

# Topically Used Herbal Products for the Treatment of Psoriasis – Mechanism of Action, Drug Delivery, Clinical Studies

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## Key words

- Psoriasis
- herbal products
- keratinocyte hyperproliferation
- inflammatory reaction
- skin barrier
- herbal drug delivery systems

## Abstract

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Psoriasis is a chronic inflammatory skin disease characterized histologically by hyperproliferation and aberrant differentiation of epidermal keratinocytes. A wide range of conventional medical therapies to treat psoriasis is established, from topical therapies and systemic medications through to phototherapy or combinations of those. However, most of these therapies have a limited efficacy and may cause a number of side effects, including cutaneous atrophy, organ toxicity, carcinogenicity, and broadband immunosuppression, which are restricting their long-term use. Therefore, it would be desirable to use herbal products as an alternative treatment for psoriasis that causes fewer side effects. For this purpose,

several electronic databases and literature references were used to summarize the current knowledge acquired on the basis of animal studies and clinical trials regarding herbal products used to treat psoriasis topically. This review discusses the mechanisms of herbal products activities through (1) inhibition of the keratinocyte hyperproliferation and inducing apoptosis, (2) inhibition of immune-inflammatory reaction, (3) suppression of phosphorylase kinase (PhK) activity, and (4) inhibition of the hedgehog (Hh) signaling pathway. Moreover, the penetration of herbal products through the psoriatic skin barrier, novel herbal drug delivery systems in psoriasis treatment, and possible adverse effects of herbal therapy are discussed.

## Introduction

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Psoriasis is a chronic autoimmune human skin disorder that is characterized by excessive proliferation of keratinocytes, scaly plaques, severe inflammation, and erythema [1]. A wide range of conventional medical therapies to treat psoriasis is established, from topical therapies [steroids, vitamin D analogues, psoralen, 5-aminolevulinic acid, salicylates, fumaric acid esters, anthralins (dithranol), tacrolimus, retinoids – e.g. tazarotene] and systemic medications (methotrexate, cyclosporine, retinoids, 6-thioguanine, mycophenolate mofetil, troglitazone and new biologic agents, such as adalimumab, alefacept, efalizumab, etanercept, infliximab), through to phototherapy or combinations of those [2]. However, most of these therapies cause a number of side effects, and limited in efficacy, inconvenience, cutaneous atrophy, organ toxicity (hepatotoxicity, nephrotoxicity, teratogenicity), carcinogenicity, and broadband immunosuppression, which are limiting their long-term use [3,4]. In turn, a short-term

treatment of psoriasis causes its remission after finishing the treatment or only relieves the patient's condition. Moreover, psoriasis is often accompanied by other diseases, such as depressive illness, cardiovascular disease, and a seronegative arthritis known as psoriatic arthritis [5]. Therefore, the invention of new alternative treatments for psoriasis causing fewer side effects would be desirable. It seems that several herbal drugs can meet these requirements and have to be seen as promising new agents for psoriasis treatment [6]. Herbal products are greatly accepted by patients because they are believed to be safer than conventional therapeutics. Moreover, herbal products present a great structural diversity and multidirectional mechanisms of action, which is not commonly seen in synthetic compounds. Herbal drugs may become an effective treatment for psoriasis, causing lower costs and less side- or toxic effects in comparison to other therapies. Therefore, researchers are still looking for novel herbal products and/or their active constituents,

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which potentially could be used for the treatment of psoriasis instead of synthetic drugs.

The goal of this review is to summarize the knowledge based on animal studies and clinical trials regarding herbal products used for the topical treatment of psoriasis and to characterize their mechanisms of action. Penetration of herbal products through the psoriatic skin barrier, novel herbal drug delivery systems in psoriasis treatment, and possible adverse effects of herbal therapy are also discussed.

## Methods



### Search strategy

PubMed, Scopus and Google Scholar were searched for articles published from 1995 up to the present. Search terms included “herbal products and psoriasis”, “herbal treatments for psoriasis”, “topical herbal medication for psoriasis”, and “herbal drug delivery systems in psoriasis treatment”. References from reviews about herbal products and psoriasis were examined for additional articles and case reports. A manual search was also conducted, based on citations in scientific literature.

### Inclusion and exclusion criteria

Selection criteria included articles which are examining herbal products used for the topical treatment of psoriasis by means of animal studies and clinical trials, and are comparing herbal products treatment vs. control treatments (placebo or active therapy). Other forms of psoriasis treatment than topical administration of herbal products (e.g. oral, systemic) were excluded from the study. Also publications in languages other than English were excluded.

