Anti-Psoriasis Agents from Natural Plant Sources

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Anti-Psoriasis Agents from Natural Plant Sources

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Abstract: Psoriasis is a chronic inflammatory immune-mediated skin disease. It affects most races, does not have any sexual predilections and can manifest at any age of life. Psoriasis is more frequent in certain racial groups and geographical areas. For these reasons, both genetic and environmental factors could be considered. In this review, we discuss promising natural compounds, their molecular targets and mechanisms, which may help the further design of new anti-psoriasis agents. Literature documents the widespread use of herbal remedies worldwide, and the presence of some phytochemicals supports the efficacy of some botanical treatments. The research on natural products has greatly contributed to the progress in the treatment of skin diseases such as psoriasis and many of these compounds are now being used. Understanding the mechanism of these molecules will contribute to the development of more specific preventive strategies for the treatment of psoriasis.

Keywords: Psoriasis, skin, botanicals, medicinal plants, mechanism of action.

1. INTRODUCTION

Psoriasis is a chronic inflammatory immune-mediated skin disease. Both genetic and environmental factors are involved in the etiology. Symptoms include the presence of erythematous red patches covered with scaly dry and whitish, pain, itchiness, and bleeding [1]. In 2013, the Executive Board of World Health Organization (WHO) recommended a resolution that requests to increase awareness of psoriasis as one of the main health problems worldwide [2].

Psoriasis is one of the most common and frequent skin diseases. Its estimated prevalence in the world’s population is about 2%, but there are many geographic and ethnic differences so that it can swing widely between 0.5 and 4%. Psoriasis is more common in colder northern climates than in the tropical regions [3]. Several studies suggested that Caucasians are more affected than other races [4,5]. The incidence seems to be the same in the sexes, but some authors identify prevalence in males. Psoriasis can make its debut at all ages of life, being able to be present in newborns as in the elderly, with a peak incidence in the range 20-30 years and 50-60 years. Particularly severe forms affect about 10% of patients; psoriatic arthritis can be present in 20-

30% of cases. About 70-80% of patients have mild psoriasis, controlled by topical therapies alone [6]. In addition to ethnicity, the prevalence of psoriasis may also be affected by exposure to the sun and the climate. However, Jacobson et al. [7] in a recent study demonstrated a weak correlation between latitude and psoriasis prevalence. This suggests that other factors, or much more plausibly combinations of factors, might be involved.

People affected by psoriasis are most at risk of developing other diseases including psoriatic arthritis, anxiety and depression, lymphoma, metabolic syndrome, cardiovascular disorders, and Crohn’s disease. Mild trauma, sunburn or chemical irritants can provoke psoriasis. There are drugs such as non-steroidal anti-inflammatory agents, β-blockers, lithium and antimalarials that can aggravate the disease.

Plants and their secondary metabolites demonstrated an important role in the discovery of new potential anti-psoriasis agents [8]. Interestingly, in America and Europe about 50% subjects affected by psoriasis use complementary and alternative medicine, including plant-based medicines [9-12].

The interest in plant-based medicines used for the treatment of psoriasis is evident analysing the literature [8,12-21]. The aim of this review is to report the most recent works on plant extracts and pure compounds for...
the treatment of psoriasis and to discuss their mechanisms of action. As reported, in many cases it is observed a greater activity of plant extracts and/or pure constituents in comparison to conventional drugs, such as corticosteroids. Aloe vera, Boswellia serrata, Curcuma longa, Hypericum perforatum, Indigo naturalis, Mahonia aquifolium, and Viola tricolor and their main active constituents boswellic acids, curcumin, hyperforin, hypericin, and berberine can be considered the most promising agents for future management of psoriasis.

2. PATHOGENESIS AND CLINICAL MANIFESTATIONS

Psoriasis is a skin disease with an etiology involving both genetic and environmental factors. The causes are still unidentified. Now the role of the immune system is widely accepted and, consequently, the genetic predispositions of psoriasis with respect to immune genes and their encoded pathways in the pathogenesis [22,23]. The immune genes are responsible for several functions that involve innate immunity, antigen presentation, the interleukin (IL)-23 axis, and T-cell development and polarization. In recent years, the contribution of some of these gene products to psoriasis has been proved targeting of some key immune components, namely IL-23, tumor necrosis factor alpha (TNF-α), and the Th17/IL-23 axis [24]. Psoriasis involves keratinocytes, antigen-presenting cells, neutrophilic granulocytes, vascular endothelial cells, and the cutaneous nervous system [25]. At onset of psoriasis, activated dendritic cells produce different mediators including TNF-α and IL-23.

TNF-α is a pro-inflammatory cytokine, produced by different cell types including lymphocytes, keratinocytes, endothelial cells, and macrophages, which amplifies inflammation response through several pathways. The IL-23/Th17 axis could be a novel targeted therapy for the treatment of psoriasis [26]. Th17 cells are a subset of T-lymphocytes that express IL17, different from the classical Th17 cells that have a significant role in the pathogenesis of inflammatory disorders including psoriasis.

Expansion and survival of these cells depend on myeloid cell-produced IL-23, which determine the Th17 cells differentiation. Other cytokines including IL-9 might support Th17-related inflammation. After activation, Th17 cells produce several mediators that induce keratinocyte proliferation and other psoriasis features. TNF-α and IL23/Th17 axis pathways affect the proliferation and production of cytokines by epidermal keratinocytes. Moreover, inflammation, observed in psoriatic lesions, leads to induction and activation of several pro-angiogenic factors.

Regulatory T cells affect the vascular endothelial growth factor (VEGF)-related angiogenic microenvironment and contribute to some psoriasis features. Therapies able to target leukocytes recruitment and/or vascular functions are a promising approach for the treatment of psoriasis.

Five types of psoriasis have been described. Plaque psoriasis, also known as psoriasis vulgaris, is the most common form of the disease (about 85% of cases). Distinctive characters are monomorphic demarcated erythematous plaques covered by silvery lamellar scales. These are mainly found on the scalp, knees, elbows, legs, and sacral area, but may be present on any part of the body in the most advanced states of the disease. The other types are: a) guttate or eruptive psoriasis; b) inverse psoriasis, also called intertriginous or flexural psoriasis; c) pustular psoriasis or generalised pustular psoriasis; and d) erythrodermic psoriasis.

Guttate psoriasis presents small lesions over the upper trunk and proximal extremities and is frequent among young adults. Inverse psoriasis shows up as very red lesions in is found in the armpits, groin, under the breasts and in other skin folds on the body. It is common in overweight people.

