Priya Patel, Kevinkumar Garala, Arti Bagada, Sudarshan Singh*, Bhupendra G. Prajapati* and Devesh Kapoor

Phyto-pharmaceuticals as a safe and potential alternative in management of psoriasis: a review

https://doi.org/10.1515/znc-2024-0153
Received July 15, 2024; accepted October 22, 2024;
published online November 12, 2024

Abstract: Psoriasis is a chronic autoimmune skin disease with a worldwide prevalence of 1–3 % results from uncontrolled proliferation of keratinocytes and affects millions of people. While there are various treatment options available, some of them may come with potential side effects and limitations. Recent research has shown that using bioactive compounds that originate from natural sources with a lower risk of side effects are relatively useful in safe management psoriasis. Bioactive compounds are molecules that are naturally available with potential therapeutic efficacy. Some of bioactive compounds that have shown promising results in the management of psoriasis include curcumin, resveratrol, quercetin, epigallocatechin-3-gallate, etc., possess anti-inflammatory, antioxidant, immunomodulatory, and anti-proliferative properties, with capabilities to suppress overall pathogenesis of psoriasis. Moreover, these bioactive compounds are generally considered as safe and are well-tolerated, making them potential options for long-term use in the management of various conditions linked with psoriasis. In addition, these natural products may also offer a more holistic approach to treat the disease, which is appealing to many patients. This review explores the bioactive compounds in mitigation of psoriasis either in native or incorporated within novel drug delivery. Moreover, recent clinical findings in relation to natural product usage have been also explored.

***Corresponding authors: Sudarshan Singh**, Office of Research Administration, Chiang Mai University, Chiang Mai 50200, Thailand; and Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand, E-mail: sudarshansingh83@hotmail.com. https://orcid.org/0000-0002-7929-3322; and **Bhupendra G. Prajapati**, Shree. S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva, Gujarat 384012, India; and Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, 73000, Thailand, E-mail: bhupen27@gmail.com. https://orcid.org/0000-0001-8242-4541
Priya Patel and Arti Bagada, Department of Pharmaceutical Sciences, Saurashtra University, Rajkot, Gujarat 360005, India
Kevinkumar Garala, School of Pharmaceutical Sciences, Atmiya University, Rajkot, Gujarat 360005, India
Devesh Kapoor, Dr. Dayaram Patel Pharmacy College, Bardoli, Gujarat 394601, India. https://orcid.org/0000-0003-4085-8936

Keywords: bioactive compounds; drug delivery; natural product; nanotechnology; psoriasis

1 Introduction

Excessive immunological abnormalities, environmental risk factors, and various genetic risk foci interact dynamically to develop psoriasis, which is known as chronic inflammatory skin condition. Psoriasis affects about 1–3 % of the global population, and major advancements have been achieved in our understanding of the illness and its therapies [1]. Its connection also causes damage to the skin and lymphocytes to continually emit enormous quantity of inflammatory cytokines, leading to several systemic problems [2]. Pathological results show that keratinocytes proliferate, differentiate abnormally, and infiltrate many lymphocytes triggering inflammation. Although the etiology of psoriasis is complex, extensive study has uncovered it. Dendritic cells (DC) are immune cells essential to developing psoriasis in its beginning and progression stages. Furthermore, research on macrophages implies that they serve an essential part in the pathophysiology of psoriasis, particularly during the beginning phase [3].

Immunity is determined by the delicate three-way balance of type 1, type 2, and type 3 helper cells with innate lymphoid cells; regulatory cells regulate the excess burden. Psoriasis is categorized as an immunological disease of type 3 dominance, triggered by interleukin (IL)17. While psoriasis has a type 3 cytokine profile, psoriatic blisters additionally demonstrate an elevated level of interferon (IFN) γ/tumor necrosis factor-α (TNF-α). In addition to being flexible and reversible, the three-way balance can also become unbalanced due to illness or drug side effects. This implies that under normal conditions, the population of regulatory cells strongly inhibits immunological activities and that in psoriasis, the functional ability of regulatory cells is compromised [4]. Physiological anomalies in keratinocytes, DCs, along with other regions of the innate immune system have been perceived among patients experiencing psoriasis [5]. In this review we explored the bioactive compounds in mitigation of psoriasis either in native or incorporated

within novel drug delivery. Moreover, recent clinical findings in relation to natural product usage have been also investigated.

1.1 Role of dendritic cell, T-cells, and neutrophils in psoriasis

In the immunological systems underlying psoriasis and other disease processes, DCs have a crucial function. Since their discovery in the lymphoid organs of mice by Steinman and Cohn in 1973, DCs have been identified as antigen-presenting cells (APCs), which are essential for the presentation of molecules to T- and B-cells [6]. The production of IFN-α and TNF-α by macrophages and plasmacytoid DC, two kinds of innate immune cells, is stimulated by the nucleic acid plus an array of antibiotic peptides generated by harmed keratin cells in early-phase psoriasis. Monocytes differentiate into inflammatory DC and resident dermal DC mature as a result of IFN-α release. The generation of cytokines such as (IL) 23, IL-12, TNF-α, as well as others by fully functional indigenous DC and the ever-growing iDC populace markedly encourages naïve T cells to split into Th1, Th17, and Th22 subsets. IL-23 facilitates the expansion and long-term survival of pathogenic Th17 cells. Keratinocytes proliferate and undergo aberrant differentiation when IL-17 and IL-22 are released. Because keratinocytes produce antimicrobial peptides, VEGF, IL-8, TNF-α, and other immune-related chemicals, some of which activate DC, they also function as immune cells. In the chronic stage of psoriasis, this intractable inflammatory cycle keeps the plaque present and deteriorates it [7].

Regulatory T cells (Tregs) in healthy individuals influence type 1 and type 17 cytokine-producing cells, and they're responsible for disease development. Tregs block immunological responses, which is how they play a crucial role in immune homeostasis and help avoid autoimmune illness. Tregs' ability to suppress is compromised in psoriasis, which results in a change in the T-helper 17/Treg ratio. While psoriasis patients' Treg dysfunction is linked to worsening of the illness, it is unclear how they are functionally controlled [8].

The CD25, alpha-chain of the IL-2 receptor, is highly expressed by Treg cells, a unique subpopulation of helper T cells. Then, it was shown that Foxp3 (Forkhead Box P3), a member of the fork head/winged-helix family, was the most important transcriptional element modulating the proliferation and survival of Treg cells. Treg cells prevent other functional immunity cells from responding by dealing with them either explicitly or by releasing cytokines like IL-10 along with transforming growth factor that dampen the immune system. Treg cells are therefore strongly linked to autoimmune disorders, chronic inflammatory illnesses, peripheral tolerance, and psoriasis [9].

The most prevalent kind of leukocytes in the bloodstream is neutrophils. Recent data suggests that neutrophils might be involved in autoimmune disorders. Psoriasis patients had considerably greater neutrophil-to-lymphocyte ratios, neutrophil activity, and NETotic cell counts than healthy controls. Patients with psoriasis had much more low-density granulocytes in their blood than in the control group. Furthermore, neutrophils may play a major role in the increased cardiovascular risk that psoriasis poses [5].

Many and varied endogenous and exogenous stimuli, including antigens, trauma, infection, or psychological stress, can set off the intricate immune responses that result in psoriasis. Through their interactions among T cells, dendritic cell types, and neutrophils, which both the adaptive and innate immune systems are linked. Psoriasis is caused by an imbalance in T cells, keratinocyte proliferation, angiogenesis, and the production of autoantigens, which draw in neutrophils. As neutrophils in the blood approach psoriatic lesions, they cause degranulation, respiratory burst, and the formation of. Neutrophils from psoriasis patients had enhanced respiratory burst, NADPH oxidases and myeloperoxidase activity. MPO also has a role in elevating degranulation and oxidative stress. Proliferating dendritic cells (pDCs) may release cytokines, chemokines, and other innate immune mediators in response to antigen specific CD8 + T cells (memory T cells in the dermis and naive T cells in the lymph node) by activating TLR receptors 7 and 9 as a result of the developed oxidative stress caused by neutrophils. These T cells have the ability to migrate to the epidermis through the major histocompatibility complex receptor on keratinocytes, where they can trigger keratinocyte progression and trigger regional inflammation. pDCs' production of IFN-α and IFN-β then encourages myeloid dendritic cells (mDCs) synthesis of inflammatory cytokines such as TNF, IL-12, and IL-23. Neutrophil-secreted proteinase 3 cleaves pro-IL-36 into active IL-36 cytokine, thereby boosting the mDC response. TNF, IL-12, and IL-23 substantially induce the immune response of Th1, Th17, and Th22 cells in the lymph node. Numerous chemokines and cytokines, including as TNF, IFN-γ, IL-1, IL-17, TNF, CCL20 (Chemokine ligand 20), and cytokines produced by neutrophils and DCs, are released in response to a viral infection. Proteinase 3 synthesizes LL-37, an autoantigen essential for the establishment of the immune response in psoriasis involving DNA chromatin and transforms resting TNFα into active sTNFα. NETs play a major role in maintaining psoriasis by supplying IL-17 and stimulating Th17 T-helper 17 cells to generate greater amounts of them. The above steps

lead to regional inflammation of psoriatic tissue which leads to the intricate responses to inflammation associated with psoriasis. Acanthosis, skin thinning, and epidermis hyperplasia are both psoriatic dermatological conditions that have been connected to the growth of IL-22. The activation of Nuclear factor kappa-light-chain-enhancer of activated B cells NF-κB, cyclic AMP Cyclic adenosine monophosphate, and JAK-STAT Janus kinase/signal transducer and activator of transcription family causes psoriasis by boosting angiogenesis, vascular proliferation, and adhesion molecules through the creation of TNF and IL-17 [10].

1.2 Pathogenesis of acne

Physical most cases, acne vulgaris (AV) results physical discomfort, mental anguish, deformity, and perhaps permanent scarring. Furthermore, individuals may have emotions of humiliation and fear, which contribute to the state of mental depression [11]. The pathophysiology of acne is multifaceted and involves overproduction of sebum, aberrant hyperkeratinization of pilosebaceous follicles, hyperproliferation of the cutibacterium acnes bacteria, and inflammatory processes [12].