### Pathology of Psoriasis

The pathophysiology of psoriasis involves both skin cells and immune cells. Psoriasis is typically characterized as inflamed skin with surface scales, thickening of the epidermis (acanthosis; granular layer is reduced or absent) caused by parakeratosis, which is a consequence of nuclei retention in SC keratinocytes caused by abnormal differentiation and hyperproliferation of epidermal keratinocytes [1,7]. Some scientific reports consider nitric oxide (NO), released from keratinocytes at high concentrations, as a key inhibitor of cellular proliferation and inducer of cell differentiation *in vitro*. Although a high-output NO synthesis is suggested by the expression of inducible NO synthase (iNOS), mRNA, and proteins in psoriasis lesions, the pronounced hyperproliferation of psoriatic keratinocytes may indicate that iNOS activity is too low to effectively deliver antiproliferative NO concentrations [8]. As a consequence, the impairment of corneocyte differentiation, including an impaired formation and secretion of lamellar body contents and the processing of lamellar body contents into lamellar bilayers, causes a reduction in the psoriatic skin barrier function [9]. Moreover, skin barrier problems in psoriasis are not only the excessive growth and aberrant differentiation of corneocytes but also almost absent normal moisturizing factors (NMFs) like water, an imbalance of skin lipids (rise in the levels of cholesterol and fall in the levels of ceramides), and dry and sensitive skin [10].

The role of the immune system and its interactive network of leukocytes and cytokines in disease pathogenesis was also described [11,12]. Psoriatic lesions are highly infiltrated with immune cells, most notably CD3<sup>+</sup> T cells and CD11c<sup>+</sup> dendritic cells [13,14].

Proinflammatory cytokines produced by these cells, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-17 (IL-17), IL-20, IL-22, IL-23, IL-12, and IL-1b, have been linked to the pathogenesis of psoriasis through causing keratinocytes hyperproliferation [7]. Moreover, IFN- $\gamma$  and IL-15 seem to increase the apoptotic resistance of the keratinocytes [15,16]. Also growth factors and genetic factors like transforming growth factor (TGF)- $\beta$ , toll-like receptor (TLR)-2, signal transducer and activator of transcription (STAT-3), coiled-coil alpha-helical rod protein 1 (CCHCR1), steroidogenic acute regulatory protein (StAR), and vitamin D receptor (VDR) are suggested to be the most critical factors governing the exacerbation of psoriasis [17,18]. The essential transcription factor in psoriasis, nuclear factor kappa B (NF- $\kappa$ B), has been shown to be a key regulatory element occurring in a variety of immune and inflammatory pathways, in cellular proliferation and differentiation, and in apoptosis [19]. An imbalance between the proapoptotic and antiapoptotic activities of NF- $\kappa$ B proteins has been demonstrated to cause differentiation and hyperproliferation in psoriatic lesions rather than in normal cells [20].

### Topically Used Herbal Products for the Treatment of Psoriasis

Many herbal topical formulations have been marketed worldwide to prevent psoriasis [21]. There are many advantages of using natural drugs, including patient compliance, less side-effects, easy availability, low-costs, and more than one mode of biochemical action for psoriasis treatment. Therefore, researchers are searching for new herbal products, which have the potential to be an alternative for synthetic drugs in psoriasis therapy.

### Animal-based studies

Herbal products with an anti-psoriasis potential tested in animal-based studies are summarized in **Table 1**. Most of the *in vivo* studies performed in animals are based on a mouse tail model of psoriasis, introduced by Jarrett and Spearman [22]. The model is based on the induction of orthokeratosis in those parts of the adult mouse tail, which have normally a parakeratotic differentiation. Antipsoriatic drug activity is defined by the percentage increase of orthokeratotic regions after topical drug treatment of a mouse tail. Ethanolic extract of *Aloe vera* leaf gel [23], ethanolic extract of *Nigella sativa* [24], ethanolic extract of *Rubia cordifolia* [25], methanol extract of *Smilax china* and the isolated flavonoid quercetin [26], *Thespesia populne* extract [27], hydro alcoholic extract of *Wrightia tinctoria* [28], and baicalin isolated from *Scutellaria baicalensis* [29] were assessed for their antipsoriatic activity using the mouse tail model. All of them exhibited a significant percentage reduction of relative epidermal thickness, promoted epidermal differentiation and normal keratinization of keratinocyte, produced significant orthokeratosis, and exhibited a higher antipsoriatic activity as the positive control (tretinoin 0.05%, tazarotene 0.1%, dithranol 1%, tacrolimus 0.03%, retinoic acid). A topically administered ointment containing methanol extract of *Kigelia africana* induced a significant and dose-dependent increase in orthokeratosis in parakeratotic areas of albino mouse tails, with significant effects on the epidermal thickness compared to the vehicle control [30].