Pustular psoriasis is characterized by white coalescing pustules (blisters of non-infectious pus) and often appears in patients with existing or previous psoriasis vulgaris while erythrodermic psoriasis is a severe and rare complication of psoriasis.

3. CONVENTIONAL THERAPIES

The conventional therapies for the treatment of mild disease are generally topical drugs such as glucocorticosteroids and vitamin D derivatives, or their combinations. Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are used for the treatment of difficult-to-treat parts, such as the intertriginous areas or the face. Mason et al. [27] showed that a combination of corticosteroids and vitamin D3 was the most effective treatment for the scalp. Unfortunately, convenience, time needed for the treatment, and adverse effects limit the use of these topical drugs. Patients affected by moderate and severe psoriasis generally use a combination of phototherapy and systemic therapy. Acitretin, ciclosporin, and methotrexate have been approved for the treatment of psoriasis as systemic drugs. Apremilast has been approved in the USA and Europe. Photoche-
motherapy or PUVA (Psoralen Plus Ultraviolet Light Therapy) is a combination of ultraviolet A (UVA) light therapy and a psoralen medication. Unfortunately, the carcinogenic effects of PUVA limit its long-term use. In recent years, several biologics such as TNF-α inhibitors (adalimumab, etanercept, and infliximab) and inhibitors of interleukin 12 and 23 (ustekinumab) have been approved for the treatment of psoriasis. Biologics have shown a good safety profile and no cumulative toxicity. TNF-α inhibitors are generally used when conventional systemic therapies have either failed, were not tolerated or were contraindicated and after phototherapy. This is due in part to the high costs.

4. OXIDATIVE STRESS AND PSORIASIS

Although endogenous antioxidants may attenuate the damaging effects of reactive oxygen species (ROS), increased and/or prolonged presence of free radicals can override ROS defense mechanisms and mediate several cellular responses that contribute to the development of a variety of skin disorders, including psoriasis [28]. Zhou et al. [28] reviewed studies that demonstrated the role of oxidative stress in the pathogenesis of psoriasis. ROS influence the cellular signal transduction pathways such as pro-inflammatory signaling pathways and modulate the expression of numerous genes [29]. The most important effects are observed in the mitogen-activated protein kinase/activator protein 1 (MAPK/AP-1), nuclear factor κB, and Janus kinase-signal transducers and activators of transcription pathways, which have been considered as initial events in inflammatory disorders such as psoriasis. Moreover, the high level of polymorphonuclear leukocytes (PMN) in psoriatic lesions leads to the release of ROS produced via NADPH-dependent oxidase/myelo-peroxidase and proteolytic enzymes, leading to lipid peroxidation and oxidative damage of skin cells. In particular, the decrease of membrane fluidity caused by lipid peroxidation products is observed in association with the exacerbation of the disease. Fatty acids and their oxidation products can bind the peroxisome proliferator-activated receptor PPARα, that controlling lipid and lipoprotein metabolism, cell proliferation, differentiation, and apoptosis of keratinocytes, is a major event in psoriasis, contributing to the hyperproliferative phenotype by induction of heparin-binding EGF-like growth factor, known to induce epidermal hyperplasia and be overexpressed in psoriasis.

Although the molecular mechanism of the regulation of ROS-mediated pathways is still unknown, antioxidants may be beneficial for the treatment of psoriasis. The role of oxidative stress in the pathogenesis of psoriasis makes to study the possible benefit of an enriched diet or of a therapeutic supplementation of natural antioxidants.

5. NATURAL PRODUCTS

5.1. Acanthus Mollis

Acanthaceae family comprises of 250 genera and about 2500 species. Among them, Acanthus mollis is a plant used in traditional medicine in southern Italy for the treatment of skin disorders including psoriasis [30]. Eicosanoids play a very important role in inflammatory processes of the skin, therefore, also in the course of psoriasis and dermatitis atypical. Neutrophils migrate into the epidermis quickly inflamed and come into close contact with the keratinocytes, releasing leukotriene A4 in the extracellular space. From this substrate, the production of leukotriene B4 starts.

12(S)-Hydroxy-5Z,8Z,10E,14Z-tetraenoic acid (12(S)-HETE) is one of the most widely eicosanoids produced by the epidermis, and is found in large quantities in psoriatic plaques [31]. The activity of A. mollis extracts seems partly due to inhibition of direct and indirect enzyme responsible for the synthesis of eicosanoids. Moreover, in vitro studies have shown that A. mollis extracts are able to inhibit cyclooxygenase (COX), lipooxygenase (LOX), and redox-sensitive enzymes, and affect the release of LT4β, eicosanoid and activation of nuclear factor NF-κB (Table 1) [32,33]. The methanol extract of A. mollis was assessed for its in vitro effects against COX-1, 5-, 12- and 15-LOX enzymes, and NF-κB activation [34-38]. A. mollis inhibited both COX-1 and 5-LOX (at a concentration of 200 µg/ml). No inhibitory activity on 12-LOX was observed.

5.2. Aloe Vera L.

Aloe vera (Asphodelaceae) has been used for more than 2000 years in the treatment of dermatological disorders [39-41]. Different studies investigated products obtained by A. vera for the treatment of psoriasis. Syed et al. [42] in a study that involved sixteen patients with mild to moderate psoriasis evaluated an A. vera cream demonstrating that the treatment effect of A. vera was significantly superior than that to placebo. Successively, Paulsen et al. [43] conducted a randomized, double-blind, placebo-controlled, study with fourteen patients.

The Psoriasis Area Severity Index (PASI) scores decreased by 72.5% of the A. vera-treated sites com-
pared with 82.5% of the placebo-treated areas after 4 weeks of treatment. However, no difference in efficacy between A. vera and the placebo was evidenced after 12 weeks. In contrast to these results, A. vera cream was more effective than 0.1% triamcinolone acetonide cream after 8 weeks [44]. The improvement in the PASI was about 66.1% in the A. vera group and 60.1% in the triamcinolone acetonide group. No complete remission was observed in either of the groups. The impact of psoriasis on the quality of life was investigated using the Dermatology Life Quality Index (DLQI). This index decreased in both groups throughout the course of the study. No significant difference between the 2 groups was found after 8 weeks of treatment.

