

## A Review on Phyto Constituents for Treatment of Psoriasis

### Abstract

Psoriasis once thought to be largely an epidermal keratinocyte problem, it is now understood that it is a disorder due to immune-mediation. Skin hyperplasia of vascular hyperplasia, epidermal keratinocytes, and permeation of neutrophils, leucocytes, and extra types of T lymphocytes in affected skin. The pathophysiology of the illness is intricate and includes both genetic and cellular elements. As a result, there are many different therapeutic approaches that work on various targets, ranging from symptomatic treatment to immune system modulation. Drugs are known to cause the condition but the precise cause of it is uncertain. Environmental factors like smoking, infections and seasonal changes are also responsible. Natural alternatives are being sought after due to the harmful impact on life quality and dangerous adverse effects of conventional treatment. There are a variety of plants that have been utilized in conventional psoriasis treatment methods that could serve as safer substitutes. The emphasis of the current review article is on pharmacological studies of anti-psoriatic plant, plant extracts, and formulation. The review has also taken into account several chemical elements extracted from plants that are accountable for antipsoriatic activity and their mechanisms of action. This review is necessary to choose these plants for more research in order to identify the chemical components that fight psoriasis and determine how they work.

Keywords: Phytoconstituents, Psoriasis, Anti-psoriatic plants, Pharmacological studies.

### INTRODUCTION

Psoriasis is an inflammatory, proliferative skin, and autoimmune condition that occurs by T-cell activation. It is distinguished by violently distinct, peach-pink or drab-red hard silvery scales patches which cause specific abrasions on skin. It also causes hyperkeratosis, dilated micro-vessels, aberrant keratinization, epidermal proliferation, and inflammatory cell infiltration. A characteristic risk factor for several diseases, for example cardiovascular disease, type 2 diabetes, and Dyslipidemia, is psoriasis. Insomnia, arthritic pain, and depression are among issues that are frequently present.[1] Any area of the body can be affected by psoriasis, but it occurs mostly on the scalp, lower back, and limb's extensor surfaces (particularly the knees and elbows). Psoriasis can clarify at any age, though it frequently appears to be around the 15-22 age range. Around the 60-69 age range, psoriasis appears to reach a second peak. Ladies are slightly more likely than males to get psoriasis at an earlier age, and family history also has a significant impact on when psoriasis first appears. With alternate periods of relapse and remission, the illness may endure for only a few weeks or for the rest of life. There is a noticeable rise in the inflammatory cytokines IL-1, IL-6, and TNF- $\gamma$  in those with psoriasis. The metabolic syndrome is linked to the chronic systemic inflammatory condition known as psoriasis. Those with metabolic syndrome also have cytokines including IL-1, IL-4, IL-6, IL-8, IL-12, and

TNF- $\gamma$  that are involved in the development of psoriasis.[2] Psoriasis is caused by a number of reasons, in addition to chronic inflammation, including environmental factors, genetics, alcohol consumption, stress and improper nutrition. Both the genetics and environment play role in the psoriasis development process. Compared to those who are not affected by psoriasis, people with psoriasis have a higher incidence of metabolic syndrome. Pustular and non-pustular psoriasis can be broadly divided into two kinds, with other subtypes occurring between these two types. The most prevalent kind of plaque psoriasis is psoriasis vulgaris. The subtypes that are typically collected with plaque psoriasis comprise erythrodermic psoriasis, that affects 75% of the body's surface, guttate psoriasis, and eruptive psoriasis, which typically affects young adults and children. Flexural areas of skin are associated with Inverse psoriasis. The first line of treatment is traditional topical therapy, which uses corticosteroids, Vitamin D and its equivalents. Psoriasis was measured using Vitamin A as a control. The proliferation rate and epithelia are affected by a number of Vitamin A derivatives. Keratin variation and thus controls its abnormalities in psoriasis which is an autoimmune disease. According to a worldwide epidemiology study, psoriasis is common in many different nations and, in certain places, it affects people of all ages. Psoriasis is common in children; in Taiwan it is 0%, in Germany it is 0.71%, and in Italy it is 2.1%. Adults

