A Review on Phytoconstituents for the Treatment of Psoriasis

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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-γ 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-γ 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.\textsuperscript{[3]}

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.\textsuperscript{[4]}

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.\textsuperscript{[5]}

On May 24, 2014, the 67\textsuperscript{th} 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.\textsuperscript{[6]} Different triggering events that cause the disease to appear or chronic diseases to flare up have been found. Understanding triggers and reducing them can be a crucial step in the management of psoriasis. Many researches from several 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.\textsuperscript{[7]}

**CLASSIFICATION OF PSORIASIS**

**Plaque psoriasis**

Plaque psoriasis is the mainly prevalent type of psoriasis, and patients may have plaques that are nummular (coin-sized), circular, or oval in shape.\textsuperscript{[8]} The lesions may start out as erythematous macules which flat and 1 cm in diameter or papules, spread outward, and then combine to create plaques that range in diameter from 1 to several centimeters. 90% of instances of plaque psoriasis are chronic.

**Guttate psoriasis**

The term “guttate psoriasis” refers to the sudden appearance of numerous tiny psoriatic lesions with a diameter of 2 to 10 mm.\textsuperscript{[9]} Although these can also affect the head and limbs, guttate lesions are typically spread centripetally. It makes up 2% of all instances of psoriasis.

**Inverse or flexural psoriasis**

Specifically perineal, inframammary, and axillary psoriasis differ morphologically from conventional plaques in a different place on the limbs and trunk. Flexural lesions are red, lustrous, well-defined plaques that lack scale and can resemble candidal, intertrigo, and dermatophyte diseases.\textsuperscript{[10]}

**Erythroderma**

Erythroderma is the term for entire or partial skin involvement caused by active psoriasis, and it can appear in one of two ways. First off, when plaques enlarge and become confluent, chronic plaque psoriasis may gradually worsen. Second, erythroderma can be a symptom of not stable psoriasis brought on by an infection, exposure to tar, medications, or stopping corticosteroids.\textsuperscript{[11]}

**Generalized pustular psoriasis**

It is uncommon and indicates an illness that is aggressive and unstable.\textsuperscript{[11]} The patient has monomorphic, sterile pustules that may merge into sheets and has pyrexial skin that is red, uncomfortable, inflammatory, and studded with these lesions.

**Palmoplantar pustulosis**

The symptoms of palmoplantar pustulosis include sterile, yellow pustules on the palms and/or soles, along with erythema and scaling.\textsuperscript{[11]}

**Psoriatic nail infection**

Little depths in the nail plate, caused by improper nail development in the proximal region of the nail matrix, are the most frequent observation. About 50% of people with psoriasis develop psoriatic nail disease.

**Pathophysiology of Psoriasis**

Dendritic cells of Myeloid are triggered early in the pathogenesis of psoriasis by cytokines released by keratinocytes, natural killer T cells, plasmacytoid dendritic cells, and macrophages. Sharply delineated, erythematous, and flaky plaques are the clinical markers of psoriatic lesions, which are caused by the interplay of Dendritic Cells (DCs), Keratinocytes (KC), and T lymphocytes.\textsuperscript{[12]}
According to research on psoriasis, the condition appears to affect the skin's outermost layer, which is made up of keratinocyte-type cells. Inflammation caused by psoriatic plaques is not just restricted to the epidermis; rather, keratinocytes and adaptive immune cells interact, causing the inflammation to spread to the skin’s dermis. Psoriasis pathogenesis can be categorized into two stages: the initial stage, that may be brought on by the Koebner phenomenon, medications, or infection, and the subsequent maintenance stage, which exhibits persistent clinical expansion (Figure 1).[13]