Only two studies were based on an UVB-induced model of psoriasis. UVB-induced photodermatitis in rats has been proposed as an experimental model for *Psoriasis vulgaris* by Nagakuma et al. [32]. The model is based on the induction of dark-brown scale on the erythematous lesion after UVB irradiation. Singhal and Kan-

**Table 1** Herbal products used for the topical treatment of psoriasis – animal studies.

Plant	Animal	Model of the study	Pharmacological data	Effect	Ref.
<i>Cassia tora</i>	albino mice	UVB-induced psoriasis	methanolic <i>C. tora</i> extract (0.05 %, 0.1 %, 0.2 %) in O/W creams; positive control: tretinoin (0.05 %) in base cream; treatment: single dose of creams with different concentrations of extract/tretinoin/cream base/crude extract	O/W creams with extracts exhibited a significant reduction in percentage of relative epidermal thickness as compared to tretinoin	[31]
<i>Kigelia africana</i> (sausage tree)	albino mice	mouse tail model of psoriasis	ointments containing 200, 100 and 50 mg/ml of methanol extracts from stem, leaves, and fruit of <i>K. africana</i> ; control: vehicle and placebo; treatment: 0.1 ml of the ointment, contact time of 2–3 h, once daily for 2 weeks	stem methanol extracts induced orthokeratosis in parakeratotic areas of mouse tail with significant effects on epidermal thickness	[30]
<i>Nigella sativa</i>	albino mice	mouse tail model of psoriasis	95 % ethanolic extract of <i>N. sativa</i> desolved in water; ratio 1 : 2; control: placebo; positive control: tazarotene gel (0.1 %); treatment: once daily for 14 days, contact with the skin for 2 h	extract produced equivalent epidermal differentiation in degree of orthokeratosis as tazarotene	[24]
<i>Rubia cordifolia</i>	BALB/c mice	mouse tail model of psoriasis	ethanolic extract was fractioned sequentially with hexane, ethyl acetate (EA), n-butanol, and water; 1 %, 2 % and 5 % EA fraction of extract was formulated into gel; control: placebo; positive control: 1 % w/w dithranol in gel; treatment: twice a day, 7 times a week for 4 consecutive weeks	EA fraction dose-dependently increased granular layer and epidermal thickness; potency of keratinocyte differentiation 5 % EA fraction is similar to that of dithranol gel	[25]
<i>Scutellaria baicalensis</i>	BALB/c mice	mouse tail model of psoriasis	creams with 1 %, 3 % and 5 % baicalin isolated from <i>S. baicalensis</i> ; control: placebo; negative control: 2,4-dinitrofluorobenzene-induced contact hypersensitivity (CHS); positive control 1: 0.1 % tazarotene cream; positive control 2: 0.03 % tacrolimus ointment; treatment: twice daily for 4 weeks	creams with baicalin inhibit CHS reaction at a less significant magnitude than that of tacrolimus ointment; 5 % baicalin cream promotes epidermal differentiation and normal keratinization of keratinocyte in mouse similar to that of tazarotene cream	[29]
<i>Smilax china</i>	Swiss albino mice	mouse tail model of psoriasis	methanol extract and isolated flavonoid quercetin; positive control: retinoic acid	flavonoid quercetin shows significant orthokeratosis, anti-inflammatory, and maximum antiproliferant activities	[26]
<i>Thespesia populne</i>	Wistar rats	mouse tail model of psoriasis	cream with 100 mg of each extract (ethanolic, pet-ether, butanolic, ethyl acetate) and 50 mg of each isolated compound (TpF-1 and TpF-2 as flavonoids, TpS-2 as sterole); positive control: 0.05 % tretinoin cream; treatment: once daily, 5 times a week for 2 weeks	pet-ether extract and TpF-2 increased orthokeratotic region	[27]
<i>Wrightia tinctoria</i>	albino mice	mouse tail model of psoriasis	hydro alcoholic extract of <i>W. tinctoria</i> leaves; control: vehicle; positive control: isotretinoic acid; treatment: once daily for 14 days	extract produced significant degree of orthokeratosis compared to isotretinoic acid and increased the epidermal thickness compared to control	[28]

sara [31] showed antipsoriatic activities of O/W creams containing methanolic extract of *Cassia tora* leaves as well as of the crude extract, by using UVB-induced psoriasis in rats. Both of them exhibited a significant percentage reduction of relative epidermal thickness and spleen index as compared to 0.05 % tretinoin as positive control. Also irradiated rat skin treated with SUEx GEL containing aqueous extract of the bark of *Pongamia pinnata* showed a significant reduction in the total epidermal thickness and retention of the *Stratum granulosum* compared to ointment base and placebo group [33]. However, there is no animal model that could replace clinical studies. Moreover, positive results of animal-based studies are not always proved in clinical trials. They can only help in the initial determination of new herbal products, which may proceed to further stages of clinical trials and become useful drugs for the treatment of psoriasis in the future.