in France make up 5.20%. Psoriasis is not as common in India as it is in western nations, yet there are still some cases and reports of them. Psoriasis is a significant condition in itself, but it can also be made worse by a number of other conditions, like as a heart attack, diabetes, arthritis, etc. It has a negative impact on health. The National Health Services place more emphasis on educating and empowering patients to reduce the negative effects of the illness. On May 24, 2014, the 67th World Health Assembly of WHO permitted a resolution on psoriasis. Every member state made a commitment to make the necessary efforts and reduce the number of psoriasis sufferers in order to combat the disease. The members were aware of the psoriasis sufferers worldwide due to insufficient care, delayed or inaccurate diagnoses, and access to care issues. The perseverance petitioned WHO to organize a worldwide report on psoriasis and involve in spreading alertness about the psoriasis in order to draw attention to the effect of the condition on public health. The goal of policymakers' efforts is to enhance the health and social inclusion of people having psoriasis. Health services research must enhance the effectiveness and quality of care so that psoriasis therapy can serve as a paradigm for other chronic skin diseases. Different triggering events that cause the disease to appear or chronic diseases to flare up have been found. Nations demonstrate that obesity or weight gain has been linked to the development of psoriasis. Smoking tobacco is a significant additional risk factor for psoriasis. Psoriasis can also be brought on by specific types of infections, such as streptococcal throat infections. Psoriasis risk is elevated in those with periodontitis. In both adults and children, stress is the primary beginning factor for psoriasis.

#### CLASSIFICATION

**Plaque psoriasis:** Plaque psoriasis is the most common type of psoriasis. About 80% to 90% of people with psoriasis have plaque psoriasis.

**Inverse psoriasis:** This type appears in your skin folds. It causes thin plaques without scales.

**Guttate psoriasis:** Guttate psoriasis may appear after a sore throat caused by a streptococcal infection. It looks like small, red, drop-shaped scaly spots and often affects children and young adults.

**Pustular psoriasis:** Pustular psoriasis has small, pus-filled bumps on top of plaques.

**Erythrodermic psoriasis:** This is a severe type of psoriasis that affects a large area (more than 90%) of your skin. It causes widespread skin discoloration and skin shedding.

**Sebopsoriasis:** This type typically appears on your face and scalp as bumps and plaques with a greasy, yellow

scale. This is a cross between psoriasis and seborrheic dermatitis.

**Nail psoriasis:** Nail psoriasis causes skin discoloration, pitting and changes to your fingernails and toenails.

#### EPIDEMIOLOGY

The worldwide prevalence of psoriasis is estimated to be approximately 2–3%. Although the disease is known to have higher prevalence in the polar regions of the world, its burden in a tropical/subtropical country like India cannot be underestimated. In a diverse country such as India, the prevalence of psoriasis may vary from region to region due to variable environmental and genetic factors. We found only six studies, mostly in a hospital setting, from North India estimating the prevalence of disease among adult dermatologic patients. A higher prevalence in males has been reported with a peak age at onset is in the third and fourth decade of life. In one of the larger studies from Northern India, point prevalence of pediatric psoriasis was estimated to be 0.0002%. The peak age at onset among boys is in the 6–10 years age group compared to girls in 11–15 years age group. A positive family history may be elicited in 9.8–28% of the children. The age at onset of psoriatic arthritis varies from 35 to 50 years with no sex predilection. Nearly 70% of the patients develop psoriasis before articular involvement; in another 15%, arthritis precedes the onset of psoriasis by more than 1 year, and in the remaining 15% of the cases, the two conditions occur within 12 months of each other. The yearly estimated incidence and prevalence of psoriatic arthritis are, respectively, 3.0–23.1 cases/100,000 and 1–420 cases/100,000 people, with similar results in Western countries and in China. Prey *et al.* in their systematic review of literature concluded that psoriatic arthritis may affect up to 24% of patients with psoriasis. Such data is lacking among Indian patients. In children, arthritis may precede psoriasis in 50% of cases. The mean age of onset in children is 9–10 years with female predominance.

#### ETIOLOGY

Psoriasis is a multifactorial disease in which both extrinsic and intrinsic factors play major roles. Genetic predisposition is considered a key contributor, especially in individuals with early onset of the disease (under 40 years).

Behavioral and environmental factors may also be involved. Mild localized trauma, stress, drugs, infections, smoking and alcohol usage, obesity, are all known to

cause or aggravate psoriasis. Climate change in general, and exposure to natural sunlight in particular, has been recognized as a possible psoriasis trigger or exacerbating factor .

Genetics is one of the most significant factors. The importance of genetic factors is demonstrated by the fact that approximately 40% of individuals with psoriasis or psoriatic arthritis have a family history of the disease . Additionally, monozygotic twins are more likely to have the disease than dizygotic twins Using genome-wide association studies, over 60 susceptibility loci have been identified, many of which contain genes involved in immune system regulation .

