015, National Psoriasis Foundation, 2016). To date the literature on combination therapy involving biologicals is limited and therefore more work is warranted to explore patient outcomes and important adverse drug effects, including but not

limited to skin cancer (Ehrlich et al., 2004, Menter et al., 2009, Boehncke & Schon., 2015, International Psoriasis Council, 2012).

Table 6. A partial summary of antipsoriatic treatments, data based on evidence-based guidelines such as German S-3, North American and international European guidelines

Psoriasis Treatments	Efficacy*	Level of evidence	Comment
Glucocorticosteroids§	60%	1	Skin atrophy if used long term
Vitamin D derivatives§	45%	1	Safest long-term treatment
Calcineurin inhibitors§	30%	2/3	Reserved for localised sites such as face and intertriginous areas
Ultraviolet B exposure	70%	2	Time consuming; cumulative dose might cause adverse effects
Psoralen plus ultraviolet A exposure	90%	2	Time consuming; cumulative dose might cause adverse effects (including malignancies)
Acitretin	15%	2	Avoid in young women; not recommended as low-dose monotherapy
Ciclosporine	45%	1	Often used for a few months only (nephrotoxicity)
Methotrexate	50%	2	Effective also in psoriatic arthritis
Fumaric acid esters	50%	2	Oral drug, available only in Germany
Apremilast	30%	1	Innovative oral drug, effective also in psoriatic arthritis
Adalimumab	70%	1	Most widely used biological for this indication
Etanercept	50%	1	Regarded as suitable also for intermittent use
Infliximab	80%	1	Very fast onset of action; recommended for generalised pustular psoriasis (off-label)
Ustekinumab	70%	1	Only four injections per year during long term treatment
Secukinumab	80%	1	Patients often achieve complete clearance of skin symptoms
Estimated proportion of patients who achieved at least 75% reduction in their Psoriasis Area and severity Index Score from baseline to end of short-term therapy. Topical therapeutic, which as monotherapy is shown to treat psoriasis only.			

Adopted from Boehncke & Schon., 2015.

CONCLUSION

Psoriasis still remains a debilitating chronic skin condition that significantly affects both the physical health and quality of life of individuals affected with it. There is no cure for psoriasis. However, topical therapies such as glucocorticosteroids, vitamin D derivatives, or combinations of both are usually sufficient to manage mild symptoms (Table 6). Localised psoriasis is often treated with topical preparations such as emollients, keratolytics, corticosteroids, tars, calcipotriol, dithranol and tazarotene. Systemic therapy, including methotrexate, acitretin and cyclosporine and/or biological drugs, such as adalimumab, efalizumab, etanercept and infliximab, is reserved for more generalized psoriasis. Both systemic and topical treatment modalities are only partially effective and can induce irritation and/or serious adverse effects. Current treatment options are only effective in reducing psoriasis symptoms temporarily. More research is required on the pathogenesis of this complex auto-immune disease to enable the development of treatments which are efficacious, and have good patient compliance and safety profiles.

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Chapter 2

SLEEP AND PSORIASIS

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ABSTRACT

Sleep plays a substantial role in our physiological and psychological health. It has been widely demonstrated that sleep is impaired in patients with several chronic and acute diseases. More recently, sleep pattern has also been investigated in dermatological diseases. Among them, psoriasis seems to present a complex relationship with sleep. Individuals with psoriasis present more sleep disturbances in comparison to general population, as obstructive sleep apnea, restless legs syndrome and insomnia. This chronic inflammatory disease is associated with comorbidities as metabolic syndrome, hypertension, obesity and diabetes, which are also involved in the pathophysiology of obstructive sleep apnea. The presence of pain and pruritus has the capacity to interrupt sleep, leading to sleep fragmentation and sleep deprivation. Moreover, psychiatric disorders, such as depression and anxiety, are more prevalent among patients with psoriasis, and may contribute to changes in sleep pattern. Scientific evidences point to an explicit relationship between sleep and psoriasis; however, there is a need for more studies to understand whether this association is bidirectional and which are the mechanisms involved.

Keywords: sleep, psoriasis, obstructive sleep apnea, insomnia, restless legs syndrome, narcolepsy

INTRODUCTION

More recently, a new factor has been investigated among individuals with psoriasis: sleep. Sleep is of utter importance to several aspects of our body: cognition [1-3], emotional and sexual behavior [4-6], metabolism and hormonal secretion [7-9], immunity [10-13], and several others. It is plausible to accept that skin homeostasis also depends from sleep. Skin is the largest organ of our body and the first main barrier against harmful exogenous agents. In addition, skin presents a local and unique immune system, tightly connected to central and peripheral nervous system [14-16]. Psoriasis is a complex chronic inflammatory disease with a genetic component that also depends on several external factors, such as stress [17-18]. Recently, psoriasis has been related to a higher prevalence of sleep disorders as obstructive sleep apnea (OSA) and insomnia, poor sleep quality and quantity [19] (Table 1). This chapter will discuss the possible factors raised by literature as main contributors to sleep disturbances and its correlates in psoriasis.

Table 1. Recent studies which evaluated sleep and psoriasis and its main findings

Authors	Main findings
Kimball et al., 2016	Pruritus severity and sleep problems are associated to activity impairment and work production
Gupta et al., 2016	Higher prevalence of sleep disturbances in psoriasis in comparison to general population: 36%-81.8% versus 2%-4% in OSA; 15.1%-18% versus 5%-10% in RLS, 5.9%-44.8% versus 10%-35% in insomnia
Cohen et al., 2015	Women with OSA have an increased risk of developing psoriasis in comparison to controls
Egeberg et al., 2015	Incidence rate ratio for OSA increases according to psoriasis severity
Güler et al., 2015	Higher frequency of RLS in patients with psoriasis in comparison to controls. Severity of RLS is associated to insomnia
Shutty et al., 2013	Individuals with psoriasis suffers more with sleep disturbances than controls, probably due to the presence of depression
Yang et al., 2012	OSA increase in 2-fold the risk to develop psoriasis

OSA: obstructive sleep, apnea; RLS: restless leg syndrome.

INSOMNIA

According to the most recent version of International Classification of Sleep Disorders [20], insomnia is defined as a "persistent difficulty in the sleep initiation, duration, consolidation, or quality, which occurs despite adequate opportunity and circumstances to sleep, and results in some form of daytime impairment." Insomnia is primarily diagnosed by clinical features. Polysomnography and actigraphy are not indicated in the routine evaluation; however, they are widely used in research. In the general population, the prevalence of insomnia varies across studies from 6.4% to 22.1% [21-24]. In addition, the prevalence of insomnia among women is higher than in men [25].

Among individuals with psoriasis, insomnia is associated especially to the psychological status of the individuals. Skin diseases cause impairments to mental health because, in addition to the clinical symptoms, affecting directly physical appearance [26]. Armstrong and colleagues [27] conducted a study with more than 5,000 patients with psoriasis and found that 94 saw their disease as a problem in daily life; 82% informed that the disease interfered in the enjoyment of life; and 88% reported that psoriasis affected the overall emotional well-being. Several emotional components as disfigurement, embarrassment, helplessness and unsightly appearance are known as contributing factors to lower well-being in psoriasis [27]. Regarding the psychiatric disorders, depression and anxiety are the most frequent among this population, being linked to its severity and duration [28-31]. Individuals with psychiatric disorders or symptoms have often comorbid insomnia symptoms, with complaints of insufficient sleep, alterations in sleep duration and sleep efficiency [32-34]. It is estimated that the prevalence of insomnia in psoriasis patients varies from 5.9%-44.8% [35]. Shutty and colleagues [36] demonstrated that individuals with psoriasis are more prone to experience insomnia and have a 6.1-fold risk to be depressed in comparison to healthy individuals. However, when evaluating the results considering depression as a control variable, the authors did not find significant differences between controls and subjects with psoriasis. Thus, it seems that in this study insomnia was primarily linked to depression, instead of psoriasis per se [36]. As mentioned, several studies evaluated the prevalence and pathogenesis of psychiatric disorders among subjects with psoriasis. However, just a few studies evaluated sleep aspects, and even less studies correlated both aspects in individuals with psoriasis.

Among the psychiatric comorbidities, pruritus is another factor associated with insomnia in psoriasis patients, contributing especially to the difficulty of

initiating and maintaining sleep [36, 37]. Pruritus is mediated by circadian factors as skin temperature and cortisol concentrations, being more frequent in the evening and night than the morning [38]. According to patient's reports, sleep is highly affected by itching. Studies have shown that sleep quality and quantity is reduced as well as the sensation of restorative sleep [39-42]. However, a good night of sleep may relief itching [41]. Among individuals with self-reported psoriasis, there is a 1.4-fold risk for developing insomnia; and among patients with physician-diagnosed chronic plaque psoriasis this risk is even greater, reaching 4.3-fold [35]. Pruritus is a very common complaint among patients with several skin diseases such as psoriasis and has a negative impact in quality of life, being considered as the most bothersome symptom [27, 43, 44]. The daily routine is also impaired by insomnia resulted from night pruritus. Recently, Kimball and colleagues [45] reported in psoriatic patients that sleep problems were mediators of the relationship between pruritus and work productivity, activity impairment and presenteeism. Also, poor sleep quality by itself was capable to negatively affect work in psoriatic patients [45].

OBSTRUCTIVE SLEEP APNEA

Probably, OSA is the most studied sleep disorder among individuals with psoriasis. However, until now scientists were not able to determine which one develops first. Psoriasis and OSA have a complex bidirectional relationship illustrated by a wide range of comorbidities in common [19]. OSA is a very common sleep disturbance, affecting 2-33% of population [46-48], associated with an increased risk for metabolic and cardiovascular diseases [49, 50] characterized by increased alterations in glucose, lipid and pro-inflammatory profile [51-53]. Of note, patients with psoriasis also present comorbidities and metabolic alterations very similar to the ones observed in OSA individuals: diabetes mellitus type II, arterial hypertension, obesity, hyperlipidemia, insulin resistance, heart diseases, dyslipidemia, inflammation and decreased vitamin D and adiponectin levels [54-65].

Due to these similarities, researchers started to investigate the presence of OSA in psoriasis individuals, trying to understand the possible mechanisms involved in this relationship. A study performed in 13,513 individuals (8,484 men and 5,029 women), among which 1,414 men and 844 women presented OSA [66], showed that after 3 years of the cohort follow-up, 0.49% of the patients with OSA developed psoriasis in comparison to 0.22% in controls.

This result suggested that OSA patients had twice the risk to develop psoriasis in comparison to individuals without OSA [66]. Karaca and colleagues [67] evaluated 33 patients with psoriasis and found that 54.5% were diagnosed with OSA after a polysomnography exam. OSA patients presented a higher apnea hypopnea index, reduced mean and minimal oxygen saturation in comparison to controls, as expected. No significant differences were found in the proportion of sleep stages [67]. Another study found that only body mass index and hypertension were associated with OSA in psoriasis patients, while serum lipid profile and glucose levels were not. However, the psoriatic patients with OSA presented more frequently snoring and lower sleep quality in comparison to those without OSA [68]. Cohen and colleagues [69] compared adult women with and without OSA. The results showed that OSA women presented a higher risk to develop psoriasis in comparison to healthy women [69].

Not only has the presence of psoriasis been importantly correlated with OSA, but also its severity. Egeberg and colleagues [70] described that the incidence rate ratio (IRR) for sleep apnea was lower in mild psoriasis cases (IRR: 1.30; 95%CI: 1.17-1.44) and higher in severe cases (IRR: 1.65; 95%CI: 1.23-2.22). In addition, the authors also evaluated the IRR considering the use or not of continuous positive airway therapy (CPAP), which is recommended for treating cases of moderate to severe OSA. The IRR in patients with mild psoriasis without CPAP was 1.62 (95%CI: 1.41-1.86) *versus* 1.82 (95%CI: 1.43-2.33) with CPAP, showing absence of significant difference. Surprisingly, in severe psoriasis patients the IRR increased in those with CPAP (IRR: 3.27; (95%CI: 2.03-5.27) in comparison to those without CPAP (IRR: 2.04; 95%CI: 1.47-2.82), indicating that the relationship between OSA and psoriasis may be more complex than initially supposed [70].

Maari and colleagues [71] proposed an intervention to improve sleep quality in a population of patients with psoriasis and OSA. This randomized clinical trial enrolled 20 patients, who received adalimumab (an inhibitor of tumor necrosis factor-α) or placebo. No differences were observed in apnea-hypopnea index before and after treatment among the groups. However, they observed an improvement in body surface area affected by psoriasis [71]. Thus, it is very difficult to establish a causality relationship between OSA and psoriasis. The influence of OSA in psoriasis development could be explained by the intermittent hypoxia and oxidative stress. This event leads to activation of pro-inflammatory pathways that would contribute to the triggering of psoriasis [19, 66]. Further studies are warranted in this area to clarify the possible mechanisms involved since there is contrasting data in the literature.

SLEEP RELATED MOVEMENT DISORDERS

This category comprehends disturbances characterized by movements that disturb sleep or its onset as restless legs syndrome (RLS), periodic limb movements, sleep related bruxism and others (ICSD-3). Only few studies evaluated the presence of these sleep disorders among individuals with psoriasis. Cicek and colleagues [72] evaluated the presence of RLS in atopic dermatitis and psoriasis patients. RLS was assessed according to clinical cardinals defined by the International RLS Study Group [73]. Among the 50 patients with psoriasis, 18% presented RLS. This prevalence did not differ statistically from the control group (10.8%) [72]. However, when evaluating the mean RLS score, psoriasis group presented a higher score in comparison to atopic dermatitis patients and controls. In addition, the authors found a significant correlation between body surface area affected by psoriasis and RLS [72]. Other studies showed a higher frequency of RLS among individuals with psoriasis in comparison to controls: 17% *versus* 4% [74] and 40% *versus* 14.2% [75]. Another work also demonstrated that in patients with RLS there is a correlation between the severity of RLS and secondary insomnia [75].

Gupta and colleagues [35] described in their systematic review other 2 studies: 1 reporting a prevalence of 15.9% of RLS among psoriasis patients [76], and another reporting that there was an increase in periodic limb movements in psoriasis individuals compared to controls [77]. There are no studies correlating the medication used in psoriasis treatment with the development of RLS [74]. Other studies also indicate a higher prevalence of RLS in other chronic inflammatory conditions [78, 79].

NARCOLEPSY

Narcolepsy is a neurological disorder characterized by chronic daytime sleepiness and disordered regulation of rapid-eye-movement (REM) sleep [80]. The main age of diagnoses is between 5 and 15 years, especially due to the poor performance at school caused by narcolepsy symptoms. Narcolepsy may be also accompanied by cataplexy (triggered by strong emotions), fragmented sleep and hypnagogic and hypnopompic hallucinations [80]. Recently, it has been confirmed that narcolepsy can be considered an autoimmune disease [80]. Martinez and colleagues [81] evaluated patients with narcolepsy based on evidences that people with an autoimmune disorder

have a higher risk to develop another one [82]. Among 26 cases of narcolepsy objectively diagnosed by polysomnography and multiple sleep latency tests, 2 also presented psoriasis [81]. Due to the lack of data in this field, it is very difficult to discuss where it lies a possible connection among these 2 conditions.

CONCLUSION AND FUTURE PERSPECTIVES

Scientific community must be aware of the importance of considering sleep while investigating dermatological conditions. Skin diseases have very complex pathogenesis, and recent studies suggest that sleep could be involved in some related mechanisms. A few studies showed that psoriasis patients have a higher prevalence of sleep disorders as OSA, RLS and insomnia. The alterations on sleep wake-cycle may promote alterations in our body homeostasis, which in turn trigger and/or aggravate psoriasis (Figure 1). However, a small amount of questions has been raised about the possible mechanisms involved, and even less has been answered until now. There is a need to join researchers from several areas, clinical and basic background, to seek and better investigate this disease, and then conduct biochemical and molecular approaches linked to the Sleep field.

FINAL CONSIDERATIONS

Several negative effects of sleep disturbances have been documented regarding behavioral, hormonal, and immunological changes, in addition to a reduction in longevity. Recent evidence has shown a close connection between sleep and skin diseases, and psoriasis is one of the most studied with regards to sleep. Overall, it seems that there is a bidirectional relationship between sleep and psoriasis. Sleep deprivation can impair skin integrity through activation of stress system and inflammation pathways, leading to higher disease severity. On the other hand, the sleep pattern of psoriasis patients is characterized by sleep fragmentation, poor quality and increased risk of sleep breathing disorders, insomnia, hypersomnolence and movement sleep disorders. Although many techniques and treatments for dealing with psoriasis have been developed, further studies about how sleep intervention such as sleep hygiene could improve the severity of this disease and the quality of life of patients.

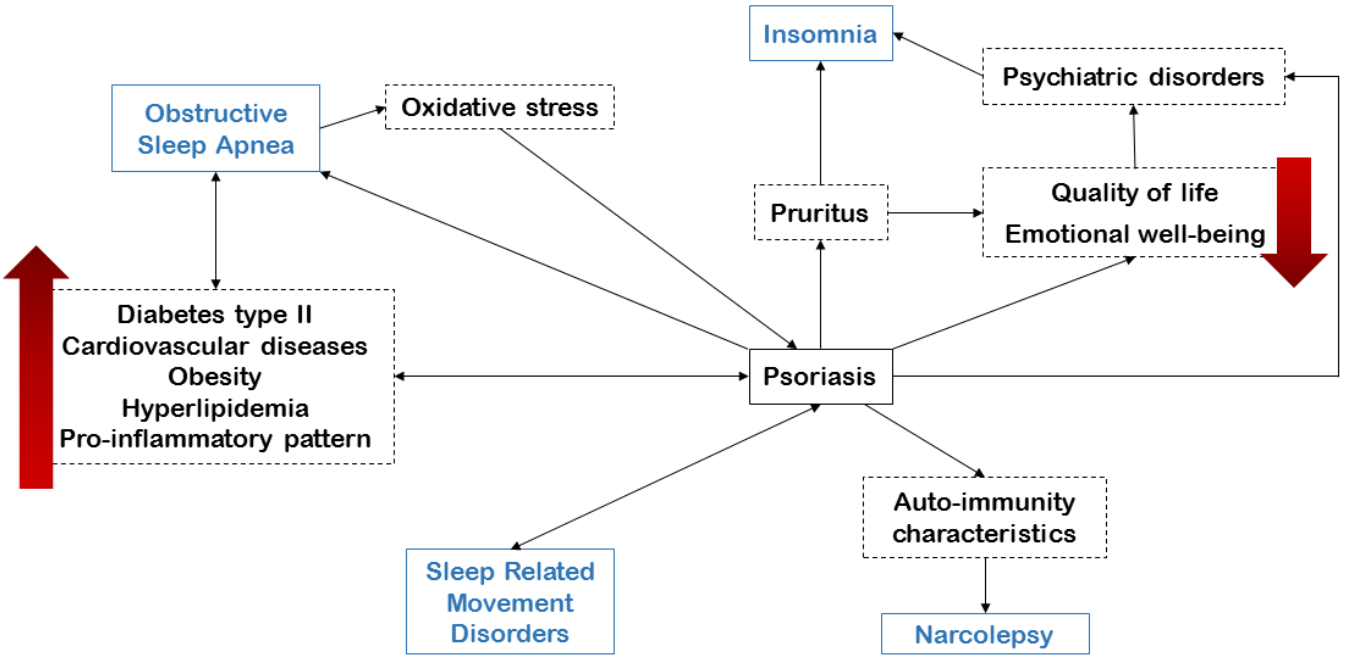

Figure 1. Main sleep disorders and possible mechanisms involved in psoriasis individuals.

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Chapter 3

DIFFERENTIAL SCANNING CALORIMETRY (DSC) AS A NEW DIAGNOSTIC AND SCREENING METHOD ON PATIENTS WITH PSORIASIS

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ABSTRACT

Psoriasis is a long-lasting skin disorder, which is appearing in different form (plaque, nail, scalp, guttate, inverse, pustular, erythrodermic psoriasis) and in some cases can affects the joints (psoriatic arthritis). Generally the diagnosis is based on full skin physical examination rarely skin biopsy is useful to determine the exact type of psoriasis, while in the cases of psoriatic arthritis radiological examinations (X-ray, ultrasound, MRI) are necessary to differential

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diagnosis. Unfortunately, there are often has not specific laboratory and radiographic findings that reliably confirmed this challenging diagnosis. Recently, there are continuous research efforts to find new methods to detect and to monitor this dermatological syndrome at any stage. Differential Scanning Calorimetry (DSC) is a thermoanalytical method which monitors small heat changes between a sample and reference material. The DSC thermogram, is the unique signature for bio-molecules reflecting the normal or pathomorphological changes under given solution conditions. Moreover, DSC is useful method to evaluate local and global conformation changes in the structure of different biological samples (blood plasma and serum, tissue samples) in several previous orthopaedical and traumatological, surgical, oncological and dermatological clinical studies. Recently, numerous articles confirmed that DSC is widely used as a new diagnostic method for detection of different diseases' seriousness, and as an applicable technique during monitoring of patients. The following chapter should give an overview of the current results where blood plasma thermal changes have been detected by DSC technique on psoriatic patients with different clinical stages, and monitored patients from symptomless and till the effect of various drug therapies (Cytostatics, Retinoids, and Biologic response modifier agents) on patients with serious symptoms. The studies demonstrated that thermal changes (transition temperature, calorimetric enthalpy) of blood plasma showed strong correlation with psoriasis severity and effectivity of medical treatment, and these measurements increased our knowledge about blood plasma structural changes in one of the most common inflammatory skin disease. In case of proper validation and further investigations of this method should promise for routine clinical use.