### Clinical studies

Herbal products with anti-psoriasis potential tested in clinical studies are listed in **Table 2**. Topical application of cream with 10 % *Mahonia aquifolium* extract [34], 0.03 % *Camptotheca acuminata* nut [35], *Aloe vera* extract [36], oleoresin from *Copeifera langsdorffii* (5 %) ointment [37], and cream with *Persea americana*

oil [38] showed significantly greater improvements in psoriatic treatment compared with calcipotriol and fluticasone propionate mixture, hydrocortisone, triamcinolone acetonide, and calcipotriol ointment, respectively. In turn, *Aloe vera* cream [39], *Baphicacanthus cusia* ointment [40], *Camptotheca acuminata* nut extract in tincture/gel/ointment [41], *Curcuma longa* microemulgel [42], *Hypericum perforatum* ointment [43], *Indigo naturalis* ointment [44], *Indigo naturalis* extract in oil [45], *Mahonia aquifolium* cream [46], *Mahonia aquifolium* bark extract ointment [47], *Strobilanthes formosanus* ointment [48], and cream with capsaicin from *Capsicum frutescens* [49] were found to be significantly more effective than the vehicle control group. There are also literature data showing no significant difference between herbal products and drug/placebo treatment. The effect of *Mahonia aquifolium* ointment appears to be less potent than that of dithranol [50]. *Aleurites moluccana* (Kukui nut) oil [51], *Aloe vera* gel [52], as well as ointment and lotion containing 20 % kunzea oil [53] showed no significant difference compared to a placebo psoriasis treatment.

The clinical studies presented in **Table 2** contain some shortcomings, which ultimately do not diminish the value of these limited research works. **Table 2** reports 10 clinical trials, which

**Table 2** Herbal products used for the topical treatment of psoriasis – clinical studies.

Plant	Type of clinical study	Participants	Treatments	Effect	Ref.
<i>Aloe vera</i>	placebo-controlled, double-blind clinical trial	60 patients (18–50 years) with slight to moderate chronic plaque psoriasis and PASI scores between 4.8–16.7	<ul style="list-style-type: none"> <li>▶ <i>A. vera</i> extract (0.5%) in hydrophilic cream (n = 30);</li> <li>▶ base cream (n = 30);</li> <li>3 times daily (without occlusion) for 5 consecutive days per week for 16 weeks</li> </ul>	<i>A. vera</i> cream had cured 25/30 patients compared to the placebo cure rate of 2/30 resulting in significant clearing of the psoriatic plaques and decreased PASI score to a mean of 2.2	[39]
<i>Aloe vera</i>	randomized, comparative, double-blind clinical trial	80 patients with mild to moderate plaque psoriasis	<ul style="list-style-type: none"> <li>▶ <i>A. vera</i> cream (70% aloe mucilage) (n = 40);</li> <li>▶ 0.1% triamcinolone acetonide cream (n = 40);</li> <li>twice daily for 8 weeks</li> </ul>	<i>A. vera</i> cream was found to be more effective than triamcinolone acetonide cream	[36]
<i>Baphicacanthus cusia</i>	vehicle-controlled clinical trial	14 patients with chronic plaque psoriasis	<ul style="list-style-type: none"> <li>▶ indigo naturalis ointment (20% <i>B. cusia</i> powder);</li> <li>▶ vehicle ointment;</li> <li>once daily for 8 weeks</li> </ul>	significant reduction of psoriasis compared to control	[40]
<i>Capsicum frutescens</i>	comparative, vehicle-controlled, double-blind clinical trial	44 patients with moderate to severe psoriasis	<ul style="list-style-type: none"> <li>▶ cream with capsaicin isolated from <i>C. frutescens</i>;</li> <li>▶ vehicle cream;</li> <li>once a day for 6 weeks</li> </ul>	capsaicin cream was found to be significantly more effective than control	[49]
<i>Curcuma longa</i>	randomized, prospective intra-individual, right–left comparative, placebo-controlled, double blind clinical trial	40 patients (18–60 years) with mild to moderate plaque psoriasis	<ul style="list-style-type: none"> <li>▶ turmeric (hydroalcoholic <i>C. longa</i> extract) microemulgel;</li> <li>▶ vehicle;</li> <li>twice a day for 9 weeks</li> </ul>	progressive reduction of thickness, followed by decrease erythema, pruritus, resulting in moderate to acceptable improvement; in some cases, significant resolution of psoriatic lesions	[42]
<i>Hypericum perforatum</i>	right–left comparative, vehicle-controlled, single blinded (only patients were blinded) clinical trial	10 patients (20–55 years) with mild plaque psoriasis	<ul style="list-style-type: none"> <li>▶ <i>H. perforatum</i> (5%) ointment;</li> <li>▶ vehicle ointment;</li> <li>twice daily for 4 weeks</li> </ul>	improvement in clinical scores was reported with <i>H. perforatum</i> ointment compared with placebo group	[43]
<i>Indigo naturalis</i>	randomized, vehicle-controlled, observer-blind clinical trial	31 patients with symmetrically comparable psoriatic nails	<ul style="list-style-type: none"> <li>▶ refined <i>I. naturalis</i> extract in oil (Lindioil);</li> <li>▶ olive oil;</li> <li>twice daily for the first 24 weeks</li> </ul>	reduction of NAPSIS scores for the Lindioil group was superior to the reduction in the control group	[45]
<i>Mahonia aquifolium</i>	placebo-controlled, double-blind clinical trial	200 patients with mild to moderate psoriasis	<ul style="list-style-type: none"> <li>▶ cream with 10% <i>M. aquifolium</i> extract;</li> <li>▶ placebo;</li> <li>twice a day for 12 weeks</li> </ul>	significant improvements in PASI and QLI in the <i>Mahonia</i> -treated group compared with the control group	[46]
<i>Strobilanthes formosanus</i>	randomized, vehicle-controlled, observer-blind clinical trial	42 patients with chronic plaque psoriasis	<ul style="list-style-type: none"> <li>▶ indigo naturalis (1.4%) ointment;</li> <li>▶ vehicle ointment;</li> <li>once a day for 12 weeks</li> </ul>	31 of 42 patients experienced clearance or near clearance of psoriasis after herbs ointment treatment	[48]
<i>Persea americana</i> (Avocado)	randomized, prospective, right–left comparative clinical trial	13 patients (10 men and 3 women) with chronic plaque psoriasis	<ul style="list-style-type: none"> <li>▶ cream with vitamin B12 and avocado oil;</li> <li>▶ vitamin D<sub>3</sub> analog calcipotriol;</li> <li>twice daily for 12 weeks</li> </ul>	cream with vitamin B12 and avocado oil was effective as calcipotriol cream with regard to PASI score	[38]