Increased sebum production in hair follicles, primarily influenced by androgen hormones like testosterone and IGH-1, is a key factor contributing to acne development, affecting the frequency and severity of acne lesions [13–15], [14–16]. In contrast to healthy follicles that release single-cell keratinocytes into the lumen, hyperkeratinization anomalies in pilosebaceous follicles result in irregular desquamated corneocytes, lipid buildup, and monofilament accumulation [17–19]. When the immune system comes into contact with *P. acnes*, it triggers an inflammatory process that damages and ruptures hair follicles, releasing bacteria, lipids, and fatty acids into the dermis layer and causing inflammatory lesions such as ulcers. Reactive oxygen species are produced by neutrophils, which damages the follicular epithelium and exacerbates acne inflammation [20–22]. Because of its connection to inflammatory, autoimmune, and malignant skin conditions, DNA methylation – a type of epigenetic modification – is becoming more and more recognized in the field of dermatology. It has been demonstrated to play a role in the etiology and development of inflammatory skin conditions, including psoriasis, atopic dermatitis, and hidradenitis suppurativa. The development of acne vulgaris is also influenced by epigenetics, which provides information on the disease's biological causes and possible treatments [23].

2 Bioactive compounds as safe and potential alternative in management of psoriasis

2.1 Therapeutic drug approaches for psoriasis

Formerly thought to be an infection of the skin that relapsed, psoriasis is now understood to be a systemic immune-mediated inflammatory disease that can co-exist with psychiatric problems, cardiovascular disease, and psoriatic arthritis. Treatment should consider factors like psoriasis phenotype, treatment history, psychosocial impact, comorbidities, medications, and individual preferences. A holistic approach is essential, flexible, and adaptable to patient needs. The development of psoriasis therapy over time century is a testament to successful translational research [24].

First-line treatments for moderate to severe instances of psoriasis, which affect less than 10 % of the total area of the body, are conventional/topical therapy, which are time-consuming, greasy, sticky, and odor-causing. Multiple techniques, comprising traditional pharmaceuticals, nanocarrier-based therapy, and herbal medicines, are used to treat psoriasis. Liposomes, chitosan coated liposome, nanostructured lipid carriers, solid lipid nanocarriers, niosomes, dendrimers, nanosuspension, metallic nanoparticles, transfersomes, and ethosomes are a few possible nanocarriers for psoriasis therapies [25, 26]. Other cutting-edge drug delivery methods that are helpful for treating psoriasis include hydrogels, microspheres, microemulsions, micelles, microneedles, and microsponges [27–31].

For mild to severe inflammatory conditions, topical treatment is the primary line of management. It includes corticosteroids, dithranol, vitamin D analogue, tretinoids, Tacrolimus, Babchi oil, and 8-methoxypsoralen [32]. It is better accepted by skin that is sensitive and lessens adverse effects. Calcipotriol, a synthetic counterpart, has disadvantages such as a quick metabolism and skin irritation. These problems have reportedly been resolved with calcipotriol-loaded liposome gel [33].

Vitamin A is retinoid, and it comes in both synthetic and natural forms. Hyperkeratosis in the skin is a result of a vitamin A deficiency. Retinoids decrease psoriasis-related epidermal hyperplasia and control gene transcription through their interaction with nuclear receptors. While for psoriasis of moderate to severe intensity that has not improved with traditional systemic treatments, biologics are

Table 1: Pharmaceutical medications for psoriasis.

Drug	Activity	Reference
Vitamin A	Reduce the epidermal hyperplasia associated with psoriasis and regulate gene transcription by means of their contact with nuclear receptors.	[24]
Fumaric acid	Preventing the expression of proinflammatory cytokines and adhesion molecules, stopping the differentiation of D-cells, and reducing the generation of intracellular free radicals.	[33]
Ciclosporin	Demonstrated that the T cells act as the disease's mediators while treating psoriasis.	[34]
Adalimumab	The current recommended initial recourse biologic for psoriasis in conjunction with psoriatic arthritis.	[35]
Certolizumab pegol	Psoriatic arthritis and psoriasis	[36]
Tofacitinib	Targeting the signaling pathways inside cells that are linked to the etiology of psoriasis, hence inhibiting Janus kinase and 3, which in turn controls the immunological response.	[37]

recommended. For psoriasis of moderate to severe intensity that has not improved with traditional systemic treatments, biologics are recommended. Various potential pharmaceutical synthetic medications for psoriasis have been shown in Table 1.

2.2 Bioactive compounds in management of psoriasis

Bioactive compounds are natural substances found in plants, animals, and other organisms that have biological activity and can have a beneficial effect on health [38, 39]. These compounds have been significantly explored and investigated for their potential therapeutic effects in the management of psoriasis. Several bioactive compound that has been studied are elaborated below.

2.2.1 Flavonoids

Plant secondary metabolites include flavonoids, a class of polyphenolic chemicals. Studies have demonstrated the therapeutic potential of flavonoids, with a particular emphasis on their potent anti-inflammatory activities in the treatment of psoriasis [40]. Flavonoids are the main type of polyphenolic compound. From plants, more than 4,000 flavonoids have been identified. It has been demonstrated that flavonoids have strong antioxidant properties and can block the enzymes microsomal monooxygenase, lipoxygenase, mitochondrial succin-oxidase, glutathione S-transferase, nicotinamide adenine dinucleotide NADH oxidase, and cyclooxygenase [41]. Bioactive compound in management of psoriasis shown in Figure 1.

The primary anti-inflammatory properties of certain flavonoids as possible psoriasis treatment agents are amentoflavone that reduces the thickness of the skinfold and ear folds, promote apoptosis, restrict the growth of Immortalized human epithelial cell line (HaCaT) cells, prevent Imiquimod (IMQ) induced increases in mRNA expression, and suppress the production of IL17A, IL-22, and NF-κB [41]. Vegetables and fruit offer an outstanding way to acquire apigenin, a flavone possessing fascinating biological characteristics with anti-inflammatory properties and antioxidant activity. It has been noted that two of the best compounds for reducing the production of inflammatory cytokines in different cell lines are luteolin and apigenin [42]. As Astilbin has demonstrated Improvements in circulating CD4 and CD81 T cells, keratinocyte proliferation, and inflammatory cytokines [43].

In a study 2,4-dinitrofluorobenzene-induced contact hypersensitivity along with the mouse-tail test was used to assess baicalin's *in vivo* anti-inflammatory and keratinocyte differentiation-inducing characteristics. The results suggest that applying a lotion containing baicalin over the skin decreases inflammation and promotes proper keratinization [44].

Anthocyanidin delphinidin is found in a large quantity in fruits and vegetables with color, especially in blueberries with intriguing anti-inflammatory and antioxidant qualities. The consequences of delphinidin upon psoriatic cutaneous keratinocyte differentiation, growth, and inflammation have been recently investigated with a rebuilt human psoriatic skin equivalent (PSE) model [45].

In vivo, isoliquiritigenin has been shown to reduce IL-6 and IL-8 levels, as well as CD4, CD8, CD11b/c, F4/80, and Vascular Endothelial Growth Factor (VEGF) expression in the ear and back skin, therefore alleviating psoriatic lesions and slowing the pathogenic development of psoriasis. Isoliquiritigenin inhibited NF-κB activation, resulting in lower levels of proinflammatory cytokines IL-6 and IL-8. Isoliquiritigenin reduced both protein and mRNA levels of NF-κB. This discovery suggests isoliquiritigenin as a potential NF-κB inhibitor and psoriasis treatment medication [41]. In another research, the mouse tail test was used to investigate quercetin's anti-psoriatic properties derived through Smilax China's tuber. The substance's antiproliferative properties were further examined *in vitro* on HaCaT cells. Quercetin with 25 and 50 mg per kilogram substantially changed

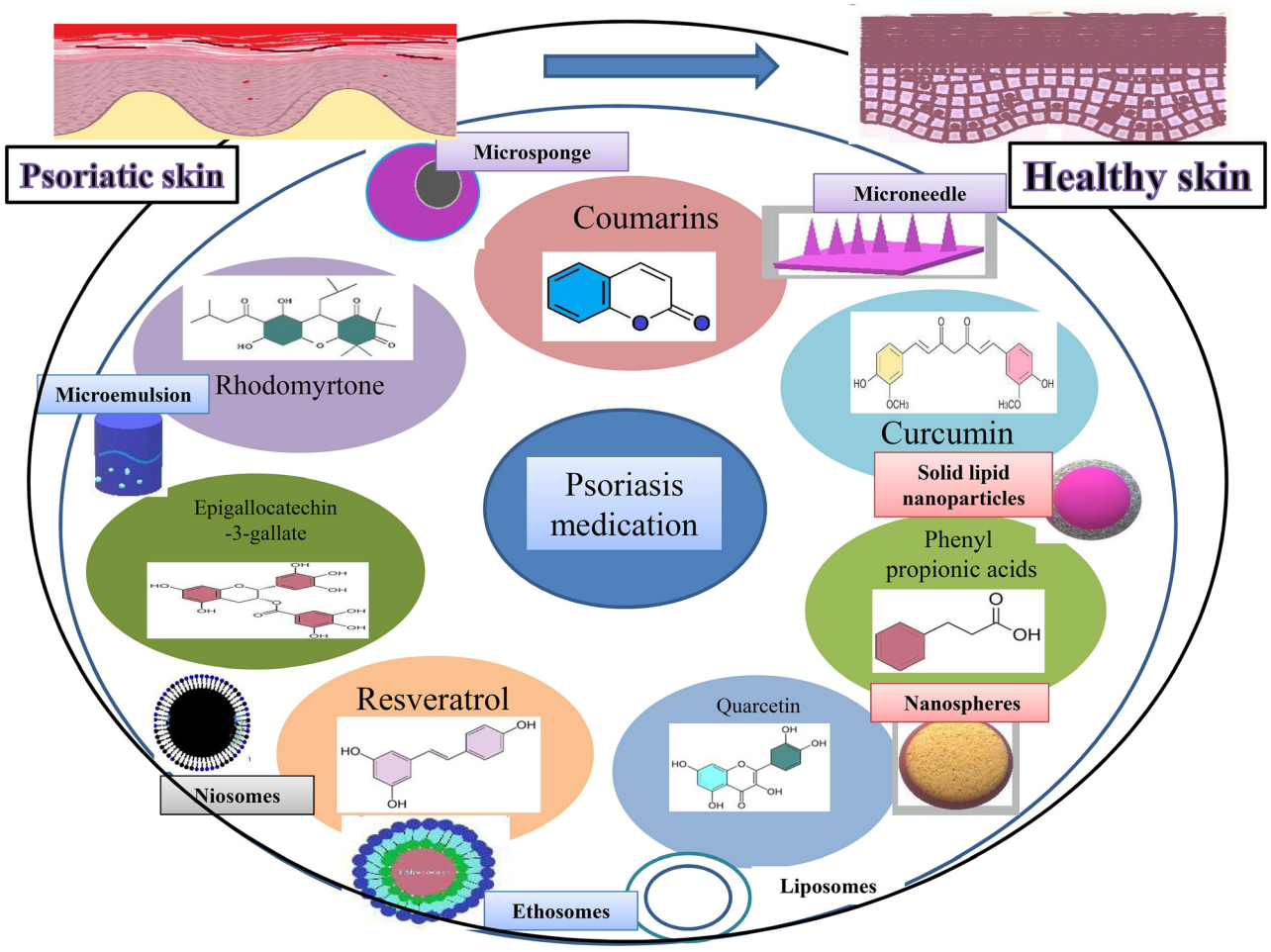

Figure 1: Bioactive compound for management in psoriasis.

epithelial width and accomplished incredible orthokeratosis in the mouse-tail test compared to the placebo group. In actuality, psoriatic lesions are distinguished by a significantly diminished or missing granular layer of the epidermis. With its capacity to function through several pathways, quercetin has been suggested as a possible treatment for psoriasis, a persistent inflamed dermatological condition with several triggers [46].

2.2.2 Phenylpropanoids

Phenylpropanoids, such as gallic acid, coumarins, phenyl propionic acids, and curcumin, have demonstrated encouraging outcomes in the treatment of psoriasis.

2.2.2.1 Coumarins

Coumarins are a crucial family of natural compounds that exhibit a benzoquinone α-pyran one core. It has been discovered that coumarins have an anti-psoriatic effect via reducing the generation of chemokines and cytokines that are associated with inflammation. Usually, phototherapy is used in conjunction with coumarins, such as psoralen, to enhance the therapeutic benefits of psoriasis. Researchers investigated the effectiveness and safety of psoralen-UVA (PUVA) therapy for 48 individuals with palmoplantar psoriasis (mean age 51 years). While 63 % of the patients were deemed successfully treated following topical PUVA treatment. However, in situations when topical PUVA treatment is ineffective after eight to 10 sessions, it was coupled with acitretin. In the course of therapy, 25 % phenyl propionic acids and other phenylpropanoids [47].

2.2.2.2 Phenyl propionic acids

Phenyl propionic acid, or ferulic acid, has demonstrated encouraging outcomes in the management of psoriasis. In a research by Lo et al., it was discovered that mice given ferulic acid had much fewer skin lesions, lower scores for scaling and erythema, and lower expression of the IL-17A gene [48]. Following intraperitoneal injections, Danshensu, a traditional Chinese herbal treatment, has shown to

ameliorate skin thicknesses and scales in psoriasis mice. The anti-psoriatic benefits of the high-dose therapy may be mediated by inhibition of YAP expression, as evidenced by the 80 % reduction in skin thickness and the reduction in YAP protein expression [49].

2.2.2.3 Curcumin

A polyphenolic substance called curcumin has been demonstrated to successfully cure psoriasis in mice. One research found that curcumin reduced Baker scores, TNF-α, IFN-γ, IL-2, IL-12, IL-22, and IL-23 levels, as well as the amount of T cells in mice's ear skin [50, 51].

2.2.2.4 Terpenoids

Terpenoids are compounds with antiviral, antibacterial, and anti-neurotoxic effects that are produced from isoprene units could be also used to treat psoriasis. In psoriasis-affected mice, betulinic acid was shown to drastically lower Psoriasis Area and Severity Index [52] scores, the goal was to reduce epidermal thickness, CD3+ T cell infiltration, and Th17, γδT production, as well as NF-κB signaling. Paeoniflorin is a clinically effective therapy for psoriasis, even though its exact mechanism of action is yet unclear. Paeoniflorin was studied in mice with IMQ-induced psoriasis to determine its mechanisms and therapeutic benefits. Psoriatic mice were administered 150 mg/kg of intraperitoneal paeoniflorin for 16 days, and their ear thickness dropped considerably. The paeoniflorin therapy decreased epidermal thickness and alleviated skin inflammation, according to the histopathology test. Paeoniflorin treatment decreased the number of CD11b- Gr-1- neutrophils and F4/80-CD68-macrophages in the skin. Pedoniflorin lowered TNF-α, iNOS, IL-1β, IL-6, IL-12, IL-23, and TNF-α levels [50] .

2.2.2.5 Alkaloids

Because of its substantial anti-inflammatory qualities, the molecule indorubin, which is present in bacteria, fungus, and plants, has shown to offer potential as a psoriasis treatment. Studies have demonstrated that indirubin suppresses EGFR stimulation along with EGF-induced CDC25B gene regulation in keratinocytes of the epidermis, hence lowering inflammatory reactions. In one research, indirubin therapy boosted keratinocyte proliferation, decreased the expression of many inflammatory mediators' mRNA, and nearly cut down on PASI scores [53, 54].

2.2.2.6 Steroids

A naturally occurring substance containing a cyclopentanoperhydrophenanthrene carbon backbone, steroids exhibit pharmacological effects those are particularly beneficial for treating psoriasis. Psoriasis therapy diosgenin dramatically reduced proinflammatory cytokine expression and elevated differentiation marker expression, accounting for half of the model group's score [55].

2.2.2.7 Organic acids

To lessen adverse effects and improve skin permeability, salicylic acid, an organic acid containing carboxyl groups, is used as a therapeutic anti-psoriasis medication in conjunction with tacrolimus, mometasone furoate, or calcitriol. Salicylic acid and mometasone furoate together proved to be a more efficient and secure combination, according to research including 408 patients [56]. Research has shown that gambogic acid, a substance found in the resin of the *Garcinia hanburyi* tree, has anti-psoriatic properties. Study demonstrates that gambogic acid administration reduces adhesion molecules, inhibits hyperplastic and inflammatory vasculature, and improves scarring, cutaneous building, along with parakeratosis in K14-VEGF transgenic mice [57, 58]. Table 2 gives the various molecular targets of bioactive compound.

2.2.3 Antiproliferative strategy to ameliorate psoriasis

Antiproliferative, having a propensity to impede or restrict the growth of cells, strategy represents a targeted and multifaceted approach aimed at addressing the characteristic of excessive skin cell growth associated with this chronic skin disorder. Psoriasis, a prevalent autoimmune

Table 2: Molecular targets of bioactive compound.

Molecular Target	Bioactive compound	Therapeutic strategies	Reference
IL17A, IL-22, and NF-κB	Amentoflavone	Reduces the thickness of the skinfold and ear folds, promote apoptosis, restrict the growth of immortalized human epithelial cell line (hacat) cells	[41]
IL-17A	Phenyl propionic acid, or ferulic acid	Fewer skin lesions, lower scores for scaling and erythema	[59]
TNF-α, IFN-γ, IL-2, IL-12, IL-22, and IL-23 l	Curcumin (polyphenol)	Reduced baker scores and cure psoriasis in mice.	[50]
TNF-α	Pedoniflorin	Decreased epidermal thickness and alleviated skin inflammation	[41]
IL-6 and IL-8	Isoliquiritigenin	Slowing the pathogenic development of psoriasis	[41]

condition which is non-communicable disease, establishes as raised, red, and scaly patches on the skin owing to an accelerated multiplication of skin cells. An antiproliferative strategy's main goal is to control and prevent this aberrant cell proliferation, which will diminish the severity of psoriasis symptoms and improve the general health of the skin. This approach encompasses several therapeutic approaches, all expected at transforming the fundamental mechanisms causing the hyperproliferation of skin cells.

One fundamental aspect of antiproliferative interventions involves the use of topical treatments [60]. These may include corticosteroids [61], which exert anti-inflammatory effects and help regulate cell proliferation. The Working Group on Topical Therapy of the International Psoriasis Council has evaluated the effectiveness and security of corticosteroids that are applied topically that provided recommendations concerning secure, prolonged application of such medications [62]. Additionally, vitamin D analogs [63], retinoids [64], and calcineurin inhibitors [65] are employed to target specific pathways engaged in the differentiation and development of cells, along with inflammation. An additional vital component of the antiproliferative strategy is phototherapy [66], which slows down skin cell turnover by using supervised UV light irradiation. Through regulating cellular activity and inhibiting excessive proliferation, two popular phototherapeutic strategies that demonstrate effectiveness in treating psoriasis are narrowband UVB and PUVA [67]. Biologic therapies have become revolutionary medical products in the antiproliferative paradigm in the past few years. These substances, which are injected or infused, work against particular elements of the immune system like interleukins and tumour necrosis factor to stop the inflammatory cascade that causes faster proliferation of skin cells [68].

In addition, systemically administered drugs such as immunosuppressants [69] and oral retinoids [70] have been employed in extreme situations to lessen aberrant skin cell turnover and stop systemic inflammation. Usually, such systemic approaches are saved for circumstances in where conventional therapies are found to be inadequate or undesirable. The antiproliferative approach aims to improve the quality of life for psoriasis sufferers in addition to managing their symptoms. These therapies try to reduce the frequency and intensity of psoriatic flare-ups, relieving the physical and psychological effects of the disease by altering the mechanisms controlling cell proliferation [71]. The antiproliferative strategy for psoriasis is a thorough and dynamic method that includes a range of topical, phototherapeutic, systemic, and biologic treatments. This approach aims to provide long-lasting relief by focusing on the abnormal cellular processes that cause psoriatic lesions, giving psoriasis sufferers a more tolerable and satisfying life.

2.2.4 Bioactive compounds for antiproliferation against keratinocytes

Keratinocytes, the predominant cells in the epidermis, play a crucial function in preserving the skin's integrity. Ungoverned keratinocyte multiplication, nevertheless, may result in a variety of dermatological issues in specific situations, such as hyperproliferative skin conditions or the beginning phases of skin malignancy.

Scientists and researchers are continuously investigating both natural and synthetic substances that possess bioactive qualities and have antiproliferative actions, especially towards keratinocytes. These substances can be produced chemically, extracted from plants, and sometimes obtained from marine organisms. These compounds can alter the complex processes controlling keratinocyte proliferation. A crucial component of the study is comprehending the molecular interactions that occur between bioactive substances and keratinocytes.

The top-performing external herbal remedies in management of psoriasis includes aloe vera, indigo naturalis, polyphenolic compounds, capsaicin, *Rubia cordifolia, Curcuma longa, Rheum palmatum, Lonicera japonica, Mahonia aquifolium,* and *Rehmannia glutinosa* [49]. Such bioactive compounds have the ability to reduce psoriatic lesions through molecular pathways associated with preventing angiogenesis, apoptosis, and suppression of inflammatory responses [72]. Table 3 listing some compounds derived from plants that are known for their potential in treating the hyperproliferation associated with psoriasis, along with a brief description of their effects.

2.3 Anti-psoriasis effects of bioactive compounds based novel drug delivery system

Bioactive ingredient delivery is severely limited in traditional psoriasis therapies that frequently use topical medicines, phototherapy, or systemic drugs. The difficulty is in getting these compounds to be as bioavailable as possible at the psoriatic lesions that result in less-than-ideal treatment results. Given the chronic nature of psoriasis, certain bioactive chemicals may be less useful in managing the condition due to their intrinsic low solubility and stability.

In the last few years, the growth of novel drug delivery systems, as shown in Figure 2, has materialized as an encouraging avenue to improve the therapeutic effects of bioactive compounds in treating psoriasis. By employing nanocarriers such as liposomes, nanoparticles, and micelles,

Table 3: Compounds that have been reported for their potential in treating the hyperproliferation associated with psoriasis.

Compound	Plant source	Mechanism of action	Potential benefits in psoriasis	Reference
Curcumin	Turmeric (*Curcuma longa*)	Anti-inflammatory, antioxidant, inhibits cell proliferation by inhibiting TNF-α-activated NF-κB, IL-6, and IL-8.	Reduces inflammation, inhibits keratinocyte proliferation.	[73]
Gucomannans	Aloe vera (*Aloe barbadensis*)	Anti-inflammatory, moisturizing, promotes wound healing.	Soothes irritated skin, may help in reducing psoriatic plaques.	[74]
Indigo naturalis	*Baphicacanthus cusia* plant	Anti-inflammatory, inhibits angiogenesis and keratinocyte growth by controlling apoptosis, proliferation, and differentiation	Traditional remedy for psoriasis, shows efficacy in studies.	[75]
Mahonia aquifolium	Oregon grape (Mahonia spp.)	Anti-inflammatory inhibits keratinocyte proliferation. Prevent 5-lipoxygenase and reduce in T-cell infiltration	Used topically for psoriasis, contains berberine with benefits.	[76]
Willow bark extract	Salix species	Contains salicylates, anti-inflammatory, keratolytic effects.	Similar to salicylic acid, helps in reducing scaling and redness.	[77]
Licorice extract	*Glycyrrhiza glabra*	Anti-inflammatory, antioxidant, may modulate immune responses.	Topical application may help in alleviating psoriatic symptoms.	[78]
Neem oil	Neem tree (*Azadirachta indica*)	Anti-inflammatory, antimicrobial, may modulate immune responses.	Traditional use in managing skin conditions, potential for psoriasis.	[79]
Oat extract	*Avena sativa*	Anti-inflammatory, soothing, may reduce itching and irritation by suppressing the keratinocytes' nuclear factor kappa B function	Suitable for sensitive skin, may offer relief from psoriatic symptoms.	[80]
Chamomile extract	*Matricaria chamomilla*	Anti-inflammatory, soothing, may promote wound healing.	Topical application for calming psoriatic skin and reducing redness.	[81]
Tea tree oil	*Melaleuca alternifolia*	Antimicrobial, anti-inflammatory, may alleviate itching.	Used for its potential to reduce inflammation and manage psoriasis.	[82]
Evening primrose oil	*Oenothera biennis*	Contains gamma-linolenic acid, anti-inflammatory properties.	May help in managing inflammation associated with psoriasis.	[83]

the solubility issues of bioactive substances are resolved, and their bioavailability simultaneously improve. These systems ensure a prolonged presence of bioactive chemicals at the target region by providing controlled and sustained release mechanisms. These carriers minimize systemic exposure and lower the risk of negative effects associated with conventional systemic drugs by adding customized delivery. This method represents a substantial improvement in the individualized and effective management of psoriasis by optimizing the therapeutic effects of bioactive substances while also improving the overall safety and efficacy of treatment.

2.3.1 Liposomes

Liposomes are lipid-based vesicles that have become more prominent in medication administration for the reason that of their unique capability to contain hydrophilic and hydrophobic bioactive substances [84, 85]. These spherical, phospholipid bilayer-based structures provide targeted distribution while preserving and increasing the bioavailability of the encapsulated drug [86–90]. Liposomes contain tiny uni-lamellar vesicles that could boost their capacity to penetrate the epidermal stratum corneum [91]. Liposomes are adaptable vesicle that effectively deliver bioactive substances to targeted locations while reducing systemic exposure and reducing adverse effects [92]. Studies revealed how the liposomal gel having the bioactive component curcumin in combination with ibrutinib substantially lowered the level of inflammatory cytokines, psoriasis and the epidermal hyperplasia associated with imiquimod [93]. Additionally, Wadhwa et al. synthesized liposomes encapsulating fusidic acid to aid in the therapeutic management of plaque psoriasis. While in comparison with conventional cream, the produced liposomes showed 1.41 and 3.40 times greater skin penetration and retention [94]. Similarly, Suttiwan and coworker reported in their investigation that the *Rhodomyrtus tomentosa* derived Rhodomyrtone serum was effective and safe for treatment of inflammatory acne lesions [95, 96], (Figure 3). Amphipathic substances, lipids have both hydrophilic and hydrophobic characteristics. They may spontaneously organise into structured patterns in aqueous solutions by self-assembly, without the need for human intervention. As a result, micellisation or micelle production occurs, which is essential for many lipid-based micelles functioning as agents that are surface-active. When combined at the nanoscale level, micellas function as transporters for hydrophobic medicines, much like

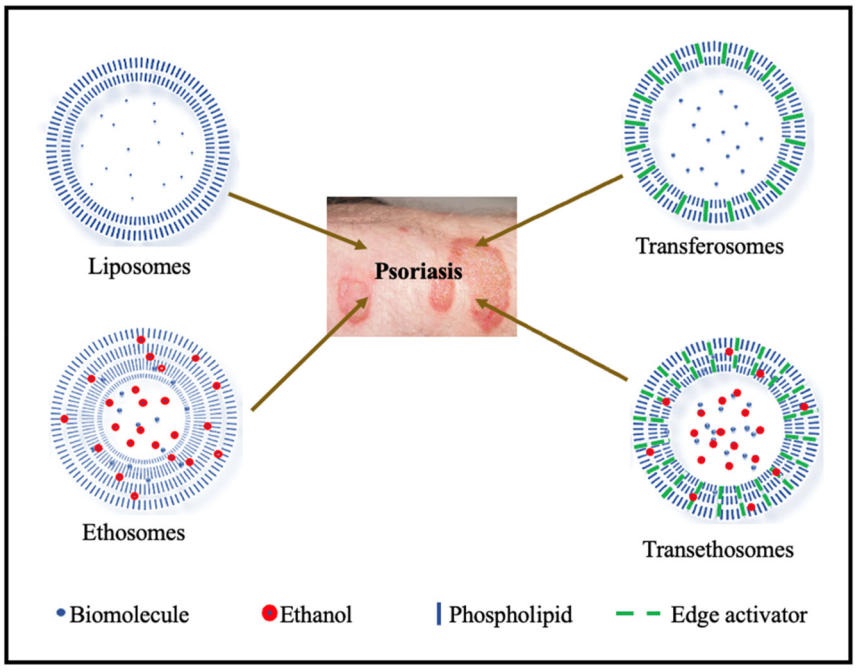

Figure 2: Novel approaches for the management of psoriasis.

lipid-based nanoparticles. Because of this similarity, medication administrations have been enhanced by increased bioavailability and decreased side effects [97] .

2.3.2 Ethosomes

Ethosomes, a variation of vesicle, incorporate ethanol in their composition, enhancing their penetration through the skin layers. Substantial interactions between ethanol along with lipidic structure of skin allow the enclosed medication to penetrate beneath the skin's layers more effectively [98]. This characteristic makes them particularly suitable for topical and transdermal drug delivery [99]. Modified ethosomes further optimize this delivery by adjusting their composition for improved stability and bioactive compound release. Ethosomes and modified ethosomes, with their skin-penetrating properties, represent promising avenues for topical applications of bioactive compounds, enhancing their therapeutic efficacy in dermatological conditions such as psoriasis. Mangiferin is a naturally occurring substance that was extracted from *Mangifera indica* L. It was added to glycerosomes, a modified ethosomes [100]. The better capability of mangiferin incorporated glycethosomes to encourage wound healing in association to the raw mangiferin was highlighted by the *in vivo* data, indicating that they might be beneficial in the management of psoriasis. Additionally, research developed ethosomes and liposomes of psoralen and their ability to penetrate and efficacy were assessed and it was found that psoralen flux of ethosomes reported 3.5 folds greater compared liposomes [101].

2.3.3 Niosomes

Niosomes are vesicles made of non-ionic surfactant, provide an alternate method of drug administration. These were developed to get beyond liposomes' inadequate physical resilience and high manufacturing expenses [102]. They are capable to encapsulate a variety of bioactive substances due to their amphiphilic nature [103]. Niosomes address issues with drug solubility by offering regulated release and enhanced stability when combined with bioactive substances. This technique is very useful for efficiently delivering bioactive substances to specific locations, which makes it a helpful tactic for improving the management of a range of illnesses, including skin disorders.

Triterpenoid celastrol is derived from tripterygium, exhibits strong anti-psoriasis properties [104]. Meng et al. used probe sonication and thin film hydration to create celastrol noisome [105]. In addition, hydrogel has been employed as a fundamental transporter to spread the topical medication's period onto the surface of the skin and preserve wetness. According to the *in vitro* penetration examination, celastrol noisome hydrogels had an active ingredient loading in the skin that had been almost 13 times greater than celastrol hydrogels. When hydrogel using celastrol niosomes was used instead of hydrogel by itself, the psoriasis area and severity index were smaller, as well as the psoriasis plaques showed less erythema along with white patches.

Niosomal gel was developed by Hashim and colleagues using acitretin, retinoid of the second generation, niosomes

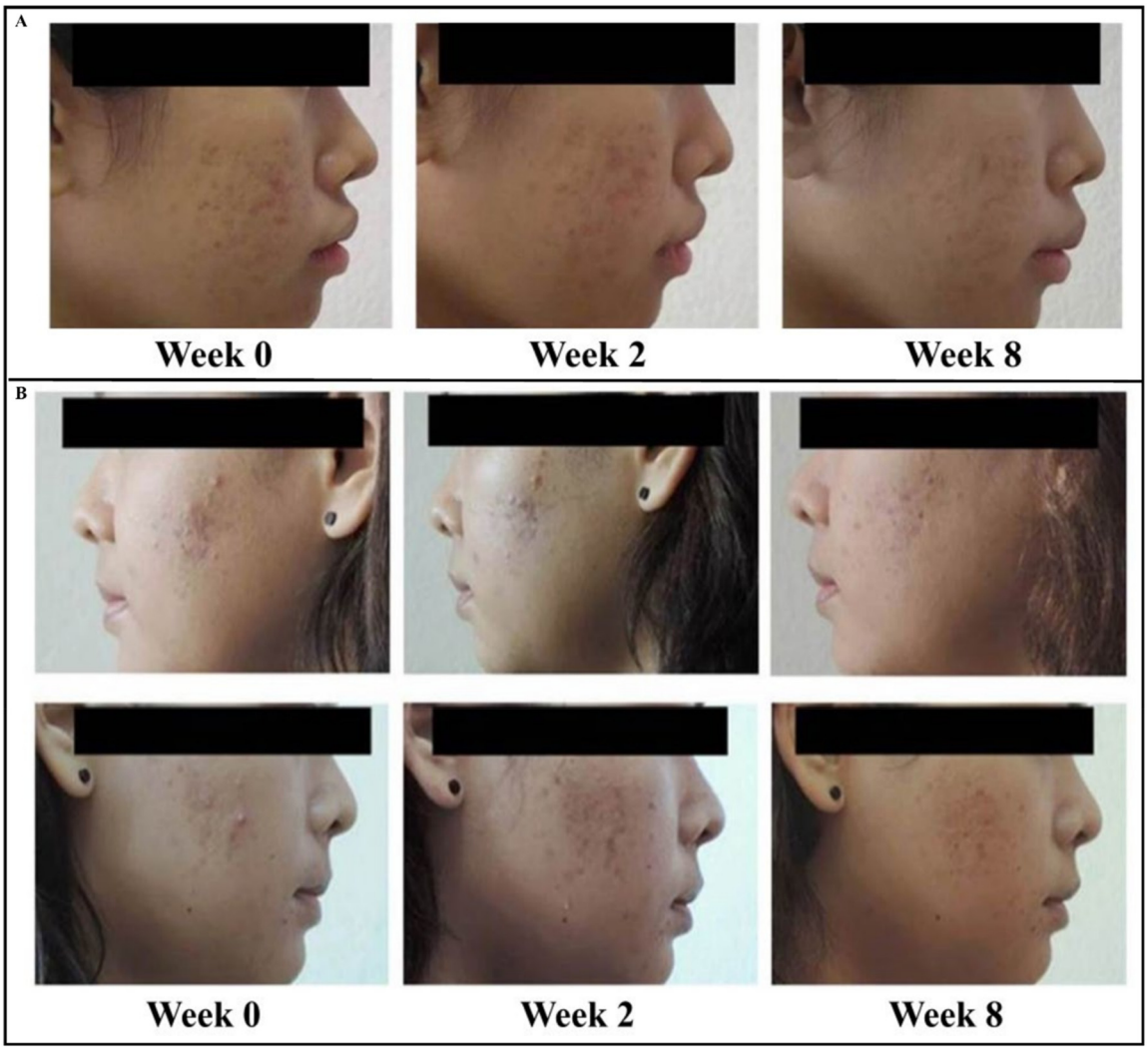

Figure 3: Case study: Patient with mild severity of acne vulgaris at the baseline set up investigator following investigator global assessment were on scale 2, reduced and left no more than one small inflammatory lesions after 8 weeks of application of rhodomyrtone serum twice a day daily. (A) In the same study another patient with moderate severity of acne vulgaris at baseline of 3 changed to 2 with no more inflammatory lesions after 8 weeks of application of rhodomyrtone serum twice a day daily. Adapted under creative commons CC BY 4.0 license from [95].

that were distributed in hydroxyl propyl methyl cellulose gel structure [106]. Comparing with standard acitretin gel, niosome-based gel demonstrated a considerable increase in drug accumulation in the functional epidermal layers with a better *ex vivo* penetration characteristic lasting for as long as 30 h. Ex vivo HaCaT cells demonstrated the acitretin niosomes' anti-psoriatic properties.

2.3.4 Transferosomes

Lipid-based vesicular transporters called transferosomes are renowned for their plasticity and flexibility in bridging the skin barrier [107]. Due to their exceptional capacity to efficiently encapsulate and distribute bioactive chemicals, these nanocarriers have drawn interest and may represent a breakthrough in the treatment of psoriasis. Transferosomes containing bioactive substances, such as immunomodulators [108], antioxidants [109], and anti-inflammatory drugs, are commonly intended for the management of psoriasis. These elements provide a more targeted and effective therapy strategy by addressing the underlying causes of psoriasis, such as autoimmune disorders and a hyperactive immune system [110]. Because of their flexibility, transferosomes can effectively permeate the different layers of skin, increasing the bioavailability of the bioactive substances they have contained [111]. By limiting systemic exposure, such selective administration lowers the possibility of adverse reactions that are frequently connected to traditional psoriasis therapies. Additionally, transferosomes are able to adjust to the particular milieu of psoriatic skin,

which is marked by inflammation and increased permeability. This flexibility maximizes the therapeutic effect while reducing the impact on healthy tissues by ensuring optimum drug release at the location of action. Scognamiglio et al., developed the transferosomes counting resveratrol, a non-flavonoid polyphenolic compound, showed better penetration through skin [112].

2.3.5 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are the primary era of lipid nanocarrier frameworks, presented within the 1990s. It is an imaginative drug delivery carrier with submicron particles (40–1,000 nm) of lipids dispersed in an aqueous surfactant solution [113]. The surfactant acts as the emulsifier in SLNs, however the lipid (fatty acid, steroids, glycerides) is stable at body and ambient temperature. SLNs are usually prepared using either a cold or a hot homogenization process, depending on the temperature stability of the drug [114]. High-pressure homogenization and ultrasonication can also be used to form SLNs [115]. In comparison to liposomes, their dynamic system allows for modifications in component formulation, such as the surfactant, which can be ionic or nonionic and is frequently utilized with a co-surfactant to minimize particle size [116].

2.3.6 Nanoemulsion

Nanoemulsions are new formulations for topical medication delivery. The key advantage of nano emulsion is that it loads less drug, reducing the danger of side effects from large dosage pharmaceuticals, and it can carry poorly water-soluble drugs to the bottom of the skin layer. The medication absorption rate can be enhanced since the drug particles are submicron in size (up to 10–200 nm). Nano emulsions are repeatable, and controlled medication release at the target location is another significant benefit [117]. Clobetasol propionate was administered by nanoemulsions, an innovative delivery technology for topical medication administration. The efficacy of psoriasis therapy was solely reliant on the extended effect of the drug, without any adverse effects. Sarfaraz Alam et al. developed oil in water nano emulsions in which the oil phase was constituted of clobetasol propionate [118]. Nanoemulsions are isotropic, heterogeneous systems composed of two immiscible liquids with adequate drug dispersion in nanodroplet sizes [97].

In order to reduce the surface and interfacial tension between water and oil – which may be ionic or nonionic surfactants must be carefully chosen. Tween® 80, amphiphilic proteins (caseinate), phospholipids (soy lecithin), polysaccharides, and polymers [119] are examples of common surfactants or emulsifying agents [120]. Since nonionic surfactants cause less local irritation than anionic surfactants, they are frequently regarded as safer than anionic surfactants, which makes them perfect for use in medicine. Additionally, they offer a steadier drug delivery mechanism since their CMC value is lower than that of their ionic counterparts with the same alkyl chain length [121].

Since methotrexate is considered the gold standard in psoriasis treatment, an attempt was made to include this medication in nanoemulsion gel. In order to target animal model-induced skin inflammation similar to that of psoriasis, a formulation based on olive oil was created. The psoriasis area and severity Index decreased by 91 % in the methotrexate tablet group, and this reduction was equal to or greater in the methotrexate nanoemulsion gel formulation. The study's findings demonstrated the efficacy of a methotrexate nanoemulsion gel formulation in treating psoriasis and lowering the rate at which symptoms diminish [122]. Using the spontaneous emulsification approach, Sahu et al. created tacrolimus and kalonji oil based NEs with cremophor RH 40 and PEG 400 to treat psoriasis. When compared to free drug in gel, the *in vitro* investigation revealed 100 % release of the drug in gel at 12 h, however the drug release from NEs and NEs gel was slower, releasing 80 and 50 % of the drug in 24 h, respectively. Consequently, as compared to NEs gel, the NEs formulation with cremophor RH 40 and PEG 400 yields a greater release rate. With NEs, the droplet size and polydispersity index were determined to be 93.42 ± 3.23 nm and 0.330 ± 0.015, respectively. Research conducted *in vivo* revealed a considerable improvement in psoriatic conditions, a 4.33-fold increase in BA, and a decrease in blood cytokines. According to a SEM investigation, skin treated with kalonji oil also exhibited a therapeutic response, but skin treated with plain oil showed a poor reaction. Additionally, the dissolution investigations of the NEs formulation and the organoleptic characterizations and drug contents did not exhibit any significant changes based on the stability experiments [123]. Similarly utilizing an ultrasonication aided cold maceration process, Kadukkattil et al. optimised *Alpinia galanga* extract [124] based NEs with different polymers, surfactant, and co-surfactant such as cremophor RH 40, tween 80, tween 20, propylene glycol, and propylene glycol 400 for the management of psoriasis. The produced NEs were found to have a mean droplet size of 59.79 ± 17.77 nm and a zeta potential of −8.05 ± 4.18 mV. Ex vivo permeation tests on porcine skin revealed flux values of 125.58 ± 8.36 µg/cm2h–1 for AGE NEs and 12.02 ± 1.64 µg/cm2h–1 for AGE per se. The mice who received NE treatment showed a substantial ($p < 0.05$) improvement

in their psoriasis. The histology showed that NEs receiving mouse treatment had a lower psoriasis area severity index (ASI) [125].

2.3.7 Foams

Colloidal solutions with gas dispersed across a liquid, solid, or gelled substrate are called foams. Because of their minimal risk for irritation, even distribution, lack of leftover oil, and non-stickiness, foams are superior to conventional formulations as new topical carriers. Foams have recently shown potential in the management of psoriasis. The properties of foams make medications ideal for treating scalp psoriasis because they break down quickly on the scalp and allow medication to enter the SC through the hair roots [126]. The foam propellant evaporates quickly, increasing the concentration of surfactant in the leftover foam and improving its permeability. Foams are also investigated to increase permeability and lessen irritation in natural products like capsaicin and oxymatrine for the topical treatment of psoriasis [57].