Keywords: psoriasis, PASI score, differential scanning calorimetry (DSC), monitoring, drug therapy, blood plasma

INTRODUCTION

Psoriasis is a lifelong, recurring and remitting inflammatory disease of the skin that is associated with genetic, environmental (trauma, infection, medications, stress, smoking, and alcohol consumption), and immunologic factors with a prevalence of 2-3% worldwide [1, 2]. This chronic and complex disease affects both sexes equally, and can occur at any age, although it most commonly appears for the first time between the ages of 15 and 25 years [3]. It has a predilection for presenting on the scalp, extensor surfaces of the limbs, hands and feet, sacral and genital regions, and sometimes accompanied with

nail changes, but the total body surface area affected can vary. According to dermal symptoms there are five types of psoriasis: plaque, guttate, inverse, pustular and erythrodermic. In about 80% of cases, plaque psoriasis presents as symmetrical, sharply demarcated, erythematous, dry, scaling, pruritic plaques affecting the top first layer of the epidermis [4, 5]. Psoriasis should be a systemic disorder; in 10-30% of the cases can also cause inflammation of the joints (psoriatic arthritis) and often involves extra-articular sites, such as the gastrointestinal tract and the eye [3, 5, 6]. Recently, mounting evidence for an association between severe psoriasis and systemic metabolic disorders (obesity, insulin resistance, hypertension, dyslipidemia, and cardiovascular disease) was found [7].

Along with local (skin look, itching, etc.) and general symptoms (e.g., sleeplessness), and the higher risk for systemic diseases, patients have negative body image and decreased quality of life, which explains that psoriasis recently has been in the focus of experimental and clinical research.

PATHOGENESIS

In the last decades, rapid progress has been made in understandings of the general cellular and molecular pathways of inflammation. Moreover, accumulating clinical and experimental evidence points out that the immune system plays a key role in disease pathogenesis. Despite all our knowledge, the complete pathogenic mechanism of psoriasis is still unclear [8-10]. The histological appearance of the plaque psoriasis due to (1) the epidermal hyperplasia due to abnormal differentiation and incomplete maturation of keratinocytes, (2) a thickened epidermis, and (3) a reduced or absent granular layer, (4) increased amount of new blood vessels (angiogenesis), and (5) invasion of numerous immune cells (T lymphocytes, dendritic cells, macrophages, neutrophils) in the dermis layer of the skin.

Firstly, the antigen presenting cells present environmental factor or foreign body as an antigen causing secretion of various cytokines and chemokines and allow the differentiation of native T cells to effector T cell subpopulations. These Th17 cells will secrete further pro-inflammatory cytokines (interferon-γ: IFN-γ; tumor necrosis factor-α: TNF-α; and interleukins: IL-2 and IL-23) increasing the proliferation of keratinocytes. IL-2 stimulates T cells, while TNF-α activates the further production of cytokines and the adhesion of molecules by keratinocytes and thereby increases the recruitment of immune cells. Recent data suggest that IL-23 as a key cytokine

with Th17 cells could be pivotal inducers of epidermal hyperplasia and thus pathologically modify epidermal differentiation in psoriasis (Figure 1). Depending on these immunological status and activity of the lesions psoriatic plaques may persist for months to years, and periods of complete remission are possible [9, 11-13].

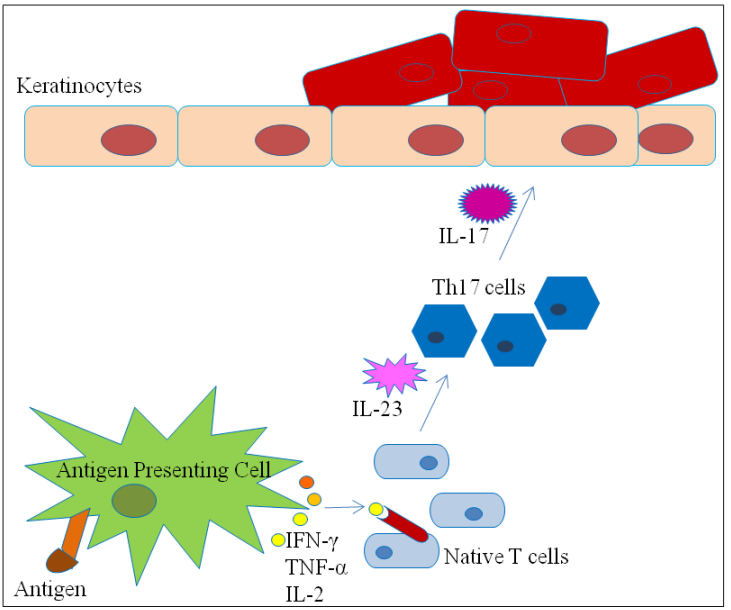

Figure 1. Schematic presentation of cellular and molecular pathways of the pathogenesis of psoriasis.

DIAGNOSIS AND MONITORING

Although there are no validated diagnostic criteria, the diagnosis and follow-up of plaque psoriasis is based on dermatological examination only, and in a majority of cases histological confirmation is not necessary. Skin biopsy may be useful to differential diagnosis only in localized pustular psoriasis, in order to exclude other clinically similar conditions. The psoriasis area severity index (PASI) is created by Fredriksson and Pettersson in 1978, as an index used to express the severity of psoriasis [14]. To make up the score, the three features of a psoriatic plaque (redness, thickness and scaliness) scaling with a number from 0 to 4 where 4 being worst. Then the extent of

involvement of four regions (head, trunk, upper and lower extremities) of the body is scored from 0 to 6. Adding up the scores give a range of 0-72, where the lowest PASI score is 0, while the potential highest is 72. According to PASI patients should be selected into four groups: symptomless (PASI: 0), mild (PASI: 1-5), moderate (PASI: 6-15), and severe symptoms (PASI: >15) (Figure 2).

Up till now, there are no generally accepted methods, or objective parameters to assess effectiveness of treatment or to follow the disease in any stage. Moreover, in a clinical practice there are no laboratory findings specific for psoriasis. The laboratory follow-up is useful only to monitor the side-effects of medical therapies [3, 15].

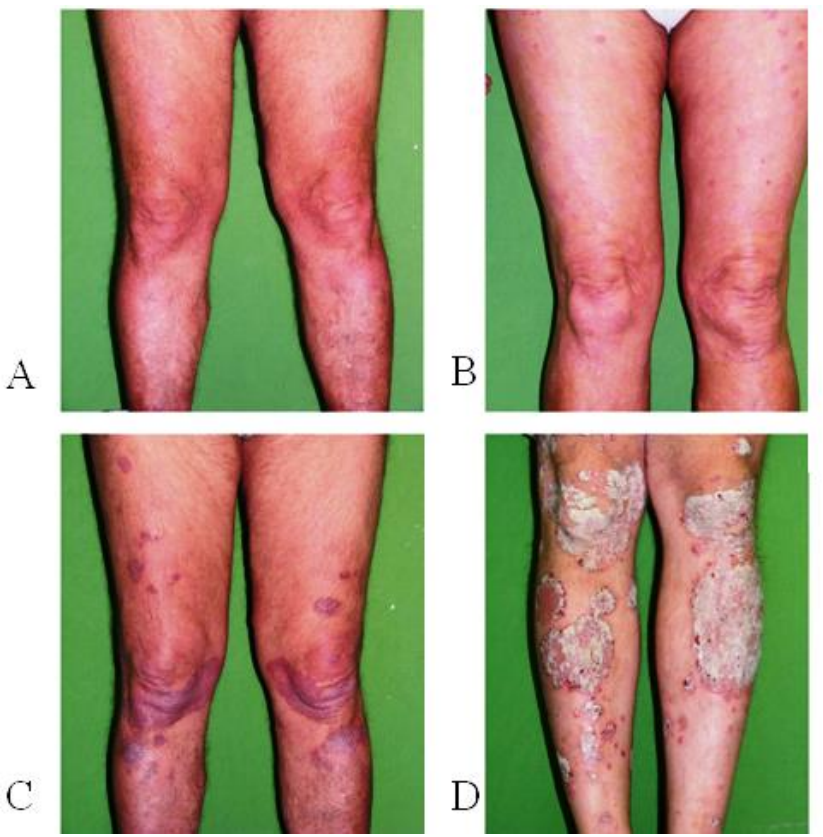

Figure 2. Symptomless (A), mild (B), moderate (C), and severe symptoms (D) patients with psoriasis.

TREATMENT

Management of psoriasis may involve principally medication treatment (local or systemic drugs), and various adjuncts such as stress reduction, climate- and phototherapy, moisturizers, and different keratolytic agents (salicylic acid, urea, etc.). Each guideline recommends that psoriasis treatment be personalized for each patient's clinical situation and discusses examples of this approach to treatment. Recommendations from a 2014 International Consensus Report on treatment optimization and transitioning for mild-to-severe plaque psoriasis include methotrexate, retinoids, and biologic agents as monotherapy, or combination of these drugs [9, 16].

Methotrexate is a popular medicine used for treating psoriasis. It has comprehensive anti-inflammatory effects: (1) it may relate to an increase in intracellular adenosine, a purine nucleoside in keratinocytes, (2) it is a folate antagonist, which means it prevents the action of folic acid, on cellular function resulting in reduction in pyrimidine, purines, and methylation of DNA, so it has immune suppressive effects on T cells. Beside its successful usage, methotrexate side effects present in more than 10% of cases, including nausea and vomiting, increased level of liver enzymes in blood, leukopenia and bone marrow suppression [17-19].

Acitretin, a second-generation retinoid has been a well-useful drug since the late 1980s. Retinoids primarily act at cytosolic proteins and intranuclear receptors, thus these agents are normalizing keratinocyte differentiation, exerts immune-modulatory and anti-inflammatory effects without a direct immunosuppressive effect. Acitretin is rapidly and extensively distributed throughout the body bound to plasma proteins without tissue accumulation. Long-term toxicity is observed after its treatment, such as teratogenic effects, hepatotoxicity, and harmful influence on lipid metabolism [19-21].

Previous reviews showed that psoriasis treatment fundamentally changed in the last decades. Discovery of new immunological pathways and a better knowledge of psoriasis pathogenesis have turned to develop new biologic response modifiers drugs against specific immunological processes that cause psoriasis. In the newest and comprehensive studies the authors summarized the influence of the promising new treatments for psoriasis [9, 13]. For treatment of biologic agents, such as TNF-α blockers (infliximab and adalimumab) and IL-23 blocker (ustekinumab) are indicated from moderate to severe lesions in adults who fail to respond to, have a contraindication to, or are intolerant to other conventional systemic therapies (Figure 3). Advantages of the biological therapy that in addition these drugs are effective in reducing of skin the

symptoms they associated with lower toxicity to distant organs and minimized general side effects (Figure 4). Disadvantages of them, biologics are more expensive than conventional treatments, and because of their intracutaneus or intravenous administration these therapies need patient's hospitalization.

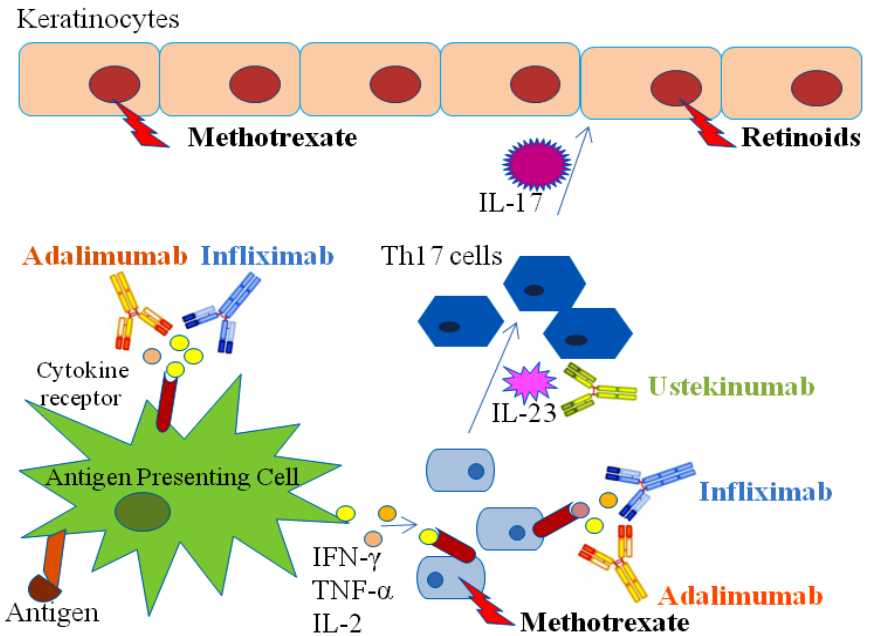

Figure 3. Schematic representation of the effect of currently used anti-psoriatic agents to target molecules and cells.

DIFFERENTIAL SCANNING CALORIMETRY

Differential scanning calorimetry (DSC) is a thermoanalytical method which is used firstly during the research of the physical properties of mineralogical and inorganic materials since 1960s years. The technique was first described by Watson and O'Neill in the Perkin-Elmer Corporation in USA [22]. Later, this validated and efficient method used for the demonstration of structural changes not only in the physical sciences, but also at behavior of numerous biological macromolecules (carbohydrate, proteins, nucleic acids, etc.) [23, 24], in different experimental animal models [25-28], and also in clinical researches [29, 30].

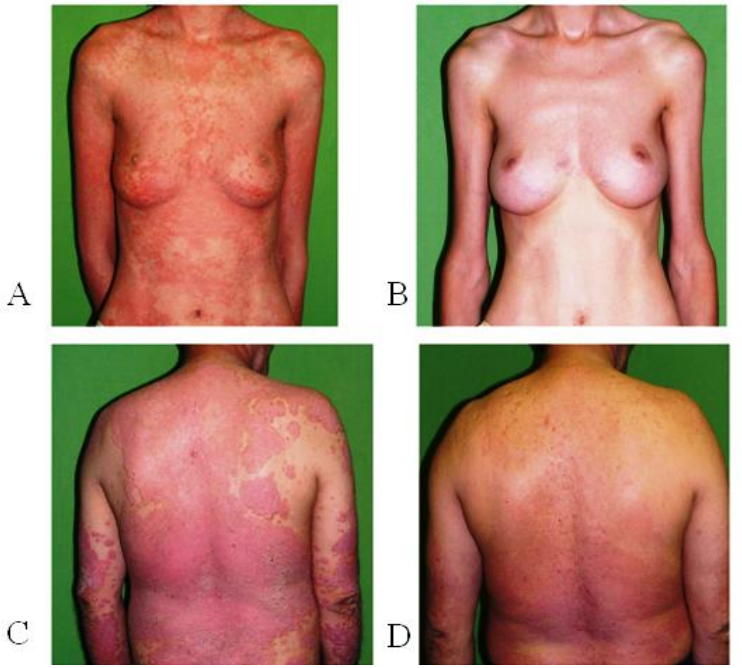

Figure 4. Influence of biological response modifier drugs in moderate (A: before treatment, B: after treatment) and in severe (C: before treatment, D: after treatment) psoriasis.

For understanding the fundamental factors and considerations of this method are the follows. Any materials - including biological samples - depending on the temperature should be in the different form of chemical compounds, or crystal structure. With changing the temperature we can reach that thermal point where the chemical form of the crystal structure or physical condition of the particular substance will be changed. This conversion is frequently accompanied by heat phenomenon. Detecting the transition temperature and meanwhile absorbed or released thermal energy by chemical structure can be identified. DSC device consists of two chambers, one contains the sample and the other contains the reference. The reference material must be "inert," so during the measurement it shall not suffer any structural changes. This method measures that electric power which is required to keep the sample and the reference substances on the same temperature during heating or cooling processes. The measurements are performed within different temperature range (in biology mainly 0-100°C), for example with 0.3 K/min temperature increase. During evaluation of DSC thermograms we get

response how changed the heat flow through the material when temperature is increased. If we warm any biological sample, it will be the heat picked up steadily, and this energy will be used only for material heating (first plateau phase, where there is no temperature difference between the sample and reference, it is the so called native state of the system). At a certain temperature the heat flow will already be decreased, because some of the heat will not increase the internal energy exclusively, but rested energy will rearrange or unseal chemical and biological bonds, namely the energy will be "absorbed" in the molecules. At this point, the curve will be descending, and the denaturation phase is beginning. This process is endotherm, because the temperature of the sample less than the reference, and more energy is required to unseal the structure, so more energy have to be fed to maintain temperature difference between the sample and the reference at zero. Protein denaturation will be resulted increased absorbed heat, and finally the heat flow will be more and more in the sample. At a certain temperature, the 50% of total amount of macromolecules will be denaturized. This is signed as maximum conversion (namely, the maximum unfolding) or as denaturation temperature with T_m (T_{max}: the peak of the curve). Later, more and more denatured proteins will be, and fewer have to convert with less and less additional energy during the measurements. When all proteins denaturized, the used energy will be increased again the internal energy of the materials only. Finally, between the sample and the reference will not be temperature difference, and heat uptake of the sample and reference chambers will be returned to second plateau phase (it can differ from the first one in case when the denatured material undergoes into other state than the first native state) [31].

ANALYSIS OF BLOOD PLASMA BY DSC TECHNIQUE

From the beginning of the XXI. century, some researchers had started to use this technique to analyze structural changes of different tissues and macromolecules in body fluids (blood sera and plasma, synovial fluid) in various inflammatory and in cancerous diseases in such a complex place like a human body. The initial studies have shown that thermodynamic alterations of the biological structures associated with the development of various diseases. It has been demonstrated that changes of thermoanalytical parameters [transition temperature T_m (°C); calorimetric enthalpy: ΔH (J/g)] specifically appear in different diseases and in their various severity stages [32-34].

Recently, importance and role of DSC analysis is incontestable for understanding the stability of biological systems in human body. DSC directly measures the stability and unfolding of proteins, lipids, or nucleic acids that occur in bio-molecules during controlled increase or decrease in temperature, making it possible to study materials in their native state [35]. Garbett at al. have shown in their early works, that DSC thermogram is an unique signature for bio-molecules reflecting the normal or pathomorphological changes under different conditions [32, 33].

More than a decade since DSC measurements of patients has been focused in the researches more and more authors confirmed importance and advantages of DSC data. Summary, these are the follows:

1) Thermal results (heat absorption, transition temperature, and calorimetric enthalpy) of blood plasma or serum are significantly different in healthy individuals and in patients with various disease, namely in systematic inflammatory disorders or in tumorous diseases [32-34, 37-39].
2) Changes of DSC data show a strong correlation with clinical stages of different diseases [3, 35-38, 40-44].
3) DSC curves completely reflect the protein composition of the plasma or serum sample [39, 40-44].
4) Significant changes in thermograms follow not only from quantitative changes of major plasma proteins, but from interactions of small molecules or peptides of these proteins also [39, 40, 42-44].
5) Additionally, the shape of DSC curves is very sensitive to conformation changes of proteins, to protein-protein or to ligand-protein interactions, to appearance of new proteins (e.g., paraproteins in cancerous diseases), or to influence of different medications to plasma proteins [32-44].

The thermal unfolding of the human plasma components can be monitored by calorimeter, used for measurements between 0 and 100°C with for example 0.3 K/min heating rate. During measurements the sample chamber contains blood plasma, while reference chamber contains normal saline (0.9% NaCl). Mass of the sample and reference has to equilibrate with a precision of ± 0.1 mg. Calorimetric enthalpy should be calculated from the area under the heat absorption curve by using two-point setting peak integration.

Currently, researches have therefore raised the possibility that beside traditional diagnostic procedures DSC provides useful information in such systemic inflammation diseases like psoriasis [3, 19].

EFFECT OF ANTI-PSORIATIC DRUGS IN BLOOD PLASMA BY DSC

In healthy control cases, three main denaturation melting points (T_{ms} ~ 56, 62 and 65°C) appeared (Table 1). These results are consistently in line with measurements of all researchers [44-46]. Following deconvolution of DSC curve of healthy plasma from the three transition temperature the T_{m1} transition can be attributed mainly to fibrinogen, T_{m2} to albumin, while T_{m3} to immunoglobulins (Figure 5).