A. vera cream showed mild side effects. A 95% ethanolic extract of the gel of A. vera leaf has recently been studied using a mouse-tail model of psoriasis [45]. This extract made significative differentiation in the epidermis as seen from its degree of orthokeratosis (85.07%), equivalent to the effect of the positive control tazarotene (0.1%) gel, which showed a 90.03% degree of orthokeratosis.

A. vera leaf gel extract also increased relative epidermal thickness, whereas tazarotene did not produce any change. Unfortunately, until now results on the effectiveness of A. vera are contradictory [40].

### 5.3. Astragalus sinicus L.

Astragalus sinicus (Fabaceae) (known as Chinese milkvetch) is a perennial legume that grows in Korea, Japan, and central and southern China. The main identified classes of constituents are alkaloids, flavonoids, and triterpene glycosides [46,47].

In a recent study, the dried roots or stems of A. sinicus were extracted with methanol and dichloromethane. The extracts were partitioned into water and n-butanol, and the latter fraction was repartitioned into aqueous methanol and n-hexane [48]. Among fractions obtained from the aqueous methanol layer, rf3 and rf4 showed the most interesting anti-inflammatory and antioxidant effects.

In particular, rf3 and rf4 exerted an effect on the JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling cascade with possible inhibitory effects in cytokine-induced keratinocytes signaling. Both fractions inhibited Th2 and Th17 cells differentiation and enhanced Treg-cell differentiation. Besides JAK/STAT signaling pathways, both fractions, but in particular rf4, inhibited the activation of nuclear factor kappa B (NF-κB) by inhibiting a) the phosphorylation and degradation of IkBα protein, b) the phosphorylation of NF-κB p65, and c) the nuclear translocation of the activated NF-κB p65 subunit. Overall, these effects

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**Table 1. Plant extracts for the treatment of psoriasis.**

<table>
<thead>
<tr>
<th>Species</th>
<th>Family</th>
<th>Parts</th>
<th>Study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthus mollis</td>
<td>Acanthaceae</td>
<td>Leaves</td>
<td>In vitro</td>
<td>[28]</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Asphodelaceae</td>
<td>Leaves</td>
<td>In vivo</td>
<td>[36-39]</td>
</tr>
<tr>
<td>Astragalus sinicus</td>
<td>Fabaceae</td>
<td>Dried roots or stems</td>
<td>In vitro and in vivo</td>
<td>[42]</td>
</tr>
<tr>
<td>Boswellia serrata</td>
<td>Burseraceae</td>
<td>Resin</td>
<td>In vivo</td>
<td>[47, 48, 50-54]</td>
</tr>
<tr>
<td>Caesalpinia bonduc</td>
<td>Caesalpinaceae</td>
<td>Leaves</td>
<td>In vitro and in vivo</td>
<td>[59]</td>
</tr>
<tr>
<td>Curcuma longa</td>
<td>Zingiberaceae</td>
<td>Rizome</td>
<td>In vivo</td>
<td>[62-67, 74-76, 78]</td>
</tr>
<tr>
<td>Dodoneae polyandra</td>
<td>Sapindaceae</td>
<td>Leaves</td>
<td>In vitro and in vivo</td>
<td>[79-82]</td>
</tr>
<tr>
<td>Hypericum perforatum</td>
<td>Hypericaceae</td>
<td>Flowers/Fruits</td>
<td>In vitro and in vivo</td>
<td>[90-97]</td>
</tr>
<tr>
<td>Illicium verum</td>
<td>Illiciaceae</td>
<td>Fruits</td>
<td>In vitro</td>
<td>[102-104]</td>
</tr>
<tr>
<td>Indigo naturalis</td>
<td></td>
<td>Leaves*</td>
<td>In vitro and in vivo</td>
<td>[106-111]</td>
</tr>
<tr>
<td>Mahonia aquifolium</td>
<td>Berberidaceae</td>
<td>Bark</td>
<td>In vivo</td>
<td>[113-120]</td>
</tr>
<tr>
<td>Memecylon malabaricum</td>
<td>Melastomataceae</td>
<td>Leaves</td>
<td>In vitro and in vivo</td>
<td>[121-122]</td>
</tr>
<tr>
<td>Picea mariana</td>
<td>Pinaceae</td>
<td>Bark</td>
<td>In vitro</td>
<td>[124]</td>
</tr>
<tr>
<td>Viola tricolor</td>
<td>Violaceae</td>
<td>Leaves and flowers</td>
<td>In vitro</td>
<td>[139]</td>
</tr>
</tbody>
</table>

*Leaves of Baphicacavthus cusia, Isatis indigotica, Indigofera tinctoria, and Polygonum tinctorium.
resulted in the inhibition of the expression and production of pro-inflammatory mediators. *A. sinicus* fractions were also *in vivo* studied. Topical application of rf3 and rf4 was able to suppress ear thickness and psoriasis progression.

5.4. *Boswellia serrata* Roxb. ex Colebr.

*Boswellia serrata* (Burseraceae) is a moderate to large sized branching tree that grows in dry mountainous regions of India, Northern Africa and the Middle East. Since ancient times, three of these species have been considered as “true Frankincense” producing trees [49].

The gum-resins of trees were mentioned in Ayurvedic and Unani texts as an effective remedy for diarrhoea, dysentery, fevers, cardiovascular diseases, mouth sores, bad throat, bronchitis, asthma, cough, vaginal discharges and skin diseases [50]. Several studies support the use of this species as antiarthritic, anti-inflammatory, antihyperlipidemic, antiatherosclerotic and analgesic agent [51].

The resinous part of *B. serrata* contains α-thujene, incensole, incensole oxide, *iso*-incensole oxide, serratol, α- and β-amyrisns, boswellic acids and tirucall-8,24-dien-21-oic acids as main constituents [52]. Boswellic acids, a natural mixture of four major penta-cyclic triterpenes, namely β-boswellic acid (1), 11-keto-β-boswellic acid (2), 3-acetyl-β-boswellic acid (3), and 3-acetyl-11-keto-β-boswellic acid (4), is reported to be effective as anti-inflammatory, immunomodulatory, antitumor, anti-asthmatic agents (Fig. 1). This mix of compounds exerted the anti-inflammatory activity by the inhibition of leukotrienes via 5-lipoxygenase inhibitory effect (Table 2). Singh et al. [53] investigated the anti-inflammatory activity of boswellic acids. The results of the study revealed that topical application of boswellic acids in both acute and chronic models exerted leukotriene inhibitory activity.