In order to include cholecalciferol and salicylic acid, Janja et al. designed an oil-in-water emulsion-based foam, and their physical and chemical stabilities were examined. A stable viscoelastic interfacial coating was guaranteed by combining nonionic and ionic surfactants with the viscosity-modifying polymer HPMC to produce physical stability in the foam. With at least a 30-fold decrease in degradation rate constant as compared to its aqueous solution, cholecalciferol was stabilized in the emulsion-based foam. Cholecalciferol was shielded from degradation by the composition of the emulsion-based foam itself and by the inclusion of the antioxidant tocopherol acetate, which scavenges radicals, to the oil phase. The irritancy potential, which was below the predetermined threshold designating a non-irritant dermal product, was also evaluated with the patient in mind [127].

2.3.8 Nanocrystals

Nanocrystals are nanometric-sized crystals (20–100 nm) that contain 100 % pure medication with no polymer conjugations. Nanocrystals increase the dissolving pressure, surface area, and curvature of particles, which are primarily responsible for boosting the drug's oral bioavailability [128]. Nanocrystals also achieve increased penetration due to their quicker follicular and intercellular penetration pathways, which is extremely favorable. They made it possible to avoid giving the medication more than once and extended its duration of action [129]. In order to cure lesions, Döge et al. fabricated nanocrystal loaded with dexamethasone and found that the nanocrystal improved the drug's skin penetration [130, 131].

2.3.9 Microsponges

Microsponges are a novel kind of perforated microparticles used as pharmaceutical administration. They consist of large-surface-area hydrogel granules. This delivery method alters the drug's clearance in the body, boost therapeutic efficacy, and reduce undesirable side effects. The medication is released into the epidermal secretions by the microsponges [28]. For the mometasone furoate, Amrutiya et al. developed microsponge; an emulsion solvent diffusion technique is used. Psoriasis and other inflammatory and pruritic disorders are treated with methotreasone furoate. The emulsion solvent diffusion method was used to generate MDS. The release profiles showed an initial burst effect followed by a biphasic release. Within the first hour, 29–36 % of the medication was released, and 8 h later, 78–95 % of the drug was discharged. A microsponge gel containing clobetasol propionate was utilised for psoriasis therapy in order to minimise the number of administrations required because of the drug's continuous release. They found that, as opposed to the typical form's 2.5 h, drug release might extend up to 12 h [132].

2.3.10 Microneedles

Microneedles have the ability to deliver medications transdermally that address key difficulties with existing topical administration methods. The use of microneedles can help medications penetrate the epidermis. This methodology might be employed to furnish an extensive assortment of hydrophilic pharmaceuticals. The microneedle gadget consists of a patchwork of micron-sized needles. Drugs will be able to penetrate the skin more readily because to this needle technology. After that, the medication is immediately absorbed via the skin, where it may quickly enter the bloodstream [133]. Using a CO_2 laser cutter, Khorshidian et al. created a low-cost, chitosan-based microneedle patch (MNP) for *in vitro* testing. The influence of the microneedle's administration of *Glycyrrhiza glabra* extract [134] on the cell population was then assessed. The effectiveness of the patch was evaluated by microscopic examination, swelling, penetration, disintegration, biocompatibility, and drug delivery. To assess the number of cells, DAPI and acridine orange (AO) staining were used. The results showed that the MNs (diameter: 400–500 µm, height: 700–900 µm) were sufficiently sharp and conical. They displayed significant swelling (two folds) in 5 min and good degradability (a burst

release) in 30 min, which can be considered a burst release. The MNP did not exhibit any cytotoxicity towards the L929. fibroblast cell line. Additionally, it showed promising results for GgE delivery. The decrease in the cell population following GgE administration was confirmed by the findings of AO and DAPI labelling. In conclusion, the artificial MNP may be a helpful suggestion for research conducted on a lab size. Additionally, skin conditions where it's necessary to regulate cell proliferation may benefit from the use of a GgE-loaded MNP [135].

2.3.11 Lipospheres

Lipospheres are lipid-based nanoparticulate carriers that are developed by adding coat lipid phospholipid molecules on the surface of an aquaphobic solid lipid core to stabilize it. Compared to other lipid-based systems, lipospheres provide a number of advantages, including less expensive reagents, reduced stability issues, improved dispersibility in aqueous settings, trouble-free manufacture, and a controlled release rate due to the phospholipid coating and a carrier [136]. Lipospheres have been effectively utilized to treat a variety of conditions, including psoriasis, orally, intravenously, and transdermally. Jain et al. developed a tacrolimus and curcumin-loaded liposphere gel formulation and tested its anti-psoriatic effectiveness. A topical gel formulation containing a combination medication contained lipospheres with particle sizes of around 50 nm. The produced gel displayed sluggish drug release for both tacrolimus and curcumin as compared to TAC-CUR solution. Furthermore, skin distribution research using dye-entrapped formulations suggested deeper dye absorption across skin layers. They then conducted effectiveness research on imiquimod-induced psoriasis plaque, with psoriatic biochemical markers as a critical assessment criterion. They found improved phenotypic and histological aspects of psoriatic skin after utilizing the new liposphere gel formulation. Like the imiquimod group, the novel formulation decreased the levels of TNF-α, IL-22, and IL-17. To put it briefly, they suggested using the developed liposphere gel formulation as a novel and promising drug for the effective treatment of psoriasis [136].

2.3.12 Nanospheres

Nanospheres (NSs) are particles smaller than 1 μm with a polymer matrix that evenly distributes the medication. NSs give increased stability, enhanced solubility, better regulation of medication release, and improved absorption [137]. NSs containing vitamin D3 were produced, and their potential for topical psoriasis therapy was investigated. The results showed a greater diffusion of vitamin D3 into the epidermis compared to the control (Transcutol®). Previous research has shown that the non-cytotoxic properties of NSs, as well as their capacity to be encapsulated without losing activity, are an attractive advantage for evaluating these systems in cutaneous applications NSs have the ability to encapsulate huge amounts of hydrophobic compounds while also enhancing their solubility due to their structure, which consists of hydrophilic blocks and a hydrophobic core. Following their assessment of these NSs for photodegradation, they discovered that hydrolysis and degradation had been prevented. As a result of its shown stability, vitamin D3 qualifies for used in a topical formulation [137]. Improved skin permeability of lipophilic medications, biocompatibility and biodegradability, increased cutaneous penetration, and resistance to degradation are a few benefits of NSs [137]. Table 4 shows various lipid carriers used for the treatment of psoriasis loaded with bioactive compounds.

2.3.13 Phototherapy

To treat moderate-to-severe psoriasis, phototherapy techniques such as narrowband UV-B, broadband UV-B, and PUVA have been employed. The narrowband UV-B has a superior safety profile and is more effective than the broadband variant. UV-B phototherapy inhibits DNA synthesis, which causes keratinocytes to undergo apoptosis and produces less pro-inflammatory cytokines. Erythema, pruritus, blistering, photoaging, and photocarcinogenesis are examples of adverse consequences. Since narrowband UV-B is more effective than broadband UV-B and has a longer period of remission, a lower risk of skin cancer, and less erythema, it is used more frequently. The combination of systemic retinoids with narrowband UV-B may improve effectiveness and lower the risk of skin cancer. The use of psoralens in PUVA treatment to inhibit UV-A irradiation and DNA synthesis is no longer recommended because of the danger of skin cancer and other side effects. For palmoplantar psoriasis, topical PUVA is employed; however, patients undergoing phototherapy must travel for their office appointments. Although it's a practical choice, space and insurance restrictions may apply to home phototherapy [138, 139]. Several topical treatments when fails to clean the skin, stable plaque psoriasis patients can benefit from phototherapies such as excimer lamp/laser and NB-UVB radiation. In order to manage psoriatic lesions, phototherapy includes repeatedly exposing the skin to UV radiation, which causes T lymphocytes and keratinocytes to undergo apoptosis. Extremely economical UVB therapy is only appropriate for specific individuals with conditions including HIV, internal cancers, and pregnant women, where systemic immune responses may not be appropriate [97].

Table 4: Various lipid carrier used in fabrication of delivering bioactive compounds for the treatment of psoriasis.

Lipid carrier	Anti-psoriatic agent	Route of drug administration	Class of bioactive compound	Remarks	References
Solid lipid nanocarriers	Thymoquinone (*Nigella sativa extract*)	Topical	Monoterpene	Reduced erythema, oedema, and thickness concerns as well as a low skin irritation score in the PASI score	[59]
	Tacrolimus	Topical	Polyketide	Greater *in vivo* skin layer penetration and a high ex vivo skin penetration value.	[140]
Nanostructured lipid carriers	Dithranol	Topical	Natural anthraquinone derivative	Decreased symptoms as measured by the PASI score and the enzyme-linked immunosorbent test, along with a drop in the severity of the illness and cytokines such TNF-a, IL-7, and 22	[141]
Liposomes	Psoralen	Topical PUVA	Linear furanocoumarins	Increased skin penetration studies by several times, accompanied with decreased psoriasis plaque symptoms and psoriatic cytokine levels (TNF-a, IL-17, and IL-22).	[142]
Niosomes	Acitretin	Topical	Retinoid	Improved drug deposition and ex vivo permeability test in HaCaT cells	[106]
Ethosomes	Anthralin (dithranol)	Topical	Anthracenes	In clinical trials, high penetration rate ex vivo and few negative effects after treatment were observed.	[143]

2.4 Clinical findings and histopathological features of psoriasis

The diagnosis of psoriasis is generally confirmed by histological analysis. The presence of neutrophil aggregates in the epidermis, perivascular lymphocyte infiltration, suprapapillary plate thinning, uniform rete ridge elongation, and dilated blood vessels are all indicative signs. Finding the histology diagnosis requires carefully examining the results [144]. Histological diagnoses for inflammatory dermatoses were often done based on a qualitative approach, meaning the clinical diagnosis may or may not be accurate. In some cases, however, the relationship between the disease's clinical severity and histological findings must be examined in order to quantitatively quantify the severity of the illness [145].