Table 1. DSC data of blood plasma in case of control and in systematically treated psoriatic patients with or witout symptoms. Number of examined cases were equal in each group (n=12/group, and n=4/subgroups). (T_m/°C peak temperature of denaturation („melting" point), ΔH/Jg^{-1} calorimetric enthalpy of transitions normalised for total sample mass. Data are rounded to two places of decimals)

Groups	Symptoms	T_m/°C			ΔH/Jg^{-1}
		T_{m1}	T_{m2}	T_{m3}	
Healthy controls	-	56.20±0.10	63.00±0.10	85.30 ± 0.10	1.29 ± 0.06
Cytostatic treatment	symptomless	55.70 ± 0.10	63.20 ± 0.06	85.10 ± 0.06	1.50 ± 0.06
	moderate	56.00 ± 0.10	64.60 ± 0.10	86.80 ± 0.10	1.60 ± 0.08
	severe	56.00 ± 0.10	63.30 ± 0.10	-	1.60 ± 0.08
Retinoid treatment	symptomless	55.90 ± 0.10	63.30 ± 0.06	85.40 ± 0.06	1.70 ± 0.07
	moderate	55.50 ± 0.10	63.50 ± 0.10	82.20 ± 0.10	1.40 ± 0.07
	severe	55.90 ± 0.10	63.90 ± 0.10	83.00 ± 0.10	1.50 ± 0.07
Biological treatment	symptomless	56.45 ± 0.80	65 ± 0.07	83.9 ± 0.07	1.49 ± 0.08
	moderate	55.75 ± 0.10	63.9 ± 0.80	-	1.45 ± 0.08
	severe	55.80± 0.80	64.10 ± 0.07	88.10 ± 0.07	1.30 ± 0.07

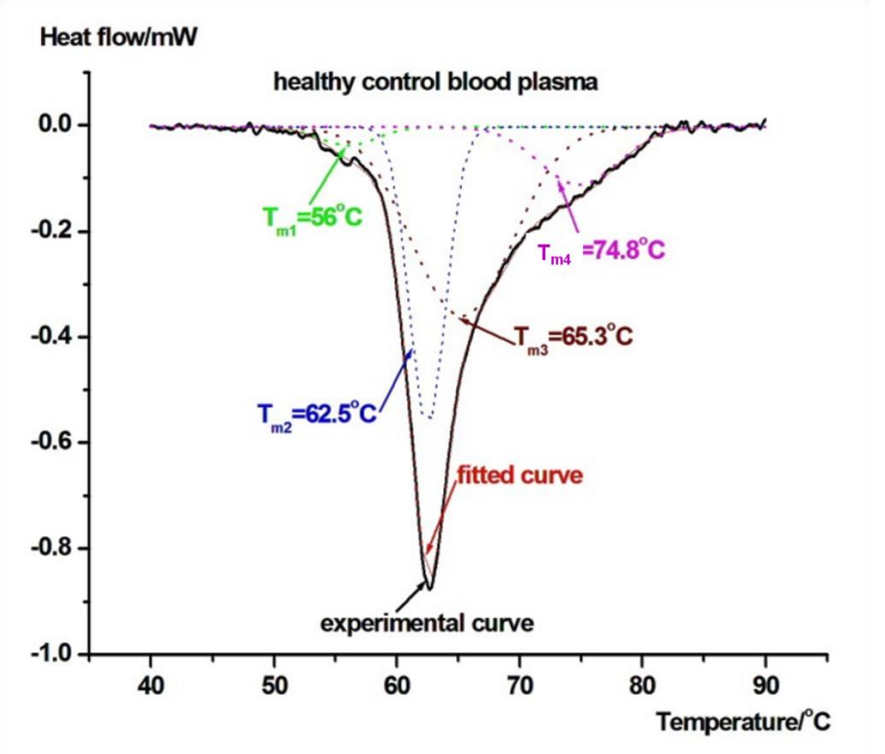

Figure 5. Deconvolution of blood plasma DSC curve from healthy individuals.

Testing the efficacy of the psoriasis treatment only possible with dermatological examination today, and it can be justified with the description of symptoms changes. Drugs as specific biomarkers present in plasma can modify the plasma thermal denaturation profile. In current research focused on the examination of blood plasma changes in context with the anti-psoriatic agent effectiveness by DSC. Psoriasis treatment with Cytostatics (Metotrexate) caused the following changes in plasma transition temperatures: regardless of disease severity the first peak (T_{m1}) did not vary significantly, but the second transition have been shifted to a little bit higher temperature (T_{m2} ~ 63 and 64°C) (Table 1, Figure 6). Moreover, the third thermal structural domain has been shifted significantly to the very higher temperature range (T_{m3} ~ 85 and 86°C) compared to controls. Increasing the third denaturation temperature has been indicated that more thermal energy apply is necessary to unpacked this densely structural domain. Presumably, this is because that the systemic inflammatory processes are reflected on changes of T_{m3} temperatures. Thus,

these results are in line with the findings that albumin level decreases and fibrinogen increases during inflammatory processes [44-46]. Besides these, the calorimetric enthalpy of plasma significantly increased, which might reflect stabilization of some plasma proteins, probably globulins, which have emphasized role during inflammation. These results can be considered as novel because no other results describing blood plasma such changes with thermoanalytical method on patients with psoriasis have ever been reported. But, similar observations have been made by some other researchers in a clinical study where in soft tissue inflammation and in rheumatoid arthritis were measured by DSC [45-47]. The present observations are in accordance with our previous results also, in which we have demonstrated similar results on patients with chronic pancreatitis, as in other systematic inflammatory disease [48].

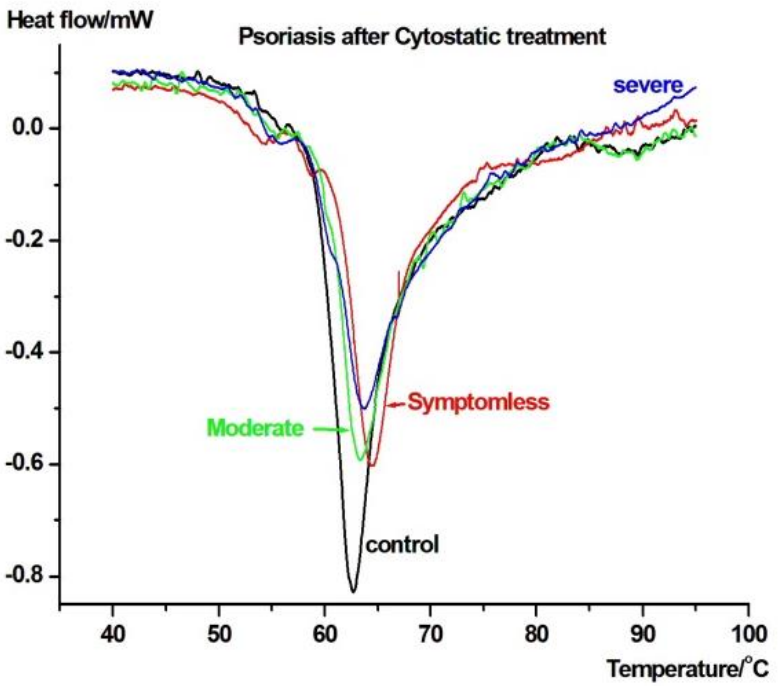

Figure 6. Thermal denaturation of blood plasma in healthy controls and after cytostatic therapy of psoriatic patients without symptoms, and with moderate and severe symptoms. Upward deflection represents endotherm process.

Systemic retinoids, which improve psoriasis through effects on epidermal proliferation and differentiation as well as immunomodulation, are also used for the treatment of this condition. After retinoid (Acitretin) treatment the melting point of plasma proteins showed mild decrease compered to controls (T_{m1} ~ 55°C) (Table 1, Figure 7). Similarly to cytostatic treatment the second transition have been shifted to a little bit higher temperature (T_{m2} ~ 63 and 64°C), while the third domain was found in significantly higher temperature range (T_{m3} ~ 82 and 85°C) compared to controls. The calorimetric enthalpy showed an increase compared to healthy plasma, while comparing to the effect of cytostatic regiments was a decreased tendency. We can conclude that all symptomatic patients' samples showed a definite calorimetric enthalpy increase between the native and denatured states of the blood plasma compared to the control, which could be the sign of different water binding of plasma proteins as well as their increased aggregation tendency in the function of the severity of disease.

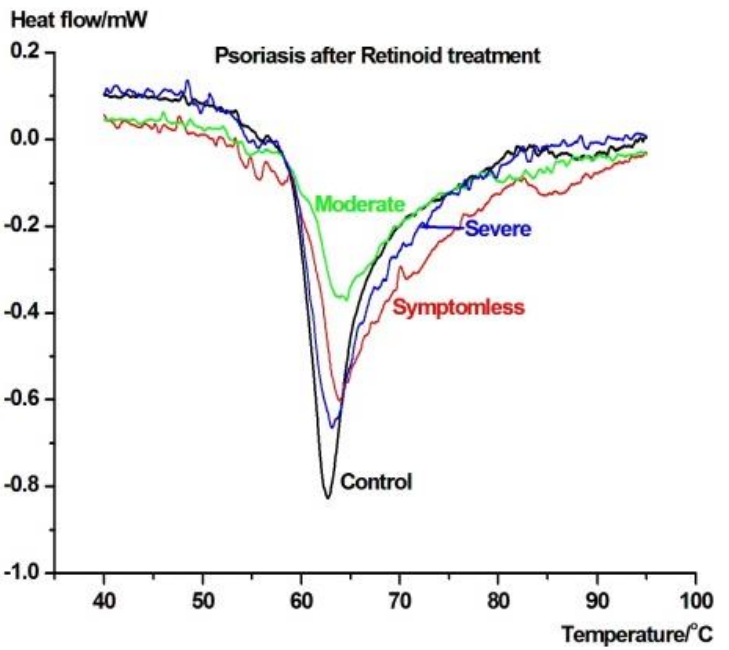

Figure 7. Characteristic of blood plasma DSC curves in healthy controls and after retinoid agent of psoriatic patients without symptoms, and with moderate and severe symptoms. Upward deflection represents endotherm process.

The newest therapeutic approach is the usage of biologic response modifier drugs. These chimeric monoclonal anti-TNF-α or anti-IL-23 antibodies caused the lowest local tissue damages and systematic side-effects to the patients, because of their specific binding to the cells' receptors did not accelerate general anti-inflammatory processes. According to DSC data the first peak (T_{m1}) did not vary significantly, but the second transition have been shifted to the highest temperature range (T_{m2} ~ 64 and 65°C) (Table 1, Figure 8). The third thermal structural domain has been shifted significantly to the highest temperature range (T_{m3} ~ 84 and 88°C) compared to controls or to plasma effect of other drugs. Increasing the third denaturation temperature has been indicated that the most thermal energy apply is necessary to unpacked this densely structural domain after applied biologic therapy (infliximab, adalimumab, and ustekinumab). The calorimetric enthalpy of plasma significantly increased, but it was lower than after cytostatic or retinoid therapy. Detection of blood plasma changes by this thermoanalytical method in psoriatic patients is novel, and similar data are not found in the literature.

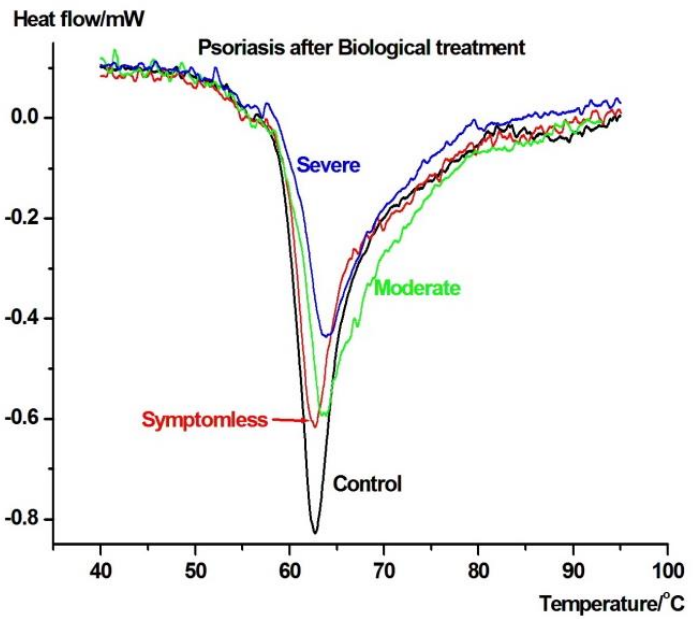

Figure 8. Heat flow changes of blood plasma in healthy controls and after biological drugs in psoriatic patients without symptoms, and with moderate and severe symptoms. Upward deflection represents endotherm process.

CONCLUSION

Present chapter demonstrated the pathogenesis and actual treatment methods in a chronic inflammatory disease, namely in psoriasis. It confirmed that DSC technique and given calorimetric parameters (transition temperature, calorimetric enthalpy) are in strong correlation with the blood plasma chances on patients with psoriasis and reflect the systemic inflammatory processes. According to the DSC parameters, significant differences were between the effects of different anti-psoriatic drugs to blood plasma status. Further studies are needed to elucidate these relationships, but these pilot studies indicates great potential for the application of DSC as a clinical diagnostic tool, for example, during disease grading and staging processes.

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Chapter 4

PSORIASIS TREATMENT: TARGETING THE IL-23/TH17 AXIS

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ABSTRACT

Psoriasis is a T helper (Th)1/Th17 induced immunoinflammatory disease and the interleukin (IL)-23/Th17 axis is believed to be crucial in the pathogenesis of this disease.

A chronic, unpredictable course of the disease, and the need for periodical alternation of drugs, makes psoriasis a disease difficult to treat. A variety of therapeutic approaches are available, ranging from topical

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agents for milder and limited forms, to phototherapy, photochemotherapy, systemic or biological agents for moderate and severe psoriasis.

Increased levels of IL-17 and Th17-related cytokines in psoriasis led to the proposal of therapeutic agents targeting IL-23/Th17 axis. Ustekinumab is a monoclonal antibody directed against the p40 subunit of IL-12 and IL-23. Secukinumab and ixekizumab are human monoclonal antibodies against IL-17A, while brodalumab is a fully human monoclonal antibody that targets IL-17 receptor A. Ustekinumab and most biologic agents targeting IL-17 were efficacious and safe in the treatment of moderate-to-severe psoriasis in adults, although, long-term data is still required. In the present chapter we will debate published data concerning the current knowledge about the importance in psoriasis of the IL-23/Th17 axis and the present and future biological agents that target this pathway, as well as their use in treatment and adverse effects.

INTRODUCTION

Psoriasis is a chronic, recurrent immunoinflammatory dermatologic condition that affects 1 to 3% of the general population. For a long period of time, psoriasis was only defined by its clinical and skin histological characteristics. It presents an abnormal cycle of epidermal development, with epidermal hyperproliferation, modified maturation of skin cells, vascular alterations and significant inflammatory features. The histological findings include also a marked acanthosis, accompanied by parakeratosis and a mixed dermal cell infiltrate, with $CD4^+$ T cells, dendritic cells, macrophages, and mast cells. In the epidermis, neutrophilic exudates and $CD8^+$ T cells are the predominant inflammatory cells. Elongated, dilated and tortuous blood vessels are found in the dermal papillae [1].

Accumulating evidence showed that genetic, environmental and immunologic factors are also involved in psoriasis onset and in its course. The T-helper (Th)1 pathway was believed to be important for psoriasis pathogenesis, however, more recent studies showed that the interleukin (IL)-23/Th17 axis has also a crucial role in psoriasis. The relevance of the IL-23/Th17 axis is highlighted by the success of the treatment of moderate to severe psoriasis with therapeutic agents targeting IL-23 and IL-17.

TH1 PATHWAY

Human CD4+ T cells may differentiate into different phenotypes, such as Th1 or Th17 phenotypes. The transcriptions factors, retinoid-related orphan receptor (ROR)c and T-bet, a T-box transcription factor, contribute to both phenotypes, and, apparently, both phenotypes may produce IL-17A and interferon (IFN)-γ [2]. The differentiation of these cells into Th1 or Th17 is mediated by IL-12 or IL-23, respectively [2].

In psoriasis, an increase in cytokines of Th1 pathway has been detected both in plaques [3] and in serum of patients [4-6], suggesting the occurrence of a systemic release of cytokines towards a Th1 dominance.

IL-12, from activated macrophages, as well as IL-2, from activated T cells, regulate the transcription of IFN-γ, and tumour necrosis factor (TNF-α). IL-2 also mediates the proliferation of activated T cells and IL-12 promotes also the survival and growth of Th1 cells.

IL-27, produced by activated monocytes, macrophages, and dendritic cells, has a synergistic action with IL-12 on the production of IFN-γ by naïve Th cells.

The IL-18 also synergizes the stimulation of IFN-γ release and it is also important to cellular adhesion [7]. Monocytes, macrophages, dendritic cells, keratinocytes, and epithelial cells are all able to produce IL-18.

IFN-γ is secreted by Th1 cells, dendritic cells and natural killer T (NKT) cells. This cytokine increases the expression of the specific receptor chain for IL-12 and plays a central role in the development of Th1 immune responses [8]. Apparently, it is important in the early stages of psoriasis, by enhancing the immune cell migration into the skin and by activating dendritic cells, monocytes/macrophages and endothelial cells. Moreover, it inhibits apoptosis of keratinocytes and stimulates proliferation of epidermal cells [9].

TNF-α is expressed by dermal macrophages, T cells, keratinocytes and CD11c+ dendritic cells [10, 11]. This cytokine has a key role in local T cell proliferation [10]. TNF-α induces the expression of several cytokines, such as IL-6, and of acute phase reactants; thus, its neutralisation contributes to diminish the levels of these acute phase products [12]. IL-6 mediates T cell activation, stimulates keratinocytes proliferation and mediates the acute phase response [4]. TNF-α also enhances IL-8 production, providing a chemotatic signal for recruitment of neutrophils [13]. TNF-α and IFN-γ increase the expression of inter-cellular adhesion molecule-***1*** (ICAM-1), which promotes skin infiltration of T cells and other inflammatory cells, such as monocytes.

The neutralization of TNF-α is the basis for some successful psoriasis therapies, which confirms that this cytokine has an important role in the pathogenesis of psoriasis.

Circulating levels of TNF-α, IFN-γ, IL-12, IL-18 and IL-27 were reported to correlate significantly and positively with psoriasis severity [4, 5].

TH17 CELLS

The Th17 cells, known to produce IL-17, contribute to autoimmunity and chronic inflammation [14]. This distinct T-helper cell population plays a central role in CD4+ T cell-mediated adaptive immunity.

The mediators that stimulate the differentiation of naïve CD4+ T cells into activated memory Th17 cells are IL-1, IL-6, IL-21, IL-23 and transforming growth factor (TGF)-β [15, 16]. IL-1β participates in the activation of naive T cells, and is one of the strongest inducers of IL-17 production. The production of IL-17 is also enhanced by IL-6 and IL-21 [17]. One the other hand, IFN-γ and IL-4 restrains the formation of Th17 cells from naive precursors.

The proliferation of Th17 cell is driven by IL-23 [18]. *In vivo* studies showed that the induction of Th1 cells appears to depend on IL-12, while the induction of Th17 cells relies on IL-23 and IL-6 [19].

In severe psoriasis, $CD4^+$ regulatory T cells (Tregs) were also able to differentiate into Th17 cells in psoriasis lesions [20]. IL-17-secreting CD8+ T cells (Tc), Tγδ cells and NKT cells seem to have also the capacity to produce IL-17 [21].

IL-6 and TGF-β are necessary for the induction of Tc17 cells [22] and the development of these cells is supported by IL-23 that might be inhibited by IFN-γ [23]. Tγδ and NKT cells induce IL-17 production through stimulation by IL-23 [24, 25].

IL-17A, the prototype of the IL-17 family, from IL-17A through IL-17F, is a pro-inflammatory cytokine; IL-17F seems to be also pro-inflammatory, however, less potent than IL-17A [26]. This cytokine, IL-17A, is a dimeric glycoprotein that circulates as a homodimer, with two IL-17A chains, or as a heterodimer of IL-17A with IL-17F.

The cytokine IL-17E induces a deviation to Th2 response and is an anti-inflammatory cytokine [27]. The other cytokines of the IL-17 family are poorly characterized. The IL-17 receptor family comprises IL-17 receptor A (IL-17RA), IL-17RB, IL-17RC, IL-17RD and IL-17RE.

IL-23/TH17 AXIS

IL-23, produced by dendritic cells and by macrophages, activate Th17 cells, by stimulating their survival and proliferation, and, thus, it is a major cytokine regulator in psoriasis. IL-23 induces the production of IL-17A and of other Th17 cytokines, namely IL-17F [28]. It is also associated with the involvement of keratinocytes in the inflammatory psoriasis lesions, and with the acanthosis and dermal infiltration by mixed inflammatory cells that are mediated by IL-22 [29]. IL-23 also stimulates the expression of TNF-α in macrophages.

IL-17 is a key master in the establishment and perpetuation of inflammation, exerting its effects on macrophages, dendritic cells, neutrophils, fibroblasts, endothelial cells, epithelial cells, keratinocytes, and lymphocytes. It induces the production of pro-inflammatory cytokines, such as IL-6, prostaglandin E2 and IL-8 [30]. The latter, IL-8, upregulates keratinocyte expression of other chemokines (e.g. CXCL1, CXCL3, CXCL5 and CXCL6), known to favor the recruitment of neutrophils [31, 32]. IL-17 seems to promote also angiogenesis by two ways; indirectly, by enhancing the proliferation of endothelial cells, via induction of vascular endothelial growth factor (VEGF) and IL-8 by fibroblasts [33]; by increasing the recruitment of endothelial progenitor cells to support angiogenesis.

IL-22 is also considered a Th17 cytokine, produced, apparently, by a separate T cell subset, the Th22 subset, induced by Langerhans cells and dermal dendritic cells [34]. The Th17 and Tc17 cells were reported to produce also IL-22, besides IL-17 [35]. The IL-22 induces epidermal hyperplasia and hypogranulosis, acting as a mediator between the immune system and epithelial cells. It induces also the production of cytokines, chemokines and acute phase proteins, by several cell types; regulates the production of antimicrobial proteins by keratinocytes, as well as the differentiation and migration of keratinocytes [36]. Its activation does not need TGF-β, and, *in vivo* activation seems to require only IL-23 [37], although, *in vitro*, IL-6 and IL-23 stimulate IL-22 production [29]. Apparently, there is an important crosstalk between IL-23 and IL-22; IL-23 induces IL-22 production, and IL-22 can mediate IL-23 induced acanthosis and dermal inflammation [29]. The epidermal hyperplasia induced by IL-23 is significantly diminished by genetic deletion or by *in vivo* blockade of IL-22 [29].

Circulating Th17 cells are increased in psoriasis, along with Th22 and Th1 cells, although in a lesser extent [38].

The levels of IL-17, IL-23 and IL-22 were found enhanced in skin lesions and in blood of psoriatic patients, and appear to correlate with the severity of the disease [4, 36]·[39-43]. Moreover, the levels of IL-23 [44-46] and IL-17 [41, 44] are diminished after successful treatment of psoriasis, confirming the major role of these cytokines in the pathogenesis of the disease.