Dendritic cells play vital role in the initial stages of disease. Specialized antigen-presenting cells have dendritic cells. While the exact mechanism of its stimulus in psoriasis is unknown. One of the suggested processes is the release of antimicrobial peptides, which are frequently over expressed in psoriatic skin and are generated by keratinocytes in reaction to injury. The three AMPs that specifically cause psoriasis are defensins, LL37, and S100 proteins. Interferon alfa (IFN-α), released by plasmacytoid dendritic cells that have been stimulated by DNA-LL37, activate myeloid dendritic cells. IL-23, IL-12 from myeloid dendritic cells is released and once they have been activated. IL-12 causes basic T cells to discriminate into TH1 cells. IL-23 sustains the existence and growth of TH17 and TH22 cells. TNF-γ and Interferon gamma (IFN-γ) are activated by TH1 cells, IL-22 is produced by TH22 cells, IL-17, IL-22 and TNF-γ are produced by TH17 cells.[14]

Different T cells that trigger the adaptive immune response cause the psoriatic inflammation. TH17 cytokines, exclusively IL-17, IL-22 and IL-21, promote keratinocyte growth in the epidermis. TNF-γ, IL-17, and IFN-α, as well as keratinocytes activation by LL37 and DNA, which considerably boost the creation of type I IFNs-α, are all induced by the psoriatic inflammation. Moreover, they actively contribute to the inflammatory cascade by the production of cytokines, chemokines, and AMP. Tyk2-Jak2 and STAT3 pathway are intracellular intermediates in the IL-23 signaling process that trigger the transcription of main inflammatory mediators. The cytokines trigger downstream keratinocyte development, enhanced endothelial cell and angiogenic mediator interaction, and immune cell penetration into lesional skin.[13]

Drugs that target TNF-γ, IL-23, and IL-17 as well as JAK/STAT signaling pathways, for example, are effective in treating plaque psoriasis. Yet, other inflammatory pathways work well for psoriatic variations. Topical medicines such as corticosteroids, keratolytic, calcineurin inhibitors, targeted phototherapy and Vitamin D analogues are used to treat mild psoriasis. Nevertheless, biologics, oral medicines, and UV-B/PUVA phototherapy are helpful for treating moderate to severe psoriasis.[16]

**Plants acting against psoriasis**

Many plants, including Centella asiatica, Aloe Vera, Panax ginseng, Saccharum officinarum, Rubia cordifolia, etc., have been found to have antipsoriatic action, according to a thorough review of the literature. Information covered includes the biological source (family, common name and plant’s botanical name), the extract or isolate of the plant portion employed, the bioactive dose, the

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**Figure 1:** Pathophysiology of Psoriasis.

Source: Gooderham MJ, Papp KA, Lynde CW. Shifting the focus—the primary role of IL-23 in psoriasis and other inflammatory disorders. Journal of the European Academy of Dermatology and Venereology.
path of administration, the humans or animals, the experimental model or scientific research, and the way of action (if reported).

The negative effects of the current psoriasis treatments have caused researchers to turn their attention to safer natural remedies. The psoralen active component in PUVA therapy, which is extensively used to treat psoriasis, comes from the plant *Psoralea corylifolia*. Herbal medicines appear to be a potential way to investigate for better, safer, and more effective antipsoriatic pharmaceuticals, keeping in mind the significant adverse effects related with synthetic treatments accessible for psoriasis treatment. There is scientific proof which supports the traditional uses of plants like *Aloe vera*, *Curcuma longa*, and *Thespesia populnea* for treating skin conditions like psoriasis. Researchers' confidence in natural resources has been restored by the addition of such plant medicines to the arsenal of contemporary treatments.[17]

In the current review paper, fifteen plant-derived chemical components with anti-psoriatic activity have been described (Table 1).