The anti-inflammatory activity of boswellic acid (1) and its derivative 3-acetyl-11-keto-β-boswellic acid (4) is attributed to the ability of both compounds to bind the 5-lipoxygenase enzyme at a selective site for penta-cyclic triterpenes that is different from the arachidonate substrate-binding site [54]. The analysis of structure-activity relationships (SARs) revealed that the penta-cyclic triterpene ring system is crucial for binding to the highly selective effector site, whereas the keto function in addition to a hydrophilic group on C4 of ring A are essential for the 5-lipoxygenase inhibitory activity of boswellic acids [55]. More recently, Altmann et al. [56] have demonstrated that boswellic acids at low concentrations inhibited the activation of mitogen-activated protein kinases (MAPK) signaling and significantly suppressed the PAF-induced Ca2+ mobilization. Moreover, boswellic acid inhibited leukocyte elastase, released in inflammatory reactions and hyper-sensitivity, underscoring its antiphlogistic effects [57].

The 3-acetyl-11-keto-β-boswellic acid (4) also caused inhibition of nuclear factor NF-κB and then a down-regulation of the expression of TNF-α through its direct inhibition of IKK (beta kinase K) [58]. Human psoriatic skin lesions exhibited strong activation of transcription factor NF-κB.

Based on this observation, Wang et al. [59] investigated the *in vivo* effect of 3-acetyl-11-keto-β-boswellic acid (4) by using a mouse model of psoriasis. After treatment with compound 4, NF-κB signaling and NF-κB-dependent cytokine production was strongly suppressed. Moreover, the application of 3-acetyl-11-keto-β-boswellic acid (4) led to resolution of the abundant immune cell infiltrates, counteracted the expression of IL-12, IL-23, and MCP-1 in lesional areas, and reduced the proliferation of keratinocytes.

Successively, Togni et al. [60] described the results of the application for 30 days of novel boswellic acid formulation (Bosexil®). The size and irritation of lesions were classified as absent, moderate, severe or very severe. The efficacy of treatment was evaluated according to the “change of conditions” of patients, according to the following scale: a) in remission: when

![Fig. (1). Chemical structure of boswellic acids 1-4.](image-url)
However, the study was carried out for a short period, twice a day for thirty days resulted in an actual improvement of the disease.

Bosexil formulation improved both erythema and itchiness without any case of worsening. Bosexil® formulation improved both erythema and itchiness without any case of worsening. Bosexil®, formulated according to the Phytosome® delivery system, could be proposing for the treatment of psoriatic and eczematous symptoms. This study has shown that through topical administration, twice a day for thirty days resulted in an actual improvement of the disease. However, the study was carried out for a short period, including a small number of patients. In addition to anti-inflammatory effects, as already reported, these molecules have the capacity to restore and protect in the time the barrier function of the skin, which is made weaker by the same psoriatic plaques. It is thought to also increase the time between periods of remission when the disease takes over the patient’s skin. In addition to serving for the treatment of psoriasis and eczemas, the formulations investigated can also be applied for other inflammatory disorders of the skin, including contact, atopic, and seborrhoeic dermatitis.

### 5.5. *Caesalpinia bonduc* (L.) Roxb.

*Caesalpinia bonduc* (Caesalpiniiaceae), known as Kat Karanj in Hindi, is traditionally used in the Malabar region, Karnataka, India, to treat inflammation and...
skin diseases, such as psoriasis [61]. Phytochemical screening reported cassane furanoditerpenes from different parts of the plant [62-64]. A decoction and a hydroalcoholic extract of C. bonduc leaves were prepared and studied for their potential anti-psoriasis effects by using a mouse-tail test [65].

*C. bonduc* decoction was fractionated with water saturated n-butanol to give a butanol and a water fraction decoction. Hydroalcoholic extract was fractionated with chloroform and water saturated n-butanol to give chloroform, n-butanol and water fraction of hydroalcoholic extract.

In the mouse-tail test, the most active fractions were n-butanol and water fraction of hydroalcoholic extract by producing remarkable orthokeratosis in comparison with the control. Moreover, the water fraction of hydroalcoholic extract also exhibited significant modification in epidermal thickness. *C. bonduc* decoction and the other fractions did not produce significant orthokeratosis but determined important changes in epidermal thickness.

Taking into account the role of LOX catalysed oxygenation products in the development of psoriasis, extracts and fractions were also tested for their ability to inhibit the enzyme. The most active fraction was the water fraction of decoction with an IC$_{50}$ value of 164.71 µg/ml, followed by decoction (IC$_{50}$ value of 291.65 µg/ml). The water fraction of decoction showed antiproliferative activity against HaCaT cell line.

### 5.6. *Curcuma longa* L.

*Curcuma longa* (Zingiberaceae) is a perennial plant with characteristic odour and slightly pungent bitter in taste. The rhizome contains three main curcuminoids, namely curcumin (5) (Fig. 2), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumeron, atlantone, and zingiberone). *C. longa* is largely used in traditional medicine especially in Ayurvedic medicine for its analgesic, antibacterial, antioxidant, expectorant, and anti-inflammatory properties [66,67].

Curcumin (5) demonstrated to be a highly pleiotropic molecule able to interact with numerous molecular targets involved in inflammation [68]. IL-23, IL-17A, and IL-17F and cytokines play a critical role in the pathogenesis of psoriasis [69]. Curcumin (5) exerts its beneficial effect in psoriatic patients since it acts in keratinocytes as an anti-inflammatory agent by inhibiting the expression of several pro-inflammatory cytokines. The topical use of a curcumin (5) gel formulation (curcumin 1 g, azone 1 g, hydroxypropyl cellulose 3 g, ethanol (96%) 17 g, and distilled water q.s. to 100 g) strongly inhibited psoriasis-like inflammation in an animal model, the development of which is based on the IL-23/IL-17A axis. Real-time PCR analysis revealed that the treatment with curcumin (5) determined a reduction of IL-17A, IL-17F, IL-22, IL-1β, IL-6 and TNF-α cytokines expression similarly to clobetasol, a glucocorticoid largely used for psoriasis treatment.

IL-17A induces the activation of the NF-κB and JUN amino-terminal kinase (JNK) signaling pathways and synergizes with other cytokines namely IL-1β, IL-6 and TNF-α that promote the activation of tissue-infiltrating neutrophils. Curcumin (5) significantly reduced the increased expression of IL-17A and IL-17F induced by imiquimod (IMQ). The receptor RORγt, activated by IL-6 and TGF-β, is necessary for the expression of IL-17A. Because there are no evidences of the influence of curcumin (5) on the expression of RORγt, it can be deduced that compound 5 down-regulated the expression of IL-17A/IL-22 by inhibiting the production of IL-1β/IL-6. The expression of IL-22 was also significantly down-regulated by 5 in IMQ-induced psoriasis-like inflammation.