Our team reported [44] that during 12 weeks of narrowband ultraviolet (UV) B or psoralen-UVA therapy, IL-23 and TNF-α decreased at the 3rd week, followed by the decrease of IL-22 and IL-17 at the 6th week, and, finally, at 12th week, a decrease in VEGF and in IL-8. In accordance, we proposed [44] an immunoinflammatory pathway for psoriasis, involving the production of TNF-α and IL-23 by dendritic cells, causing activation and proliferation of Th1 cells, Th17 cells and monocytes/macrophages that lead to the induction of IL-17 and IL-22. IL-22 induces keratinocyte hyperplasia and mediates IL-23-induced dermal inflammation and achantosis. IL-17, and also TNF-α, activates keratinocytes to secrete IL-8, resulting in neutrophil mobilization and activation. Keratinocyte activation also results in induction of angiogenesis, by the production of VEGF.

The IL-23/Th17 axis seems to be a key master in psoriasis pathogenesis, and its inhibition appears to be crucial for clearing of psoriasis lesions. This axis also explains some of the typical histological characteristics of the psoriatic lesions, such as hyperplasia of psoriatic keratinocytes, induced by IL-22, and neutrophil infiltration, through IL-8 production, induced by IL-17 (Figure 1).

THERAPEUTIC STRATEGIES IN PSORIASIS

The main goal of psoriatic therapies is to control the disease and its clinical manifestations, contributing to improve the quality of life of the patients. The choice of treatment for psoriasis depends on many factors, including the severity of the disease, the skin type, the effect on patient's quality of life, the response to previous psoriatic treatments, patient's age and clinical history.

In clinical practice, broad global assessment of psoriasis activity and its impact on patient's quality of life, as well as patient's clinical and therapeutic history, are used to define the severity of patient's disease and to choose the

more appropriate treatment. There are several approaches to measure psoriasis severity; one of the most used is the Psoriasis Area and Severity Index (PASI) score, which considers the area of the affected skin surface and the severity of the lesions, by evaluating the degree of scaling, erythema and induration of the lesions.

The chronic, unpredictable course of the disease makes psoriasis as a disease difficult to treat. A variety of approaches are available for its treatment, ranging from topical agents, for milder and limited forms of psoriasis, to phototherapy, photochemotherapy, systemic and biological agents, for moderate and more severe forms.

The goal of the more recent therapeutic strategies is to target specific steps of the immune pathways involved in the development of psoriasis. The TNF inhibitors are available since more than a decade, and have greatly increased the treatment choices for patients with severe psoriasis. Etanercept is a recombinant human TNF-receptor fusion protein that competitively inhibits the effects of endogenous TNF, by interacting with cell-surface receptors [47]. It was reported that after 12 weeks of treatment with etanercept, 38% and 54% of patients are clear or nearly clear of psoriatic lesions, respectively [48]. Infliximab is a chimeric monoclonal antibody that specifically inhibits TNF-α [47], and seems to promote a rapid effect in very severe psoriasis, unstable psoriasis, erythrodermic psoriasis and pustular psoriasis [49]. After infliximab therapy, about 90% of the patients become clear or, at least, minimally affected [48]. Adalimumab is a monoclonal antibody specific to TNF-α that prevents binding of TNF to its receptors, causes lyses of cells to which TNF-α is bound on its surface, and decreases the expression of cellular adhesion molecules [49].

Increased circulating Th17 cells and increased levels of IL-17 and Th17-related cytokines in psoriasis patients led to the proposal of therapeutic agents targeting the IL-23/Th17 axis (Figure 1). Ustekinumab is a monoclonal antibody directed against the p40 subunit of IL-12 and IL-23. Briakinumab also targets IL-12 and IL-23, but the development of this drug, to use in psoriasis treatment, was discontinued in 2011. Concerning biologic agents targeting IL-17, secukinumab and ixekizumab are human monoclonal antibodies directed against IL-17A, while brodalumab is a fully human monoclonal antibody that targets IL-17 receptor A.

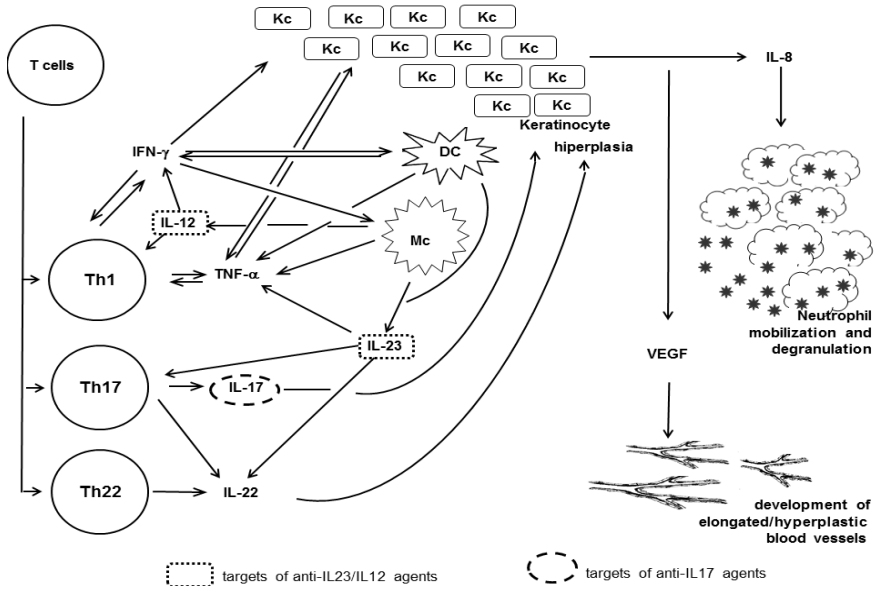

Figure 1. A simplified diagram of T-helper (Th)1 and Th 17 pathways and the targets of anti-IL23/IL12 (rectangular dot lines) and anti-IL17 (oval dot lines) agents (DC, dendritic cells; IL, interleukin; INF, interferon; Kc, keratinocytes; Mc, macrophages; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor).

USTEKINUMAB

IL-12 and IL-23 are heterodimeric cytokines composed of two glycosylated and disulfide-linked subunits. Both cytokines share p40 subunit, which forms heterodimers with p35 in IL-12 and with p19 in IL-23. Ustekinumab inhibits Th1 and Th17 inflammatory pathways, by binding to IL-12 and IL-23 cell surface receptor complexes, blocking these cytokines (Figure 1). Indeed, it antagonizes both the actions of Th1 cells, inhibiting the release of mediators, such as TNF-α, and of Th17 cells, inhibiting keratinocyte activation and proliferation. Ustekinumab reduces the expression of IL-12- and IL-23-induced cell surface markers that mediate skin homing, activation and cytokine release.

The results from randomized double-blind placebo-controlled trials (PHOENIX1 and PHOENIX 2) [50, 51] showed that ustekinumab is efficacious for the treatment of moderate and severe forms of psoriasis. A subcutaneous (SC) regimen of ustekinumab, 45 mg or 90 mg at weeks 0 and 4

and then every 12 weeks, resulted in a fast and long-lasting improvement in PASI scores for most patients. For patients responding only partially to this initial regimen, and for patients with more than 100 kg body weight, it was necessary to use the dose of 90 mg of ustekinumab, or to treat the patient every 8 weeks, to achieve a full response. Ustekinumab contributes also to improve the health-related quality of life of psoriasis patients, as assessed by the Dermatology Life Quality Index (DLQI) [52]. Moreover, this treatment enhances significantly the productivity of the patients, by reducing the number of missing days at work, and by improving work limitations [53].

Considering data from the clinical trials, ustekinumab was approved for the treatment of moderate to severe plaque psoriasis by Food and Drug Administration (FDA) in 2009. Indeed, a meta-analysis involving six randomized control trials [54] showed that psoriasis patients treated with ustekinumab 45 mg or with 90 mg achieved a better therapeutic effect than the placebo group; moreover, the efficacy for the ustekinumab 90 mg group was more significant than in the 45 mg group. The 6 trials considered in this meta-analysis reported as adverse effects headache, upper respiratory tract infection, nasopharyngtis, infection, serious infection, cardiovascular events, and malignant tumors. In another systematic review and meta-analysis [55], evaluating nine controlled trials, from 1990 to August 2013, ustekinumab was effective after 12 weeks of treatment of moderate to severe psoriasis patients, and safe over a period of 5 years. However, the clinical trials did not report a significant superiority in the efficacy of the 90 mg dose over the 45 mg dose, for short-term therapy.

Several studies concerning ustekinumab efficacy were performed more recently. A study involving 908 patients with moderate to severe psoriasis showed that ustekinumab treatment (45 or 90 mg of SC ustekinumab, at weeks 0 and 4) achieved a significantly higher clinical improvement than the treatment with etanercept (50 mg twice weekly for 12 weeks) [56]. Moreover, the safety profile of continued ustekinumab exposure, up to 3 [57], 4 [58] and 5 [59] years, was considered favorable. In another retrospective analyze of 71 patients treated up to 2 years, ustekinumab appeared to be more efficient than what was reported by previous randomized clinical trials [60]. More recent data showed no increased risk of malignancy through 3 years [61], or of serious infections [62]. Concerning drug survival, a parameter that reflects the long-term therapeutic performance in a real-life setting, ustekinumab showed a significantly longer drug survival than the anti-TNF-α agents, adalimumab, etanercept and infliximab [63].

SECUKINUMAB

Secukinumab was the first IL-17 inhibitor to be approved by FDA (January of 2015). As referred, secukinumab is an antibody that selectively neutralizes IL-17A.

A randomized Phase I clinical trial involving 36 patients with psoriasis vulgaris treated with a single dose of secukinumab (3 mg/kg intravenously (IV)) showed at the 12th week a 63% reduction in PASI (opposed to 9% with placebo) [64]. Moreover, a decreased production of inflammatory cytokines and chemokines, and a reduction in T-cell infiltration were observed in skin plaques [64].

In a randomized, double-blind, placebo-controlled Phase II dose-range study [65], 125 patients with moderate to severe plaque psoriasis received either SC secukinumab (25, 75, or 150 mg) or placebo, at weeks 0, 4, and 8; or a single dose of 25 mg secukinumab at week 0 followed by placebo. After a follow-up period of 12 weeks, the two highest doses (75 and 150 mg) significantly improved the PASI 75 score (57% and 82%, respectively), as compared with placebo (9%). These 12 weeks were followed by a 24-week follow-up period, and it was reported that the PASI 75 responses remained along this period, for the two highest doses.

In a Phase II, randomized, double-blind, placebo-controlled, regimen-finding study [66], 404 patients with moderate to severe plaque psoriasis were randomized to receive SC placebo (n = 67) or 150 mg of secukinumab in three different regimens: single (week 0; n = 66), early (weeks 0, 1, 2, and 4; n = 133), or monthly (weeks 0, 4, and 8; n = 138). After 12 weeks, PASI 75 responders from treated groups were re-randomized to either a fixed-interval regimen of 150 mg secukinumab (SC) at weeks 12 and 24 or to a treatment-at-start-of-relapse regimen, also at a dose of 150 mg. After the first 12 weeks, the early and monthly regimens showed higher PASI 75 response rates, and the early regimen the highest PASI improvement. Considering the maintenance period, the fixed-interval regimen showed better results than the treatment-at-start-of-relapse regimen. Nonetheless, both were very effective, as less than 10% of patients, on either of the regimens, experienced relapse at 15th week, after the last study drug administration.

In two phase III, double-blind, 52-week trials [67], ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis),

738 (in the ERASURE study) and 1306 (in the FIXTURE study) plaque psoriasis patients received 300 mg or 150 mg of SC secukinumab (once weekly for 5 weeks, and every 4 weeks afterwards), placebo, or (in the FIXTURE study only) etanercept at a dose of 50 mg (twice weekly for 12 weeks and once weekly afterwards). It was reported that the PASI 75 score at 12th week was higher for each of the secukinumab doses used, as compared with placebo; or, in the FIXTURE study, when compared with etanercept.

In a 52-week, double-blind study [68], 676 patients with moderate to severe plaque psoriasis were treated with secukinumab (SC; 300 mg) or with ustekinumab (SC; 45 mg for patients with a body weight ≤100 kg; 90 mg for patients with a body weight > 100 kg); the primary end point was PASI score 90 at 16th week. Secukinumab was superior to ustekinumab in clearing skin of the patients and in improving health-related quality of life; a similar safety profile was reported for both treatments over 16 weeks.

IXEKIZUMAB

In a randomized, double-blind, placebo-controlled, Phase I trial [69], 40 moderate to severe psoriasis patients were randomized to receive 5, 15, 50, or 150 mg of ixekizumab (SC) or placebo, at weeks 0, 2, and 4; patients were followed for a period of 20 weeks. After 2 weeks, as compared to week 0, significant dose-dependent reductions in keratinocyte proliferation, hyperplasia, epidermal thickness, infiltration of T-cells and dendritic cells into the dermis and epidermis, and in keratinocyte expression of innate defense peptides, were observed. At 6th week, biopsy of the lesions showed almost skin normalization, in patients treated with the two highest doses (150 and 50 mg ixekizumab). Clinical efficacy was significantly higher at 6th and 20th weeks for patients who received 15, 50, and 150 mg ixekizumab, as compared to placebo and to patients who received 5 mg ixekizumab.

In a randomized, double-blind, placebo-controlled, Phase II trial [70], 142 patients with moderate to severe plaque psoriasis received placebo or 10, 25, 75, or 150 mg of ixekizumab (SC) at weeks 0, 2, 4, 8, 12, and 16. At week 12, the proportion of patients who achieved PASI 75 response was significantly higher in the groups that received ixekizumab (except for the lowest dose, 10 mg) than in the placebo group. At 8th week, significant reductions in the mean DLQI scores were observed, and this was sustained along 16 weeks, in patients treated with the three highest doses.

In two prospective, double-blind, multicenter, phase III studies (UNCOVER-2 (n = 1224) and UNCOVER-3 (n = 1346)) [71], ixekizumab, administered (SC) as 80 mg every 2 weeks (n = 351 and n = 385, respectively) or every 4 weeks (n = 347 and n = 386, respectively) after an initial dose of 160 mg, showed higher efficacy, when compared to placebo (n = 168 and n = 193, respectively) and to etanercept treatment, 50 mg twice weekly (n = 358 and n = 382, respectively), over a 12 week follow-up period.

A 52-week multicenter, randomized, blinded, parallel-group study comparing the efficacy and safety of ixekizumab versus ustekinumab in moderate to severe plaque psoriasis patients is ongoing, and the results are expected to be published soon (A study of ixekizumab (LY2439821) in participants with moderate-to-severe plaque psoriasis (IXORA-S); ClinicalTrials.gov identifier: NCT02561806).

Recently, at 22nd of March, FDA approved ixekizumab, for the treatment of moderate to severe plaque psoriasis.

BRODALUMAB

In a phase I, randomized, placebo-controlled trial [72], 8 plaque psoriasis patients received a single dose of 350 mg SC and another 8 patients received 700 mg IV. Two weeks after, a dose-dependent improvement in PASI score and static Physician Global Assessment (sPGA) were observed. In patients treated with 350 mg of brodalumab, 75% and 62.5% of the patients achieved PASI 50 and PASI 75, respectively; none of the placebo (n = 5) subjects achieved PASI 50. These two doses were associated with significant reductions in epidermal thickening, in keratin 16 levels and in Ki67-expressing cells, as well as with an improvement in mRNA levels of several IL-17-modulated keratinocyte-derived factors and of cytokines known to be directly regulated by IL-17R. The IL-17A, IL-17C and IL-17F mRNA levels reduced to non-lesional levels over 6 weeks [72].

In a randomized, double-blind, placebo-controlled, dose-ranging phase II study [73], 198 plaque psoriasis patients were randomized to receive placebo (n = 38); or brodalumab (SC) in the doses of 70 mg (n = 39), 140 mg (n = 39), or 210 mg (n = 40), at day 1 and weeks 1, 2, 4, 6, 8 and 10; or 280 mg of brodalumab (SC) at day 1 and weeks 4 and 8 (n = 42). After a follow-up period of 12 weeks, brodalumab diminished significantly the PASI scores. At the 12^{th} week, in patients receiving 140 mg of brodalumab, 77% and 72% achieved PASI 75 and a PASI 90, respectively; 82% and 75% of patients

receiving 210 mg showed a PASI 75 and a PASI 90, respectively; the placebo group showed 0% improvement [73]. DQLI, sPGA, and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) scores were improved (compared with placebo) for the 140 mg and 210 mg groups.

According to Papp et al. [74], brodalumab present an acceptable safety profile. It has been reported, as the most common adverse events, nasopharyngitis, upper respiratory tract infection, arthralgia and back pain. The two phase 3 studies (AMAGINE-2 and AMAGINE-3) [75] involving patients with moderate to severe psoriasis treated with SC brodalumab (210 mg or 140 mg every 2 weeks; after the 12^{th} week, with a maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks) or with ustekinumab (45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients >100 kg; at 12^{th} week, continued to receive ustekinumab every 12 weeks) reported that brodalumab treatment leads to significant clinical improvements. It was found that at week 12, PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% *vs* 22% [AMAGINE-2] and 37% *vs* 19% [AMAGINE-3], $P < 0.001$), suggesting its superiority in achieving total skin clearance at week 12.

However, in 2015, during the phase III program, brodalumab therapy was associated with events of suicidal ideation and behavior alterations, which might restrict its interest and compromise future investigations.

CONCLUSION

The advances in the understanding of psoriasis pathology allowed the development of new therapeutic strategies and the proposal of new therapeutic drugs, especially for the severe cases and for the non-responders to classical therapies. Increased levels of Th17 cells, IL-17 and Th17-related cytokines in psoriasis led to the proposal of therapeutic agents targeting IL-23/Th17 axis, such as ustekinumab and IL-17 inhibitors.

Biological agents affect the immune system and reduce inflammation, raising the fear that infections and malignancies might arise, as possible side effects of the use of these drugs.

Data on ustekinumab therapy showed the efficacy of this agent, associated with a safety profile. However, it should be noticed that ustekinumab has been used in clinical practice for a short period, since 2009.

IL-17A has an important role in host defense, raising the concern that its inhibition might be a potential risk of serious infections and other immune-mediated diseases. Secukinumab and ixekizumab were well tolerated in the reported trials; however, the duration of these trials is still short. The most common adverse events reported in these trials included worsening of lesions, nasopharyngitis, upper respiratory tract infection, arthralgia, erythema at injection site, pain in the extremities, nausea, headache and pruritus; however, some of these adverse events may be associated with other factors rather than with the biologic therapy itself.

Data concerning the use of agents targeting IL-17 in Crohn's disease and rheumatoid arthritis has not been as favorable as in psoriasis [76]; further studies are warranted to establish the value of these biological agents in the treatment of other inflammatory diseases and to better understand the complexity of the interactions that exist between immune cells and cytokines.

In conclusion, further longer-term studies are needed to assure the long-term efficacy, safety and tolerability of all the biological agents.

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Chapter 5

NATURAL HEALTH PRODUCTS FOR PSORIASIS MANAGEMENT

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ABSTRACT

Psoriasis is an incurable skin disorder characterized by the presence of inflammatory plaques on the skin. Although there are multiple therapeutic options to treat this disease, patients worldwide are dissatisfied. Consequently, they frequently use natural products to overcome undesirable effects and ineffectiveness of treatments. These alternative remedies are used together with conventional medications, so it can account for synergism, lack of adherence or adverse events of antipsoriatic therapies. In this chapter, the psoriasis physiopathology is analyzed on the basis on current etiopathogenic concepts. Additionally,

the prevalence of natural health product use in psoriatic patients is examined. A complete review of most important extracts and isolated compounds from natural origin is also considered taking into account preclinical and clinical studies recently published (2000-2016). Moreover, the strengths and weaknesses of investigations with natural products for psoriasis will be discussed to a better understanding of their importance in holistic treatment of this disease.

Keywords: psoriasis, natural products, treatments, extracts

INTRODUCTION

Psoriasis is an inflammatory skin disease characterized by erythematous pruritic plaques, which has been associated with a significant impairment of patient quality of life comparable to other chronic medical conditions, such as diabetes, cancer and hypertension [1]. Psoriasis has a wide spectrum of clinical manifestations. The classic and most common presentation of psoriasis is plaque psoriasis, found in approximately 80–90% of patients [2]. The psoriatic plaques are well-demarcated, erythematous with silvery scales. Plaques may coalesce into polycyclic or serpiginous patterns and are usually distributed symmetrically occurring on the elbows, knees, lower back, although they can also be present anywhere on the body, including the genitals.

The known environmental triggers that have been associated with psoriasis worsening include: streptococcal infection, physical trauma (e.g., tattoos and surgical incisions), certain medications such as antidepressants (lithium), antihypertensives (β-blockers) and synthetic antimalarial drugs (chloroquine). Additionally, emotional stress, smoking and alcohol have been related with psoriasis onset [3-5].

Plaque psoriasis is a chronic disease and spontaneous remission is rare [4, 6], although seasonal variation can be responsible to an improvement in the summer and a worsening in the winter. One-third of patients experience the Koebner phenomenon in which cutaneous trauma to non-lesional skin induces the development of psoriatic lesions [7]. Patients with psoriasis frequently have other chronic diseases, including cardiovascular conditions, depression and metabolic syndrome [8]. Indeed, it has been estimated that approximately 25% of patients also suffer from psoriatic arthritis [9]. Additionally, nail involvement occurs in 30–50% of patients and may clinically resemble a fungal infection with pitting, onycholysis, thickening and hyperkeratotic debris under the nail plate [10].

The histology of psoriatic plaques is distinguished by excessive hyperplasia caused by an accelerated epidermal growth. The classic histological features of psoriatic skin explain the clinical appearance of the disease. The epidermis is greatly thickened (acanthosis) as the keratinocytes move through the epidermis over 4-5 days with a tenfold acceleration. As the normal differentiation process cannot occur, there is a loss of the normal granular layer, together with a thickened *stratum corneum* (hyperkeratosis) and a retention of nuclei in the upper layers of corneal layer (parakeratosis). Additionally, the proliferating keratinocytes fail to secrete lipids, causing that corneocytes adhere, thereby producing the classic scales of psoriatic plaques. The tortuous and dilated dermal blood vessels are responsible for the erythematous appearance of lesions. In addition to epidermal hyperproliferation, the presence of an inflammatory infiltrate distinguishes psoriatic skin. Collections of neutrophils termed Munro's abscesses are found within the *stratum corneum*. Furthermore, an influx of T cells is present in both, epidermis and dermis, along with an increased number of dermal dendritic cells, macrophages and mast cells [10, 11].