PASI – Psoriasis Area and Severity Index; QLI – Quality of Life Index; NAPSIS – Nail Psoriasis Severity Index

were carried out on groups consisting of 10–20 patients (3/10), 30–50 patients (4/10), 60–80 patients (2/10), and more than 100 patients (1/10). In practice, the first phase of clinical trials involved usually 100–500 participants, because only studies carried out with more than 100 patients provide the opportunity for statistical analyses. Only one of the above described clinical trials was performed on 200 subjects. The participants in this randomized, double-blind, placebo-controlled study used either the topical cream Reliëva (a homeopathic product containing a proprietary *M. aquifolium* extract) or control (placebo) [46]. Other clinical trials included a nonrepresentative number of participants and therefore the conclusions of these studies cannot be generalized to the entire population affected by psoriasis. Moreover, participants (men and women) aged from 18 to 60 years

with mild chronic plaque psoriasis (1/10), mild to moderate chronic plaque psoriasis (4/10), moderate to severe chronic plaque psoriasis (1/10), and chronic plaque psoriasis without determining psoriasis area (4/10) were condensed in clinical trials. Plaque psoriasis, also known as *Psoriasis vulgaris*, affects about 90% of all cases of psoriasis, which makes the described research potentially useful to treat this type of psoriasis. These clinical studies included randomized trials (5/10), vehicle-controlled (8/10), comparative (5/10), observer-blind (2/10), single-blind (1/10), and double-blind clinical trials (5/10). It is known that only well-controlled double-blind clinical trials can prove the efficacy of herbal products in psoriasis treatment. Moreover, such research is expensive, long lasting and requires a special permission from the regulatory authorities. Also compared to multi-



directional synthetic drug studies, clinical and toxicological studies to prove the efficacy and safety of herbal products are rare. Several factors might contribute to the explanation of such discrepancies, for example a lack of standardization and quality control of the herbal products used in clinical trials, the use of different dosages of herbal medicines, inadequate randomization in most studies and an improper selection of patients, the numbers of patients in most trials are insufficient for the attainment of statistical significance, wide variations in the duration of treatments using herbal medicines, and lacking or insufficient results of toxicological studies. Unfortunately, the most of the above-mentioned factors can be related to the clinical trials described in **Table 2**.

