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Pharmacological Benefits of Herbal Formulations in the Management of *Psoriasis vulgaris*

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Abstract

Psoriasis is a chronic inflammatory skin disease, with an important impact on the patient's quality of life. Its incidence and prevalence are continuously increasing. The complex ethiopathology of this disorder is only partially known; there is a clear genetic predisposition, which associates a number of environmental triggering factors such as an unbalanced diet and lifestyle. The conventional therapeutic options are not always satisfactory in terms of efficiency and safety, therefore, complementary and alternative medicine approaches are frequently chosen by patients, mostly as self-medication. This review, based on recent literature flow data, outlines the pharmacological benefits of herbal formulations with antipsoriatic activity. It also reveals the molecules responsible for their effects, as well as their interference with the metabolic and immunopathogenic mechanisms of this disease. An important number of plants have been proved to act as antipsoriatic agents, many botanical-based preparations containing key-phytochemical molecules (belonging mainly to phenolics, triterpenoids and phytosterols or unsaturated fatty acids, as mentioned in specific phyto-pharmaceutical databases). Specific mechanisms of action, which can explain their activity (such as lipoxygenase inhibition, antioxidant, anti-inflammatory, anti prostaglandin), were recently described. Only some of these formulations have been actively tested *in vitro* or *in vivo*. Most publications in the field agree on the need for more *in vitro* and *in vivo* studies, especially clinical assessment on patients with *Psoriasis vulgaris*. These would provide more accurate data on the efficacy and safety of such herbal formulations for this disease.

Keywords: activation pathways in psoriasis, anti-inflammatory activity, complementary and alternative medicine, medicinal plants, phytochemicals, *Psoriasis vulgaris*

Background

Psoriasis vulgaris is a chronic inflammatory skin disorder, with a worldwide distribution and an increasing incidence and prevalence. Recent epidemiological studies show its impact on a level of 1.5-4%, with important local variations depending on ethnicity and climate (Jacobson *et al.*, 2011).

Psoriasis vulgaris has a complex ethiopathology, scientifically proven by a genetic predisposition associated with environmental triggering factors, such as unbalanced diet, stress, trauma and infection being the most frequently mentioned ones (Griffiths *et al.*, 2007).

Most studies on the immunopathogenesis of psoriasis point to a primary T cell-mediated hyperproliferation of keratinocytes, leading to the well-known lesions (Nickoloff and Nestle, 2004; Homey and Meller, 2008; Jeon *et al.*, 2013).

Epidermal infiltrate of oligoclonal CD8+ T and dermal presence of CD4+ T cells is actually a constant feature of chronic psoriasis lesions. These cells could be responding to specific antigens present in the HLA-Cw6 binding pocket of keratinocytes, or to bacterial superantigens, which cause an important activation of T-cells. The activation and remission episodes might be due to the changing balance between effector and suppressor CD4+ and CD8+ T cells. Additionally, natural killer T cells, dendrite cells and a

number of cytokines (interleukins, interferon) are present in these lesions. The complex and only partially elucidated interaction between T cells, their resulting cytokines and dendrite cells leads to the pathogenic inflammation.

A number of pathogenic models for psoriasis have been discussed and there are still many unknown aspects on the matter. Type 1 pathway of cytokines and inflammation producing gene products have been linked to this disorder. The activated T helper 1(Th 1) and T cytotoxic 1(Tc 1) cells release IFNγ, which through signal transducer and activator of transcription 1 (STAT1) induces a large group of inflammatory genes. Th17, the latest characterized subset of Th cells, are also involved in the immunopathogenesis of psoriasis (Fig. 1).