Although there are many available treatments for psoriasis, including topical, phototherapy, systemic and biotechnological therapies, the use of complementary and alternative medicine is very frequent among patients, with 43-69% prevalence. These therapies include the use of herbs, special diets and dietary supplements. It is not surprising, considering the chronic and frustrating nature of this disease which lead patients to be highly unsatisfied with their conventional treatments. According to literature, this kind of treatment is used in combination with antipsoriatic medications, so it can account for synergism, lack of adherence or adverse events of antipsoriatic therapies [4, 5]. As most of patients do not discuss about the use of these therapies with their dermatologists, it is important to review the most important plant remedies use worldwide for psoriasis in order to provide patients and dermatologists with scientific information that allow them take decisions about their use in clinical practice [12].

In this chapter, current ethiopathogenic hypothesis of psoriasis will firstly be presented. Additionally, the prevalence regarding the use of complementary alternative medicine for patients will be examined on the basis of recent reports. A complete revision of most important natural products for psoriasis will be provided, with an up-to-date evidence-based information taking into account preclinical and clinical studies published between 2000-2016. Additionally, we will discuss about challenges to be overcome in order to use plants as antipsoriatic treatments.

CURRENT ETHIOPATHOGENIC CONCEPTS OF PSORIASIS

Psoriasis was initially thought to be a variant of leprosy. Until the early 1980s, psoriasis was considered a disease caused by epidermal keratinocyte proliferation, with the cutaneous inflammatory infiltrate as a secondary consequence [3]. However, experimental models and clinical results using immunomodulating therapies have refined this etiopathogenic perspective and so far, psoriasis is mostly considered as an autoimmune disease. Current research on the pathogenesis of psoriasis examines the complex interactions between genetic susceptibility, immunologic mechanisms and environmental stimuli [10], (Figure 1).

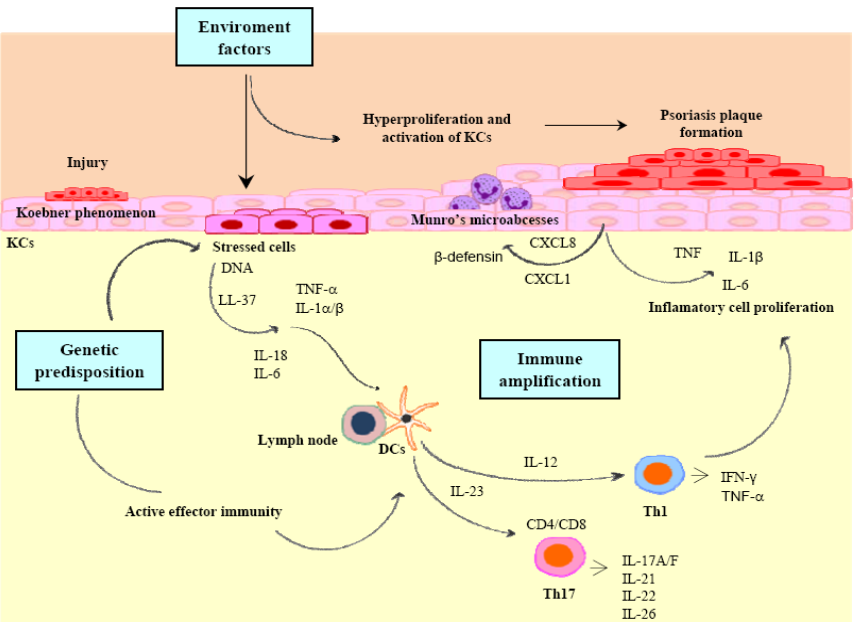

Figure 1. An ethiopathogenic hypothesis for psoriasis. Environmental stress, physical trauma (Koebner phenomenon) or bacterial products in genetic predisposed individuals activates keratinocytes (KCs) and dermal dendritic cells (DCs). DCs migrate into skin-draining lymph nodes by promoting the differentiation of T cells in Th17 and Th1. Th1 and Th17 cells-related cytokines and chemokines interact with KCs by inducing the release of more cytokines and chemokines (TNF, IL-6, IL-1, CXCL8, CXCL1) which amplify the inflammatory network. These mediators also increase the mitotic activity of KCs promoting psoriasis plaque formation. Neutrophils are recruited (Munro's microabsceesses) in response to proinflamatory cytokines, chemokines and β-defensin. These complex interactions are responsible for the perpetuation of the disease.

Evidence from mouse models and translational research strongly indicates that psoriatic plaques result from both, a primary defect in keratinocytes and an inappropriate innate and adaptive immune response mediated mainly by resident and infiltrating T cells [11, 13]. Complex interactions between antigen presenting cells (APCs), natural killer (NK) cells and neutrophils as well as adaptive T cells are involved in psoriasis pathogenesis. Moreover, the proinflammatory cytokines produced by these cells, including tumour necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ), IL-17, IL-22, IL-23, IL-12 and IL-1β and antimicrobial peptides (AMPS) contribute to the initiation and perpetuation of cutaneous inflammation characteristic of psoriasis [14, 15].

In addition to maintaining a mechanical barrier, keratinocytes (KCs) play a dynamic and critical role in the initiation, maintenance and regulation of immune responses in the skin [16]. They are part of the innate immune system and respond to antigenic stimuli in a fast, nonspecific manner. Although KCs are not classical APCs, they can process and present antigen to T cells. KCs behavior in normal and diseased skin is determined mostly by its state of activation or differentiation. Complete terminal differentiation, in which KCs express keratins (K) 1, 2 and 10, is critical not only for the mechanical integrity of the skin barrier, but also for defense against desiccation and invasion by foreign pathogens. Additionally, fully differentiate KCs play a dynamic immunological role in the innate immune response of the skin [17]. In the homeostatic state, differentiation is favored and only basal KCs (expressing K5 and K14) can regenerate and differentiate through the spinous and granular layers of the epidermis to become corneocytes [3]. Psoriatic KCs display a different phenotype (expressing K6, K16 and K17) compared to normal ones; they are hyperproliferative and migratory and can change their cytoskeleton by amplifying their cell-surface receptors, also producing constituents of the basement membrane. They can also produce cytokines and angiogenic factors, such as vascular endothelial growth factor (VEGF), that are required not only for immediate repair of a breach in tissue integrity but also for recruitment of circulating lymphocytes [3]. Another critical role of KCs is the induction of AMPs which are markedly increased in psoriasis and decrease following antipsoriatic treatment. When the epithelial barrier is breached, KCs release of IL-1α, IL-1β and IL-18 occurs. These mediators are powerful initial inducers of AMPs. IL-1α, IL-1β, IFN-γ, and TNF can differentially regulate the expression of genes that code for human β-defensin 2, S100A7 (psoriasin), calprotectin, secretory leukocyte protease inhibitor, lactoferrin and lipocalin 2. IL-18 also induces expression of α-defensins and LL-37 [3]. The latter, in addition to its powerful antimicrobial activity, can

also act synergistically with IL-1β to increase the production of IL-6, IL-8, and IL-10 as well as chemokines such as CCL-2 and α-defensins. This increase in cytokines and chemokines, leads to an intensification in the neutrophil and macrophage infiltration, which amplify inflammation [3].

Psoriatic skin lesions are highly infiltrated most notably with CD3+ T lymphocytes, CD4+ T helper cells and CD11c+ myeloid dendritic cells within the dermis and CD8+ T cells and neutrophils in the epidermis [18-20]. Both mature CD4+ and CD8+ T cells can respond to the peptides presented by APCs. While the specific antigen that these T cells are reacting has not yet been elucidated, several antigenic stimuli have been proposed. These include self-proteins, microbial pathogens and microbial super antigens [21]. T cells can be also activated without antigens or superantigens, but rather with direct contact with other cells [22]. The antigen presentation and network of costimulatory and adhesion molecules optimize T cell activation and dermal dendritic cells release of IL-12 and IL-23 promote a T_H1 and T_H17 response, respectively [23, 24]. *In situ* in psoriasis lesions, abundant IL-23 is available from macrophages and DCs (myeloid and plasmacytoid) [25].

Cytokines produced by immunocytes (lymphocytes and macrophages) as well as non-immunocytes (endothelial cells and keratinocytes) are responsible for the generation of an inflammatory network in psoriasis. APCs which also produce cytokines, such as IL-18, IL-23 and TNF-α, contribute to the inflammatory infiltrate of psoriatic plaques. Both IL-18 and IL-23, released by APCs stimulate T_H1 cells to produce IFN-γ, whereas IL-23 stimulates T_H17 cells. Psoriatic lesions are characterized by a relative increase of T_H1 (IL-2, IFN-γ TNF-α and TNF-β)/ T_H17 compared to T_H2 (IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13) type cytokines. Clearly, a T_H1/T_H17 type pattern governs the immune effectors cells and their respective cytokines present in psoriatic skin [10, 26].

T_H1 cell polarization results in an increased production of IFN-γ and TNF-α. These T_H1 cells migrate into psoriatic lesions by T cell chemokines (CXCL9, CXCL10 and CXCL11), which are produced by myeloid cells and keratinocytes. The growth factors released by these helper T cells sustain neoangiogenesis, stimulate epidermal hyperproliferation, alter epidermal differentiation and decrease susceptibility to apoptosis that characterize the erythematous hypertrophic scaling psoriatic lesions [27]. In contrast to T cells of healthy skin, psoriatic lesional T cells produce abundant IL-17 when activated [28]. T_H17 cells produce a number of cytokines such as IL-22, IL-17A, IL-17F and IL-26. IL-22 acts on outer body barrier tissues such as the skin and has anti-microbial activity. Psoriatic patients have elevated levels of

IL-22 in the skin and blood. Blocking the activity of IL-22 in mice prevented the development of skin lesions [29].

The IL-17 cytokines induce the expression of proinflammatory cytokines, colony-stimulating factors and chemokines which recruit, mobilize and activate neutrophils [10]. IL-17 mRNA was found in lesional psoriatic skin but not in unaffected skin [38]. Moreover, cells isolated from the dermis of psoriatic skin have been shown to produce IL-17 [28].

Besides conventional T cells, increasing interest has now innate γδT cells resident within the dermis. γδT cells constitutively express the IL-23 receptor (IL-23R) and in the presence of IL-23, rapidly produce high amounts of IL-17, thus amplifying T_H17 responses. Accumulations of γδT cells have been found in psoriatic plaques [30] such as Vγ9Vδ2 T cells (a novel proinflammatory subset that seems to mediate an immediate tissue response upon koebnerization) [31], suggesting that these innate cells may play some role in psoriasis pathogenesis.

Overall, interactions between T lymphocytes, keratinocytes, APCs and other cells from innate immunity in individuals genetically predisposed are involved in psoriasis pathogenesis. However, it has much to learn about how immune cells or keratinocytes are activated primarily or secondary as consequence of an antigen that should still be identified. Additionally, it is important to better understand how DCs, T cells and keratinocyte activation contribute to psoriatic inflammation considering the heterogeneity of this disease and the difference in treatment response between patients. This information will serve to generate testable hypothesis that could help researchers to develop new specific and safe therapies in order to improve patient's quality of life.

CONVENTIONAL ANTIPSORIATIC TREATMENTS OF PSORIASIS

The treatment against psoriasis is based on the degree of severity of each patient [32]. Psoriasis Global Assessments (PGA) is used to determine the severity of psoriasis. PGA specifically breaks down psoriasis into severe, moderate to severe, mild to moderate, mild, almost clear and clear [33]. Furthermore, treatment response in clinical trials as well as the efficacy of those treatments are measured using the Psoriasis Area and Severity Index (PASI.) Different parameters are taken into account on the PASI evaluation.

The area affected, signs of erythema, thickness and scaling are assessed to yield a result. $PASI_{50}$ and $PASI_{75}$ refer to clinical improvement of psoriasis in 50% and 75% respectively after a particular treatment. Indeed, the US National Psoriasis Foundation stated that for a psoriasis treatment to be considered successful there needs to have an improvement of at least 50%. Both $PASI_{50}$ and $PASI_{75}$ are valuable when comparing the success of different treatments [34].

A cure for psoriasis is yet to be found. There is however, a range of treatment approaches used to alleviate and control the symptoms present in this skin disease. Topical treatments are a fist therapeutic option for mild or localized psoriasis [35]. Topical medications such as corticosteroids, vitamin D analogs, topical retinoids, ditranol and coal tar are amongst the available choices to treat this first form of psoriasis [36]. Moreover, it is estimated that 20%-30% of people with psoriasis have a more severe form of this disease. For these patients, a second-line therapeutic option is often preferred. Phototherapy, biological and non-biological systematic agents are included in the therapeutic arsenal for more severe psoriasis cases [9].

TOPICAL TREATMENTS

Corticosteriods

Inflammatory dermatoses, such as psoriasis, are often treated with topical corticosteroids (CS), either as monotherapy or complementary medication; usually to systemic treatment. CS are classified according to their potency and are still a first option treatment in psoriasis. They are found in various preparations such as gels, creams, and sprays [37, 38].

The action mechanism of CS can be divided into a genomic and nongenomic pathway. The first one involves the binding to the glucocorticoid receptor (GR) in the cytoplasm and the consequent migration to the nucleus. Anti-inflammatory transcription genes are then promoted and transcribed. Tyrosine amino transferase (TAT), phosphoenolpyruvate carboxynase (PEPCK) and IL-10 are among the genes promoted in this first pathway. Proinflammatory agents including nitric oxide, prostanoids and adhesion molecules are also downregulated with the use of CS. On the second pathway, membrane-bound receptors and second messengers are involved. The level of activation and responsiveness of monocytes, T cells and platelets are

modulated [32]. This happens through a cellular increase of inhibitory factor IkBα, which binds to NF-kB thus inhibiting the activation of T cells [39].

Coal Tar

A range of anti-inflammatory and antipruritic properties are attributed to coal tar. It induces epidermal differentiation through the activation of the aryl hydrocarbon receptor (AHR) [40]. AHR translocates to the nucleus and target genes are promoted when the receptor is activated. These genes restore defective differentiation in skin barrier proteins. For example, filaggrin, which is a valuable protein in skin differentiation [41].

Dithranol

The exact mechanism of dithranol is not completely elucidated. However, it is known that it accumulates in the mitochondria. Recent studies have shown that it decreases important TCA cycle metabolites like citrate and malate. The resulted effect is an overall inhibition on keratinocyte proliferation. This is the result of an oxidative respiration inhibition and ATP synthesis restriction caused by the decreased of important metabolites. Other intermediates also seem to decrease with the intake of dithranol. These include malonate nicotinamide, and hypotaurine, affecting cellular metabolism [42].

Vitamin D Analogue (*Calcipotriol*)

As with the previous drug, the exact action mechanism of calcipotriol is not completely understood. It is, however, a vastly used drug against psoriasis. It is known that calciptriol decreases CD4+ and CD8+ T cells and thus their production of proinflammatory, proliferation, and differentiation agents such as IL-17A, IFN-y and IL-22. Nuclear Vitamin D Receptor (VDR) is exhibited on keratinocytes and activated T cells. VDR translocates to the nucleus when activated by calciptriol. It then binds to DNA sequences and target genes are consequently augmented or inhibited. This results in an overall inhibition of keratinocyte proliferation and CD4+ and CD8+ T cell decrease [43].

Topical Retinoids

Retinoids in general have an effect in the proliferation and differentiation of epidermal cells [44]. Tazarotene is a retinoid developed in the 1990´s as a weapon against psoriasis. It is known that retonic acid receptors-α and γ are activated by tazarotene, inducing normalization in keratinocyte differentiation, a reduction in keratinocyte proliferation and a decrease on expression of inflammatory markers like IL-6. Lastly, because of moderate efficacy and considerable irritation, the prescription of this drug is limited [35, 45].

PHOTOTHERAPY

In the cases of patients who suffer of more severe psoriasis, phototherapy is an alluring option due to its efficacy and cost effectiveness. Psoriatic lesions are treated with radiation while unaffected skin is not involved in such procedure. Targeted ultraviolet B (UVB) phototherapy, localized narrowband (NB-UVB) and ultraviolet A plus topical psoralen (PUVA) are some variants of phototherapy used to treat psoriasis [32].

In a general sense, the division of epidermal cells is affected by UV. It reduces division of these cells. Cytokine and INF-alpha expression, as well as keratinocyte proliferation is also impaired by UV. UV forms pyrimidine dimers which cause the effects mentioned above. Additionally, NB-UVB utilizes a 311-313nm wavelength range as opposed to broadband UVB which uses a wavelength between 208-320nm. NB-UVB is considered more efficient because the most effective wavelengths used in treating psoriasis are 311-313nm [40, 46].

PUVA requires the ingestion of 8-methoxypsoralen or another psoralen derivative, which are photosensiting drugs. Apoptosis is induced through p53 activation, the mitochondria is depolarized and reactive oxygen species are produced upon PUVA usage. Also, the inhibition of autophagy and suppression of cell migration in keratinocyte are observed when using this type of phototherapy [47].

Studies have shown that PUVA seems to be more effective than NB-UVB. It however, has greater risks as it is associated with carcinomas and other unwanted skin diseases. Meanwhile, NB-UVB is accepted as it has lesser risks, becoming a more patient-friendly option [48].

SYSTEMIC NON-BIOLOGIC AGENTS

Oral Retinoids

The first retinoid introduced two decades ago was etretinate, but because of its long life and associated side effects, it was replaced by its active metabolite, acitretin [41]. With a better pharmacokinetic profile, acitretin became highly used in psoriasis as a systemic retinoid. Acitretin specifically offers the advantage of being non-immunosupressive and having a better safety profile [49].

Even though the complete action mechanism of acitretin is not fully understood, it is known that it enters the body through endocytosis. Cytosolic proteins carry it then to the nucleus, activating nucleic acid receptors, which regulate the transcription of genes. Overall, the proliferation rate of epidermic acanthosis is reduced because terminal differentiation in keratinocytes is promoted [50].

Methothrexate (MTX)

MTX has been used in the treatment of psoriasis since a long time, even with the development of biological drugs. Different actions including anti-inflammatory, antiproliferative, and immunosuppressant properties are attributed to MTX. Additionally, MTX is considered an antimetabolite as it is a synthetic analogue of folate. Thus, its effect on the cell is associated with inhibition of DNA synthesis. The induction of apoptosis in lymphocytes is another mechanism associated with this drug. This results in an overall impairment of the expression of adhesion molecules. MTX is still a standard amongst the available options in treating psoriasis [51]. Moreover, studies in which a biologic agent and MTX are combined show an increase in efficacy than biologic monotherapy itself [52].

Calcineurin Inhibitors (Cyclosporine)

Cyclosporine is among the calcineurin inhibitors which is used against psoriasis [53]. The complete activation of T cells is interfered upon cyclosporine intake. This happens because cyclosporine forms a complex with cyclophilin. This complex inactivates calcineurin phosphorylase and thus

prevents the transcription of interleukin-2, which crucial in the activation of T cells [54]. Additionally, cyclosporine consumption must be done with precaution because of long term toxicity [47]. Strategies of combination therapy are often used to minimize this toxicity. Combination with topical agents and even a systemic agent like MTX have proven to be efficacious. Other studies involving combination therapy with glucosamine and an anti-TNF treatment have demonstrated good efficacy and safety in treating psoriasis [48]. Calcineurin inhibitors (pimecrolimus and tacrolimus) can also be used as topical treatments for psoriasis.

BIOLOGIC AGENTS

Biological drugs are considered as the newest and most advanced treatments for psoriasis. The most used are the TNF-inhibitors: adalimumab, infliximab and etanercept, which form part of the arsenal against psoriasis. Recently, certolizumab and golimumab have been added to the list. As anti-TNF agents, they block the TNF activity which has a fundamental role in the pathogenesis of psoriasis. The advantage of these drugs is their efficacy. On the other hand, they should be administered with care as patients react differently to each TNF-antagonist. There is also a risk of infections, including, tuberculosis if prolonged administration of anti-TNF drugs were to take place. Other antibodies, targeted against interleukin-17 for example Ixekizumab, are being developed to overcome the disadvantages of TNF-antagonists [44, 55].

Aside TNF-inhibitors, other biological agents are also used in psoriasis treatment. Alefacept is a fusion protein approved by the FDA. Studies have shown an improvement on psoriasis upon Alefacept intake. It binds to the CD2 receptor resulting in a memory-effector T lymphocyte reduction, which is associated with an improvement of psoriasis [56]. Ustekinumab is a monoclonal antibody which has also proven effective in treating psoriasis. Phase I studies showed reduction in inflammatory cytokines such as IL-12 and IL-23. Phase 3 trials of Ustekinumb also showed a reduction in PASI scores demonstrating its efficacy [57].

PATIENTS SATISFACTION WITH CONVENTIONAL THERAPIES ACCORDING TO WORDLWIDE SURVEYS

Psoriasis is a chronic disease with physical, psychosocial and economic implications that commonly interfere with patients' daily functional capacity and consequently with their quality of life [58]. Psoriasis, especially in severe cases, is associated with major impairments in physical and psychosocial well-being, as manifested by higher risks of cardiovascular disease, obesity, suicidality, and mortality. While numerous treatments for moderate-to-severe psoriasis have been demonstrated to improve clinical disease and health-related quality of life (HRQoL), several studies have suggested that up to 25%-38% of psoriasis patients were dissatisfied with their current treatments [59].