### Herbal Products Penetration Through Psoriasis Skin

Novel drug delivery systems such as liposome, niosome, ethosome, microemulsion, nanoemulsion, solid lipid nanoparticles (SLNs), and nanostructured lipid carrier systems (NLCs) present desirable attributes for the use in extremely dehydrated and thickened psoriatic skin that has a lipid imbalance and is sensitive to irritants [54,55]. They offer an enhanced penetration through skin with less toxic effects compared to free drugs (liposomes), slow down drug release and reduce systemic toxicity (niosomes), enable drugs to reach the deep skin layers and/or the systemic circulation (ethosomes), provide long-term stability and high solubilization capacity for hydrophilic and lipophilic drugs (microemulsions), prolong action on the skin and protect the drug from instability (nanoemulsions), cause only negligible skin irritation, and ensure the compatibility of the drugs (NLCs) [54]. Moreover, topical drug delivery systems with herbal formulations enhance the therapeutic effects of herbal drugs and facilitate their penetration through the skin [56,57].

Studies performed on liposomal vesicles (combination of methotrexate and menthol) incorporated in vesicular gel base [58], elastic liposomal formulation of colchicine isolated from *Colchicum autumnale* and *Gloriosa superba* [59], and capsaicin-containing liposomes, niosomes and emulsomes [60] confirmed their potential to enhance skin accumulation, prolong drug release, and improve the site-specificity of active constituents as effective drugs in the treatment of psoriasis. Niosomes loaded with ammonium glycyrrhizinate from *Glycyrrhiza glabra* showed no toxicity, good skin tolerability and improved the drug's anti-inflammatory activity in mice and human [61]. Psoralen from *Fructus psoraleae* loaded in ethosomes increased the lipid fluidity and cell membrane penetrability, which made it possible to enhance the skin deposition *in vitro* and *in vivo* and can be used to cure psoriasis [62]. Microemulsion gel-based systems of babchi oil (*Psoralea corylifolia*) and chitosan-coated microemulsions are a potential vehicle for the topical delivery of psoralen and methoxypsoralen (extracted from *Ammi majus*) for the treatment of psoriasis [63,64]. Microemulsion systems of 5% tea tree oil distilled from *Melaleuca alternifolia* are promising vehicles for a transdermal drug delivery [65]. Skin delivery of nanoemulsion system loaded turmeric oil (15%) from *Curcuma longa* [66], nanoemulsion O/W containing rice bran oil [67], and nanoemulsion with glycyrrhetic acid from *Glycyrrhiza glabra* [68] significantly increased the transdermal permeability of these compounds, showed anti-inflammatory activities and a low irritation potential, and so can be used for psoriasis treatment. NLCs and SLNs showed a good ability to increase the drug accumulation in various skin layers. NLCs may as well be a more potent carrier for the

topical delivery of capsaicin, to allow for an effective therapy of psoriasis [69].

### Mechanisms of Action of Herbal Products Used in Psoriasis Treatment

In general, herbal products used in the treatment of psoriasis work by (1) inhibition of the keratinocyte hyperproliferation and induction of apoptosis, (2) inhibition of immune-inflammatory reactions, (3) suppression of phosphorylase kinase (PhK) activity, (4) inhibition of the hedgehog (Hh) signaling pathway.

A number of studies show that the inhibition of keratinocyte hyperproliferation, induction of apoptosis, and modulation of keratinocyte differentiation have been considered as targets of anti-psoriatic strategies. Animal-based studies support the efficacy of the herbal products for the treatment of psoriasis via inhibition of keratinocyte hyperproliferation. The ethanolic extract of *Aloe vera* leaf gel showed antipsoriatic activity by a significant differentiation of the epidermis, seen as orthokeratosis as well as an increase in the relative epidermal thickness when compared with the control group in mice [23]. The ethanolic extract of *Nigella sativa* seeds extract produced a significant epidermal differentiation from its degree of orthokeratosis comparable to tazarotene gel (0.1%) in albino mice [24]. However, most desired for the treatment of psoriasis are herbal products that inhibit epidermal hyperplasia and inflammation simultaneously. Tuhuai extract reduced epidermal hyperplasia and inflammation in normal hairless mice, which makes it a valuable drug for treatment of psoriasis [70]. Baicalin isolated from *Scutellaria baicalensis* acts by inhibiting inflammatory reactions and inducing the differentiation of keratinocytes at the same time [29]. Moreover, baicalin cream (5%) promotes epidermal differentiation and normal keratinization of keratinocyte in mouse skin similar to tazarotene cream (0.1%). The flavonoid quercetin from the rhizome of *Smilax china* shows significant orthokeratosis, reduction in epidermal thickness, anti-inflammatory, and maximum antiproliferant activities compared to mice treated with retinoic acid [26]. The treatment of psoriasis by inhibition of keratinocyte hyperproliferation through herbal products was also confirmed in clinical studies. *Indigo naturalis* ointment modulates the proliferation and differentiation of keratinocytes in the epidermis as well as inflammatory reactions by inhibiting the infiltration of T lymphocytes in patients with chronic plaque psoriasis [40]. Analysis of biopsies taken from patients after *I. naturalis* ointment treatment showed that the expressions of proliferating marker Ki-67 and inflammatory marker CD3 were decreased, while differentiation markers, such as filaggrin, were increased in the epidermis. Moreover, *I. naturalis* as well its major active constituent indirubin inhibited the proliferation and abnormal differentiation of epidermal keratinocytes through decreasing proliferating cell nuclear antigen (PCNA) and increasing involucrin at both mRNA and protein levels in patients with psoriatic lesions [71].