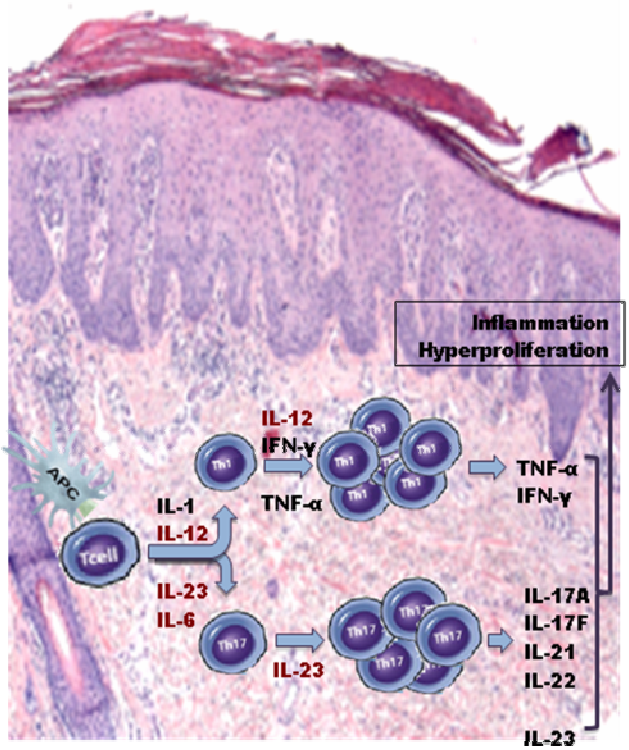

Fig. 1. Th1 and Th17 in the imunopathogenesis of psoriasis

Clinically, psoriasis is characterized mainly by its cutaneous involvement, but it can also affect joints and nails. Its typical signs, the red scaly patches, can cover large areas of the body, being easy to notice and therefore stigmatizing, with a strong impact on the quality of life (Kurd *et al.*, 2010).

These scaling of psoriatic lesions are due to particular histological features. The cellular cycle of keratinocytes is decreased from the normal period of 30 days to 3-5 days, in which they transit from the basal to the cornified layer. These cells present parakeratosis, an altered differentiation pattern, nuclei being present even in the cornified layer. In addition, there is an aberrant expression of antigens associated to the differentiation. The local erythema is caused by the hyper proliferation of the vascular endothelial cells, which are contorted and dilated. Pathognomonic features of psoriasis are the Munro's microabscesses, formed by the focal migration of neutrophils into the epidermis (Schon *et al.*, 2005).

Psoriasis is a chronic recurrent condition, so remission periods and acute episodes alternate in an unpredictable way. While some patients can be in remission for years, others may present rapid progression to severe forms.

The morphology, distribution and severity of the cutaneous manifestations are highly variable, ranging from small, localized papules, to large plaques, covering the whole body, intensely symptomatic.

The treatment is also chronic, having a significant impact on the patient's quality of life. According to the clinical form and severity, patients can use topical products, or require systemic therapy. The classical therapeutic options include immunosuppressive agents such as different corticosteroids, azathioprine, cyclosporine, methotrexate, or one of the biologic agents (Gottlieb, 2005). New insights into the immunologic mechanisms of psoriasis might lead to the development of more targeted therapeutic interventions (Asadullah *et al.*, 2002).

Currently available options have variable efficacy and frequently associate well-known side effects. In addition, not all patients are responsive to them; some cases are actually worsened. Another problem arises from the important costs of these therapies.

All these decrease the adherence to treatment, affect the trust patients have in their physicians and increase the percentage of those starting to use self-medication (Magin *et al.*, 2009). Kivelevitch *et al.* (2012) suggest that up to 30-40% of the population is non-adherent to the various therapeutic options. It is reported that for their skin diseases patients show an increasing preference towards natural approaches, likely due to the perceived decreased risk for adverse effects of such therapies (Magin *et al.*, 2006).

For a proper efficacy assessing of natural compound's safety, both *in vitro* research and *in vivo* preclinical (on animal models) and clinical studies are essential. *In vitro* research can help assess the safety of the compounds and provide important details on their specific cellular and also molecular activity. Development of animal models is of a real value for such studies, especially xenotransplantation models using human skin grafted on to immunodeficient mice. They allow studying the behavior of different cell types in human tissue. Even if no animal model mimics psoriasis completely, many aspects are present in these (Danilenko, 2008), which also helped prove that specific T cell subsets can induce psoriatic lesions in uninvolved skin from psoriasis patients, supporting the immunopathogenic pathways discussed above (Schon, 1999). Clinical studies are the final step, critical for a valid assessment of efficacy and safety.

Complementary and alternative medicine (CAM) promotes plant based formulas approaches the use of natural products, mainly based on individual plants extracts or complex formulas (dietary supplements) combined with diet-based therapies, which demonstrated their efficacy, but many times their benefits are proven only by limited reported experience.