Traditionally, psoriasis has been treated with topical medications, phototherapy, and conventional systemic medications, but patient satisfaction with these has been low due to side effects, inconvenience and toxicity. Biologic medications have improved treatment of the psoriasis symptoms, showing positive effects on quality of life, clinical outcomes and productivity of patients [60, 61]. Despite recent advances in treatment options, approximately one of three patients in the United States with moderate to severe psoriasis is untreated. Furthermore, up to 50% of patients with moderate to severe psoriasis are still treated only with topical medications. Thus, non-treatment and under-treatment are significant issues in this disease, thereby contributing to a dissatisfaction with treatments [62].

In 2014, Callis Duffin et al., assessed patient-reported satisfaction with systemic and phototherapy treatments for moderate-to-severe psoriasis in clinical practice in order to correlate satisfaction with disease severity, using the Treatment Satisfaction Questionnaire for Medication, version II TSQM-11. Authors demonstrated greatest satisfaction with biologics (either as monotherapy or combined with methotrexate), over all other treatment options. They performed a cross-sectional study with 1182 patients with moderate-to-severe psoriasis in the Dermatology Clinical Effectiveness Research Network in the United States. Satisfaction scores were highest for patients receiving biologic monotherapies, biologic-methotrexate combinations and phototherapy (83.3). These patients reported to be "very satisfied," whereas satisfaction was lower for those receiving topical therapies or acitretin (66.7), which reported to be "satisfied" [59].

Patients treated with biologic medications place importance on satisfaction and treatment frequency options. In a study performed during 2012-2013, patient reported to be satisfied with treatments and dosing frequency of biologics. It was used a health care claims database to identify patients with moderate to severe plaque psoriasis. Participants completed the Treatment Satisfaction Questionnaire for Medication. A total of 426 patients completed the survey (263 biologic-experienced and 163 biologic-naïve patients). Patient satisfaction with psoriasis treatment was significantly higher in the biologic-experienced cohort. Scores effectiveness was significantly higher for biologic-experienced patients [74] than biologic-naïve [60] patients. Global satisfaction was significantly higher for biologic-experienced [70] than biologic-naïve [56] patients. The scores were not significantly different [63].

The National Psoriasis Foundation conducts biannual surveys to collect data from more than 76 000 patient members with psoriasis and psoriatic arthritis in order to determine: the extent of nontreatment and undertreatment of psoriatic diseases, trends in treatment use, treatment satisfaction and reasons for medication discontinuation among patients. From 2003 through 2011, a total of 5604 patients with psoriasis or psoriatic arthritis completed the survey. Patients who were untreated ranged from 36.6% to 49.2% of patients with mild psoriasis, 23.6% to 35.5% of patients with moderate psoriasis and 9.4% to 29.7% to patients with severe psoriasis. Among those receiving treatment, 29.5% of patients with moderate psoriasis and 21.5% of patients with severe psoriasis were treated with topical agents alone. The most frequently used phototherapy modality was UV-B, whereas methotrexate was the most commonly used oral agent. Although adverse effects and a lack of effectiveness were the primary reasons for discontinuing biological agents, the inability to obtain adequate insurance coverage was among the top reasons for discontinuation. Overall, 52.3% of patients with psoriasis and 45.5% of patients with psoriatic arthritis were dissatisfied with their treatments [62].

In 2013, European dermatologists recruited psoriasis patients into an observational study to compare clinical improvement and treatment satisfaction with biologic versus other therapies in patients with plaque psoriasis. These analyses included a total of 2151 patients receiving: topicals (n=453), phototherapy (n=666); conventional systemics (n=683), and biologics (n=349) treatments. The percentage with severe disease declined from 70% to 15% after biological treatment, whereas with topicals, the decline was 22% to 10%. When patients used phototherapy, the worsening of disease decayed from 20% to 11 while when they used conventional systemics it declined from 49% to 15%. Significantly more patients receiving biologics were satisfied

with their treatments (59%) versus those with topicals (45%), phototherapy (34%) or conventional systemics (50%). Significantly more dermatologists were satisfied with biologics (60%) versus topicals (35%), phototherapy (26%) or conventional systemics (42%) [64.

In 2007, Wasel et al., conducted an online survey of Canadians in order to evaluate the severity and impact of psoriasis on the lives of Canadians patients. A total of 514 qualified respondents completed the survey. The majority of respondent (65%) reported suffering from moderate, severe or very severe psoriasis at the time of the survey. Use of systemic medication (oral/injection) and/or phototherapy was reported by 18% of respondents. These forms of treatment were more commonly used by individuals with body surface area (BSA) involvement (25%) and particularly in those with ≥ 10% BSA involvement (39%). Dermatology Life Quality Index (DLQI) score indicated a moderated or more effect in 19% of individuals with an affected BSA 0 to 2%, 51% of individuals with ≥ 3% BSA involvement, and 67% of individuals with ≥ 10% BSA involvement [65]. In 2006, European Federation of Psoriasis Patient Associations (EUROPSO) undertook a Europe-wide survey to explore patient's perspectives of psoriasis on their lifestyle and wellbeing and to gain insight into the effectiveness and satisfaction with currently available therapies for psoriasis. In total, 18 386 responses were received (36%), of whom 17 990 had psoriasis. Higher satisfaction (score of 8–10) was expressed for the systemic therapies methotrexate (30%), ciclosporin (28%) and fumarates (26%), as well as PUVA treatment (38%). Lower satisfaction (score of 1–4) was expressed for tazarotene and etretinate (42% and 38%, respectively) [66]. In 2003, Christophers et al., conducted a survey at three outpatient clinics in Europe to estimate the unmet need for safe and effective antipsoriatic treatments. A total of 301 patients participated in the survey, with approximately 100 patients from each centre. Therapies most frequently used by patients were UVB (67%), methotrexate (51%), PUVA (46%), retinoids (40%) and cyclosporin (31%). A majority of the patients (89%) were treated with at least one systemic agent or phototherapy. More than 90% of the patients undergoing treatment with these agents reported abnormalities and nearly 80% of the patients reported one or more of the following: hypertension, abnormal liver enzymes, hyperlipidaemia, increased alcohol intake, renal problems and photosensitivity. Overall, 42% of the patients were dissatisfied with the current treatment options for psoriasis. Lack of patient satisfaction was higher among patients who were treated with a greater number of agents and also in those who had more frequent relapses of the disease [67].

Overall, these studies show that although treatment satisfaction of psoriatic patients with new treatments such as biologics has increased last years, there are still a great disconformity among them with available therapeutic options. This reality drives them to use other alternative therapies such as natural health products.

PREVALENCE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE USE IN PSORIATIC PATIENTS

There is little scientific information available on unconventional therapies used in psoriasis although there are some reports that show an increased use of complementary and alternative medicine (CAM) options (Figure 2). The prevalence of CAM use varies within general population (9.8% to 76%) [68]. In psoriatic patients, CAM use is common, with prevalence estimations varying between 42 and 69%. Herbal therapies seem to be the most commonly used modality [12].

CAM modalities include traditional Chinese medicine (TCM), herbal therapies, dietary supplements, climatotherapy, and mind/body interventions. Most often, patients use CAM as 'complementary' therapy, as opposed to 'alternative' therapy, i.e., rather than using CAM as monotherapy, most patients are taking CAM in combination with conventional treatment modalities in an effort to do everything possible to control their disease. Other reasons that lead patients to choose CAM include a preference for 'natural' approaches to their skin disease, a perceived lower risk of side effects and dissatisfaction with the efficacy or toxicity of conventional medicine.

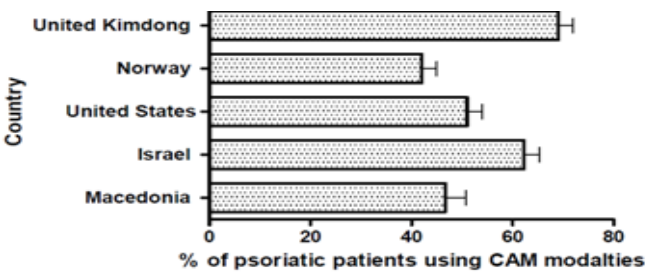

Figure 2. Use of Complementary and Alternative Medicine (CAM) among psoriatic patients according to worldwide studies. In the United Kimdong 69% of psoriatic patients use CAM; in Norway 42%; in the United States 51%; in Israel 62.3% and in Macedonia 46.7%.

In order to collect comprehensive information on CAM use, Damevska et al., (2014) recruited 44 inpatients (36.1%) and 78 outpatients (63.9%) from the University Clinic of Dermatology, at Skopje Medical Faculty in Macedonia. Fifty-seven patients (46.7%) used one of the CAM methods in the previous year, including topical and systemic antipsoriatics, dietary supplements and diet (Figure 2). Forty-one different nonconventional topical treatments were used. Seven patients (5.7%) took nonconventional systemic medication, of whom a small percentage of the patients (5.8%) took oral herbal mixtures of an unclear composition and 15.5% used dietary supplements. There were three patients who reported current adherence to a diet as treatment for psoriasis [69].

To study CAM use among patients with psoriasis, Ben-Arye, et al. (2003) conducted semistructured interviews to psoriatics individuals in a dermatology clinic at major university hospital in northern Israel. Consent was obtained for 78 patients. Post-visit questionnaires were given to 5 physicians. Among the study participants, 48 to 62.3% used CAM for psoriasis treatment during the study period or in the past, with 45.8% having used a CAM treatment during the last year. Almost two thirds of users (58.3%) had seen a CAM practitioner. The most often practiced modalities were herbal therapy (64.6% of CAM users), diet therapies (20.8%), homeopathy (18.8%) and traditional Chinese medicine including acupuncture (18.8%) and nutritional supplements and vitamins (12.5%) [70].

A high prevalence of CAM use was also found in a North Carolina study that analyzed 317 respondent questionnaires in which 51% used CAM after exclusion of sunlight and nonprescription tanning equipment. A study conducted at a university hospital in Norway found that 42% of 506 patients had used CAM currently or in the past [18]. In a study at a specialist psoriasis clinic in the United Kimdong, 34 of 50 patients (69%) had tried 81 different CAM treatments (mean number of treatments per patient, 2.4) [71].

According to a study performed by Smith et al., (2009), CAM modalities are frequently used with conventional antipsoriatic therapies, not as a reemplacement of them and patients do not discuss about it with their physicians [72]. This situation should not be neglected by dermatologists mainly considering three key factors: 1) a high proportion of psoriatic patients worldwide uses this kind of therapy (around 69%), so is more frequent than thought; 2) natural products are not always safe, the combination with conventional therapies can lead to adverse events; 3) antagonic or pharmakokinetic interactions could take place, thereby decreasing the effectiveness and adherence of patients to therapies. For these reasons, it is

very important to know the most important natural health products used for the treatment of this disease and the current state of the preclinical or clinical investigations.

NATURAL HEALTH PRODUCTS FOR PSORIASIS

As previously analyzed, psoriasis can be a disease difficile to treat, so it is not a surprise that patients use preparations from natural origin. Literature shows that some of these preparations are, in most cases, extracts from plant origin (Table 1), which have been tested both *in vitro* and *in vivo*. The following sections will describe some natural products from plant and animal origins and how they have been studied for psoriasis treatment.

NATURAL EXTRACTS FROM PLANT ORIGIN

Aloe Vera Extracts

Aloe vera (*Aloe barbadensis miller*) is a green succulent plant, belonging to the Liliaceae family, widely spread in some of the dry regions of Africa, Asia, Europe and America. "The plant of immortality," as Egyptians called it, has been used since ancient times for its health, beauty, medicinal and skin care properties. Two thousand years ago, Greek scientists considered it the universal panacea; Alexander the Great and Christopher Columbus used it for treating soldier's wounds. Scientific research added new data regarding the use of *A. vera* for various medical purposes, especially dermatological conditions including wound healing, herpes simplex, atopic dermatitis, seborrheic dermatitis, acne, diaper dermatitis, lichen planus, aphthous stomatitis, human papilloma virus and frostbite [73]. *A. vera* contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids [74]. Some *in vitro* and *in vivo* studies assessed the efficacy and safety of *A. vera* in psoriasis [68].

A. vera gel has been used to treat psoriasis in various folk systems of medicine. Dhanabal et al. (2012) have observed that the extract produced a significant differentiation in the epidermis, as seen from its degree of orthokeratosis (85.07-3.36%) when compared with the negative control (17.30-4.09%). The extract showed an overall antipsoriatic activity of 81.95%,

compared with 87.94 for tazarotene (positive control) in the mouse tail model for psoriasis [75].

Clinical studies on the use of *A. vera* preparations in plaque psoriasis are few. To further substantiate these observations, studies by Choonhakarn et al. (2010) compared *A. vera* cream with 0.1% triamcinolone acetonide cream in a double-blind clinical study. Authors have shown that the topical application of *A. vera* for 8 consecutive weeks was effective in decreasing the PASI score from 11.6 to 3.9. Additionally, this treatment improved the quality of life of patients with mild to moderate psoriasis [76]. However, contradicting these observations Paulsen et al. (2005) in their double-blind, placebo-controlled right/left comparison study (2-week wash-out period followed by a 4-week treatment period with two daily applications and follow-up visits after 1 and 2 months) have observed that the commercial *A. vera* gel was not better than the placebo in healing stable plaque psoriasis suggesting that detailed studies with large number of patients are warranted with standardized aloe preparation [77]. These results suggest that although there are some promising data, clinical effectiveness needs more scientific confirmation.

Mahonia Aquifolium Extracts

Mahonia aquifolium (Oregon grape) is a flowering plant belonging to the Berberidaceae family. It is native from North America, being spreading on the west coast from Southeast Alaska to Northern California. *Mahonia* is an evergreen shrub, with leathery, pinnate leaves, often with of spiny leaflets and dense clustered racemes of yellow flowers, sometimes fragrant, followed by black or purple berries. The use of *M. aquifolium* for medical purposes goes back to Indian tribes, which were using it to treat dyspepsia. Nowadays, it is still of significant medical interest for its analgesic, anti-inflammatory, antioxidant and hepatoprotective effects; these are due principally to its rich content in alkaloids like berberine, palmatine, jatrorrhizine, berbamine and oxyacanthine [78].

Meta-analysis including both scientific *in vitro* and *in vivo* relevant data agrees on the efficacy of *M. aquifolium* preparations for plaque psoriasis [68, 79]. Clinical data show promising results for topical formulations (ointments or creams) of *M.aquifolium* for psoriasis compared to placebo or to classic therapeutic options (corticoids, vitamin D derivatives). Preparations of *Mahonia* were well tolerated, with rare side effects. Bernstein et al. (2006) reported results from a double-blind, placebo-controlled clinical trial in which

the efficacy of Reliéva (a homeopathic product containing a proprietary *M. aquifolium* extract) on PASI scores of 200 patients (100 active patients, 100 control patients) was analyzed [80]. For the PASI score, the Reliéva-treated active group showed a significantly greater reduction. Eighty-one patients (41%) had a PASI score between 0 and 6 and 119 (59%) had a PASI > 6. The tolerability of the active *M. aquifolium* (Reliéva) topical cream was excellent. The side effects reported were minor, mainly rash, a burning sensation and clothing stain. Clothing stains were removed with a simple wash. Gulliver and Donsky, (2005) reported 3 trials and review the clinical data on the use of *M. aquifolium* 10% topical cream for the treatment of 33 patients with mild to moderate psoriasis. In Mahonia-treated patients, the first symptom to improve was scaling. The results indicate statistically significant improvement in PASI score and Dermatology Life Quality Index after 4 weeks of treatment. In some cases, improvement was observed after the first week of mahonia treatment. The thickness of Mahonia-treated plaques declined over a period of 2 to 4 weeks and redness gradually improved [81].

Picea Mariana Bark Extract

Picea mariana, also known as black spruce, is a North American coniferous tree which is widely distributed in northern parts of United States and Canada. Black spruce is native from Quebec and is considered as the most widespread conifer species in Canadian forest [82]. Native American used young shoots of spruce in decoctions to treat coughs due to their expectorant and diaphoretic qualities. A poultice of the inner bark of black spruce was traditionally used as a topical anti-inflammatory [83].

Recently, it has been demonstrated that the ethyl acetate fraction isolated from the aqueous extract of *Picea mariana* bark, which is mainly composed by neolignans and lignans (3.57% w/w) [84], efficiently blocks the TNF-induced activation of psoriatic keratinocytes. Indeed, this extract downregulates NF-kB pathways and produces a diminution of nitric oxide production and expression of the nitric oxide synthase, an enzyme upregulated in psoriasis that generate high amounts of nitric oxide. Moreover, this polyphenolic extract produces a diminution of ICAM-1 expression, cytokine production (IL-6 and VEGF), chemokine formation (IL-8 and fractalkine) and trappin-2/elafin generation, a marker of aberrant differentiation of psoriatic keratinocyte [85]. Additionally, this extract is a powerful inhibitor of the prostaglandin E2 (PGE2) production

of psoriatic keratinocytes. This effect was attributed to a direct influence on cyclooxygenases (COX1 and COX2) activities.

This investigation demonstrated the immunopharmacological role of a polyphenolic extract from *Picea mariana* bark on the inhibition of TNFα-induced responses by psoriatic keratinocytes. In fact, it was demonstrated that this polyphenolic extract obtained from the residues of Canadian forest industry, provides a highly effective means to reduce the inflammation induced by TNF-α. Moreover, most the pharmacological effects, attributed to polyphenols present in Picea mariana bark, appear to be more efficient than those observed with dexamethasone, demonstrating the therapeutic potential of the molecules present in this species for the management of psoriasis.

Green the Extract

Camellia sinensis best flourishes in warm climate, and can grow in altitudes varying from sea level to 2100 meters above sea level [86]. Generally, its particular taste and health benefits makes *C.sinensis* a highly consumed tea. Regarding its phytochemical composition, catechins, a group of flavonoids, compose up to 80% of all polyphenols found in this plant. Additionally, within catechins four main ones have been identified: epicatechin (EC), epicatechingallate (ECG) epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG), with the latter one being highly pharmacologically active [87]. Several studies have shown the therapeutic potential of Green tea extract in autoimmune conditions such as psoriasis. First, interactions of EGCG with growth factors, especially with the fibroblast growth factor (FGF) and vascular endothelial growth factor (VGEF), result in an inhibition of these. An anti-inflammatory activity has also been associated to green tea [88]. This effect is reached by elevating the Tollip protein, which is an inflammatory signaling regulator. Also, EGCG has proven to decrease the number of infiltrating inflammatory leukocytes, playing a role in the anti-inflammatory activity [89]. Other studies have shown a visible improvement and preventive effect of green tea extract used on mice with similar epidermal characteristics to psoriatic lesions [90]. Moreover, a cytokine neutralizing effect is also attributed to *Camellia sinensis*. Reduced epidermal growth of up to 90% was observed when *C.sinensis* was associated with V. vinifera or S.nigra [91]. The overall effects of EGCG, a major component of green extract, on growth factors, inflammatory signaling and cytokine secretion make it an attractive alternative against psoriasis.

Neem Bark Extract (*Azadirachta Indica*)

Azadirachta indica belongs to the botanical family, "Meliacea." Found in Africa and throughout India, *A.indica* is also known as "Neem," "Nimba" and "Margoa Tree." It can reach up to 16 meters high on average. *Azadirachta indica* is characterized by a straight and tough trunk with red brown bark that secrets resin. Mature leaves are bright green while immature ones are reddish to purple [92]. Several metabolites have been identified in Neem extract, among these nimbidin, azadirachtin and epoxyazadiradione offer therapeutic effects on the physiopathology of psoriasis. A mixture of tetranortriterpenes compose nimbidin, and an elevated anti-inflammatory activity is attributed to it. Studies have shown an inhibitory effect of nimbidin on both the release of lytic enzymes by neutrophils and certain functions of macrophages. Inhibition of chemotaxis, phagocytic capacity and release of pro-inflammatory interleukines such as IL-1 are the resulted effects of nimbidin on macrophages and neutrophils [93]. Also, PASI scores lowered in a study conducted when Neem extract was used in the treatment for psoriasis [12]. Moreover, an inhibitory activity on TNF-biological induced responses is attributed to azadirachtin. Studies show that azadirachtin binds and inhibits TNF response, exerting an action on the immune system [94]. Epoxyazadiradione is a limonoid extracted from Azadirachta indica, and an anti-inflammatory activity is also attributed to it. One study showed the inhibitory effect of epoxyazadiradione on the Macrophage Inhibitory Factor (MIF). MIF is responsible for pro-inflammatory reactions. Thus epozyazadiradione offers an anti-inflammatory activity in diseases, potentially reducing progression of them [95]. Finally, some safety concerns have risen in regards to dermatological reactions and genotoxic effects. Nonetheless, no accumulative effects have been observed during *in vivo* studies [96].

Givotia Rottleriformis Extract

Givotia rotteriformis belongs to the Euphoribaceae family and it is a moderately-sized tree. Its occurrence is limited to India and seeds are used sometimes in form of a crushed seed liniment [97]. Both, seeds and the bark, are used as herbal medicine. Also, composition of this plant shows biologically active flavonoids rutin, quercetin, kaempferol and luteolin. These flavonoids show anti-inflammatory activity and an inhibitory effect on keratinocyte proliferation which have been related to the antipsoriatic properties of this plant [98]. Additionally, an ethanol extract from this plant

can increase the orthokeratotic regions by 45.93% in a mouse tail psoriatic model [99].