The psoriasis-susceptibility (PSORS1) locus on chromosome 6p21 (location of the HLA genes) is thought to be a major genetic determinant of psoriasis . HLA-Cw6 is the most important allele for susceptibility to early-onset psoriasis and it has also been associated with guttate psoriasis, among other MHC genes linked to psoriasis . HLA-B17 has been linked to an increased risk of psoriasis and severe psoriatic arthritis .

Psoriasis susceptibility loci have been also found in genes that encode the common component of the IL-12 and IL-23 receptors . Psoriasis appears to be predisposed to or protected by certain receptor polymorphisms . Furthermore, highly associated to psoriasis are the *IL12B* gene, which encodes for the p40 subunit of IL-12 and IL-23, as well as the *IL23A* gene, which encodes for the p19 subunit of IL-23 and IL-39. Despite the lack of evidence, pustular psoriasis appears to be genetically unique, with different susceptibility genes implicated (*IL36RN*, *APIS3* in Europeans, and *CARD14* in other ethnicities) .

Beta blockers, lithium, and antimalarial medicines are the most commonly employed pharmaceuticals that can induce psoriasis-like eruptions or worsen the psoriasis. Notably, TNF inhibitors, which are commonly used to treat psoriasis, have also been associated with the development of psoriasis-like eruptions .

Infections, both bacterial and viral, have been linked to worsening of psoriasis. The initiation or exacerbation of psoriasis in correlation with HIV infection, as well as poststreptococcal flares of guttate psoriasis, are known contributors .

Low vitamin D levels have been observed in psoriasis patients, although the function of vitamin D in psoriasis is unknown . Even after adjusting for factors such as the Fitzpatrick skin phototype and estimated sun exposure, serum levels of 25-hydroxyvitamin D were lower in the patients with psoriasis in a case-control study that compared 43 patients with psoriasis and 43 matched

controls with other non-photosensitive dermatologic diseases .

For many psoriatic patients, psychological distress is a causal or sustaining component in disease manifestation .

In a previous study comprising 400 patients with newly developed psoriasis, 46% of plaque psoriasis patients and 12% of guttate psoriasis patients associated the onset of their disease to a life crisis, such as divorce, severe or life-threatening disease in the patient or a family member, death in the family, financial burden, dismissal, or harassment in school . Further research is necessary to determine the effect of stress on the progression of psoriasis.

#### PATHOPHYSIOLOGY

Psoriasis is characterized by an abnormally excessive and rapid growth of the epidermal layer of the skin. Abnormal production of skin cells (especially during wound repair) and an overabundance of skin cells result from the sequence of pathological events in psoriasis. The sequence of pathological events in psoriasis is thought to start with an initiation phase in which an event (skin trauma, infection, or drugs) leads to activation of the immune system and then the maintenance phase consisting of chronic progression of the disease. Skin cells are replaced every 3–5 days in psoriasis rather than the usual 28–30 days. These changes are believed to stem from the premature maturation of keratinocytes induced by an inflammatory cascade in the dermis involving dendritic cells, macrophages, and T cells (three subtypes of immune cells). These immune cells move from the dermis to the epidermis and secrete inflammatory chemical signals (cytokines) such as interleukin-36 $\gamma$ , tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , interleukin-6, and interleukin-22. These secreted inflammatory signals are believed to stimulate keratinocytes to proliferate. One hypothesis is that psoriasis involves a defect in regulatory T cells, and in the regulatory cytokine interleukin-10. The inflammatory cytokines found in psoriatic nails and joints (in the case of psoriatic arthritis) are similar to those of psoriatic skin lesions, suggesting a common inflammatory mechanism.

Gene mutations of proteins involved in the skin's ability to function as a barrier have been identified as markers of susceptibility for the development of psoriasis.

Deoxyribonucleic acid (DNA) released from dying cells acts as an inflammatory stimulus in psoriasis and stimulates the receptors on certain dendritic cells, which in turn produce the cytokine interferon- $\alpha$ . In response to these chemical messages from dendritic cells and T cells, keratinocytes also secrete cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$ , which signal

downstream inflammatory cells to arrive and stimulate additional inflammation.

Dendritic cells bridge the innate immune system and adaptive immune system. They are increased in psoriatic lesions and induce the proliferation of T cells and type 1 helper T cells ( $T_H1$ ). Targeted immunotherapy, as well as psoralen and ultraviolet A (PUVA) therapy, can reduce the number of dendritic cells and favors a  $T_H2$  cell cytokine secretion pattern over a  $T_H1/T_H17$  cell cytokine profile. Psoriatic T cells move from the dermis into the epidermis and secrete interferon- $\gamma$  and interleukin-17. Interleukin-23 is known to induce the production of interleukin-17 and interleukin-22. Interleukin-22 works in combination with interleukin-17 to induce keratinocytes to secrete neutrophil-attracting cytokines.