The prevalence of CAM application is stronger in developing countries, but there is an increasing demand also in developed countries. Natural formulas of dietary supplements (known as natural remedies) have an important preventive role and are reported to be used by patients with various dermatologic problems, more

frequently than by the general population. It is estimated that up to 50% of dermatologic patients use CAM, alone or in combination with conventional therapies (Fuhrmann *et al.*, 2010; Jensen, 1990). Plant-based preparations are used not only in CAM, but also in conventional dermatology (e.g. use of psoralens, podophyllin, pyrethrins, oatmeal).

Plant-based preparations include individual medicinal herbs or combined formulas, which may enhance their efficacy and reduce side effects (Bensky and Barolet, 1990). According to Mantle *et al.* (2001), approximately one-third of them are useful skin disorders, including psoriasis, compared to only 1-3% of synthetic drugs.

Psoriasis patients frequently use alternative therapies, especially herbal products. Their preference for natural approaches is mostly explained by the perceived decreased potential for adverse effects of CAM therapies (Magin *et al.*, 2006). Thus, for a proper management of their patient's condition, it is important for physicians to be aware of the current evidence concerning plant-based preparations.

Recently (Deng *et al.*, 2013) made a meta-analysis of Chinese plants with antipsoriatic activity. The most commonly used herbs were *Sophora flavescens* root and *Lithospermum erythrorhizon* root, which were proven to have anti-inflammatory, anti-proliferative, anti-angiogenic and tissue repair actions. These actions may explain their benefits of the topical multi-herbal formulations in psoriasis.

Tabs. 1 and 2 summarize data about the main effects of *Aloe vera* and other plants in the management of *Psoriasis vulgaris*, in relation to their composition in bioactive compounds. The efficiency and safety of plant-based preparations is critically evaluated, considering the involvement of natural molecules on the cellular mediated

Tab. 1. Bioactive components from *Aloe vera*, with antipsoriatic activity (from Duke Phytochemical and Ethnobotanical Databases, 2013)

Compound	Activity
Provitamin A (beta-carotene), vitamin C and E	antioxidant
Bradykinase	enzyme with anti-inflamatory activity
Enzymes: aliiase, alkaline phosphatase, amylase, carboxypeptidase, catalase, cellulase, lipase and peroxidase	breakdown of carbohydrates and lipids
Calcium, chromium, copper, zinc selenium, magnesium, potassium	essential minerals for the various enzymatic reactions, some having also antioxidant potential
Polymannan	anti-inflammatory and immunostimulatory properties
Alprogen	glycoprotein with antiallergic properties
C-glucosyl chromone	a novel anti-inflammatory compound
Anthraquinones (aloin and emodin, aloesin)	analgesic, antibacterial and antiviral properties, a moderate photoprotective effect
β-sitosterol, campesterol, cholesterol and lupeol	anti-inflammatory action, antiseptic and analgesic potential
Auxins and gibberellins	plant hormones efficient in wound healing and inflammation
Salicylic acid	anti-inflammatory and antibacterial activity
Lignin	enhances cutaneous absorption of other ingredients, when mixed in topical preparations

Tab. 2. Other plants with antipsoriatic activity and the key-molecules with their associated activity (according to Duke Phytochemical and Ethnobotanical Databases, 2013 and other references)

Plant name (Latin, common)	Key-molecules	Other References
Allium sativum var. *sativum* L. (garlic) *Angelica sinensis* (angelica) *Balanites aegyptiacus* (Brussel-Sprout) *Daucus carota* (carrot) *Glycine max* (soybean) *Morus alba* (white mulberry)	Arachidonic acid Carotenoids Phospholipids	Pazyar and Feily, 2011
Capsicum annuum (bell pepper, cherry pepper) *Capsicum frutescens* L.(hot pepper) *Zingiber officinale* (Ginger)	Capsaicin Capxanthin	
Curcuma longa (turmeric) Zingiber officinale (ginger)	Curcumin	Hatcher *et al.*,2008 Noorafshan & Ashkani-Esfahani, 2013 Jantarat, 2013
Indigo naturalis (indigo)		Lin *et al.*, 2012
Hippophae rhamnoides(seabuckthorn)	PUFAs Phytosterols	Zeb, 2004 Khan *et al.*, 2010; Kumar *et al.*, 2011

immunological mechanisms, in the antioxidant defense and apoptotic effects. The interference of natural molecules with cellular pathways can explain scientifically their beneficial effects at low doses, without secondary effects. These findings are assessed in recent studies and reviews, standing as a proof of the benefic potential of natural phytochemicals in such a chronic skin disease.