Centella Asiatica Extract

Also known as Gotu Kola, *Centella asiatica* has been used in traditional medicine for thousands of years. In China and other Asian countries such as India and Pakistan, it has been used in dermatology to treat wounds, burns and other skin conditions including scleroderma [100]. The effectiveness of *C. asiatica* to heal wounds is useful in treating psoriasis. Many phytochemicals with antioxidant, anti-inflammatory and anti-proliferative properties are found in *C. asiatica* [101]. Specifically, pentacyclic triterpenoids such as asiaticoside, madecassoside, asiatic acid, and madecassic acid, are constituent of this plant. Furthermore, increased collagen synthesis, antioxidant levels and angiogenesis is promoted by these terpenoids [102, 103]. Also, inhibition of keratinocyte proliferation has been attributed to this plant. As a result, the efficacy of this plant in treating psoriasis is due to the overall effects of terpenoids in the whole biological process involved in wound healing.

Formulations of *Centella asiatica* are present in ointments, cutaneous powders, and cream. Regarding toxicity, headaches, dizziness and drowsiness may appear. Data suggesting hepatotoxicity is available, but with recommended doses, side effects are infrequent.

Hamamelis Virginiana Extract

Similar to *C. asiatica*, *Hamamelis virginiana* forms part of medicinal plants which have been used for many years to treat various skin conditions [104]. *Hamamelis virginiana* is colloquially known as “Witch Hazel” and is a high shrub found in North America. Among the phytochemicals found in this plant are tannins, gallic acid, catechins and proanthocyannin. Both, bark and leaves, of this plant are used as they contain the pharmacologically active components mentioned above. Thus, the therapeutic effect attributed to *Hamamelis virginiana* is attributed to such components. Moreover, it is well known that interleukins play a fundamental role initiating inflammation in patients with psoriasis. Tannins found in *H. virginiana* have the ability to neutralize various cytokines through hydrogen bonds. It has been reported that proanthocyanidins and hamamelitanins found in *Hamamelis virginiana* also

inhibit 5-lipoxygenase and synthesis of leukotriene B4. Additionally, an antioxidant activity as well as a collagenase and elastase inhibiting effect are attributed to this medicinal plant, maintaining fibroblasts in normal shape and thus contributing to the overall therapeutic effect in psoriatic lesions.

Opoplanax Elatus Extract

Oplopanax elatus Nakai is a perennial deciduous shrub of the Araliaceae family, which is mainly distributed in Northeast China, Korea and Russia in the Far East [105]. The chemical components of the leaves of this plant have been widely investigated [106]. Earlier work indicated that this plant contains various bioactive secondary metabolites, such as volatile oils, aliphatic acids, saponins from leaves, flavonoids from leaves and anthraquinones from barks. The chemical constituents of its roots and stems are not clear to date [106]. *O. elatus* has been used for treating neurasthenia, hypopiesis, schizophrenia, cardiovascular problems, diabetes mellitus, rheumatism. Additionally, it also possesses antifungal, fever relieving, pain-easing, anti-aging, antioxidant, anti-inflammatory, analgesic and anticancer activity [105, 106]. Dou, et al. (2009) discovered that the 60% extract of the bark of *O. elatus* plant possesses anti-psoriasis activity [106].

Oplopanax elatus has been used in Korean and Chinese traditional medicine for anti-inflammatory and analgesic purposes. Saponins, anthraquinones and the antibacterial essential oil, have been identified from this plant [107].

Cassia Tora Extracts

Cassia tora (C. tora) is a wild crop of the Leguminosae/Fabaceae family that grows in most parts of India as a weed, and has been traditionally used for the treatment of psoriasis and other skin diseases such as, eczema, dermatomycosis and leprosy [108]. Several anthraquinones have been isolated from the seeds of *Cassia* species, and sennosides, which are well known for their medicinal importance, have been detected in the leaves of the plant [109].

Vijayalakshmi and Geetha (2014) investigated the anti-psoriatic potential of standardized ethanolic extract (70% v/v ethanol) and three flavonoids, namely luteolin-7-O-β-glucopyranoside (**1**), quercetin-3-O-β-D-glucuronide (**2**) and formononetin-7-O-β-D-glucoside (**3**), isolated from the leaves of *C.*

tora on a UV-B induced photodermatitis model. In the ultraviolet ray photodermatitis model for psoriasis, the exposure of the rat's skin to UV radiation using a UV-B bulb (wavelength 280-315 nm) induced proinflammatory reaction in the skin similar to that observed in psoriasis. Histopathological analysis of the section revealed the absence of Munro's microabscess, elongation of rete ridges, and capillary loop dilation in ethanol extract (400 mg/kg), isolated compound **2**, **3** and standard group. The ethanolic extract (400 mg/kg) and isolated compounds **1**, **2** and **3** exhibited a significant percentage reduction of relative epidermal thickness when compared with a positive control. Authors concluded, using this animal model, that the flavonoids from *Cassia tora* leaves have significant antipsoriatic activity [110].

Singhal and Kansara (2012) determined the antipsoriatic activity of three different concentrations of O/W creams (Test 1–0.05%, Test 2–0.1%, and Test 3–0.2%) of methanolic extract of *Cassia tora* L. leaves by using ultraviolet-B-induced psoriasis in rat. Histopathological analysis revealed that there were absence of Munro's microabscess, elongation of rete ridges, and capillary loop dilation in Test 2 (0.1%) and standard group. O/W creams and methanolic extract of *Cassia tora* L. leaves exhibited significant reduction in percentage of relative epidermal thickness and spleen index as compared to positive control. They concluded that topical O/W creams and crude extract containing methanolic extract of *Cassia tora* L. leaves have potent antipsoriatic activity in ultraviolet-B-induced psoriasis in rat [111].

Argemone Mexicana Extract

Argemone Mexicana of belonging to Papaveraceae family is a widely distributed medicinal plant in India. *A. mexicana* contains numerous isoquinoline alkaloids of the protoberberine type and related including sanguinarine. The total alkaloid fraction in the dried roots and stems is 0.25%, mainly consisting of protopine and berberine. Protopine is considered as narcotic and it significantly reduces morphine-withdrawal effects. Berberine has improving effects on the circulation in small doses and also has hallucinogenic properties. Other pharmacological effects of berberine include spasmolytic, antibacterial and to some degree antifungal and antiprotozoal activities. The alkaloid fraction from the roots showed the anti-inflammatory activity in rabbits and rats [112].

Arora, et al. (2009) purified Arabinogalactan-Protein (AGP) isolated from an extract obtained from the leaves and/or stems of *A. Mexicana*. AGP, exhibits vastly superior anti-psoriatic activity and other useful immunological and pharmacological activities compared to the extract and fractions of the leaves and/or stems of the plant, as disclosed in US PatentApplication Publication No. 2003/0194456 A1 [113]. A comparison of biological activities of aqueous extract and AGP composition, showed efficacy of AGP as an immunomodulator, regulating cytokine production (IL-2 inhibition, IFN-y inhibition, or IL- 10 induction). Moreover, AGP was found inhibitory to nerve growth factor (NGF) induced human keratinocytes proliferation in range of 0.0001μg/ml to 40 μg/ml [114].

Cissampelos Sympodialis Eichl Extract

Cissampelos is one of the major genera of Menispermaceae comprising 21 species. These plants are mostly climbers or lianes. The leaves of *C. sympodialis* are peltate with deltoid blades and petioles wollenat extremities. The genus Cissampelos has a wide global distribution panning five continents as well as several islands. *C. sympodialis* is found only in South America (Brazil) where is used to treat several inflammatory disorders, bronchitis, asthma, rheumatism and gastrointestinal, urinary tract and skin infections [115]. Several chemical compounds belonging to the alkaloids class have been isolated from the leaves and roots, such as: bisbenzylisoquinolinic (warifteine, methylwarifteine, roraimine, and simpodialine); morphinic (milonine); aporphinic (laurifolin) and oxoaporphinic (liriodenine) alkaloids. Quality control studies have shown that both alcoholic fractions of the leaves (AFLs) and alcoholic fractions of the roots (AFRs), present alkaloids as their principal compounds [116].

The immunomodulatory effect of the aqueous fraction of the ethanolic extract of the leaves (AFL) of *C. sympodialis* has been described. This effect was associated with inhibition of IL-2 production and increased production of both IL-10 and IL-4. Feily and Namazi (2009) suggested that *C. sympodialis Eichl* leaf extract could be a novel and safe addition to the antipsoriatic weaponry due to its potent effect in decreasing the nitric oxyde production, inflammatory cytokines generation together with an increase in the production of anti-inflammatory cytokines (which are known to ameliorate this disease) [117].

Table 1. Natural extracts from plant origin studied for psoriasis treatment

Extract	Study/Model	Most important result	Reference
Ethanolic extract of *Aloe vera* leaf	Preclinical study/Mouse tail model for psoriasis	Significant increase in relative epidermal thickness	[75]
Aloe vera cream	Clinical study	Decreasing the PASI and improved the patient's quality of life.	[76]
Mahonia aquifolium extract (homeopathic preparation)	Clinical study	Significant reduction in PASI score	[80]
Mahonia aquifolium 10% topical cream	Clinical study	Significant improvement in PASI score and DLQI	[81]
Polyphenolic extract of *Picea mariana* bark	Preclinical study/Culture of normal and psoriatic keratinocytes	Reduction of inflammation induced by TNF-α by impacting on NF-kappaB pathway	[85]
Green tea polyphenols	Preclinical study/Culture of normal human epidermal keratinocytes and flaky skin mouse model	Induces caspase 14 in keratinocytes and reduces psoriasiform lesion in the mouse model	[90]
Tetranortriterpenes from *Azadirachta indica*	Preclinical study/wistar rats and culture of macrophages and neutrophils	Anti-inflamatory activity	[93]
Flavonoids of *Givotia rottleriformis*	Preclinical study/HaCaT cell line and Male Swiss albino mice	Antiinflamatory and anti-proliferative activity on HaCaT cells. Significant reduction in epidermal thickness	[98]
Centella asiatica extract	Preclinical study/Cell Culture of SVK-14 keratinocytes	Keratinocyte antiproliferative effect	[102]
Oplopanax elatus extract	Clinical study	Anti-psoriatic activity	[106]
Flavonoids extract of *Cassia tora*	Preclinical study/Rat ultraviolet B ray photodermatitis model	Anti-psoriatic activity	[110]
Arabinogalactan-Protein (AGP) isolated from an extract of *Argemone Mexicana*	Preclinical study/ Normal human keratinocytes	Immunomodulator and antiproliferative activities	[114]
Indigo naturalis extract	Preclinical study/Normal keratinocytes and skin samples	Upregulates claudin-1 expression	[119]

Indigo Naturalis Extract

Indigo naturalis is a dark-blue powder prepared from leaves of plants such as *Baphicacavthus cusia*, *Polygonum tinctorium*, *Isatis indigotica* and *Indigofera tinctoria* by traditional Chinese herbal medicine wich is widely used in clinical practice for treating various infectious and inflammatory skin diseases, such as carbuncles, furuncles, eczema and also psoriasis over the past 40 years in China [118]. Lin et al. (2013) showed that *I. naturalis* extract promotes claudin-1 expression and enhanced tight junction (TJ) function in primary human keratinocytes, suggesting that the PKC pathway is involved in *I. naturalis*-induced claudin-1 expression. Indeed, three major components of *I. naturalis*, indirubin, indigo, and tryptanthrin, exerted a synergistic effect on upregulating TJ function, with indirubin accounting for the majority of the effect [119].

Prior to this study the same authors demonstrate that *I. naturalis* and its major component, indirubin, inhibit proliferating cell nuclear antigen (PCNA) expression and increase involucrin expression at both, the mRNA and protein levels in cultured human keratinocytes under a condition with no cytotoxicity. The anti-psoriatic effect of indigo naturalis results from, at least in part, inhibition of proliferation and promotion of differentiation in human epidermal keratinocytes [118]. Topical *I. naturalis* ointment shows to be both, safe and effective, for the treatment of chronic plaque psoriasis [120, 121].

ISOLATED COMPOUNDS FROM PLANTS

Resveratrol

Resveratrol, is a stilbene present in high quantities in grapes and red wines. This compound reaches about 40.61 $\mu g.g^{-1}$ in the aqueous extract from Thompson seedless dried grapes [122]. Other edible and non-edible sources of resveratrol include dark chocolate (0.4 $\mu g.g^{-1}$) [123], peanuts (0.03-0.14 $\mu g.g^{-1}$) [124] and the roots of the *Polygonum cuspitadum* used in ancient Chinese and Japanese herbal medicines (2960-3770 $\mu g.g^{-1}$) [125]. Additionally, it is also present in bark of forest trees, such as *Picea mariana* which contain at least 104.19 $\mu g.g^{-1}$ of *trans*-resveratrol, being considered as a new and profitable source of this molecule [84].

Resveratrol has demonstrated to have significant antipsoriatic properties both, in preclinical and clinical studies. This molecule significantly reduced

skin thickness, in an Imiquimod induced psoriasis mouse model [126]. Resveratrol also ameliorated Psoriasis Area Severity Index (PASI) and scaling in mice. Gene expression of IL-17A, IL-17F, IL-19 and IL-23p19 was decreased by resveratrol. This result is particularly interested considering that IL-17A, IL-17F and IL-23 are major instigator cytokines in psoriasis [126]. Resveratrol can also increase in the expression of genes associated with retinoic acid stimulation [126].

A multi-center, double bind study was performed on psoriatic patients with a clinical diagnosis of mild to moderate chronic psoriasis, in order to compare the efficacy of resveratrol vs. calcipotriol, a treatment widely used for psoriasis treatment [127]. Patients were randomized in four groups: a) control group (ointment without resveratrol); b) resveratrol treated group (1% resveratrol ointment); c) calcipotriol treated group (50 mg/g); d) combination of resveratrol/ calcipotriol (1% resveratrol/50 mg/g calcipotriol). Results showed 10% for control group showed marked improvement compared with 80% patients treated with resveratrol [127]. Additionally, 95% patients that received the combination calcipotriol/resveratrol had significant improvement whereas effectiveness of treatment with calcipotriol was observed only in 47% of patients [127].

Luteolin

Luteolin, also known as 3',4',5,7-tetrahydroxyflavone, is a flavonoid present in fruits, vegetables, trees and medicinal herbs [128]. Luteolin has multiple biological properties, and it has been used for treating diseases such as cancer and hypertension [129]. Its antinflammatory activity has been related to its anticancer properties and also with its antipsoriatic activity. Luteolin, at concentrations of 10-100 mM is able to inhibit the production of vascular endothelial growth factor (VEGF), IL-6 and IL-8 in keratinocytes under TNF stimulation in a dose-dependent manner. Additionally, it is able to inhibit the TNF-induced NF-kappa B activation which is involved in inflammatory transcription [130]. This flavonoid can also reduce the TNF-induced mRNA expression of NFKB1 and RELA, two genes encoding for p50 and p65 NF-kappaB subunits [130]. These results support the antinflammatory potential of this molecule for psoriasis treatment.

Quercetin

Quercetin, a flavonol occurring in fruit and vegetables is a food component which has been proven beneficial impact on health [131]. It is one of the most potent antioxidant among polyphenols. Quercetin has also been demonstrated to display the antiviral, antibacterial, anticarcinogen and anti-inflammatory effects [132]. Vijaylakshmi et al., (2012) isolated quercetin from the methanolic extract of the rhizoma of *Smilax china* and evaluated for anti-psoriatic efficacy [133]. Using mouse tail test, isolated flavonoid quercetin (25 and 50mg/kg) produced significant orthokeratosis 32.18% and 39.80% when compared to control. In epidermal thickness, a significant reduction with respect to control was observed in groups treated with retinoic acid and isolated quercetin. Quercetin (50 mg/kg) showed anti-inflammatory effect with a significant inhibition of leukocyte migration. Moreover, maximum antiproliferant activity was shown by isolated flavonoid quercetin ($IC_{50,}$ 62.42±10.20 μgmL^{-1}). Authors conclude that this is the first report on the anti-psoriatic effect of the quercetin which is promising for further investigations addressed to prove its anti-psoriatic activity.

Boswellic Acid

Recently the acetyl-11-keto-β-boswellic acid (AKβBA) has been identified as a NF-kB inhibitor targeting the IkB kinase (IKK). AKβBA is a natural pentacyclic triterpenoid that can be isolated from oleogum resins of various *Boswellia* species commonly known as frankincense. Extracts thereof have been used in traditional medicine and in small clinical trials for the treatment of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Wang et al., (2009) analyzed the effect of the AKβBA as a NF-kB inhibitor on the CD18 hypomorphic ($CD18^{hypo}$) mouse model of psoriasis [134]. They treated affected animals with either 30 μmol/kg or 100 μmol/kg AKβBA. After 35 days of treatment, an improvement of the disease was observed in affected $CD18^{hypo}$ mice treated with 30 μmol/kg (PASI score of 7.0 _ 1.7 vs 3.7 _ 3.1, p = 0.1987) and 100 μmol/kg AKβBA (PASI score of 7.5 _ 1.3 vs 2.5 _ 1.2, p =0.0057).

Immunohistochemical analysis of the skin of $CD18^{hypo}$ mice treated with AKβBA (100 μmol/kg) revealed profound suppression of the phosphorylation of IkBα and p65 activation in the dermal layer indicating inhibition of the NF-

kB signaling and the subsequent NF-kB-dependent cytokine production. Indeed, the TNF-α production of macrophages was profoundly suppressed. Additionally, application of the compound counteracted the intradermal MCP-1, IL-12 and IL-23 expression in lesional skin areas, leading to resolution of the abundant immune cell infiltrates. This compound also significantly reduced the increased proliferation of keratinocytes. Overall, the AKβBA treatment was accompanied by a profound improvement of the psoriasis disease activity score in the $CD18^{hypo}$ mice with reconstitution of a nearly normal phenotype within the chosen observation period.

Curcumin

Curcumin is a natural polyphenol product and major constituent of the perennial herb *Curcuma longa* (also named turmeric) derived from the rhizome of the plant, which belongs to the Zingiberaceae family. It is cultivated in most parts of Southeast Asia and has a long history of use as a traditional medicine in India and China [135]. The powdered extracts of turmeric-dried roots may contain volatile and nonvolatile oils, proteins, fat, minerals, carbohydrates, moisture and curcuminoids. The curcuminoids are a mixture of three principal compounds: curcumin (curcumin I; 77%), demethoxycurcumin (DMC; curcumin II; 17%), and bisdemethoxycurcumin (BDMC; curcumin III; 3%) [136]. The structure was discovered in 1910 by the German scientists J Milobedzka and V Lampe [137]. The chemical name of curcumin is 1,7-bis-(4 hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione and its chemical formula C21H20O6 [136].

Based on the available pharmacological data obtained from *in vitro* and *in vivo* research, as well as clinical trials, an opportunity exists to translate curcumin into clinics for the prevention of chronic inflammatory diseases including obesity, diabetes, cardiovascular, neurodegenerative diseases, cerebral edema, allergy, bronchial asthma, inflammatory bowel disease, rheumatoid arthritis, renal ischemia, psoriasis, scleroderma, acquired immunodeficiency syndrome and certain types of cancers [138].

Kurd et al., (2008) studied the safety and efficacy of oral curcumin in patients with moderate to severe psoriasis in a prospective phase II, open-label, Simon's two-stage clinical trial [139]. Twelve patients with chronic plaque psoriasis were enrolled in this study and were given a 4.5 g curcumin capsule per day for 12 weeks. This was followed by a 4-week observation period. Curcumin was well tolerated and all participants completed the study.

However, the response rate was low and possibly caused by a placebo effect or the natural history of psoriasis. Nevertheless, two patients who responded to the treatment showed 83–88% improvement at 12 weeks of treatment. There were no study-related adverse events that necessitated participant withdrawal. Small sample size and the lack of a control group were the limitations of the study.

Heng and colleagues (2000) investigated the phosphorylase kinase (PhK) activity which correlated with antipsoriatic activity after the administration of curcumin [140]. Four groups (active untreated psoriasis group, calcipotriol-treated group, curcumin-treated group, and non-psoriasis group) were set and each group included 10 patients. Curcumin (1%) was given as an alcoholic gel. Dovonex ointment containing 0.005% calcipotriene was also used in the calcipotriol-treated group. The results showed that PhK activity was highest in active untreated psoriasis group, lower in calcipotriol-treated group and curcumin-treated group, and lowest in non-psoriasis group. Furthermore, there were significant differences in PhK activity among the four groups. In addition, five of 10 patients had a 90% resolution of psoriasis with 2-6 weeks' treatment of curcumin and the others with 3-8 weeks with curcumin showed 50-85% improvement. The index level decreased from 1204±804.3 to 207.2±97.6 after the curcumin treatment, which was associated with a corresponding reduction in keratinocyte transferring receptor expression. This study showed that curcumin might be a potential drug to treat psoriasis due to its efficacy and lack of toxicity.

Epigallocatechin Gallate

(-)-Epicatechin-3-gallate (EGCG), (-)-epigallocatechin and (-)-epicatechin are the main catechins found in *Camelia sinensis*. Indeed, EGCG covers 50-80% of all catechin composition in green tea [141]. A number of different studies have demonstrated the role of this phytochemical in treating psoriasis. It is well known that psoriasis involves an inflammatory process associated with angiogenesis [142]. Various studies have demonstrated the anti-angiogenetic activity of EGCG. Singh et al. reported that an inhibition of angiogenesis takes place through an augmentation of FOXO transcriptional activity [141]. It has been reported that vascular endothelial growth factor (VEGF) and CXCL8/IL8, two important mediators in angiogenesis, are strongly inhibited by EGCG in association with Ginkgo bilboa extract in normal human keratinocytes (NHKs) activated with tumor necrosis factor

alpha (TNF-α) [141]. Pro-inflammatory cytokines and chemokines such as IL-1, TNF-a, IL-8 and adhesion molecules including ICAM are regulated by transcription factor NF-kB. *In vivo* experiments showed a TNF-a reduction upon oral administration of green tea, demonstrating the anti-inflammatory potential of EGCG [143].