Some studies show that the inhibition of fibroblast-secreted cytokines could regulate keratinocyte proliferation and differentiation as well slow down the process of inflammation in psoriasis [72]. Ethanolic extracts from *Alpinia galanga*, *Curcuma longa* and *Annona squamosa* showed effects on the downregulation of NF- $\kappa$ B signaling molecules in the HaCaT keratinocyte cell line, reflecting their potential use in treating diseases with inflammation and hyperproliferation such as psoriasis [73]. *Copeifera langsdorffii* oleoresin, also known as Copaiba balsam, exhibits an anti-inflammatory activity through inhibiting NF- $\kappa$ B nuclear translocation and secreting proinflammatory cytokines [37]. Pre-

incubation of LPS-stimulated human THP-1 monocytes with increasing concentrations of the oleoresin purified fraction reduced the release of proinflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) and counteracts LPS-driven NF- $\kappa$ B nuclear translocation. Water-soluble polysaccharide (GP-I) purified from *Gynostemma pentaphyllum* showed a significant antiproliferative effect and decreased TNF- $\alpha$ , a vital proinflammatory cytokine in psoriasis [74]. Extracts of *Acanthus mollis*, *Achillea ligustica*, *Artemisia arborescens*, and *Inula viscosa* inhibited 5-LOX and COX-1 activity as well as NF- $\kappa$ B activation [75]. Moreover, *A. ligustica*, *A. arborescens*, and *A. mollis* increased the biosynthesis of 15(S)-HETE, an anti-inflammatory eicosanoid. Herbal products treatment of psoriasis through inhibition of cytokines was also confirmed in animal-based studies. The topical application of a mixture of herbal extracts (*Tinospora cordifolia*, *Curcuma longa*, *Celastrus paniculatus*, *Aloe vera*) lead to the downregulation of overexpressed cytokines in mice, initially induced with psoriasis-like dermatitis through topical application of imiquimod [17]. Some research found that phosphorylase kinase (PhK) enzyme is expressed on a significantly higher level in psoriatic epidermis as in normal epidermis [76]. PhK integrates multiple calcium/calmodulin-dependent signaling pathways including those involved in cell migration and cell proliferation. Therefore, a modulation of PhK activity by drugs/herbal products may be an effective treatment of psoriasis. Curcumin is a selective PhK inhibitor [77]. It was observed that the PhK activity was highest in active untreated psoriasis, lower in the calcipotriol and curcumin treated group, and lowest in normal skin. A decreased PhK activity in curcumin and calcipotriol treated psoriasis patients was associated with corresponding decreases in keratinocyte transferrin receptor expression, severity of parakeratosis, and density of epidermal CD8+ T cells.

Some reports suggest that the Hh pathway is activated in lesional psoriatic skin, and that treatment with the Hh pathway antagonist cyclopamine may lead to a rapid resolution of the disease [78]. Cyclopamine isolated from *Veratrum californicum* was found to be more effective than topical clobetasol-17 propionate in the treatment of guttate and plaque type psoriasis [79]. Besides, inflammatory cells including CD4+ lymphocytes were found to disappear rapidly after the treatment with cyclopamine as well as *hedgehog/smoothened* signaling was inhibited. On the other hand, some research found that the Hh pathway is not activated in psoriasis [80]. It was observed that Hh target genes (*PTCH1* and *GLI1*), whose expression is elevated in response to Hh signaling, were downregulated in lesional skin. Therefore, the proposed use of Hh antagonists as antipsoriatic agents is very questionable.

