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Review Article

Phytotherapeutic Potential of Natural Herbal Medicines for Management of Psoriasis: Current Status

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ABSTRACT

Psoriasis is a complex multifunctional inflammatory autoimmune skin disease, which is mainly characterized by activation of T-cell (T-lymphocyte), abnormal proliferation keratinocyte, local vascular changes and activation of the neutrophil. A number of therapies are being used to treat psoriasis including topical, systemic and phototherapy recpectively but none of them is able to cure the disease completely, precluding the long-term serious side effects for the human body. In contrast to these, herbal therapies can play an important role for treatment of psoriasis. With this endeavor, this review reports the recent developments and patent showing potential of herbal therapy for treatment of psoriasis along with future prospect in the field of traditional and novel drug delivery system (NDDS) for treatment of psoriasis.

Keywords: Psoriasis, Keratinocyte, Hyperproliferation, Herbal drug, Novel drug delivery systems.

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INTRODUCTION

The immune system is a complex of various tissues, organs, proteins and special cells, which helps to protect the human body against disease. The largest part of our body (skin) perform various function including immunological and physical protection through some cellular and humor constituents including keratinocyte, dendritic cells (DCs), β-defensins, mannose-binding lectins and immunoglobulin.[1] These components are responsible to generate adaptive immune responses against the exogenous injuries.

Psoriasis is a most common and chronic autoimmune disease among various skin diseases including lupus, scleroderma and atopic dermatitis (AD) which has significantly negative effect on quality of life style of patient along with their families resulting in emotional, physical and social burden.[2]

The term psoriasis is originated from the Greek word *psora* which reflect with "itching".[3] Psoriasis is a complex multifunctional inflammatory autoimmune skin disease, which is characterized by activation of T-cell (T-lymphocyte), abnormal proliferation in keratinocyte, local vascular changes and activation of the neutrophil.[4,5]

According to Epicast report, there were approximately 36.5 million prevalent cases of psoriasis in 2012 across the world and it was estimated that this number will reach approximately 40.93 million prevalent cases by 2030.

With a prevalence of India, it is observed that most of the psoriatic patients are individuals between 30-40 years of age.[6] Understanding the morphological difference between normal and diseased skin can make the discussion more clear. The lack of safe and effective treatment for psoriasis has directed many researchers towards the development of novel therapies. Parallel to various topically or systemically used synthetic medicines; herbal therapy can play potential role for treatment of psoriasis.[7,8] Against this background, the present review emphasizes the future prospect of herbal therapy and recent developments along with patents reported in the field of traditional and novel drug delivery system (NDDS) for treatment of psoriasis.

CAUSES OF PSORIASIS

Various environmental factors including stress, hypocalcemia infections (e.g., streptococcal pharyngitis) physical trauma (Koebner or isomorphic phenomenon) and some medications including beta blockers, IFNs, antimalarials and systemic corticosteroids are responsible for psoriasis. Apart from these some other factors such as higher body mass index (BMI) rapid weight changes, alcohol consumption, vitamin D deficiency and habit of tobacco are also associated to increase psoriatic inflammation.[9]

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GENERAL SYMPTOMS

The general symptom of this disease includes silvery scales on bright red, pitting on nails, genetic predisposition, well demarcated plaques (usually on the *sclap*, elbows and knees) and chronic inflammation. People with psoriasis are also have risk of coronary artery diseases.[3,10]

TYPES OF PSORIASIS

Historically, the disease has been classified on the basis of clinical appearance (Table 1). According to morphology and localization, plaque psoriasis is a most common type of psoriasis, covers around 85% of psoriatic population. In this type of psoriasis, scalp, trunk and buttocks are mainly infected but inflammation may occur at anywhere on the body. The degree of severity of disease is classified as mild, moderate, and severe, which is further measured by means of patient's body surface area (BSA) affected by psoriatic lesions. Normally 3-10% BSA is considered to be moderate while more than 105 is considered to be severe.[11,12]

PROBABLE MECHANISMS OF PSORIASIS

The mechanism of the occurrence of psoriasis is not clear yet. Progression of psoriasis is assumed to be based on number of cumulative events which are involved in the activation of immune cell along with secretion of various signaling molecules such as cytokines, chemokine and growth factors that lead to congealing of epidermis, hyperkeratosis and neovascularization.[23,24] External factors, such as medication, infection or trauma can stimulate the formation of complex antimicrobial peptides (AMPs) which are released from keratinocytes in genetically

Table 1: Clinical classification of psoriasis.