## DIAGNOSIS

Psoriasis is a clinical diagnosis, and a skin biopsy is usually not necessary for classic presentations of the disease. The characteristic lesions are sharply demarcated, scaly, erythematous plaques. The plaques may be pruritic and/or painful. They can be ovoid, round, or irregular in morphology and are often symmetrically distributed. When the xerotic scale is removed with scraping, points of fine bleeding may be seen (the “Auspitz sign”). Lesions may develop at sites of trauma or injury, known as the Koebner phenomenon.

The plaques are most frequently found on the extensor surfaces (elbows and knees), the scalp, and the intergluteal cleft. The palms and soles may be affected in the variants of palmoplantar psoriasis and palmoplantar pustulosis. Other forms of psoriasis include generalized pustular, guttate, erythrodermic, and inverse psoriasis.

The extent and severity of psoriasis can be measured using the Psoriasis Area and Severity Index (PASI), which includes evaluations of body surface area (BSA) involvement, erythema, induration, and scaling. This generates a severity score ranging from 0 to 72. Although more commonly used in clinical trials than in the context of clinical practice, the PASI can be a useful measurement in assessing response to a given treatment. For example, PASI-75 indicates that the patient’s psoriasis has improved by 75% or greater from baseline. The Physician Global Assessment (PGA) is another simplified measurement tool that rates the severity of psoriasis at a single point in time. It is important to note that one of the limitations of the PASI and PGA is that there can be high interobserver variability.

In addition to assessing the severity of psoriasis, it is also important to include evaluations of subjective symptoms and quality of life burden. Furthermore, given the high

probability of systemic comorbidities, including arthritis and cardiovascular, metabolic, and psychiatric disorders, patients should be screened for such conditions and have an established primary care physician who can help manage the patient’s overall health.

## TREATMENT

Although there is no cure for psoriasis, there are multiple effective treatment options. Topical therapy is the standard of care for treatment of mild to moderate disease. A large proportion of patients would benefit from topical therapy, which can be initiated at the primary care level. If topical agents do not elicit an adequate response or if they are not practical owing to the affected body surface area, these patients can be referred for assessment by a dermatologist, at which point systemic therapy with topical adjuncts might be more suitable. Presence of psoriatic arthritis might also call for systemic therapies in collaboration with a rheumatologist.

## TOPICAL THERAPY

*Corticosteroids:* Considered the cornerstone of topical treatment, corticosteroids are often well tolerated and effective for patients with mild psoriasis. Despite widespread use for more than half a century, large RCTs and head-to-head comparisons are rather limited. A Cochrane review of 177 RCTs, however, showed that corticosteroids performed at least as well as vitamin D3 analogues, with standardized mean differences ranging from  $-0.89$  (95% CI  $-1.06$  to  $-0.72$ ) to  $-1.56$  (95% CI  $-1.87$  to  $-1.26$ ) for potent and very potent corticosteroids, respectively. Overall, topical steroids in various formulations, strengths, and combinations are efficacious initial therapy for rapid control of symptoms. For instance, salicylic acid, a keratolytic agent, can be combined with steroid therapy to help treat plaques with thicker scales, for better penetration of medication. Although uncommon, long-term use is complicated by possible side effects of local skin changes, tachyphylaxis, and hypothalamic-pituitary-adrenal axis suppression. *Vitamin D3 analogues:* Calcipotriol, a vitamin D3 analogue, is a first-line topical agent for treatment of plaque psoriasis and moderately severe scalp psoriasis. It reduces symptoms by modulating keratinocyte proliferation and differentiation, and by inhibiting T lymphocyte activity. Multiple randomized trials have shown calcipotriol to be safe and efficacious for patients with mild plaque psoriasis and not inferior to most corticosteroids with respect to efficacy. Further, a Cochrane meta-analysis of 177 RCTs showed that vitamin D3 analogues are more effective than all other

topical medications, except the most potent of corticosteroids; standardized mean difference ranged from  $-0.7$  (95% CI  $-1.04$  to  $-0.30$ ) to  $-1.66$  (95% CI  $-2.66$  to  $-0.67$ ) for twice-daily bexocalcidiol and once-daily paricalcitol, respectively. Given their efficacy and safety profile, vitamin D3 analogues are commonly used as monotherapy or, more often, as combination therapy. Side effects include mild irritant dermatitis and rarely hypercalcemia with excessive use. These agents should not be used in combination with salicylic acid or before phototherapy. *Combination products:* Combination of calcipotriol and betamethasone dipropionate was shown to be more effective for psoriasis than either monotherapy alone in a Cochrane review of 177 RCTs. Clinical trials have also demonstrated reduced incidence of adverse events with concomitant or sequential use of vitamin D3 analogues and topical corticosteroids. Based on a systematic review of 6 RCTs with 6050 patients, the mean reduction in Psoriasis Area and Severity Index score at 4 weeks was 74% with combination therapy, compared with 59% and 63% with calcipotriol and betamethasone dipropionate, respectively. The combination gel is well tolerated and can be applied once daily, avoiding the facial, genital, and flexural areas.