Recently, a relevant literature reveals the efficacy of plants and herbal preparations to be used as food supplements or teas or as ingredients of dermocosmetic formulas (May *et al*., 2012; Kuchekar and Bhise, 2012; Bhuchar *et al*., 2012; Chandrasekaran *et al*., 2012) some of them being investigated by clinical trials (Su *et al*., 2011; Kaur and Kumar, 2012; Al-Khafaji, 2012; Rahman *et al*., 2012; Li *et al*., 2012; Lu *et al*., 2012; Deng *et al.,* 2013, Yu *et al*., 2013), as well by topical treatments (Bos and Spuls, 2008).

The topical formulations based on conventional excipients are replaced by new biocompatible and biodegradable vehicles (liposomes, microemulsions, solid-lipid nanoparticles for bioactive molecules), in order to improve their efficacy and safety as well to allow a controlled delivery (Katare *et al*., 2010). Such vehicles are very compatible with lipophilic or hydrophilic plants extracts as well with pure compounds (psoralens, corticosteroids, levulinic acid, theophiline, vitamin D analogies).

Plants with antipsoriatic potential: scientific evidence and preclinical/clinical studies

Aloe vera (*Aloe barbadensis miller*) is a green succulent plant, belonging to the Liliaceae family, widely spread in some of the dry regions of Africa, Asia, Europe and America. "The plant of immortality", as Egyptians called it, has been used since ancient times for its health, beauty, medicinal and skin care properties. Two thousand years ago, Greek scientists considered it the universal panacea; Alexander the Great and Christopher Columbus used it for treating soldier's wounds (Surjushe *et al.*, 2008).

To the anecdotal use, scientific research added new data regarding the use of *Aloe vera* for various medical purposes, especially dermatological conditions including wound healing, herpes simplex, atopic dermatitis, seborrheic dermatitis, acne, diaper dermatitis, lichen planus, aphthous stomatitis, human papilloma virus and frostbite. For these indications, studies like those of Surjushe *et al.* (2008), or Feily and Namazi (2009) report various efficacy and sometimes, conflicting results.

Aloe vera contains around 75 potentially active constituents; in relation to their cutaneous benefits, its most relevant compounds are described in Tab. 1 (Atherton, 1998; Surjushe *et al*., 2008). Some *in vitro* and *in vivo* studies assessed the efficacy and safety of *Aloe vera* in psoriasis (Morelli *et al.*, 2010; Deng et *al.*, 2013)

Its anti-inflammatory activity is most likely the most relevant one for this pathology. *Aloe* has been reported to inhibit the cyclooxygenase pathway and to reduce prostaglandin E2 production (Hutter *et al.*, 1996).

Clinical studies on the use of *Aloe vera* preparations in plaque psoriasis are few in number; Syed *et al.* (1996) and Choonhakarn *et al*. (2010) agree on its efficacy in topical applications, reporting improvement of PASI and DLQI scores (more than with placebo, but less than with steroids); but there is also conflicting data Paulsen *et al.* (2005). Therefore, although there are some promising data, clinical effectiveness needs more scientific confirmation.

Use of topical *Aloe vera* gel is generally well tolerated, rarely causing allergic reactions, as reported by Mantle *et al.* (2001). It should be avoided in patients with known hypersensitivity to *Aloe vera* or plants of the *Liliaceae* family (e.g. garlic, onions, tulips). Through oral ingestion, it may lower blood sugar levels, so caution is advised in patients with diabetes, hypoglycemia, or glucose intolerance.

Cayenne pepper (*Capsicum frutescens*), due to its main ingredient, **capsaicin**, has important medical benefits in decreasing the intensity of different types of neurological induced pain. Topical capsaicin has modulating effects on substance P, thus it is efficient in a number of neuralgias: post herpes zoster neuralgia, diabetic neuropathy, notalgia paresthetica, reflex sympathetic dystrophy and also for hemodialysis-induced pruritus (Reuter *et al.*, 2010).

In vitro studies Yu CS (2011), as well as *in vivo* data, including a double-blind clinical trial, report efficacy for topical capsaicin in psoriasis, especially the pruritic forms (Ellis *et al.*, 1993; Bernstein *et al.*, 1986; Arnold and van de Kerkhof, 1994). The use of topical capsaicin can be limited by the temporary erythema and burning sensation on the site of application.