Moreover, curcumin (5) enhanced the proliferation of epidermis γδ T cells but inhibit dermal γδ T cell proliferation. In mouse skin cells γδ T type are very abundant, and act in order to monitor local immune. IL-23, in turn, is essential for the maintenance of homeostasis, and cell differentiation γδ-T.

Curcumin (5) demonstrated to stimulate the proliferation of γδ T cells [70]. The increased skin thickness and inflammation in IMQ-treated mouse ear skin was inhibited by curcumin (5) [71]. An improved level of activation of signal transducer and activator of transcription 3 (STAT3) was found in human psoriatic lesions [72]. Curcumin (5) also suppressed the phosphorylation of STATs. STAT3 alters the proliferation and differentiation of keratinocytes, and induced inflammatory molecules [73].

In psoriatic lesions, STAT3 activation was promoted by increased levels of cytokines and growth factors. For example, IL-22 strongly triggers STAT3. In fact, it inhibited both IL-6-induced STAT3 and IFN-α-induced STAT1 phosphorylations [74]. Therefore, curcumin (5) inhibits inflammatory factors that contribute to inflammation and the proliferation of keratinocytes in psoriatic patients.

Moreover, curcumin (5) has shown its inhibitory effect on NF-κB, MAPK and cytokines [75]. NF-κB me-
mediates several gene expressions, critical for the regulation of inflammation and autoimmune diseases [76].

Recent studies demonstrated that the route of signal transduction induced by IL-1 is a key step in the formation of autoimmune diseases mediated by IL-17A, such as psoriasis [77]. Consequently, the link between IL-1R1 and IL-1β starts the process of signal transduction, culminating in the activation of NF-κB, JNK and p38 MAPK. NF-κB is closely related to the onset of psoriasis, as it combines the action of keratinocytes and lymphocytes [78]. Curcumin (5) can inhibit the activation of NF-κB inhibiting the phosphorylation of IkB. The nuclear receptor RORγt, which is activated by IL-6 and TGF-β is involved in the expression of IL-17A both in vitro and in vivo [79]. In the pathogenesis of psoriasis, phosphorylase kinase (PhK) increased activity has been demonstrated.

Heng et al. [80] evaluated the effect of curcumin (5) PhK suppression in patients with psoriasis. Forty patients were distributed into four groups: untreated psoriasis; psoriasis treated by calcipotriol (a vitamin D3 analogue and an indirect inhibitor of PhK); curcumin (5) (diferuloylmethane); non-psoriatic people. In psoriasis treated with curcumin (5) and calcipotriol the lower level of PhK activity was found in association with a decrease in keratinocyte transferrin receptor expression and a reduction of the severity of parakeratosis. The suppression of PhK activity by curcumin (5) is linked to the resolution of psoriatic plaque. In another study, 20 patients with chronic plaque psoriasis received capsules with curcumin (5) 4.5 g every day for 12 weeks, followed by an observation period of 4 weeks [81]. At the end of the treatment only two patients showed 83-88% improvement. This study was limited by the small sample size and the lack of group control. In consequence, obtained results should be prudently evaluated.

More recently, Carrion-Gutierrez et al. [82] have investigated the effect of oral administration of curcumin (5) together with real visible light phototherapy (VLRT) or simulated visible light phototherapy (VLSLT) in 21 patients with plaque psoriasis. In contrast to the patients treated with VSLT (30%), patients treated with VLRT showed a remission to moderate or severe plaques (81%).

In another recent study, a microemulgel containing curcumin (5) reduced the mean redness score and thickness after 9 weeks of treatment. The microemulgel was remarkably more effective than the placebo in decreasing the the area of lesion and scaling lesions [83]. Niu et al. [84] confirmed the effects of curcumin (5) associated with phototherapy demonstrating a reduction of human skin keratinocytes proliferation, induction of apoptosis, inhibition of NF-κB activity and activation of caspase-8 and caspase-9.

5.7. Dodoneae polyandra Merr. & L.M. Perry

Dodoneae polyandra (Sapindaceae) is an Australian Northern Kaanju medicinal plant. D. polyandra leaf extract showed anti-inflammatory effects in an acute mouse ear oedema model induced by croton oil and 12-O-tetradecanoylphorbol-13-acetate (TPA) [85]. Two furanoclerodane diterpenoids, namely polyandric acid A (6) and B (7), were identified as main active components.

Both compounds demonstrated potent anti-inflammatory activity in the TPA-induced mouse ear oedema model [86]. Polyandric acid A (6) demonstrated to inhibit interleukin-1β production in an acute skin inflammation model, and to reduce ear thickness and myeloperoxidase accumulation in a chronic model [87]. A significant reduction of IL-6 secretion in primary neonatal human keratinocytes was also observed. Recently, the D. polyandra leaves resin has been inserted in an oil-in-water cream formulation at strength of 5% w/w [88]. Keratinocytes released high amounts of TNF-α and IL-1β, pro-inflammatory cytokines that in turn initiate several inflammatory responses and exacerbation of the symptoms. D. polyandra cream significantly reduced the production of IL-1β in the ear tissue, inflammatory cell infiltration and ear oedema. The release from the formulation of diterpenoids 6 and 7 was studied by using an in vitro test using a Franz diffusion cell with a synthetic polyvinylidene difluoride (PVDF) membrane as a measure of batch consistency. However, the amounts released of both compounds were low (approximately 4 and 2% after 8 hours for compounds 6 and 7, respectively). Many factors, including the physico-chemical properties of the sample, the composition of the vehicle and the interactions between them, influence these results.

5.8. Hypericum perforatum L.

Hypericum perforatum L. (also known as St. John’s wort) (Hypericaceae) is one of the most investigated medicinal plants worldwide in the last two decades. H. perforatum is known for its antidepressant effects, but it is also traditionally used as oil and tincture for the treatment of burns, cramps, decubitus, lumbago, and rheumatism. The European Medicines Agency accepts the use of H. perforatum for the symptomatic treatment of skin inflammations and minor wounds [89,90]. Anti-
inflammatory, and antimicrobial properties, and stimulation and differentiation of tissue growth have been reported for *H. perforatum* and its constituents hypericin (8) and hyperforin (9), suggesting their potential benefits for the treatment of skin diseases including psoriasis. *H. perforatum* extracts exhibited interesting antioxidant properties through different in vitro assays [91-95].