#### SYSTEMIC THERAPY

*Phototherapy:* Phototherapy is a mainstay treatment of moderate to severe psoriasis, especially in psoriasis that is unresponsive to topical agents. It is available as psoralen plus UVA, broadband UVB, and narrowband UVB (NB-UVB). Owing to its efficacy and safety advantages, as shown in multiple RCTs, NB-UVB therapy is often used as first-line treatment. In fact, NB-UVB therapy can be given to almost any patient, including children and pregnant women. There is no evidence that NB-UVB increases the risk of skin malignancy. Despite its safety, limited availability of phototherapy centres (fewer than 50 centres across Canada) and the need for frequent visits (3 times a week for 3 months initially) renders this option extremely inconvenient for patients.

*Acitretin:* Acitretin is a synthetic retinoid indicated for treatment of moderate to severe psoriasis. Its role as an adjunctive therapy to other systemic agents has been well documented to enhance efficacy, lower doses, and reduce occurrence of side effects. However, large robust trials studying its efficacy and safety as monotherapy are lacking. Common side effects include mucocutaneous dryness, arthralgia, gastrointestinal upset, and photosensitivity. This medication can sometimes cause transaminitis and elevated triglyceride levels. Acitretin is a potent teratogen that is best avoided in women of

childbearing age and potential; it is recommended that women not get pregnant for 3 years after discontinuing the medication.

*Methotrexate:* Methotrexate is an inhibitor of folate biosynthesis, used for its cytostatic and anti-inflammatory properties in the treatment of moderately severe to severe psoriasis, as well as psoriatic arthritis. Despite substantial clinical experience with this drug, large robust studies of its efficacy and safety are extremely limited. One randomized, double-blind, placebo-controlled study showed 75% improvement in Psoriasis Area and Severity Index score in almost 40% of patients with methotrexate, compared with 18.9% of patients with placebo at 16 weeks. A well-known side effect is hepatotoxicity. Other more common side effects include nausea, vomiting, diarrhea, and fatigue.

*Cyclosporine:* Cyclosporine is a calcineurin inhibitor indicated for treatment of moderate to severe psoriasis. There is also some evidence for its efficacy in psoriatic arthritis. It has been shown to cause significant improvement or complete remission in 80% to 90% of patients within 12 to 16 weeks in a 1-year open, multicentre, randomized study with 400 patients. Advantages over other systemic agents include rapid onset of action and less concern about myelosuppression or hepatotoxicity. Adverse effects include nephrotoxicity, hypertension, elevated triglyceride levels, gingival hyperplasia, tremors, hypomagnesemia, hyperkalemia, numerous drug interactions, and malignancies such as skin cancers and lymphoma.

#### BIOLOGICAL THERAPY

*Biologic therapy:* Biologics have emerged as highly potent treatment options in patients for whom traditional systemic therapies fail to achieve an adequate response, are not tolerated owing to adverse effects, or are unsuitable owing to comorbidities. There is no single sequence in which biologics should be initiated or switched; however, a meta-analysis of pivotal phase III studies has shown that infliximab might be the most efficacious, followed by ustekinumab, adalimumab, and etanercept. Choice of therapy depends on clinical needs, benefits and risks, patient preferences, and cost effectiveness (around \$20 000 to \$25 000 a year on average). Previous randomized trials and retrospective studies have shown that biologic therapy was not associated with increased risk of malignancy or serious infection.

#### CONCLUSION

Psoriasis is a multisystem inflammatory disease that is underdiagnosed and undertreated despite its prevalence

and considerable effect on quality of life. Beyond skin and joint involvement, psoriasis is also associated with an array of important medical and psychiatric comorbidities that require timely therapy to improve long-term outcomes. Primary caregivers are well positioned to provide diagnosis and treatment of patients who seek initial evaluation at the primary care level. Patients with psoriasis for whom topical therapy fails can be referred to a dermatologist for further evaluation.

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