Indigo naturalis is a dark-blue powder obtained by crushing, fermenting and adding calcium to the leaves of indigo-producing plants such as: *Baphicacanthus cusia, Strobilanthes formosanus, Polygonum tinctorium* and *Isatis indigotica*. *Indigo naturalis* has been used for many years by traditional Chinese medicine for the treatment of various dermatoses.

A number of components have been isolated from *indigo naturalis*, the most active ones being indigo, isoindigo, tryptanthrin and indirubin. Experimental data on them report anti-proliferative effects on epidermal keratinocytes, anti-inflammatory activities and effects on regulatory T cells (Plitzko *et al.*, 2009; Lin *et al.*, 2009; Li *et al.*, 2011). These could explain in part the efficacy of *indigo naturalis* in plaque psoriasis, which has been confirmed by patients and discussed by Reuter *et al.* (2010) and Deng *et al.* (2013).

In psoriatic lesions *indigo naturalis* has been shown to upregulate claudin-1 expression and restore tight junction function; synergistic effect was reported for indirubin, inigo and tryptanthrin (Lin *et al.*, 2013). Clinical studies by Lin and his group (2007, 2008, 2011) on topical formulations of *indigo naturalis*, including oils and ointments, report efficacy in plaque psoriasis, nail psoriasis, also recalcitrant forms, in both adult and pediatric patients. Few cases of itching for a couple of days after starting the therapy were the only adverse events indicated.

These results suggest that topical application of *indigo naturalis* may be a safe and effective therapy for psoriasis, but due to the limited number of patients included in the studies and variety of the *indigo naturalis* preparations used, more *in vitro* and *in vivo* research is needed.

Mahonia aquifolium (*Oregon grape*) is a flowering plant

belonging to the Berberidaceae family. It is native from North America, being spreading on the west coast from Southeast Alaska to Northern California. *Mahonia* is an evergreen shrub, with leathery, pinnate leaves, often with of spiny leaflets and dense clustered racemes of yellow flowers, sometimes fragrant, followed by black or purple berries.

This plant is used for various purposes: a number of cultivars and hybrids have been developed as decorative plants; the resistant holly-like leaves are sometimes used by florists for greenery; its fruits are used in the traditional diets of Pacific Northwest aboriginal people; the juice is used to make wine; dyes are extracted from the inner bark and roots (yellow dye), as well as from the berries (purple dye).

The use of *Mahonia aquifolium* for medical purposes goes back to Indian tribes, which were using it to treat dyspepsia. Nowadays, it is still of significant medical interest for its analgesic, anti-inflammatory, antioxidant and hepatoprotective effects; these are due principally to its rich content in alkaloids like berberine, palmatine, jatrorrhizine, berbamine and oxyacanthine (Chao *et al.*, 2013).

For plaque psoriasis, meta-analysis including both scientific *in vitro* and *in vivo* relevant data agrees on the efficacy of *Mahonia aquifolium* preparations (Deng *et al.*, 2013; Reuter *et al.*, 2010).

In vitro studies report *Mahonia* alkaloids to reduce the expression of adhesion molecules, proliferation and activation markers (Augustin *et al.*, 1999), inhibition of inhibition of 5-lipoxygenase and antioxidant properties of protoberberine and aporphine alkaloids (Misík *et al.*, 1995; Müller and Ziereis, 1994).

Clinical data reported by Bernstein *et al.* (2006), Gulliver and Donsky (2005) and Wiesenauer and Ludtke (1996) show promising results in psoriasis cases for topical formulations (*Mahonia aquifolium* ointments or creams) compared to placebo or to classic therapeutic options (corticoids, vitamin D derivatives). Preparations of *Mahonia* were well tolerated, with rare side effects including rash, a burning sensation when applied and staining of clothes.

Olive (*Olea europaea*) oil and olive leaves extract have been used since ancient times to moisturize and help rejuvenate damaged skin. Nowadays, many health benefits of olive oil are supported by scientific data and new positive attributes keep being discovered.

Both olive oil and olive leaves extract contain oleic and palmitic acids and a spectrum of polyphenols: flavonoids, lignans and secoiridoid glucosides. These compounds have anti-inflammatory and anti-oxidant effects, benefiting a number of skin conditions (e.g. atopic dermatitis, acne, seborrheic dermatitis, diaper dermatitis), stretch marks and scars (Viola and Viola, 2009).