To avoid toxicity of systematic drugs, Psoralen and UVA treatment is used for treating psoriasis. However, there is a risk of cancer when this treatment is prolonged. A study involving *in vitro* and *in vivo* models showed inhibition of PUVA induced erythema and DNA damage upon usage of green tea extract. These results suggested an epidermal protection from PUVA therapy by green tea, which is rich in EGCG. Moreover, it is believed that caspase 14 facilitates epidermal differentiation in normal skin cells whereas in skin conditions such as psoriasis this enzyme is absent. Hsue et al. found that EGCG activates caspase 14 in NHEKs [144]. However, psoriatic keratinocytes lack nuclear entry of caspase 14, affecting proper cornification. Thus, green tea may induce caspase 14 expression and nuclear localization promoting differentiation and skin barrier formation, improving the treatment of psoriasis and other skin disorders that lack normal differentiation [144]. Studies conducted by Balasubramanina et al. found that EGCG increased the level of involucrin promoter on NHKs. Involucrin is a transglutamase substrate and this enzyme is required in skin cell death and differentiation. Balasubramanian demonstrated that the 6-fold increase on mRNA levels corresponded to transglutamase 1 (TG1), while mRNA for TG2 showed no increase. All of these information indicates that differentiation of keratinocytes is increased by EGCG [145].

Lastly, photodynamic therapy (PDT) is a suggested treatment in psoriasis and other illness such as skin cancer. This treatment involves that application of a sensitizing agent, light and molecular oxygen. Qi et al., investigated whether EGCG enhanced PDT response in T cell mediated skin diseases. Results from this study revealed an increase on the photocytotoxic effect of PDT when EGCG was applied as co-treatment. A dose-dependent photocytotoxic effect was observed and suggests that EGCG can be used to enhance PDT treatment in T cell mediated skin diseases such as psoriasis [146].

Capsaicin

Found throughout the genus *Capsicum*, capsaicin (8-Methyl-N-vanillyl-6-nonenamide) is present in pepper spicy. Capsaicin and other related compounds are also called capsaicinoids [147]. Psoriasis is characterized not only by inflammation but also by pruritus and is even reported to be a limiting condition. Patients report depression, lack of concentration and sexual desire because of this condition. Although numerous treatments are available for pruritus such as emollients and local anesthetics, capsaicin has been thoroughly studied as a potential treatment for pruritus and other conditions associated in psoriasis [148]. Reimann et al. conducted a study evaluating the efficacy and safety of capsaicin when used to treat pruritus. The study involved 40 patients whom itching was alleviated in its totality by capsaicin. Conclusions from such study suggested that capsaicin can form part in the treatment of dermatoses including psoriasis [149]. However, in a systematic review in which randomized clinical trials investigating the effectiveness of capsaicin on pruritus managing were analyzed, Gooding el al concluded there was not sufficient evidence convincingly enough that capsaicin is effective, although it is a promising option to continued further research [148]. In 2012, however, Chhabra et at undertook a study which showed that when applied topically, capsaicin is an effective treatment of pruritic psoriasis [147].

The action mechanism of capsacin can be broken into two. Capsaicin binds the vanilloid receptor subtype 1(VR1). This is an ion-channel receptor located on the membrane of pain and heat sensing neurons, which it is associated to inflammatory pain transduction. Additionally, capsaicin is able to deplete substance P (neuropeptide) from nerve terminals on the skin [147, 148]. Moreover, hypoxia-inducible factor 1-alpha (HIF-1α) plays an important role in epidermal differentiation of psoriatic skin cells. A study investigating the mechanism of capsaicin in treating psoriasis vulgaris by in situ hybridization of the translation of HIF-1α gene in psoriatic epidermis showed that before treatment, mRNA corresponding to this gene had a rate of 100%, meanwhile after the treatment with capsaicin, it decreased to an 18.2%. Such decrease on the HIF-1α gene translation has been related to an inhibition of epidermal hyperproliferation and an induction of normal differentiation [150].

Nowadays, treatment of chronic inflammatory illness such as psoriasis has taken a step into anti-body based therapy, with the objective to target signaling pathways. Desai et al. evaluated the efficacy of capsaicin (CS-CYLiPin) and anti-TNFα siRNA encapsulated in nanocarriers (CYliPin) against inflammation in skin conditions. In regards to psoriasis, *in vivo* testing on mice

showed that PASI scores for CS-CYLiPin decreased to 0 after 5 days of treatment. Combination of capsaicin and siTNF-alfa showed a faster healing process. Also, solutions containing naked capsaicin or si-TNFα did not show healing at the end of the 5th day. Overall this study suggests a synergism between capsaicin and anti TNF-α siRNA. In addition, it demonstrated that new carrier systems such as CyLiPns can offer new therapeutic approaches with an improve of the capsaicin delivery in the skin [151]. In the same year, Agrawal et al. aimed to explore the potential of solid lipid nanoparticles (SLNs) and nanostructured lipid carries (NLCs) in improving delivery of capsaicin in *in vitro* and *in vivo* studies. On such studies the amount of capsaicin permeated and retained in the *stratum corneum* was higher when using NLCs when compared to SLNs or plain drug solution, and no irritation on both NLCs and SLNs were observed. Thus showing the ability of NLCs to increase drug accumulation and effectively deliver capsaicin in skin layers [152]. Both of these studies suggests new approaches to increase the effectiveness of capsaicin when treating psoriasis.

Furanocoumarins

Furanocoumarines are chemical components of plants from different families including *Umbelliferai*, *Rutaceae* and *Moroaceace* [153]. A photodynamic action is associated to furanocoumarins and its photobiological activity is of great interest in many areas. Estrogenic, antimicrobial, hypnotic and antiproliferative properties are among the pharmacologic properties attributed to furanocoumarins. In fact, the antiproliferative property is used when treating psoriasis and such capacity is associated to the ability of furanocoumarins to affect DNA [154]. PUVA is a therapy option against psoriasis and it is composed of xanthotoxin (a furanocoumarin) plus UV light. Studies have revealed that furanocoumarins photoreact with nucleic acids inducing the formation of diadducts and mono-adducts resulting in an inhibition in nucleic acid replication and transcription. Keratinocytes and other cell types can be targeted with furanocoumarins to induce such phototoxic reactions [153]. It is important to note however, that furanocoumarins represent a hazard to a certain extent as they have the ability to induce genetic mutations. Low concentrations of 8-methoxypsoralen when activated by UV-A was sufficient to increase the frequency of chromosome aberrations in Syrian hamsters. To reduce the risks associated with PUVA treatment, Conforti et al. synthesized different series of methylangleicns which are

furanocoumarins that do not photoinduce interstand cross-lonks in DNA but that photobind with macromolecules as monoadducts. Some synthetic methylanglecins displayed high phtobiological and antiproliferative activity, which makes them promising options for clinical evaluations [154].

Moreover, a study investigation related to drug-drug interaction between a naturally occurring furanocoumarin (xanthotoxin) and immunosuppressant cyclosporine (both used to treat psoriasis) showed that bioavailabitly to cyclosporine increased upon xanthotoxin administration. The area under the plasma concentration-time curve (AUC) and C_{max} also increased for cyclosporine without modification on the t_{max} or half-life of cyclosporine. These results suggest a possible use of furanocoumarins in combination to other treatments for psoriasis.

NATURAL PRODUCTS FROM ANIMAL ORIGIN

Fish Oil and Omega-3

Concentrates with ω-3 fatty acid remain a topic of general interest for the pharmaceutical and food industries, for the production of drugs with enhanced performance and for the production of nutritional supplements. As known, fat is a source of energy but is also a vital structural component of cellular membranes and is involved in many important cell-signaling pathways. Dietary ω-3 polyunsaturated fatty acids ameliorate numerous biological and physiological functions in human body, being particularly valuable in treating some diseases [155]. Márquez et al. (2011) evaluated the efficacy of the intake of omega-3 fatty acids in patients with mild or moderate plaque psoriasis by means of the addition of Oravex® (Thea Laboratories, Barcelona, Spain [280 mg of eicosapentaenoic acid, 40 mg of docosahexaenoic acid, 50 mg of thyme extract, 50 mg of olive leaf extract, 20 mg of green tea extract, 7.5 mg of zinc, 27.5 μg of selenium per capsule] [155]. Thirty patients were recruited, 15 of whom were given topical treatment with tacalcitol, forming the control group. The remaining 15 patients were given topical tacalcitol and 2 capsules of Oravex® daily. Three visits, the baseline, intermediate (week 4) and final (week 8), were held over an 8-week period. The main efficacy endpoints were the PASI, Nail Psoriasis Severity Index (NAPSI) and Dermatological Life Quality Index (DLQI). PASI presented an improvement of 6.8 points in the Oravex® group, whereas in the control group it was only 3.5 points. DLQI

was also greater in the group treated with Oravex®, with an improvement of 6.67 points versus 3.03 in the control group.

Whey Protein Extract

Complex whey protein products have been shown to have some potential for applications in the treatment of cancer, hepatitis B, human immunodeficiency virus (HIV), cardiovascular diseases and osteoporosis. XP828L, recently commercialized as Dermylex, is a patented new oral dietary ingredient made of a protein extract isolated from bovine sweet whey. The bioactive profile of XP828L has been related to the presence of bioactive whey proteins and (or) peptides (β-lactoglobulin, α-lactalbumin, lactoferrin, glycomacropeptide, immunoglobulins G) in the extract and to growth factors (predominantly TGF-β_2). Preliminary clinical data in an open-label study performed by Poulin et al. (2005) showed the safety and efficacy of XP-828L in patients with mild to moderate psoriasis.

A randomized, double-blind, placebo-controlled study recently confirmed the efficacy of XP-828L in the treatment of mild to moderate psoriasis [156]. In this study, patients receiving 5 g/d of oral XP-828L twice daily for 112 days had an improved physician's global assessment (PGA) score compared with patients under placebo ($p < 0.05$). This study thus confirmed the efficacy of this natural health product (NHP) against a placebo and positioned XP-828L as an interesting alternative or concomitant treatment for mild to moderate psoriasis. However, *in vivo* data in humans and animals suggest a daily dose of 800 mg could be more efficient than a 5-g dose. However, no well-structured clinical study has confirmed this hypothesis. Drouin et al. (2008) examined the effect of XP-828L at a daily dose of 800 mg on the quality of life and disease severity in patients with mild-to-moderate psoriasis [157]. XP-828L at 800 mg per day (n=16) or placebo (n=10) was given orally for 56 days. This treatment decreased significantly the Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI) improving the quality of life and decrease disease severity in patients with mild-to-moderate psoriasis.

In another study an increase in oxidative stress and decrease in glutathione (GSH) levels have been demonstrated to be associated with psoriasis, both locally and systemically. Total body GSH levels are best raised by ingestion of GSH precursors. Immunocal (Immunotec Inc.) is a nonprescription, oral, whey protein supplement that has been indicated as a GSH precursor. In order to determine if a nondenatured bioactive whey protein isolate, which previously

demonstrated to increase glutathione levels, could clinically improve psoriasis, Prussick et al., (2013) performed a clinical study. Authors recruited seven patients with psoriasis to take orally a nondenatured bioactive whey protein isolate (20g per day) [158]. Patients were found to have a beneficial clinical improvement. They concluded that the positive preliminary outcomes from this pilot study support the realization of a randomized, double-blind, clinical trial for evaluating whether this protein isolate would result in statistically significant improvement of psoriasis.

Propolis and Bee Venom

Apitherapy is the medical use of various products of honey bee including raw honey (antioxidant properties), pollen, royal jelly (antitumor and antibacterial activity and a capacity to stimulate collagen production), propolis and venom. The main components of propolis are: flavonoids (that include quercetin, apegenin, galangin), simple phenols (caffeic acid phenyl ester) and terpens. The therapeutic potential of apitherapy is still partially understood; however, the anecdotal evidence according to the American Apitherapy Society depicts its effectiveness in treating many diseases including rheumatic diseases, and dermatological conditions as eczema, psoriasis, cutaneous warts and herpes virus infection.

In order to evaluate bee venom and propolis as new therapeutic modalities for localized plaque psoriasis [159], forty-eight patients were randomized into four treatment groups: 1) Group I; intradermal bee venom twice weekly; b) Group II; topical propolis ointment in vaseline base; c) Group III; oral propolis capsules 1 g/day; d) group IV; intradermal bee venom, oral and topical propolis. Changes in PASI score and IL-1β were significantly higher in Groups I and IV compared to Groups II and III. All treatments were tolerable with minimal adverse effects. The authors concluded that the intradermal bee venom and oral propolis are safe and effective treatments for localized plaque psoriasis with minimal tolerable side effects. Intradermal bee venom has superior results than oral or topical propolis when used alone or in combination with propolis.

Due to recognition of bee propolis as potent antioxidant and anti-inflammatory natural product, Oršolić et al. (2013) demonstrated that topical application of ethanolic extract of propolis (EEP) may improve psoriatic- skin lesions by suppressing functional activity of macrophages and reactive oxygen species production [160]. Taken together, it is suggested that EEP can safely

be used in the prevention of psoriasis-related inflammatory changes without causing any toxic effect.

FORMULATIONS USING COMBINATION OF NATURAL PRODUCTS FOR PSORIASIS

Psirelax

Psirelax is an herbal topical medication indicated for the treatment of psoriatic patients. The formulation includes natural ingredients such as quince seeds jelly, base cream, anti-oxidants (e.g., palm tree oil, wheat germ oil), skin softening agents (e.g., sweet almond oil), absorption aids (e.g., jojoba oil), tissue regenerating and protecting agents (e.g., grape seed oil), preservatives (e.g., paraben) and thickening agents (e.g., bee wax). Psirelax is an herbal topical medication indicated for the treatment of patients with psoriasis. Its efficacy was determined in an open-label study in 22 patients (15 men, 7 women) suffering from chronic plaque psoriasis [161]. There was 59% reduction in PASI, from a mean of 5.9 ± 4.0 before treatment to 2.4 ± 2.4 after treatment ($p<0.001$). In 8 patients (36%) PASI decreased in more than 75% (PASI75). In 16 patients (73%) PASI decreased in more than 50% (PASI50). Application of Psirelax was associated with a decrease in disease severity, as assessed by the patients and physicians.

Traditional Chinese Medicine Preparation

Traditional Chinese medicine (TCM) is an alternative therapy that can be used in the treatment of dermatologic disorders, including various forms of psoriasis [162]. In TCM, psoriasis is commonly classified into three main syndromes, namely blood heat, blood dryness and blood stasis. According to TCM proponents, this kind of treatment typically involves the application of herbs and vitamins as well as the use of a wide range of therapeutic methods, such as massages, acupuncture, diet and lifestyle modification [163].

Thus, the use of TCM herbal preparations containing e.g., *Indigo naturalis*, *Rhizoma smilcis glabre*, *Radix angelicae dahuricae*, *Radix salviae milthiorrhiza*, *Radix rehmanniae glutinosae*, *Radix angelicae sinensis*, *Dictamnus dasycarpus*, *Lithospermum erythrorhizon*, *Radix paeoniae*

lactiflorae, *Radix rubiae*, *Flos carthami tinctorii* and *Radix glycyrrhizae uralensis*, seems to be justified in the treatment of psoriatic. The rationale for their use in Chinese medical terms relates to their effects on clearing internal heat, activating blood to remove stasis and strengthening any deficiencies. The aim is to restore the balanced state of the body to allow psoriasis to resolve. Most of the key actions reflect anti-inflammatory properties, modulation of cytokine production or inhibition of angiogenesis. All these may be relevant in reducing the severity of psoriasis. Nevertheless, adverse reactions during TCM treatment range from mild (transient hepatitis, dermatitis) to severe fatal illnesses (anaphylactic shock, liver failure). Liver complications, including elevated liver enzymes, are one of the best documented adverse effects of TCM preparations, whereas allergic contact dermatitis is a commonly observed skin side effect to herbal preparations. Moreover, since numerous herbal formulations contain psoralens, their use can result in photosensitivity [162-165].

Easy access to TCM preparations (available as over the counter products) makes them popular among patients. One study, revealed that 51% of psoriatic patients opted to use alternative therapies. Although the demand for TCM preparations seems to be great and ever growing, scientific evidence confirming their efficacy is scarce in European medical journals. In fact, almost all reports on the TCM preparations' modes of action are found in Chinese medical literature. To date, there have been no randomized, placebo-controlled clinical trials, which could confirm their safety and efficacy [163].

STRENGTHS AND WEAKNESSES OF INVESTIGATIONS WITH NATURAL PRODUCTS FOR PSORIASIS TREATMENT

As previously analyzed in this chapter, a significant proportion of psoriatic patients worldwide are using natural products in order to manage their psoriasis. The origin of this interest appears to reside in three factors: a) the currently available therapies are often limited by their efficacy and toxicity; b) patients are discouraged and consequently are looking for other unconventional therapeutic alternatives; c) the misconception of the safety of natural products. As patients uses these products in combination with other conventional therapeutic options, they can account for toxicity, infectivity and lack of adherence to treatments.

Dissatisfaction of patients with available treatments is described in scientific literature, which is accompanied by a significant decrease in their quality of life. The chronic nature of psoriasis and the need for less toxic and affordable products, justify the investigations with other natural alternative therapies.

According to this review it is possible to observe that the nature of metabolites used to treat psoriasis is diverse. There are alkaloids (laurifolin, berberine, palmatine, berbamine etc.); polyphenols (resveratrol, luteolin, epigallocatechin gallate, etc.), terpenoids (asiaticoside, madecassoside, asiatic acid, madecassic acid, etc.), fatty acids (omega-3) and proteins (whey proteins) among others. These compounds use different pathways involved in the pathogenesis of the disease. If one considers the complexity of psoriasis at cellular, genomic and genetic levels (in lesions there are an altered expression of more than 1300 genes) [166], it is not a surprise that different molecules with different mechanisms show positive effects. Indeed, it could be questionable if it is an adequate pharmacologic strategy to search "one" effective medication instead of "various treatments" that could be used in different stage of the disease as part of a holistic vision of psoriasis management. This applies for natural products which should be also considered among therapeutic options. However, to tailor more effective treatments (natural, biotech or synthetic) is necessary to understand the etiopathogenic basis of psoriasis by stratifying patients into more homogeneous groups. This is important because, from a clinical viewpoint, it has been considered that every patient has his/her own form of psoriasis [167].

Some methodological problems can be appreciated in the studies performed with natural products for psoriasis. It includes: a) little knowledge of the toxicology of natural products; b) use of extracts and natural molecules pharmacokinetically poorly studied; c) misunderstanding about pharmacokinetic and pharmacodynamic interactions of natural products with conventional therapies; d) uses of models not representative of psoriasis in preclinical studies; e) insufficient number of patients in clinical trials; f) lack of adequate comparison in terms of efficacy and safety with other therapeutic options in clinical studies. These problems have conspired against the use of natural treatments in clinical practice on more rigorous bases.

In some cases, studies performed with natural products were preclinical researches. As to *in vitro* studies, they frequently use normal human keratinocytes (NHK) or immortalized ones (HaCaT). This kind of cells have important differences regarding psoriatic keratinocytes (PK). Psoriatic keratinocytes have an activated phenotype responsible of an aberrant

production of cytokines and chemokines compared to NHK [85]. HaCaT keratinocytes show strong up-regulation of stress responses compared to NHK induced by plant polyphenols and TNF, concomitant with stronger NF-kB activation [168]. These results strongly suggest that due to differences in signal transduction, transcription and post-translation events between HaCaT, NHK and PK, it is not recommending to extrapolate pharmacologic results from HaCaT or NHK to PK.

Regarding preclinical *in vivo* tests, it is important to know that, with the exception of few cases in primates, psoriasis is exclusive to humans. As consequence, most of available mice models are not able to fully reflect the complex characteristics of this disease. The most representative are xenotransplantation models which have been useful to validate the efficacy of new drugs in preclinical studies [169]. Therefore, a rigorous preclinical program for the development of a natural antipsoriatic health product should use a multi-step panel of psoriatic animal models showing different hallmarks of the disease in order to avoid incorrect assumptions of the product efficacy in humans [170].

The understanding of the toxicity mechanisms of natural health products at early stages of their development and the use of interspecies biomarkers of toxicity, could help to predict possible interactions with other therapies in further stages of development.

If one analyses table 1, it is evident that they are only few clinical studies using natural health products for psoriasis, the number of patients being relatively low. It limits the power of trials and the probability to obtain statistically significant results after natural health product therapy. In most studies here revised, there are not appropriate comparisons with conventional therapies. This is a methodological problem that does not properly allow the evaluation of the risk/benefit of natural health products in relation to others available treatments. Consequently, it is not possible to know the position of natural products within the current antipsoriatic therapeutic arsenal. Moreover, clinical studies performed with natural health products are mostly short-term studies, which is inconsistent with the long-term treatment required for psoriasis. Therefore, it is important to design clinical studies with these products beyond a year in order to obtain data about their long-term safety and efficacy.

It is also imperative to advance in the study of pharmacokinetic of the natural products. This aspect is extraordinary important because in some cases the lack of efficacy can be attributed to a low bioavailability and not to the inability to block a particular pathway involved in psoriasis. As most of these

products in clinical practice are used together with conventional therapies, preclinical and clinical evaluations should be performed for the assessment of pharmacokinetic or pharmacodynamic interactions together with conventional treatments.

Considering that natural compounds have a very high chemical diversity compared to synthetic compounds and a wider range of biological activities [171], their use in psoriasis could represent an interesting alternative to expand the available therapeutic armamentarium. An example of a molecule derived from plants is the psoralen, obtained from *Psoralea corylifolia* seeds currently used in PUVA therapy as photosensitizing agent. Natural products may provide health benefits when properly used as part of a reasoned antipsoriatic management program. The urgent need for new antipsoriatic drugs justifies the investigation with these kind of products. The structural richness of these molecules and the possibility to act on multiple pathways could be advantageous for the treatment of this disease.

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