After utilizing a 4-mm punch biopsy to gather the tissues, hematoxylin-eosin (H&E) staining was used. Ten representative features of psoriasis were examined histo-pathologically on each slide: dilated blood vessels, perivascular and dermal lymphocyte infiltrates, spongiform pustules of Kogoj, elongation of the rete ridges, elongation of the dermal papillae, edoema of the dermal papillae, intermittent parakeratosis, absence of a granular layer, perivascular and dermal lymphocyte infiltrates, and sporadic neutrophil aggregates in the stratum corneum. The five-point rating system was used to rank these 10 histopathological traits: 0, none; 1, faint; 2, moderate; 3, marked; and 4, highly prominent. The psoriasis histopathologic score was calculated by adding the grading values from 10 samples. Histopathological differences were assessed based on the clinical type of psoriasis using two measures: (i) the mean grade and total frequency of each of the 10 histopathological abnormalities, and [146] the psoriasis histopathologic score [145].

As 98 lesions from 98 people (57 men, 41 women; mean age, 34.1 years) were analyzed, the clinical manifestations of psoriasis were divided into four categories: guttate (15.3 %), popular (40.8 %), tiny plaque (32.7 %), and large plaque (11.2 %). Figure 4 shows sample patients from each of the four clinical groups along with the histology that corresponds with them [145].

One significant way to understand the disease's processes is to examine the histopathological component of the skin (Figure 5). Psoriasis has three main HP features: leukocyte infiltration, vascular dilation (both present in the dermis), and epidermal hyperplasia. Full understanding of the natural history of the illness requires correlations between elements of HP and clinical characteristics. A straightforward lymphocytic infiltration around larger blood arteries distinguishes the early macule at the beginning of the disease. Epidermal hyperplasia, the following stage of normal growth, causes scaly papules with parakeratosis to appear. Generally speaking, rete ridge elongation, parakeratotic, neutrophilic infiltration, and a thinner subpapillary plate characterize the traditional HP look of psoriasis plaques. The lesions' histology is mostly reversible; fibrosis and a decrease in neutrophils

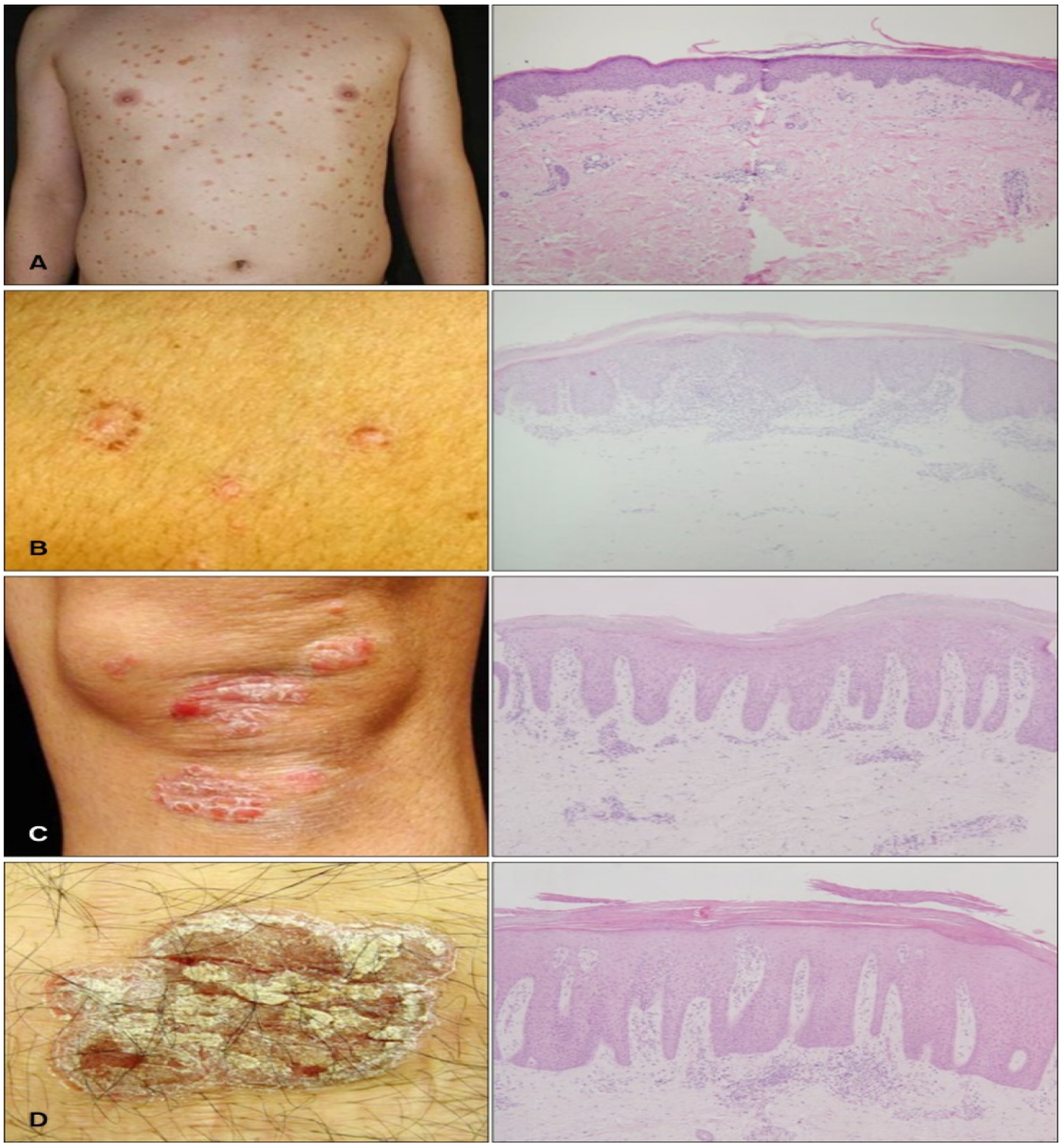

Figure 4: Categorization of the corresponding psoriatic lesions' clinical categories and histological characteristics (H&E, × 100). There are four types of plaque: Guttate (A), papular (B), tiny (C), and giant (D). Reproduce from [145] under creative commons attribution non-commercial license −3.0.

are the initial signs [147]. The function and release of exosomes from psoriatic keratinocytes were studied by Jiang et al. in relation to the course of the illness. Their results showed a substantial correlation between the production of proinflammatory proteins that aid in the development of psoriasis and keratinocyte exosomes. The function that keratinocyte exosomes play in stimulating neutrophil activation helps to explain this [148]. Their work's most notable discovery is that keratinocyte exosomes and neutrophils have intimate "communication" during psoriasis inflammation. Skin cells, immune cells, and other biological signaling molecules have a pathogenic interaction [149].

Understanding the immunopathology underlying this illness might allow us to better manage the course of the lesions, resulting in a significant improvement in patients' quality of life. However, nothing is known about the precise predictors of this condition, or the circumstances that might lead to clinical remission [150]. Nikhil et al. made an effort to connect the pathogenesis of psoriasis with its histological characteristics in their research. A substantial correlation

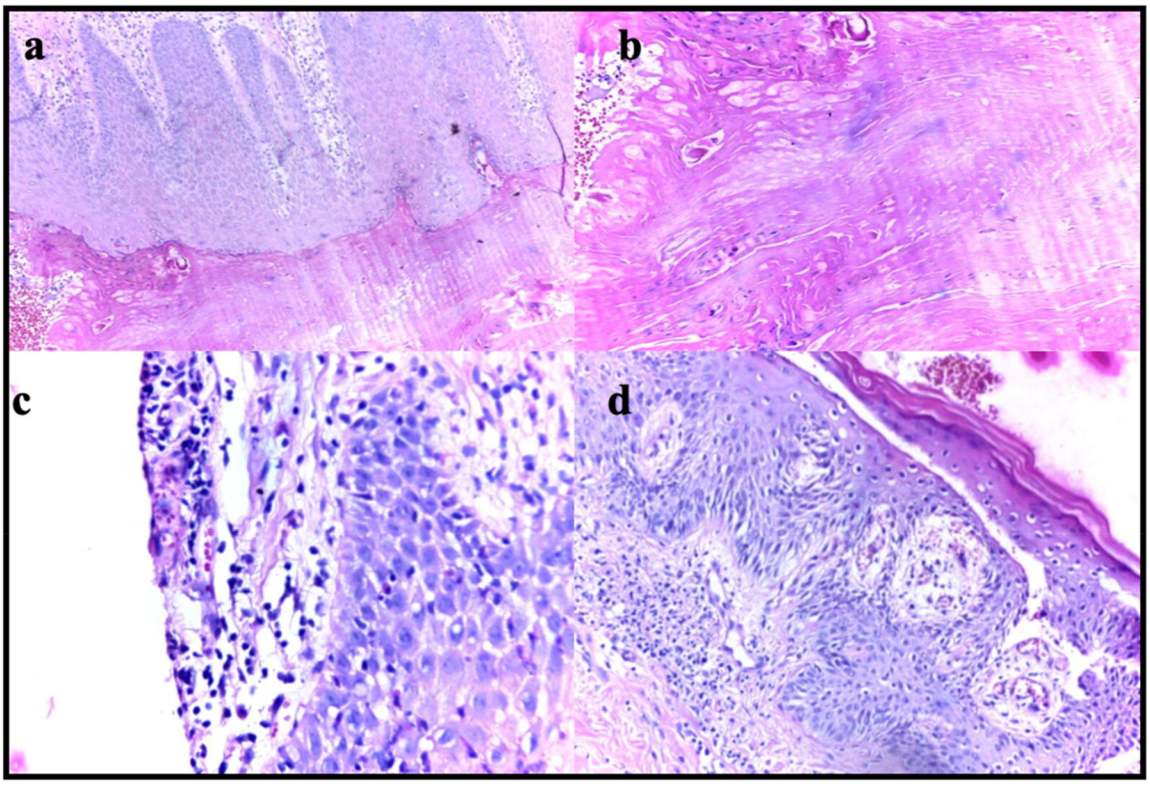

Figure 5: Histopathology patterns of psoriasis, chronic phase (regular acanthosis, hypogranulosis, hyperkeratosis, parakeratosis) at 100X (a) and chronic phase (parakeratosis, hyperkeratosis, munro micro-abscesses) at 200X (b) magnification, whereas acute phase (congested capillaries, pustules of Kogoj, perivascular lymphocytic infiltrate) at 200X (c) magnification and acute phase (elongation and fusion of rete ridges, congested and tortuous capillaries in the edematous dermal papillae, perivascular lymphocytic infiltrate) at 200X (d) magnification. Reproduce from [147] under creative commons attribution non-commercial license −4.0.

was found between the degree of epidermal hyperplasia and the inflammatory infiltrate, the grade of inflammation and pustule of Kogoj, the inflammatory infiltrate, and the capillary proliferation. They also found that 100 % of the cases had inflammatory infiltration [151]. The authors conclude that psoriasis' immunopathogenesis is mostly based on an inflammatory response. In this investigation, we discovered 100 % incidences of inflammatory infiltration [152].