Hyperforin (9) has shown radical scavenging properties in human HaCaT keratinocytes irradiated with solar-simulated radiation. A cream with compound 9 significantly protected porcine ear skin after solar radiation [96].

The anti-inflammatory activity of different *H. perforatum* extracts and pure compounds were investigated in a mouse ear model [97]. In another study, hypericin (8) considerably inhibited IL-12 production in lipopolysaccharide-activated mouse macrophages with an IC₅₀ value of 1.45 µg/ml and the activation of the IL-12 gene promoter, suggesting that hypericin (8) negatively regulated IL-12 production at the transcription level [98]. Different mechanisms such as inhibition of COX-1, 5-lipoxigenase, and PGE2 production were described for the anti-inflammatory activity of hyperforin (9) [99-101].

*H. perforatum* and hyperforin (9) demonstrated anti-inflammatory activity on T cells and stimulated keratinocytes differentiation. In a recent study, *H. perforatum* ointment was used to treat ten patients with plaque-type psoriasis [102]. Erythema, thickness, and scaling were evaluated in determining PASI. *H. perforatum* ointment applied twice daily produced a reduction of PASI scores in mild plaque-type psoriasis. *H. perforatum* formulations were also studied for their potential side effects. Adverse effects of *H. perforatum* application may be irritation and/or sensitization and photosensitization. However, available clinical data suggests that the risk is low. In an irritation test, bath oil with *H. perforatum* extract was administered to the surface of the arm of volunteers. The skin areas were analysed for photometric measurements of erythema, and transepidermal water loss (TEWL). The bath oil with *H. perforatum* did not cause irritation [103]. Previously, Schempp et al. [104] demonstrated that topical application of *H. perforatum* oil or ointment on the forearms of volunteers caused no or only mild photosensitization, respectively. Despite available clinical data demonstrated the low phototoxic potential of topical hypericin (8) treatment, caution in the application of *H. perforatum* extracts should be used since higher penetration rates of compound 8 may occur in skin lesions. Moreover, in fair-skinned people and after protracted solar irradiation, improved susceptibility to the photosensitizing effects of preparations containing hypericin (8) may occur. The synergism in the activity of hypericin (8), hyperforin (9), and other constituents may elucidate the interesting biological properties of *H. perforatum*.

*H. perforatum* oil is still recommended in traditional medicine for treatment of burns and sunburns. However, only a few clinical trials have been conducted.

![Chemical structure of compounds 5-9.](image-url)
which allow an estimation of its beneficial value in applications relative to the treatment of other skin diseases.

5.9. *Illicium verum* Hook. f.

*Illicium verum* (Illiciaceae) is a plant originally distributed in most countries of Asia, commonly known as star anise. *H. verum* fruits are used in Eastern Asian traditional medicine for treating asthma, colic, stomach ailments, skin inflammation, and rheumatic pain [105-107].

The anti-inflammatory activity of *I. verum* was demonstrated in two studies in which plant extract suppressed chemokines, cytokines, and adhesion molecules in TNF-α/IFN-γ-stimulated HaCaT cells and atopic dermatitis-like skin lesions [108, 109]. In another study, the inhibitory effects of *I. verum* extract and two constituents, namely *p*-anisaldehyde (10) and trans-anethole (11) (Fig. 3), on IFN-γ-induced ICAM-1 expression and their regulatory mechanisms were investigated in the HaCaT cell line [110]. Specifically, *I. verum* significantly inhibited IFN-γRα expression and consequent phosphorylation of Jak2, which is predominantly autophosphorylated in IFN-γ-treated HaCaT cells, and STAT1. *I. verum* decreased ICAM-1 mRNA and protein.

Studies have shown that suppressor of cytokine signalling (SOCS) proteins are key physiological regulators of inflammation. Among SOCS proteins, SOCS1 inhibits IFN-γ signaling through the Jak/STAT pathway [111]. Sung et al., [110] demonstrated that *I. verum* increased the expression of SOCS1, which attenuated the phosphorylation of Jak2, with a consequent inhibition of the phosphorylation of STAT1 and reduction of the expression of inflammatory genes. Moreover, *I. verum* inhibited the IFN-γ-induced adherence of Jurkat T cells to HaCaT cells by inhibition of the expression of ICAM-1. The *I. verum* tested compound *p*-anisaldehyde (10) demonstrated to inhibit ICAM-1 expression and adherence of T cells. This activity is comparable to that demonstrated by trans-anethole (11).

5.10. Indigo Naturalis

*Indigo naturalis* is a Chinese herb, also known as “Qing dai”, prepared from the leaves of *Baphicacavus cusia*, *Isatis indigotica*, *Indigofera tinctoria*, and *Polygonum tinctorium*. *I. naturalis* has been traditionally used to treat various inflammatory disease and dermatosis [14]. Topical application of *I. naturalis* to treat more than 10,000 patients with psoriasis considerably improved skin psoriasis [112,113].

Lin et al. [112] evaluated the effectiveness and safety of *I. naturalis* on treating plaque-type psoriasis in fourteen patients affected by psoriasis. The histological change in skin tissues was also object of this work. Patients were treated with *I. naturalis* ointment or vehicle ointment for 8 weeks.

At the end of treatment, induration, scaling, erythema and clearing percentage were evaluated. A clear improvement of skin histology was achieved. The topical application of *I. naturalis* ointment may be a safe and effective therapy for the treatment of psoriasis. Its action is mediated, at least in part, by modulating the differentiation and proliferation of keratinocytes and by inhibiting the infiltration of T lymphocytes and, consequently, the inflammatory reactions observed in lesions.

Successively, *I. naturalis* treatment showed an increased involucrin expression and a decreased proliferating cell nuclear antigen (PCNA) in psoriatic lesions [114]. Moreover, *I. naturalis* extract (10-500 µg/ml) was applied to keratinocytes and cell viability was determined. After the treatment, cultured keratinocytes decreased. An increase of the G0/G1 arrest was observed in a dose-dependent manner. In treated keratinocytes, a decrease in PCNA-stained nuclei and an increase in cytosolic involucrin were evident. These results demonstrated the anti-psoriatic effects of *I. naturalis* related, at least in part, to the modulation of keratinocytes differentiation and proliferation.