**Nanomedicine in the management of psoriasis**

Topical administration of capsaicin demonstrates potential therapeutic use in the prevention of cutaneous vasodilatation and blocking of axon reflex vasodilatation caused by a number of substances. Capsaicin regulates (HIF-1) Hypoxia-Induced Factor-1 translation through temporary receptor potential, causing proper differentiation, and preventing hyperproliferation of the psoriatic epidermis. The synthesis of SLN (Solid lipid
nanoparticles) and NLC (Nanostructured lipid carriers) with and without capsaicin is done using the solvent diffusion method for high drug retention in the afflicted skin. Comparing NLCs and SLNs to plain capsaicin solution, a high flux is seen. The skin of albino rats exhibits more capsaicin penetration, according to capsaicin NLCs (capsaicin delivery).[24] The stratum corneum drug retention in SLNs and NLCs is much higher than in capsaicin solution alone, being 3.13 times for SLNs and 4.5 times for NLCs respectively. Lipid formulations of SLNs and NLCs result in more capsaicin penetration when compare alone to capsaicin solution. NLC’s formulation of capsaicin has a great chance of regulated and sustained medication delivery in an effective dosage. In order to effectively treat skin conditions, the localized depot and subsequent extended residency of capsaicin are maintained. In the case of psoriasis, NLCs exhibit more skin permeation through deep and hyper-proliferative skin than SLNs, suggesting that NLCs may be a much better choice than SLNs for such diseases. NLCs displayed small size with more drug entrapment, superior skin permeation with good drug retention, and no signs of skin irritation. NLCs may therefore be investigated as a medication carrier for topical drug delivery.²⁷,²⁸ Capsaicin (CAP), which blocks TNF-yr, is thought to have promise for the management of psoriasis. By suppressing TNF-yr, the mediator of psoriasis, in psoriatic cells of the stratum corneum, it prevents the development of NF-kB. Furthermore, capsaicin prevents the axon reflex vasodilatation created by several erythematogenic substances. CAP inhibits cutaneous vasodilatation as well. Capsaicin reduces substance P, a crucial aspect in the etiology of psoriasis. The drug gathering in various layers of skin has enhanced with CAP-loaded emulsional gel, demonstrating the maximum therapeutic efficacy and fewest negative effects. As a result, emulsional gels loaded with capsaicin have a local effect and may be used to treat psoriatic infection.²⁹

Curcumin and caffeine combined in a topical gel formulation on a nano-sponge demonstrated efficacy in the psoriasis treatment. When compared to using curcumin alone without caffeine, the combined antipsoriatic impact shortens the time needed to treat psoriasis. The results of the histological analysis support the positive antipsoriatic activity of the developed mixture of curcumin and caffeine nanogel. Nanogels have demonstrated continuous release of drug over 12 hr. Coffee inhibits phosphodiesterase, while methyl xanthine raises AMP levels inside cells, which blocks inflammatory pathways and slows the psoriasis evolution. Cyclodextrin Nano-sponges offer the maximum drug loading and regulated release of drug, as well as bioavailability and stability for a spectrum of therapeutic molecules. The created gel was seen to be translucent, clear, uniform, and free of lumps and aggregates. Topical gel with a nano-sponge foundation has good spreading capabilities. The formulations displayed a primary drug burst release during the early few hours, which may have been caused by the gel matrix’s unentrapped drug content. This early burst was then followed by persistent drug release from the Nano-core sponges over a longer length of time.³⁰

In a Nano-emulsion formulation Tacrolimus and kalonji oil (functional excipient) were combined to deliver two antipsoriatic medications topicaly at the same time. A natural excipient with effective antipsoriatic properties is kalonji oil. Tacrolimus, a calcineurin inhibitor and successful treatment for autoimmune illness, has an immunosuppressive impact. Based on tacrolimus’ solubility and possible psoriasis-related activity, kalonji oil was employed. Tacrolimus’s solubility is supported by the increased hydrophobicity of kalonji oil compared to other synthetic oils on the market. The creation of Nano-emulsions involved the application of the spontaneous emulsification method. To optimize the therapeutic effect, treatments are combined. For the delivery of several therapeutic drugs topically, Nano-emulsions are particularly effective. Nano-emulsion gel having tacrolimus and kalonji oil reduced the severity of the psoriatic lesions, demonstrating its ability to reduce inflammation. The intrinsic properties of kalonji oil, as opposed to other oils used in amalgamation with tacrolimus for double action, in the formulation of Nano-emulsion. The anti-inflammatory properties of kalonji oil aid in the inhibition of a number of inflammatory cytokines. The Nano-emulsion created using tacrolimus and kalonji oil had a noticeable impact on cytokine levels.³¹,³²