Clinical Classification	Characterization	Associations
Chronic Plaque Psoriasis[13,14]	Well circumscribed, erythematous, silvery scale, either as single lesions or as a generalized disease. Usually involving the scalp, knees, elbows, low back, umbilicus, and gluteal cleft.	Most common; accounting for approximately 90% of all cases of psoriasis
Flexural[15]	Also known as *inverse psoriasis,* minimally scaly, affecting predominantly the axillae, groin, submammary area, genital, natal cleft region.	Prone to secondary bacterial or yeast infections
Nail[16]	Pitting, distal onycholysis, oil drop sign, splinter haemorrhages, leukonychia, crumbling, red lunula.	More common in people with psoriatic arthritis.
Scalp[17]	One of the most common sites of psoriasis that is difficult to treat.	-
Palmoplantar[18]	Localized to the hands and soles of feet with yellow-brown macules. Confluent redness and scaling without obvious plaques to poorly defied scaly or fissured areas to large plaques covering the palm or sole.	Commonly associated with sterile inflammatory bone lesions
Guttate[19]	The acute eruption of "dew-drop," salmon-pink, fine-scaled, small papules on the trunk or limbs.	Second most common type (2%) in children and young adults. Associated with group A *Streptococcus* infections.
Pustular[20]	Sheets of monomorphic pustules on painful, inflamed skin Most commonly localized to the palms or soles. Confluent pustules on an erythematous base von Zumbusch type: generalized with acute fever, chills, nausea, headache, and joint problems possible. Acrodermatitiscontinua of Hallopeau: distal fingers; fingernails possibly floating away on lakes of pus and permanent nail destruction common.	Life-threatening Potential complications include high-output cardiac failure, sepsis, and hypercalcemia
Erythroderma[21]	Erythema with scaling over more than 80-90% of the body surface area. Life-threatening emergency.	Potential complications include high-output cardiac failure, renal failure, hypothermia, sepsis hypoalbuminemia
Annular[22]	Subacute or chronic; systemic symptomsdemarcated erythematous scaly plaques with central clearing.	Systemic symptoms are less common than with the Hallopeau type.

predisposed individuals. For example, antigen presenting cells including Toll-like receptor 7 (TLR7) and (TLR9) respectively can bind to cathelicidin antimicrobial peptide (CAMP) on the surface of plasmacytoid dendritic cells (pDCs), which helps local expansion and the activation of antigen specific CD8+ T cells in the dermis and local lymph nodes.[25] Consequently, these activated cells migrate into the epidermis and attack on the major histocompatiblity complex (MHC) receptors on to the surface of keratinocytes, which triggers the release of soluble factors locally such as innate immune mediators, chemokine's and cytokines that could be able to increase proliferation of keratinocyte and local inflammation.[26] On the other hand some inflammatory mediators are released such as interferon-α (IFNα) and IFNβ which indirectly increase the secretion of additional pro inflammatory mediators such as IL-12, IL-23 and tumor necrosis factor (TNF) that helps to release additional chemokines and cytokines and promotes the defense mechanism of the host which leads to recruitment of extrainflammatory cells towards new lesion.[27] Some interleukins are responsible to contribute the characteristic psoriatic histological phenotype, including acanthosis, parakeratosis (incomplete keratinization with retention of nuclei) and epidermal hyperplasia. Activation of key transcription factors in psoriasis such as Janus kinase (JAK)–signal transducer, nuclear factor-κB (NF- κB) and cyclic AMP leads to further production of IL-17 and TNF respectively.[28] The Overexpression of growth factor of vascular endothelial receptor promotes the vascular proliferation into the skin which leads to the establishment of chronic psoriatic inflammation.[29] The pictorial representation for mechanism is given in Figure 1.

CO-MORBIDITIES ASSOCIATED WITH PSORIASIS

Moderate to severe psoriasis is linked with some other diseases, which may have a significant impact on patients.[10] Co-morbidities may increase with age and it is believed that nearly 3/4 population of psoriatic patients may have 1-3 co-morbidities. In one study it

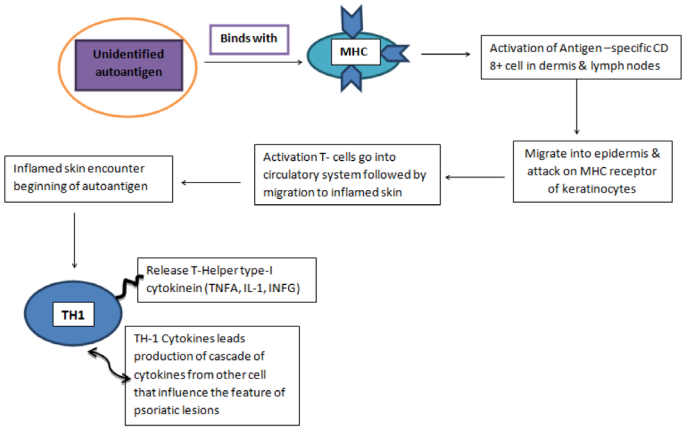

Figure 1: Mechanism for Psoriasis.

was found that patients with high severity of disease have 3-4 year shorter life than healthy people.[30] Patients older than 65 years had a statistically significant higher incidence of cardiac disease with increased risk for myocardial infarction and increased risk of higher blood glucose level which leads to diabetes mellitus.[31] Other important co-morbidities associated with this disease are psoriatic arthritis, metabolic syndrome, Crohn's disease, dyslipidemia, obstructive sleep apnea, ulcerative colitis, depression, liver disease, chronic obstructive pulmonary disease and cancer, which lead to impairment in quality of life.[32] Thus, psoriasis leads to significant psychological and psychosocial co-morbidities, which further lead to poor treatment outcomes and worsening of disease.

TREATMENT STRATEGIES

Psoriasis is a long-term diseased condition, which requires a long-term treatment therapy. The aim for the treatment of psoriasis is to reduce the severity and extent of the disease as well as to improve patient care with a major emphasis on their health-related quality of life (HRQOL) along with control on long-term disease.[33,34] Generally, three major ways are available as treatment options for psoriasis including topical, systemic and phototherapy respectively.[35] Topical therapy is the best way to treat mild to severe disease, which should be initiated at primary level of the disease. Systemic therapy may be the alternative option where topical therapy do not elicit a satisfactory responses.[19] A detailed discussion on available antipsoriatic drug therapy along with mechanism of action and potential side effect is presented in Table 2.