The ability of *I. naturalis* extract to increase the expression of claudin-1 and tight junction (TJ) function was investigated in human keratinocytes and psoriatic lesions [115]. *I. naturalis* was able to up-regulate both mRNA and protein expression of claudin-1 and function of TJ in a concentration-dependent manner. *I. naturalis* increased also the activity of protein kinase C (PKC).

*I. naturalis* and indirubin (12), the major *I. naturalis* active constituent, were investigated in primary and immortalized keratinocytes for their potential to decrease the expression of CDC25B that demonstrated to have an important role in the hyper-proliferation of keratinocytes [116,117].

Both *I. naturalis* and indirubin (12), tested at different concentrations, down-regulated the expression of CDC25B at both the mRNA and protein levels. The growth-dependent expression of CDC25B was demonstrated by the increased expression in serum-stimulated
and immortalized keratinocytes. *I. naturalis* and its main constituent 12 also inhibited the activation of EGF receptor that is highly expressed in psoriatic lesions.

### 5.11. *Mahonia aquifolium* (Pursh) Nutt.

*Mahonia aquifolium* is a species of flowering plant in the family Berberidaceae, native to western North America. This plant is traditionally used for the treatment of inflammatory diseases of the skin, such as psoriasis. The use of *M. aquifolium* for medical purposes dates back to the Indian tribes, who used to treat dyspepsia. Its extract has analgesic, anti-inflammatory, antioxidant and hepatoprotective properties. These properties are mainly due to the presence of alkaloids as berberine, palmatine, jarttorrhizine, berbamine and oxytocanthine [118].

Berberine (13) is an isoquinoline alkaloid with a great variety of effects including anti-inflammatory properties. Cyclooxygenase-2 (COX-2) plays a key role in the synthesis of prostaglandins, thus causing the onset of inflammation. Berberine (13) reduced the levels of prostaglandin E2 in a dose-dependent manner by inhibition of COX-2 expression [119].

The oral ingestion of berberine (13) for four weeks reduced the presence of TNF-α, interferon gamma (IFN-γ) and interleukin-1 alpha (IL-1α) [120]. It also seems to have an inhibitory effect against the release of nitric oxide (NO), an important mediator of inflammation [121]. The products of the lipoxygenase metabolism play an important role in the pathogenesis of psoriasis. Some benzylisoquinoline alkaloids isolated from *M. aquifolium* were tested for their potential lipoxygenase inhibitory activity. Among these, berberine (13) and oxycanthine were the most active. Moreover, both alkaloids are able to inhibit lipid peroxidation. These data suggest that inhibition of the peroxide tone could play an important role in the inhibition of lipoxygenase. This mechanism could explain the efficacy of *M. aquifolium* extract in the treatment of psoriasis [122].

Wiesenauer *et al.* [123] examined *M. aquifolium* bark extract for the treatment of psoriasis. Eighty-two patients were told to apply two types of ointment (verum/placebo) one to the left side of their body the other to the right. After 4 weeks, patients as well as physicians assessed the therapy's success on a three-level ordinal rating scale.

In a randomized clinical trial, patients were subjected to two different treatments: one cream formulated with *M. aquifolium* extract and the other one with calcipotriol and fluticasone propionate.

Out of 32 participants, 30 patients successfully completed the experience, 27 patients achieved an improvement of the disease, with passage of state from severe to moderate and only three patients did not see any improvement [124]. In a subsequent study, 33 participants with skin lesions on both arms were assigned to two groups. In the first group, *M. aquifolium* cream was applied on one arm and placebo on the other one. In the second group, a cream of calcipotriol and tazarotene was applied on one side, and placebo on the other side. After four weeks of treatment, an improvement in redness and irritation was observed [125].

A randomized double-blind trial, which involved the use of a cream containing an extract of *M. aquifolium* (consisting mainly in psoberine), was conducted in the US and Canada. Two hundred subjects participated either using the homeopathic product containing a *M. aquifolium* extract (cream Reliéva) or placebo twice a day for 12 weeks of treatment. The PASI was evaluated at the beginning and end of the treatment. The Quality of Life Index (QLI) was evaluated at 0, 4, 8, and 12 weeks.

Improvements in both PASI and QLI in the *M. aquifolium*-treated group were observed. Infrequent side effects such as rash when applying the cream and clothing stain were detected [126].


*Memecylon malabaricum* (Melastomataceae) is a shrub or small tree with blue flowers. *M. malabaricum* is traditionally used for the treatment of skin diseases including psoriasis [127]. The hydroalcoholic extract, aqueous extract of *M. malabaricum* leaves and their fractions were investigated for their potential antipsoriatic properties.

Decoction was fractionated with water saturated n-butanol to give an n-butanol and a water fraction. Hydroalcoholic extract was fractionated with chloroform and water saturated n-butanol to give chloroform, n-butanol and water fractions. Samples were studied in vitro by using HaCaT cells, for their lipoxygenase and thymidine phosphorylase inhibitory activity, and in vivo by mouse-tail test [128]. *M. malabaricum* hydroalcoholic extract and its water fraction caused maximum orthokeratosis in the mouse tail test. Except for hydroalcoholic extract, all tested samples produced a reduction in epidermal thickness. The chloroform fraction of hydroalcoholic extract revealed the maximum
activity against HaCaT cells. *M. malabaricum* samples demonstrated to inhibit LOX with a decreasing activity of samples in the order water fraction of decoction > decoction > water fraction of hydroalcoholic extract > butanol fraction of decoction > hydroalcoholic extract. High levels of the thymidine phosphorylase enzyme are found in psoriatic lesions. *M. malabaricum* decoction was the only active extract in this test. Quercetin and rutin were identified as main constituents of *M. malabaricum* extracts and fractions.

5.13. *Picea mariana* (Mill.) B.S.P.

*Picea mariana* (Pinaceae) is a North American species traditionally used for its anti-inflammatory properties. Its resin is used to promote healing of wounds and to treat skin rashes purulent wounds, and burns [129]. Moreover, *P. mariana* improves several inflammatory skin disorders such as psoriasis. In a recent study, the ability of *P. mariana* bark extract to inhibit the TNF-α-induced effects on psoriatic keratinocytes (PK) in comparison with normal human keratinocytes (NHK) was investigated. *P. mariana* extract, which contains several classes of compounds such as simple phenols, phenolic acids, neolignans and lignans, flavonoids, and proanthocyanidins, showed interesting anti-inflammatory effects against lesional psoriatic keratinocytes [130]. In particular, the extract down-regulated the NF-κB pathways associated with TNF-α stimulation, reduced the NO production and the expression of inducible nitric oxide synthase (iNOS), ICAM-1 expression, IL-6 and VEGF production, IL-8 and fractalkine formation, and trappin-2/elafin generation. Previous works reported the ability of some main constituents of *P. mariana* extract, such as *p*-coumaric acid (14), pinnoresinol (15), and resveratrol (16), to inhibit the production of NO through the inhibition of the expression of iNOS mRNA [131-133].