Psoriasis-related skin inflammation reveals an overexpressed protein that could be the target of new Nano carriers to increase medication absorption by the skin. As a new drug delivery system for curcumin, ethosomes made from modified propylene glycol and hyaluronic acid are joined through covalent bonding. Due to air, temperature, and light, babchi oil (Psoralea corylifolia) is susceptible to issues including oxidation and deterioration. However, there are still more issues with babchi oil that need to be researched, such as skin irritation and toxicity. Despite its effective antipsoriatic properties, these shortcomings prevent routine utilization of BO. Furocoumarins, which are the major ingredients of babchi oil and slow DNA synthesis as well as cell proliferation, have antipsoriatic properties. The use of phytoconstituents as nanocarriers for drug delivery has garnered considerable interest from the scientist because it has demonstrated to be a successful tactic for treating skin problems. Moreover, cyclodextrins have been scientifically proven to enhance local irritancy and aid in drug delivery, which is very important in the psoriasis treatment. Babchi oil Nanostructure gel based on cyclodextrin can be used to treat psoriasis and investigated in human clinical studies for potential future commercial exploitation.³³

The occurrence of Thymoquinone (TQ), a lipid-soluble benzoquinone with specific expertise in therapeutic antagonistic effect in skin diseases such as pigmentation, hypersensitivity, vitiligo, and also in the early skin tumors stages which also includes psoriasis, has been credited with the significant antipsoriatic action of Nigella sativa seeds. Thymoquinone has drawbacks
<table>
<thead>
<tr>
<th>Common Name</th>
<th>Botanical Name</th>
<th>Part used</th>
<th>Antipsoriatic component</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babchi</td>
<td><em>Psoralea caryifolia</em></td>
<td>Seeds</td>
<td>Babichi Oil</td>
<td>Furocoumarins, the primary ingredients of babichi oil, which likewise inhibit DNA synthesis and cause cell proliferation to slow down, have been shown to have anti-psoriatic properties.</td>
<td>[36]</td>
</tr>
<tr>
<td>Bell pepper</td>
<td><em>Capsicum annuum</em></td>
<td>Fruits</td>
<td>Capsaicin</td>
<td>In the case of psoriasis, NLCs exhibit high skin permeation through deep and hyper-proliferative skin than SLNs, suggesting that NLCs may be a much better choice than SLNs for such diseases.</td>
<td>[37]</td>
</tr>
<tr>
<td>Kalonji</td>
<td><em>Nigella sativa</em></td>
<td>Seeds</td>
<td>Thymoquinone</td>
<td>Ethosomal vesicular system could be use as delivery medium to increase drug solubility, trapping, and penetration.</td>
<td>[38]</td>
</tr>
<tr>
<td>China root</td>
<td><em>Smilax china</em></td>
<td>Roots</td>
<td>Quercetin</td>
<td>The created NLC formulation serves as a practical drug delivery system for the management of psoriasis.</td>
<td>[39]</td>
</tr>
<tr>
<td>Turmeric</td>
<td><em>Curcuma longa</em></td>
<td>Rhizome</td>
<td>Curcumin</td>
<td>HA-ES system designed to boost the skin's absorption of the medication curcumin by targeted drug delivery.</td>
<td>[40]</td>
</tr>
<tr>
<td>Aloe</td>
<td><em>Aloe barbadensis</em></td>
<td>Leaves</td>
<td>Aloe emodin</td>
<td>Stem less, leaves fleshy green, thick and green or grey colour.</td>
<td>[41]</td>
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<tr>
<td></td>
<td><strong>miller</strong></td>
<td></td>
<td>acemannam, salicyclic</td>
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<td></td>
<td></td>
<td></td>
<td>acid.</td>
<td></td>
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<tr>
<td>Cayenne red</td>
<td><em>Capsicum annuum</em></td>
<td>Fruits</td>
<td>Capsaicin</td>
<td>Flower purplish or off white colour. Stem thickly branched Fruit yellow, green, or red when ripe.</td>
<td>[42]</td>
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<tr>
<td>pepper</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Wintergreen</td>
<td><em>Gaultheria procumbens</em></td>
<td>Leaves</td>
<td>Methyl salicylate and</td>
<td>Flowers pink or white, bell-shaped corolla fruits red colour.</td>
<td>[43]</td>
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<td></td>
<td></td>
<td></td>
<td>procyanidin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chamomile</td>
<td><em>Matricaria recutita</em></td>
<td>Flowers</td>
<td>Chamazulene quercetin,</td>
<td>Leaves-narrow bipinnate or tripinnate. Flowers-paniculate flower heads.</td>
<td>[44]</td>
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<td></td>
<td></td>
<td></td>
<td>apigenin, and Basabolol.</td>
<td></td>
<td></td>
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<tr>
<td>Christmas berry</td>
<td><em>Psoropermum febrifugum</em></td>
<td>Stem bark</td>
<td>Fatty acids.</td>
<td>Small scrub flowers, white or creamy colour.</td>
<td>[45,46]</td>
</tr>
<tr>
<td>Milk thistle</td>
<td><em>Silybum marianum</em></td>
<td>Seeds</td>
<td>Silymerin, Vitamin E</td>
<td>Leaves-white pattern of veins flowers-purple colour.</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>taxifolin, linolenic acid and linoleic acid.</td>
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including low hydro solubility, great hydrophobicity, chemical instability, low bioavailability, and limited penetration despite fits significant therapeutic potential. Ethosomal vesicular systems are potential delivery vehicles for bypassing these restrictions since they increase drug solubility, trapping, and penetration. As a result, ethosomal gel with TQ loading demonstrated promising results for the treatment of psoriasis.