CHALLENGES AND OPPORTUNITIES FOR AVAILABLE TREATMENT

Currently conventional therapy is being used for the treatment of mild to moderate psoriasis.[56] Such Patients being treated with various topical therapies such as tazarotene, corticosteroids, psoralen, Vitamin D analogues, calcineuin inhibitors, 5-aminolevulinic acid, salicylic acid, an ester of fumaric acid, anthralins (dithranol), and tacrolimus as well as some systemic medication such as cyclosporine, 6-thioguanine, mycophenolatemofetil, and methotrexate.[57] Some other biologic agent such as alefacept, adalimumab, efalizumab, infliximab, etanercept or various combination of those are also being used as a treatment option for psoriasis.[58] However, most of the available therapies are associated with problems such as decreased safety profile as well as increased side effects and limited efficacy for long term use. For example, topical corticosteroids may result in cutaneous atrophy and dyspigmentation as a major side effect which limit their long-term use.[59] Some corticosteroids are also being used with several vitamin D analogues to modulate immune system as well as to increase normalization of keratinocyte maturation.[60] Tazarotene is effective as a topical agent, which is considered to be the first-aid treatment for facial

Table 2: Available treatment options for psoriasis.

Topical Therapy	
Calcineurin inhibitors (a) Tacrolimus[36] *Mechanism of action* This drug inhibits the activity of calcineurin phosphatase (cytoplasmic enzyme), which further inhibits the translocation of NFAT (nuclear factor of activated T cells) in the T cells. (b) Dithranol[37] *Mechanism of action* The drug accumulates inside the mitochondria and acts by impairment of energy supply to the cell by free radicals released from the oxidation of dithranol and interferes with the DNA replication, which slows down the extreme cell division that occurs in psoriatic plaques. (c) Tar[38] *Mechanism of action* Coal tar causes suppression of the hyperplastic skin occurring in some proliferative disorders.	*Side effects* Burning, itching sensation, Flu-like symptoms, headache, cough, discoloration of surrounding skin, Irritation Staining and carcinogenic risk.
Vitamin D_3 analogue: Calcipotriol[39] *Mechanism of action* It acts by reducing the production of pro-inflammatory cytokines such as interleukin (IL)-8. It also increases the production of anti-inflammatory cytokines like IL-4 and IL-10. Calcitriol[40] *Mechanism of action* It acts by increasing the calcium absorption in the intestine and kidney and leads to increase in the calcium level in the serum, consequently decreased bone desorption, decreased level of serum phosphatase and parathyroid hormone, increased resorption of renaltubule phosphate.	*Side effects* Pruritus, sharp pain, erythema, burning, and rare hypercalcemia, Anorexia, headache, thirst, sweating and polyuria.
Keratolytic agents: Salicylic acid[41] *Mechanism of action* Salicylic acid acts by reducing the intercellular bonding of corneocyte by decreasing the pH of the stratum corneum, which leads to hydration and swelling of corneocyte. Omega-3 fatty acids[42] *Mechanism ofaction* It acts by inhibition of lymph proliferation, antigen presentation and adhesion molecule presentation. Omega-3 fatty acid also inhibits the responses generated by Th1 and Th2 and inhibits the production of a pro-inflammatory cytokine. Glycolic acid[43] *Mechanism of action* It affects the lower layers of stratum corneum by disrupting adhesion of corneocytes presents within.	*Side effects* Inflammation and burning sensation on the applied area, rash, itching, wheezing, difficulty inswallowing or breathing.

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Table 2: **Cont'd.**

Topical Therapy	
Corticosteroids: a) Class-I (superpotent) and Class II (potent) Clobetasol propionate, Diflorasone diacetate, Halobetasol propionate, Betamethasone dipropionate, Amcinonide, Mometasone furoate, Fluocinolone acetonide[44,45] *Mechanism of action* They control the activities of cellular proteins by modifying the expression of the gene and through non-genomic mechanisms, which lead to a broad range of anti-inflammatory, vasoconstriction actions and immunosuppressant. b) Class III (upper mid strength) and Class IV (mid strength) Triamcinolone acetonide, Betamethasone valerate, Flurandrenolide, Hydrocortisone valerate[46] *Mechanism of action* They stimulate the action of phospholipase A2 inhibitory proteins, called lipocortins, which inhibit the release of arachidonic acid and regulate the biosynthesis of inflammation-causing substances such as leukotrienes and prostaglandins. c) Class V (lower mid strength) Prednicarbate[47] *Mechanism of action* This drug involves the downregulation of Il-1 α, which inhibits the cytokine in keratinocytes and leads to anti-inflammatory effects.	*Side effects* Skin infections, perioral dermatitis, skin atrophy, hypertrichosis, striae, skin thinning, telangiectasias, purpura, acneiformeruptions, burning, itching, irritation, dryness, folliculitis and secondary infection. *Side effects* Irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, polyuria, polydipsia, polyphagia, weight gain, increased susceptibility toinfection, *Side effects* gastrointestinal ulceration, pancreatitis, osteoporosis, hyperglycemia, steroid myopathy, burning sensation, itching, rash, folliculitis, reddening of skin, weeping skin lesion may occur.
Retinoids: Acitretin[48] *Mechanism of action* Acitretin modulates the mitotic activity and differentiation of the keratinocytes leads to reduced intra-epidermal movement of neutrophilic granulocytes.	*Side effects* Vitamin A toxicity (cheilitis, xerosis, nose bleeds, alopecia, increased skin fragility).