### Adverse Effects of Herbal Therapy

The risk of adverse events increases with the topical administration and the long-term use of herbal-based formulations. Only few of the animal-based and clinical studies discussed above included a safety profile of herbal products. No side-effects or adverse events were reported for the psoriasis treatment with *Aleurites moluccana* oil [51], *Curcuma longa* microemulgel [42], *Hypericum perforatum* ointment [43], *Indigo naturalis* extract in oil [45], and *Strobilanthes formosanus* ointment [48] in patients participating in clinical trials. Local adverse events, mainly drying up, stinging, and itching of the skin on test areas, were observed after the topical application of *Aloe vera* gel [36,52]. The only clinical trial which verified the possibility of acute dermal toxicity showed that methanolic *Cassia tora* leaves extract incorporated

in O/W creams was safe up to a dose of 2000 mg/kg [31]. Moreover, for human safety reasons the assessment of new substances is still evaluated for irritant potentials by application to animals followed by observation of visible changes such as erythema and oedema [81]. Testing for skin irritation in animals is not always predictive for humans, but is still the most widely used method in toxicity research for herbal extracts applied topically. It is well known that some herbal remedies may cause allergic reactions, erythema, and edema and several can be responsible for photosensitization [82,83]. Some herbal preparations can cause organ toxicity, hitting liver, kidneys, heart, and other organs [84–86], or possess cancerogenic properties [87]. Moreover, herbal products are often mislabeled (unknown purity and standardization of active constituents) and may contain additives or contaminants (heavy metals, pesticides) that are not listed in formulation [88–90]. Some herbal products may interact with conventional drugs and some are toxic if used improperly or at too high doses [91]. Moreover, there are no regulations governing which herbal products can be marketed for various ailments as well as no authorities register adverse effects [92]. An increasing number of herbal formulation available for sale should prompt governments to introduce regulations on research which should be carried out before such products are released to the market.

### Challenges and Perspectives for the Treatment of Psoriasis by Herbal Products

The review of the literature shows that a great growth has taken place in the worldwide interest in the potential of herbal medicines for the treatment of psoriasis over the last 20 years. Parallel to various synthetic medicines used topically (corticosteroids, vitamin D analogues, retinoids) and systemic (methotrexate, retinoids, cyclosporin), or targeted (biological) therapies (e.g. alefacept, efalizumab, etanercept) also herbal products play an important role as therapeutic agents for psoriasis treatment [93–95]. The long tradition of herbal products used in the treatment of many diseases is not sufficient to consider them as effective and safe drugs. To confirm their effectiveness as new promising alternative agent for the therapy of psoriasis a lot of research must be performed. Studies showing antiproliferative activity of herbal products and their ability to modulate cell differentiation in HaCaT cell lines [96–101] do not provide sufficient evidence that these herbal products will be effective in the treatment of psoriasis. Also promising results obtained in the studies performed on animals are not always consistent with the results of clinical trials. Therefore, only well-controlled double-blind clinical trials and toxicological studies can prove the efficacy and safety of herbal products in psoriasis treatment. In general, numerous difficulties associated with the evaluation of the efficacy and safety of herbal medicines, standardization of plant materials, and quality of herbal products cause that only a few herbal drugs have been approved for clinical applications so far, and finally reach the market [102]. Unfortunately, until now there are no approved herbal drugs dedicated for the treatment of psoriasis. However, in my opinion, the great progress in herbal medicine should make it possible that the first highly efficient and completely safe herbal product designed for the therapy of psoriasis will be available on the world market in the near future. Herbal products can make substantial contributions to drug innovation by providing novel chemical structures and/or multidirectional mechanisms of action, which are not commonly seen in synthetic compounds. The development of topical drug delivery systems facilitates plant extract penetration through the skin and enhances the

therapeutic effects of herbal products in psoriasis treatment. Moreover, the growth of interest in natural medicine may force pharmaceutical companies to invest in extensive preclinical and well-controlled randomized clinical trials to prove the safety and efficacy of herbal medicines. Moreover, new branches of biological sciences, including pharmacogenomic, metabolomic, and microarray methodology, as well as the techniques of analytical chemistry, such as HPLC and GC/MS, would likely enable progress in the assessment of pharmacological qualities and safety of herbal products. These all allow for creating international guidelines that precisely define the requirements for studies about the use of herbal medicine. It seems that establishing global regulatory mechanisms for the introduction of herbal drugs to the world market is desirable and necessary.

## Conclusion

Herbal products are being increasingly used in the treatment of skin diseases like psoriasis. Some of them specifically inhibit epidermal hyperplasia and/or inflammation, which can be widely used to treat psoriasis. Unfortunately, most studies provide only limited information about the efficacy and safety of topically used herbal products in the treatment of psoriasis. Therefore, more scientific evidence and documentation is desired for the promotion of herbal treatment of psoriasis, which must be substantiated by reliable clinical trials with standardized materials and formulations.

## Conflict of Interest

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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