The full relationship between serum total bilirubin levels and psoriasis improvement in patients suggests that bilirubin has therapeutic potential in psoriasis. When applied topically, bilirubin nanoparticles are an effective nanomedicine for the treatment of psoriasis. BRNPs effectively stop tumour growth in vivo. Previous studies have shown that BRNPs can enter the stratum corneum, a skin layer that has been disrupted in psoriatic skin, and integrate into activated keratinocytes. Therefore, bilirubin Nanoparticles hold considerable promise for the topical management of psoriasis. Moreover, BRNP (Bilirubin nanoparticles) have a great clinical effect and were used to treat additional diseases caused by Reactive Oxygen Species (ROS) since they have antioxidant properties and are biodegradable when they are oxidised in response to ROS. A summary of some selected plants having antipsoriatic activity shown in Table 2. Advanced psoriatic drug delivery systems are also available, and some of these patented systems are listed in Table 3.

The negative effects of the current psoriasis treatments have caused experts to turn their attention to safer natural remedies. The active ingredient in PUVA therapy, which is extensively used to treat psoriasis, is psoralen, which comes from the plant 

Psoralea corylifolia. Herbal medicines appear to be a potential strategy to investigate for better, safer, and more helpful antipsoriatic treatments, taking note in mind the significant side effects linked with synthetic drugs to manage psoriasis. There is scientific proof to support the traditional uses of plants like Curcuma longa, Thespesia populnea, Aloe vera for treating skin conditions like psoriasis. Researchers’ faith in natural resources has been restored by the addition of such plant medicines to the arsenal of contemporary treatments.
Herbal remedies are still considered to be a significant source of many cutting-edge drugs and are seen as a precious gift of nature for the management of many disorders. Natural medicines have, up to this point, continually attracted attention due to their eco-friendliness and remarkably low side effects. The selection of traditional plants with therapeutic efficacy for future research is anticipated to be greatly aided by this review article for scientists studying natural products.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES