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Table 2: Cont'd.

Topical Therapy	
Systemic Therapy	
Efalizumab[49] *Mechanism of action* Efalizumab exerts its inhibitory action by reducing the movement of T-cell from the blood vessels into the tissue and leads to inhibited interaction with the endothelial cells. Etanercept[50] *Mechanism of action* Etanercept interacts with soluble pro-inflammatory cytokine called TNF-α, which leads to block the cascade of inflammation as it plays a major role in the development and regulation of inflammatory processes. Infliximab[51] *Mechanism of action* It also exerts its action by interacting with soluble pro-inflammatory cytokine called TNF-α, which leads to either neutralized pro-inflammatory activity or removal of the affected cells. Methotrexate[52] *Mechanism of action* This is a folic acid antagonist, which acts as a competitive inhibitor of the enzyme dihydrofolate reductase and prevents the conversion of dihydrofolic acid to tetrahydrofolic acid. Cyclosporine[53] *Mechanism of action* Itinhibits the activity of the calcium-calmodulin calcineurin complex and promotes the translocation of NFAT and promote the production of NFAT-dependent cytokine.	*Side effects* Flu-like reactions, leukocytosis and lymphocytosis, rebound, exacerbation and arthralgia. Local reactions, infections, sore throat, headache, dizziness, fatigue, hair loss, and rash, liver fibrosis/cirrhosis, pneumonia/alveolitis, bone marrow depression, renal damage, necrosis of soft tissue and bone, an increase of blood pressure, liver failure, nausea, anorexia, vomiting, diarrhea, hypertrichosis, gingival hyperplasia and tremor.
Phototherapy	
Ultraviolet B therapy[54] *Mechanism of action* Ultraviolet B radiation exerts its effect by binding with the nuclear DNA leads the generation of pyrimidine dimers and other photoproducts, which cause inhibition in DNA synthesis. Indirectly inhibits the proliferation of lymphocytes, which ultimately causes decreased proliferation in keratinocytes. Psoralen plus ultraviolet A therapy (PUVA) and Methoxsalen[55] *Mechanism of action* UV activated psoralen combines with DNA to induce strong binding between the two strands of the double-helical DNA and interferes with DNA synthesis. Thus it prevents the aberrant proliferation of a cell in psoriasis plaques.	*Side effects* Risk of skin cancer, most notably squamous cell carcinoma (SCC) and to a lesser extent basal cell carcinoma and malignant melanoma and premature skin aging. Pruritis, mild transient erythema, edema, headache, dizziness, acneiform eruption andsevereskin pain.

and flexural psoriasis that improves symptoms with less skin atrophy than other topical corticosteroids.[61] The onset of action of these agents is slow yet their adverse-effect profile is very low. Patients suffering from severe psoriasis are often treated with systemic therapies, which include methotrexate acitretin and cyclosporine in combination with phototherapy. Systemic agents and phototherapy exhibit a number of side effects such as hyperlipidemia, hypertension, renal toxicity, skin cancer and hepatotoxicity.[62] To overcome these problem, novel drug carrier are being developed that exhibit sustained release with reduced dosing frequency for improved therapeutic benefits to psoriatic patients.[63] Apart from novel drug delivery system for conventional drugs, herbal products are greatly been accepted by patients as these therapy is safer and having advantage of ease of availability, low cost, patient compliance and minimum side effect in comparison to other conventional therapeutics. Moreover, natural products have great diversity in molecular structure as well as have multidirectional mechanism of action to treat the disease. Therefore researchers are showing interest towards novel herbal products as an alternative for synthetic drugs for the treatment of psoriasis.[64]

ANTIPSORIATIC ACTIVITY OF HERBAL PLANTS

A number of herbal formulations are being used in market around the globe for treatment of psoriasis. The medicinal plants play a vital role in pharmacological research and drug development, since medicinal plants have many advantages over other medicines including various side effects, ease of availability at lower cost and patient compliance. Therefore researchers are seeking for potential herbal products as an alternative to synthetic drugs in psoriasis therapy.[65] Some of the herbal plants used in psoriasis along with their active constitute and mechanisms of action are shown in Table 3.

The efficacy of the herbal products is supported by *in vivo* studies for the treatment of psoriasis, which reveals that the inhibition of keratinocyte hyperproliferation, inhibition of hedgehog (Hh) signaling pathway, modulation of keratinocyte differentiation and suppression of phosphorylase kinase (PhK) activity are considered to be a major targets for antipsoriatic strategies.[92] The documented evidence in support of antipsoriatic herbal formulation is discussed in following text.

An ethanolic extract (95%) of Aloe vera leaf gel was evaluated as the treatment option for psoriasis using mouse tail model. The formulation shown significant differentiation in the epidermis, as measured from its degree of orthokeratosis (85.07± 3.36%) that was almost equivalent to the effect of 0.1% tazarotene gel, which was used as a standard positive control.[93]

A polysaccharide was purified from *Gynstemma pentaphyllum Makino* and investigated as antipsoriatic activity along with it's *in vitro* mechanism of action by using cultured HaCat cells as psoriasis relevant experimental model. They concluded that water-soluble polysaccharide (GP-I) can be a promising antipsoriatic agents in clinical therapy.[94]

Table 3: Medicinal plant used in psoriasis.

Botanical Name: *Aloe barbadensis* Miller[66] **Family Name:** Liliaceae. **Common Name:** Aloe vera. **Active Constituent:** Lignin. **Mechanism of action:** Lignin is responsible for curing psoriasis, which majorly acts through penetration mechanism that allows AV to penetrate into inner skin layers.[67]
Botanical Name: *Azadiracta indica*[68,69] **Family Name:** Meliaceae. **Common Name:** Neem. **Active Constituent:** Azadirachtin. **Mechanism of action:** Azadirachtin penetrates in the deep layer of skin to heal the disease where vitamin E and omega 6 and 9 fatty acids of Neem oil exert a moisturizing effect on skin and help in reduction of the scales and dryness.[70]
Botanical Name: *Curcuma longa*[71] **Family Name:** Zingiberaceae. **Common Name:** Turmeric. **Active Constituent:** Curcumin. **Mechanism of action:** Curcumin inhibits nuclear factor kappa B, group of proteins, which regulates inflammation during psoriasis. It also accelerates healing of skin and increases its regenerating potential. Tumour necrosis factor alpha and interleukin are important proteins during inflammation of psoriasis. Curcumin effectively inhibits the activity of these proteins and inhibits the activation of other biochemical pathways that could lead to the advancement of the disease.[71]
Botanical Name: *Glycine max*[72] **Family Name:** Fabaceae. **Common Name:** Soybean. **Active Constituent:** Genistein. **Mechanism of action:** Genistein is treated as the main isoflavone in soybean, which exerts potent anti-inflammatory and anti-oxidant properties. Immunological evidence suggested that modulates inflammatory responses by reducing production and expression of some proinflammatory biomarkers such as TNF-α, IL-6, IL-1β, and IL-8. Genistein is also believed to exert anti-proliferative activity by inhibiting NFκB signaling.[73]
Botanical Name: *Oenothera biennis* L.[74] **Family Name:** Onagraceae. **Common Name:** Evening Primrose oil. **Active Constituent:** Linoleic acid and Gamma-linolenic acid. **Mechanism of action:** Linoleic acid and Gamma-linolenic acid help in rehydration and restoration of the skin. This essential oil also benefits psoriasis by lessening the dryness, itchiness and boosts the generation of prostaglandins naturally and helps to control skin inflammation.[75]

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Table 3: Cont'd.

Botanical Name: *Nigella sativa* Linn.[76] **Family Name:** Ranunculaceae. **Common Name:** Black Cumin. **Active Constituent:** Thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol. **Mechanism of action:** These active constituents are capable to suppress the hyperproliferation and abnormal differentiation of keratinocytes.[77]
Botanical Name: *Psoraliya corylifolia* Linn.[78] **Family Name:** Fabaceae. **Common Name:** Bakuchi. **Active Constituent:** Psoralens, bakuchiol, bakuchalcone, isopsoralen.[79] **Mechanism of action:** Psoralen is a photoactive furocoumarin, which has the capacity to absorb radiant energy at a ultra-violet range of 200-320nm to form photoproducts with pyrimidine base, which inhibits DNA synthesis to decrease proliferation of cells and therefore helpful in dermal disorders like psoriasis.
Botanical Name: *Silybum marianum*[80] **Family Name:** Asteraceae. **Common Name:** Milk Thistle. **Active Constituent:** Silicristin, silibinin and silidianin, collectively known as Silymarin. **Mechanism of action:** *Silibum marianum* inhibits the activation of human T-cell, which occurs in psoriasis.[81]
Botanical Name: *Angelica sinensis*[82] **Family Name:** Apiaceae. **Common Name:** Dong quay. **Active Constituent:** Furocoumarin i.e. psoralen. **Mechanism of action:** Exposure to UV-A causes epidermal DNA cross-linking and decreases the rate of epidermal DNA synthesis.[83]
Botanical Name: *Indigo naturalis*[84] **Family Name:** Fabaceae **Common Name:** Qing-Dai **Active Constituent:** Indirubin **Mechanism of action:** Inhibits the TNF-alpha-dependent inflammatory pathways, to down-regulate inflammatory markers, which have observed in psoriatic skin.[85]
Botanical Name: *Capsicum annum*[86] **Family Name:** Solanaceae. **Common Name:** Chili peppers **Active Constituent:** Capsaicin **Mechanism of action:** Acts by depleting the neuropeptide substance locally in the skin, which is known to elicit itching during psoriasis.[87]
Botanical Name: *Matricaria recutita*[88] **Family Name:** Asteraceae **Common Name:** Chamomile. **Active Constituent:** Chamazulene. **Mechanism of action:** Act by the inhibition of lipoxygenase, which further forms leukotriene B4 (LTB4) and reduces inflammations.[89]
Botanical Name: *Smilax china*[90] **Family Name:** Smilacaceae **Common Name:** China root. **Active Constituent:** Flavonoid quercetin. **Mechanism of action:** Acts with reduction of leucocyte migration that significantly reduces the thickness of epidermal.[91]

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The topical effect of St Johns wort (*Hypericum perforatum* L.) was evaluated in plaque psoriasis in a case study where 10 patients were treated with ointment and observed significant antipsoriatic activity within 4 weeks as they observed that modified psoriasis area severity index (PASI) score was significantly lowered at the site of application of ointment.[95]

The novel antipsoriatic activity of herbal cream containing methanolic extract of *Cassia tora* leaves was prepared to obtain a controlled drug delivery system which was claimed that *Cassia tora* leaves extract show significant anti-psoriatic activity in ultraviolet-B-induced psoriasis in rat and can be also used as a natural antioxidant.[96]

The efficacy of herbal preparation of Durr Derma was evaluated in adult patients having moderate to severe skin psoriasis, which contains black cumin as the main component along with some other active ingredients like olive oil, cocoa butter, Vitamin B_{12} and tea tree oil Vitamin A. They included 8 males and 4 females and treated them two times in a day for 12 weeks. The success rate of treatment was determined by the psoriasis area and severity index (PASI) score, which was found to be lower than 75% in 10 out of total 12 treated patients within 10 weeks while remaining patients had shown PASI reduction by 50%. The results revealed that this herbal preparation could be a promising treatment option for psoriasis.[97]

Herbal formulation of *Solanum xanthocarpum* stem was prepared and further the anti-psoriatic activity was confirmed in Imiquimod-induced psoriatic mice model, after treatment for 15 days with both oral and topical formulation. They determined the level of TNF- α, IL-1 β, IL-6 and IL17 in the animal tissues as well as psoriasis area severity index (PASI). It was concluded that topical formulation has shown better anti-psoriatic activity than oral formulation.[98]

Poly herbal aqueous formulation (SIRB-001) was developed which consist of 3 herbs including *Lonicera japonica, Rheum palmatum* L. and *Rehmannia glutinosa* L. in the ratio of 1:1:3, respectively, which demonstrated efficacious anti-psoriatic

effects via multiple arms (anti-inflammatory, antiproliferative, proapoptotic anti-angiogenic) at the cellular level. They concluded that SIRB-001 exhibited well *in vitro* antipsoriatic properties in cell-free enzymatic assays, keratinocytes and immune cells.[99]

Double-blinded, randomized and dosage-controlled trial study was performed to determine the safety and efficacy of indirubin in the Lindi oil ointment in different concentrations to treat chronic plaque psoriasis. Lindi oil ointement 200, 100, 50 or 10 μg g^{-1} of indirubin was applied twicein a day for 8 weeks to the adult patients suffering from plaque psoriasis for more than 1 year and observed 75% to 90% reductions in PASI scores within 8 weeks. The authors finally concluded 200 μg/g of indirubin with lindi oil ointment was the most effective concentration to treat psoriasis topically.[100]

The effects of glabridin (Glab) was investigated on proinflammatory cytokines, oxidative/anti-oxidative indexes, histopathological changes and PASI scores in IMQ-induced mice and observed significantly suppressed levels of NF-κB subunit p65, nitric oxide (NO), interleukin (IL)-6, and IL-1β in HaCaT cells stimulated by lipopolysaccharide. In addition, they also observed the reduced expression of IL-17A, IL-22 and IL-23 in HaCat cells stimulated by TNF-α. The results indicated that Glab had beneficial effects on psoriasis and concluded that the underlying mechanism can be associated with the down-regulation of pro-inflammatory cytokines and the improvement of antioxidant status.[101]

HERBAL NANOTECHNOLOGY FOR PSORIASIS TREATMENT

Most of the herbal drugs from herbal origin are poorly water soluble due to presence of hydrophobic active ingredients which results in low bioavailability and increased systemic clearance. Therefore increased or repeated dose is require, that leads to limited clinical used of herbal medicines.

An alternative option is required to increase water solubility of herbal drugs as well as to localize the drug in particular site for improved patient compliance and better efficacy.[102,103] In recent years, nanoparticles and micro particles have been used widely for herbal medicines and have gained unique position for delivery of various bio actives, proteins, peptides and drugs for treatment of various skin diseases and considered to be an important one as they improve the selectivity, increase patient compliance, effectiveness and thereby reduce dose with low toxicity.[104] Several herbal active constitutes have been incorporated with different particle systems to treat various skin related immune diseases followed by biological evaluation to estimate their safety and efficacy. Table 4 states some herbal active constitutes loaded with nanoparticles for skin related immune diseases.

The number of publications relating to nanoformulation containing herbal constituents for treatment of psoriasis has been increased exponentially. For example, Laxmi *et al.* developed psoralen containing gel formulation using natural gums and polymers and further evaluated for stability, viscosity, content uniformity and pH. The perfusion study was observed using dialysis membrane in phosphate buffer with pH ranging from 6.8 to 7.0 at 37°C. The study revealed that formulation containing egg xanthan and albumin gum showed better incorporation of drug. Finally, on the basis of *in vivo* studies, the drug activity was found to be 43.3% with enhanced differentiation of orthokeratotic cell in the epidermal scales.[113]

A novel microemulsion of 5% tea tree oil was developed using Tween 80 as surfactant and Isopropyl alcohol and Isopropyl myristate as cosurfactant for treatment of psoriasis. The formulation was further tested for droplet size, PDI, pH, viscosity and surface morphology. The average droplet size was found to be between the ranges of 84-115 nm with a PDI of 0.764 which demonstrating uniformity in the emicroemulsion. The TEM image was also found to be spherical shaped having smooth boundary of the oil particles. Further *in vitro* skin diffusion studies clearly demonstrated the increased ability of microemulsions to deliver the drug through topical application.[114]

The therapeutic and clinical benefit of a topical turmeric microemulgel was evaluated on 34 patients with mild to moderated plaque psoriasis in a placebo-controlled, double blind and randomized clinical trial. The results showed improved health with lower side effects. The authors concluded on the basis of these results that microemulgel may be considered as an alternative therapeutic option for plaque psoriasis.[115]

Topical nanogel formulation of Acitretin and Aloe-emodin was prepared by using natural polymer chitin for the treatment of psoriasis. The formulated nanogel was optimized on the basis of amplitude, particle size, drug release and time of probing. Non-fickian release pattern was observed during *in-vitro* drug release at pH 5.5 suggesting prolonged release nature of the drug. It was also observed that retention of drug was high at the inner layer of skin, which is essential to treat disease like psoriasis. Biocompatibility of the drug was confirmed during the histopathological investigation after *in vivo* skin irritation study on Perry's mouse tail model.[116]

A novel nanovesicular gelof *Berberis aristata* extract was developed and evaluated for its anti-inflammatory and antipsoriatic activity. The transferosomes of modified lipid film hydration technique were prepared by using soya phosphatidyl choline and edge activator such as sodium deoxycholate, Span 80 and Tween 80. Imiquimod (IMQ) (immune modifier) was topically applied on the shaved mice to develop psoriasis-like inflammation and then studied the histopathological status of inflamed skin. Histopathological studies revelaed a marked reduction in thickness of epidermise as compared to conventional gel formulation. The results also revealed the inhibition of edema by novel formulated gel (55.76%) is greater than conventional gel along with low irritation.[117] An antipsoriatic nanovesicular gel of Acitretin (Act) was formulated for topical delivery to overcome some side effects such as skin irritation, low aqueous

Table 4: Herbal drug containing nanoparticles:

Formulation details	Benefits of Formulation
Biological Source: *Capsicum annuum*.[105] API: Capsaicine. Polymeric nanoparticle Formulation: SLN/NLC. Encapsulation Efficiency: 88%	Enhanced skin permeability.
Biological Source: *Capsicum annuum*.[106] API: Capsaicine. Polymeric nanoparticle Formulation: Lipid-polymer hybrid nanoparticles. Encapsulation Efficiency: 92%	Nanoparticles system coated with cationic lipid contributed to the enhancement of skin permeation.
Biological Source: *Capsicum annuum*.[107] API: Capsaicine. Polymeric nanoparticle Formulation: Niosome, microemulsions. Encapsulation Efficiency: 86.71%	Better permeation.
Biological Source: *Ammianus*.[108] API: Methoxsalen. Polymeric nanoparticle Formulation: Microemulsions.	Controlled drug release.
Biological Source: *Psoralea coryfolia*.[109] API: Psoralenbabchi oil. Polymeric nanoparticle Formulation: Microemulsion gel.	Improved the penetration of psoralen and babchi oil.
Biological Source: *Curcuma longa*[110] API: Turmeric oil, Curcuminoids. Polymeric nanoparticle Formulation: Nanoemulsion,Solid lipid nanoparticles. Encapsulation Efficiency: 70%	Enhanced stability with better *in vivo* activity.
Biological Source: *Tripterygium wilfondil* Hook F.[111] API: Diterpenoid triepoxide Polymeric nanoparticle Formulation: Poly (DL-lactic acid) nanoparticles Encapsulation Efficiency: 85.7%	Enhanced solubility and reduced toxicity.
Biological Source: *Tripterygium wilfondil* Hook F.[112] API: Triptolide Polymeric nanoparticle Formulation: Solid lipid nanoparticle.	Enhanced anti-inflammatory and reduced hepatotoxicity with transdermal delivery of triptolide.

solublity, instability and serious systemic adverse effects. The optimized niosomal vesicles were incorporated in gel base matrix and further investigated for *in vivo* antipsoriatic activity using mouse tail model experiments. Finally, better skin tolerability and negligible skin irritation were revealed by histopathologic examination and primary irritation index.

A nanoemulsions of rice bran oil was developed by low energy emulsification methods, The formulation contain 10% rice bran oil, 0.05% antioxidant 10% surfactants and 0.05% preservatives in distilled water which was further and then evaluated its moisturizing activity, physical stability and irritation potential on healthy and diseased skin volunteers. The results of *in vivo* assessments and irritation potential studies indicated that newly formulated nanoemulsion had an anti-psoriatic potential.[118]

A nanoemulsion of turmeric oil composed of 42% Smix (1:1), 15% turmeric oil and 43% distilled water was prepared by using titration method and further evaluated for physical stability, irritation potential and *in vivo* anti-psoriatic activity and anti-inflammatory activity. The results reveal that formulated nanoemulsion was stable during the period of study and free form irritation in organotypic HET-CAM model. It was observed that anti-inflammatory activity in cacrageenan-induced paw edema was reduced to 70.35%.[119]

Some niosomes were prepared for liquorice extracts of ammonium glycyrrhizinate (AG), made up of surfactants (Tween 85 and Span 20) and cholesterol at various concentrations and demonstrated their utility for treatment of dermatitis, eczema and psoriasis with same efficacy as corticosteroids. The newly formed vesicles were characterized by their zeta potential (ζ), dimensions, anisotropic properties, drug entrapment efficiency, stability, cytotoxicity and skin tolerability. *In vitro* release profiles of ammonium glycyrrhizinate niosomes were evaluated in murine and human models of inflammation by using cellulose membranes. Overall result demonstrated that AG-loaded non-ionic surfactant vesicles showed good skin tolerability and anti-inflammatory activity in mice without any toxicity.[120]