5.14. *Viola tricolor* L.

*Viola tricolor* is a medicinal plant used in European traditional medicine for the treatment of inflammatory skin disorders including psoriasis [32,134]. Its traditional use is described in the Pharmacopoeia of Europe [135]. The analysis of literature revealed antioxidant, anti-inflammatory, and antimicrobial properties of *V. tricolor* [136-140]. The anti-inflammatory and antinociceptive activities of a gel containing the extract of *V. tricolor* flowers were recently investigated on thermal burn induced by UVB irradiation [141]. Paw edema, neutrophilic cell infiltration, and static and dynamic mechanical allodynia were used as models. The gel was studied in order to evaluate its stability by analyzing viscosity, pH, and organoleptical aspects. Changes in the mechanical allodynia models, paw edema, and myeloperoxidase activities were found after treatment with the gel containing *V. tricolor*. No significant changes were revealed in the stability study (studies were carried out at temperature below 25 °C).

The main classes of constituents identified in *V. tricolor* are catechins, cumarins, flavonoids, phenylcarboonic acids, polysaccharides, and salicylic acid derivatives [138,139,142]. *V. tricolor* is also a rich source of small disulphide-rich peptides, called cyclotides. These molecules, which usually consist of 28-37 amino acid residues, possess many biological activities, including antimicrobial, anti-HIV, uterotonic, and hemolytic properties. Cyclotides are also described as promising immunosuppressive agents [143-145].

Fig. (3). Chemical structure of compounds 10-16.
Since lymphocytes play an important role in the inflammatory diseases, recently Hellinger et al. [146] examined the effect of a *V. tricolor* aqueous extract on the function and cell division of activated human lymphocytes. The extract inhibited in a concentration-dependent manner the cell division of activated T-lymphocytes. Authors demonstrated that this effect is not cytotoxic. In fact, the extract induced overtime neither necrosis nor apoptosis. External stimuli start the secretion of the growth factor IL-2 that consecutively promotes interaction with its receptor that is upregulated on activated T-cells. *V. tricolor* inhibited the secretion of IL-2 and reduced the production of IFN-γ and TNF-α, but not affected the expression of the IL-2 surface receptor and the level of degranulation activity.

The phytochemical screening confirmed the presence of cyclotides as active compounds. Cyclotides demonstrated to induce a reduction of the IL-2 cell surface marker expression and IL-2 cytokine expression and secretion [147].

**CONCLUSION**

Psoriasis is a very multifaceted disease involving complex pathogenic interactions between the innate and adaptive immune system. Current treatment is aimed at relieving symptoms such as itching, flaking, dry mucous membranes and their sensitivity to acidic foods or relational problems due to exposure of body parts with conspicuous spots. Topical treatments with glucocorticosteroids, vitamin D derivatives, or combinations of both are used to manage mild disease while calcineurin inhibitors are used to maneg difficult areas, such as the intertriginous areas or the face. Several adverse effects, practicability, and convenience often limit the use of these drugs. Patients with moderate-to-severe diseases are treated with a combination of phototherapy and systemic therapy.

Unfortunately, this therapy is usually used for short-term control of the disease and the long-term use of PUVA is limited by its carcinogenic potential.

In the past decade, plants have demonstrated to play a significant role in the discovery of new agents for the treatment of psoriasis. Many plants and different classes of phytochemicals, mainly flavonoids, have been identified for their interesting antioxidant effects. Skin is a target of oxidative stress mainly due to ROS originating from the environment and skin metabolism itself. Thus, the possibility to use natural antioxidant agents is of great interest.

The most promising results were obtained with *Aloe vera*, *Boswellia serrata*, *Curcuma longa*, *Indigo naturalis*, *Mahonia aquifolium*, and *Viola tricolor* and their main constituents namely boswellic acids, curcumin, berberine, and indirubin. Their anti-inflammatory, antioxidant, anti-proliferative, immuno-modulatory, wound healing and/or anti-pruritic properties may partly explain the reported effects of these natural products. These multiple effects make these plant extracts and/or pure compounds potentially become suitable for the treatment of psoriasis. Moreover, in addition to monotherapeutical applications of natural compounds, it is possible to prospect the use of combinations with well-established immunosuppressive drugs because most of these substances are associated with side effects if given at an effective dosage. Then, the dose, and consequently the side effects, can be reduced below a certain level. Further studies on these possible combinations are necessary to highlight the potentiality in the treatment of psoriasis.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
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<tr>
<td>DLQI</td>
<td>Dermatology life quality index</td>
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<tr>
<td>EC₅₀</td>
<td>Half maximal effective concentration</td>
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<tr>
<td>IC₅₀</td>
<td>50% inhibitory concentration</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IMQ</td>
<td>Imiquimod</td>
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<tr>
<td>iNOS</td>
<td>Inducible nitric oxide synthase</td>
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<tr>
<td>JAK</td>
<td>Janus kinase</td>
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<tr>
<td>LOX</td>
<td>Lipooxygenase</td>
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<tr>
<td>MAPK</td>
<td>Mitogen-activated protein kinases</td>
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<tr>
<td>NF-κB</td>
<td>Nuclear factor kappa B</td>
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<tr>
<td>NHK</td>
<td>Normal human keratinocytes</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
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<td>PASI</td>
<td>Psoriasis area severity index</td>
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<td>PCNA</td>
<td>Proliferating cell nuclear antigen</td>
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<tr>
<td>PhK</td>
<td>Phosphorylase kinase</td>
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<td>PK</td>
<td>Psoriatic keratinocytes</td>
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<td>PUVA</td>
<td>Psoralen plus ultraviolet light therapy</td>
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<tr>
<td>PVDF</td>
<td>Polyvinylidene difluoride</td>
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<tr>
<td>QLI</td>
<td>Quality of life index</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<td>SARs</td>
<td>Structure-activity relationships</td>
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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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