Olive oil has been used in psoriasis, based on anecdotal evidence, since Hippocrates, when doctors were instructed to rub olive oil on psoriasis lesions. Scientific evidence on the matter is still limited, but there are few studies reporting efficacy of olive oil mixed with other natural ingredients, likely due to their anti-inflammatory and hydrating effects (Al-Waili, 2003; Bjorneboe *et al.*, 1988).

Sea buckthorn (*Hippophae rhamnoides*) is a deciduous shrub belonging to the Elaeagnaceae family, which is cultivated in various parts Europe and Asia for its nutritional and medicinal benefits. Its fruits, but also seeds and other parts, are appreciated for their contents rich in vitamins (A, B1, B9, B12, C, E, K and P), carotenoids (beta carotene, lycopene, and zeaxanthin), flavonoids, phytosterols and unsaturated fatty acids. These components confer *sea buckthorn* therapeutic benefits including cardiovascular protection, antiulcer activity, antitumoral, anti-inflammatory, antioxidant, antibacterial, antiatherogenic and hypoglycemic effects (Patel *et al.*, 2012).

Sea buckthorn extracts have antibacterial, anti-inflammatory, antioxidant and regeneration-promoting properties, being historically used for various skin conditions like dermatoses and wound healing. It is now being tried as a natural remedy for psoriasis, in an effort to control the periodic flare-ups. Scientific studies in this direction show promising results (Ganju *et al.*, 2005, Patel *et al.*, 2012).

Chamomile is the common name given to daisy-like plants of the Asteraceae family (*Matricaria recutita, Chamomilla recutita*). It has a long history of medical use, either in oral administration, as tea, or for topical applications.

Various chemical compounds are present within chamomile, each with different effects. Antiseptic properties are due to bisabolol and its derivatives, and also to chamazulene, farnesene and matricin. Anti-inflammatory effects are principally due to a number of flavonoids: apigenin, quercetin, luteolin and patuletin. Anecdotic use of chamomile extracts includes various inflammatory skin conditions like atopic dermatitis, rosacea, seborrheic dermatitis, mucous membrane inflammations, for and also wound healing (Ross, 2008).

The anti-inflammatory effects of chamomile, and partially also the antiseptic ones, justify possible benefits on psoriatic lesions (Graf, 2000; Aertgeerts *et al.*, 1985). Still, scientific studies on the matter are very limited, so more research in this direction is needed to properly assess its efficacy in psoriasis.

Because chamomile can cause uterine contractions, leading to miscarriage, pregnant women are advised not consume it. There is also risk of allergic reaction, contact dermatitis, or even anaphylaxis. It is still unclear whether individuals with, reported allergies to chamomile were actually exposed to it, or to plants with similar appearance (Facchinetti *et al.*, 2012).

Potential antipsoriatic activities have been reported also for preparations of *Alpinia galangal, Sphaerantus indicus, Annona squamosa, Camptotheca acuminate* nut, *Daucus carota L.*, *Curcuma longa*, Kukui nut, Neem tree and for topical formulae mixing various herbs, but here is limited scientific assessment on their regard (Brown *et al.*, 2005; Deng *et al.*, 2013; Pandey *et al.*, 1994; Saelee *et al.*, 2011).

Conclusions

Psoriasis patients frequently use plant-based preparations. Physicians should be aware of the likely use of these therapeutic options, and the current evidence concerning their efficacy and safety.

Experimental data indicate mainly *Aloe vera*, capsaicin, chamomile, *indigo naturalis*, *Mahonia aquifolium*, but also

of *Alpinia galangal, Annona squamosa, Camptotheca acuminate nut, Capsicum frutescens, Curcuma longa,* Kukui nut and Neem tree, as having anti-inflammatory, anti-proliferative and other actions of benefit to psoriatic lesions. The majority of evidence coming from clinical trials, though not numerous, agrees on the beneficial effects of these preparations, and their good safety profile, no serious side effects being reported.

Due to the limited number of *in vitro* data, and small size of most clinical studies, the proper magnitude of efficacy and safety cannot be measured with accuracy, so the current promising results should encourage more scientific research assessing the potential of these preparations.

Future *in vitro* research, followed by clinical assessment of selected plant-based formulations, will supply more scientific evidence in support of their efficacy in psoriasis. In addition, carefully chosen combinations, along with new delivery systems with increased topical absorption and improved stability, might increase the efficacy of these natural remedies.

Increasing the knowledge on their molecular mechanisms of action and scientifically proven benefits will help include plant-based preparations in the daily clinical management of psoriasis.

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