Kazi and his teammates prepared various CAP-bearing systems including niosomes, liposomes and emulsomes by using film hydration method to improve topical delivery of a drug and compared various *in vitro and in vivo* parameters. TEM photographs were used to confirm the spherical shape and nanometric size of the carrier system. They found higher accumulation of drug in emul-gel formulation through skin retention studies by *in vitro* and *in vivo* experiments and concluded this formulation can be potential for topical delivery of CAP in anti psoriatic therapy.[121]

A topical formulation of psoralene ethosomes were prepared to improve entrapment, skin permeation and deposition efficiency which was further evaluated real time drug release *in vivo* in rat model by microdialysis. During *in vitro* and *in vivo* studies, the group observed 6.56 times greater skin deposition of psoralen by ethosomes as well as area under curve and peak concentration

Table 5: Recent patents for Psoriasis and skin related therapy.

Patent publication Number(s)	Year	Authors	Brief description of patent	Reference
WO2011/042485	2013	Alexandra *et al.*	The invention provides novel pharmaceutical compositions of macrollide immunosuppressants.	[125]
US008715736B2	2014	Sachdeva *et al.*	Describe the various methods and formulation com prise active Substances encapsulated within Surface modified Nanostructured lipid carrier nanoparticles for treating a condition of the skin.	[126]
US008992994B2	2015	Roy *et al.*	Reported the nonoemulsions comprising nano size droplets of one or more anti-psoriasis agents that exhibit greater permeability, and improved bioavailability.	[127]
WO 2018/236206 Al	2018	Oi Ming *et al.*	Nanoformulation comprises of vitamin A, C and E to get synergistic effect to treat common skin disorders.	[128]
US 2019/0231897 A1	2018	Balasamy *et al.*	A platinum (II) complex loaded on a mesosilicalite nanocarrier for treatment of psoriasis	[129]

by 2.34 and 3.37 times respectively than shown by tincture. The percutaneous permeability was also found to be greater for abdomen than scapulas or chest. Overall they concluded that enhanced permeation and skin deposition by ethosomes could be helpful to reduce toxicity as well as to improve the efficacy of psoralen in long term psoralen treatment.[122,123]

Skin permeation, efficacy and localization of drug in different skin layers of nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) was investigated and their potential of improving topical delivery of capsaicin (CAP) along with toxicity was explored through *in vitro* and *in vivo* studies. The SLNs were prepared by solvent diffusion methods which were further characterized for average particle size, zeta potential and entrapment efficiency.

They observed that higher amount of CAP could be encapsulated with the NLCs as compared with SLNs. They also noted that the cumulative amounts of CAP (permeation and retention, respectively) through the skin were higher by NLCs as compared with SLNs.[124]

Apart from the reported publication patents can represents an invention in a particular field of technology therefore some patent reports are also added in the following text of this review. Table 5 represents some of the latest formulations which have been recently patented for treating psoriasis.

CONCLUSION AND SUMMARY

The increase of incidence of psoriasis has spurred several efforts to identify herbal formulation with potential therapeutic benefits. Initial efforts towards the development of herbal formulation faced many challenges with regards to efficacy, safety, poor water solubility and bioavailability with increased systemic clearance. Therefore, more scientific documentation and evidences are warranted for the promotion of herbal treatment of psoriasis using a combination of various novel colloidal carriers such as NLCs, SLNs, liposomes, niosomes and transferosomes for effective and safe delivery of various anti-psoriatic drugs. The development in the nano formulation is continuous as to be a viable strategy to target with the aim to inhibit multiple pathways responsible for the pathogenesis of psoriasis. Focused research efforts to establish the superiority of novel drug delivery systems incorporating herbal treatment for psoriasis are needed. Although this appears to be promising yet scientific proof beyond doubt must be made available. Carbon nanotubes (CNTs) and Quantum dots (QDs) based drug delivery may also be worth exploring in view of their unique properties.

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CONFLICT OF INTEREST

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

ABBREVIATIONS

Act: Acitretin; **AD:** Atopic dermatitis; **AG:** Ammonium Glycyrrhizinate; **BSA:** Body surface area; **CAD:** Coronary artery disease; **CAMP:** Cathelicidin antimicrobial peptide; **CAP:** Capsaicin; **CNTs:** Carbon nanotubes; **DCs:** Dendritic cells; **Glab:** Glabridin; **Hh:** Hedgehog; **HRQOL:** Health-related quality of life; **IFNα:** Interferon-α; **IL:** Interleukin; **IMQ:** Lmiquimod; **JAK:** Janus Kinase; **LTB4:** Leukotriene B4; **MHC:** Major histocompatibility complex; **NDDS:** Novel drug delivery systems; **NF-κB:** Nuclear factor-κB; **NLCs:** Nanostructured lipid carriers; **NO:** Nitric oxide; **PASI:** Psoriasis area severity index; **pDCs:** Plasmacytoid dendritic cells; **PhK:** Phosphorylase kinase; **PUVA:** Psoralen plus ultraviolet A therapy; **QDs:** Quantum dots; **SCC:** Squamous cell carcinoma; **SLNs:** Solid lipid nanoparticles; **TLR7:** Toll-like receptor 7; **TNF:** Tumor necrosis factor; **T-cell:** T-lymphocyte.

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