2.5 Future challenges

Because they are safe and convenient, herbal sources are becoming more and more reliable. The main factors to consider for herbal therapy and screening plant extracts for anti-psoriatic efficacy include T-cell trafficking, activation, and inhibition of cytokinase, as well as counteroffensive tactics. Psoriasis can be treated using next generation immunosuppressants and anti-inflammatory medications. Future issues include patient care and monitoring, as well as biological surveillance of the patient's history and chronic inflammatory mediators.

Cytokines such as HMGB1, IL-15, and IL-23 can affect TNF-α levels. Elucidating the fundamental process by which the illness is transferred from one generation to another is another aspect of the research that must be researched in order to explore some additional herbal medications for the treatment of psoriasis [153].

As nanotechnology evolves, we see an increasing number of applications in pharmaceuticals. Because of this, adding nanomaterials to nanotechnology-based drug delivery systems is futuristic; by 2025, the market is predicted to have grown six times, to around US$334 billion, from more than a decade ago [154]. Within the next 20 years, nanomedicine will see rigorous scientific advancement as clinical demands push a greater emphasis on material design [155]. As a result, a new paradigm in psoriasis therapies is shifting towards this unique therapeutic platform [156].

2.6 Conclusions

This review has shown that naturally produced chemicals are expected to play an important role in future psoriasis

therapies. Nature, on the other hand, contains a wealth of unexplored resources. Phytochemicals have been claimed to have several health advantages, and continuous study is being done to establish their physiological effects. The traditional use of natural chemicals in psoriasis therapy is inexpensive due to plant availability and easy product production procedures. However, commercializing natural chemicals for psoriasis therapy may result in a depletion of natural resources and difficulties in creating consistent quality adulteration. However, the use of synthetic drugs has resulted in several side effects, including psoriasis. In recent years, research in this field has produced several therapy alternatives for treating psoriasis. Herbal extracts can be used in combination with synthetic drugs to treat psoriasis. Dual usage may result in a lower synthetic medication dosage and a repeat of undesirable effects. To ensure the safety and efficacy of psoriasis therapy, herbal medications must be standardized through regulatory regulations and quality control systems. More research with bigger sample size is required to evaluate the therapeutic efficacy of these natural compounds. Fresh plant resources should also be investigated in this area.

Abbreviations

DC	Dendritic cells
IL	Interleukin
Tregs	Regulatory T cells
IFN	Interferon
TNF-α	Tumor necrosis factor-α
APCs	Antigen-presenting cells
NADH	Nicotinamide adenine dinucleotide
PSE	Psoriatic skin equivalent
IMQ	Imiquimod
PASI	Psoriasis Area and Severity Index

Acknowledgments: This work was partially supported by CMU Proactive Researcher Scheme (2023), Chiang Mai University for Sudarshan Singh. Moreover, authors are grateful to Ganpat University for providing necessary facilities. In addition, Dr. Prajapati would like to extend his sincere appreciation to the Faculty of Pharmacy, Silpakorn University, Thailand, for their generous support that enabled the completion of this work.

Research ethics: Not applicable.

Informed consent: Third party material such as figures has been reproduced with permission from concern publication house.

Author contributions: Conceptualization, SS and BGP; methodology, PP, KG, AB, and DUK; software, KG, AB, and DUK; validation, SS and BGP; investigation, KG, AB, and DUK; resources, SS; data curation, SS; writing original draft preparation, KG, AB, and DUK; writing review and editing, SS; visualization, BGP; supervision, BGP and SS; project administration, PP, SS, and BGP. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Use of Large Language Models, AI and Machine Learning Tools: None declared.

Conflict of interest: All other authors state no conflict of interest.

Research funding: None declared.

Data availability: Data can be made available on request to corropondening authors.

References

1. Yamanaka K, Yamamoto O, Honda T. Pathophysiology of psoriasis: a review. J Dermatol 2021;48:722–31.
2. Yamanaka K, Mizutani H. “Inflammatory skin march”: IL-1–mediated skin inflammation, atopic dermatitis, and psoriasis to cardiovascular events. J Allergy Clin Immunol 2015;136:823–4.
3. Wang A, Bai Y. Dendritic cells: the driver of psoriasis. J Dermatol 2020; 47:104–13.
4. Buckner JH. Mechanisms of impaired regulation by CD4+ CD25+ FOXP3+ regulatory T cells in human autoimmune diseases. Nat Rev Immunol 2010;10:849–59.
5. Wang W-M, Jin H-Z. Role of neutrophils in psoriasis. J Immunol Res 2020;2020. https://doi.org/10.1155/2020/3709749.
6. Jariwala SP. The role of dendritic cells in the immunopathogenesis of psoriasis. Arch Dermatol Res 2007;299:359–66.
7. Vičić M, Kaštelan M, Brajac I, Sotošek V, Massari LP. Current concepts of psoriasis immunopathogenesis. Int J Mol Sci 2021;22:11574.
8. Nussbaum L, Chen Y, Ogg G. Role of regulatory T cells in psoriasis pathogenesis and treatment. Br J Dermatol 2021;184:14–24.
9. Hu P, Wang M, Gao H, Zheng A, Li J, Mu D, et al. The role of helper T cells in psoriasis. Front Immunol 2021;12. https://doi.org/10.3389/fimmu.2021.788940.
10. Chiang C-C, Cheng W-J, Korinek M, Lin C-Y, Hwang T-L. Neutrophils in psoriasis. Front Immunol 2019;10:2376.
11. Vasam M, Korutla S, Bohara RA. Acne vulgaris: a review of the pathophysiology, treatment, and recent nanotechnology based advances. Biochem Biophy Rep 2023;36. https://doi.org/10.1016/j.bbrep.2023.101578.
12. Kraft J, Freiman A. Management of acne. Cmaj 2011;183:E430–5.
13. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003;49:S1–37.
14. Fox L, Csongradi C, Aucamp M, Du Plessis J, Gerber M. Treatment modalities for acne. Molecules 2016;21:1063.
15. Moreno-Vázquez K, Calderón L, Bonifaz A. Seborrheic dermatitis. An update. Dermatol Rev Mex 2020;64:39–49.
16. Shamloul G, Khachemoune A. An updated review of the sebaceous gland and its role in health and diseases Part 1: embryology, evolution, structure, and function of sebaceous glands. Dermatol Ther 2021;34: e14695.

17. Knutsen-Larson S, Dawson AL, Dunnick CA, Dellavalle RP. Acne vulgaris: pathogenesis, treatment, and needs assessment. Dermatol Clin 2012;30:99–106.
18. Roy H, Nayak BS, Maddiboyina B, Nandi S. Chitosan based urapidil microparticle development in approach to improve mechanical strength by cold hyperosmotic dextrose solution technique. J Drug Deliv Sci Technol 2022;76. https://doi.org/10.1016/j.jddst.2022.103745.
19. Tan JK, LF SG, Alexis AF, Harper JC. Current concepts in acne pathogenesis: pathways to inflammation. Semin Cutaneous Med Surg 2018;37:S60–2.
20. Nishal S, Jhawat V, Phaugat P, Dutt R. Rheumatoid arthritis and JAK-STAT inhibitors: prospects of topical delivery. Curr Drug Ther 2022;17: 86–95.
21. Chauhan P, Meena D, Jindal R, Roy S, Shirazi N. Dermoscopy in the diagnosis of palmoplantar eczema and palmoplantar psoriasis: a cross-sectional, comparative study from a tertiary care centre in North India. Indian J Dermatol 2023;68:120.
22. Kim J, Oh C-H, Jeon J, Baek Y, Ahn J, Kim DJ, et al. Molecular phenotyping small (Asian) versus large (Western) plaque psoriasis shows common activation of IL-17 pathway genes but different regulatory gene sets. J Invest Dermatol 2016;136:161–72.
23. Liu X-Q, Zhou P-L, Yin X-Y, Wang A-X, Wang D-H, Yang Y, et al. Circulating inflammatory cytokines and psoriasis risk: a systematic review and meta-analysis. PLoS One 2023;18:e0293327.
24. Claire R, Griffiths CE. Psoriasis and treatment: past, present and future aspects. Acta Derm Venereol 2020;100. https://doi.org/10.2340/00015555-3386.
25. Das U, Kapoor DU, Singh S, Prajapati BG. Unveiling the potential of chitosan-coated lipid nanoparticles in drug delivery for management of critical illness: a review. Z Naturforsch C Biosci 2024;79:107–24.
26. Singh S, Chunglok W, Nwabor OF, Ushir YV, Singh S, Panpipat W. Hydrophilic biopolymer matrix antibacterial peel-off facial mask functionalized with biogenic nanostructured material for cosmeceutical applications. J Polym Environ 2022;30:938–53.
27. Jyothi S, Krishna K, Shirin VA, Sankar R, Pramod K, Gangadharappa H. Drug delivery systems for the treatment of psoriasis: current status and prospects. J Drug Deliv Sci Technol 2021;62. https://doi.org/10.1016/j.jddst.2021.102364.
28. Mohite P, Asane G, Rebello N, Munde S, Ade N, Boban T, et al. Polymeric hydrogel sponges for wound healing applications: a comprehensive review. Regener Eng Trans Med 2024. https://doi.org/10.1007/s40883-024-00334-4.
29. Shah S, Chauhan H, Madhu H, Mori D, Soniwala M, Singh S, et al. Lipids fortified nano phytopharmaceuticals: a breakthrough approach in delivering bio-actives for improved therapeutic efficacy. Pharm Nanotechnol 2024. https://doi.org/10.2174/0122117385277686231127050723.
30. Mohite P, Munde S, Pawar A, Singh S. Unleashing the potential of cyclodextrin-based nanosponges in management of colon cancer: a review. Nanofabrication 2024;9. https://doi.org/10.37819/nanofab.9.1823.
31. Mohite P, Rahayu P, Munde S, Ade N, Chidrawar VR, Singh S, et al. Chitosan-based hydrogel in the management of dermal infections: a review. Gels 2023;9:594.
32. Angsusing J, Singh S, Samee W, Tadtong S, Stokes L, O'Connell M, et al. Anti-inflammatory activities of yataprasen Thai traditional formulary and its active compounds, beta-amyrin and stigmasterol, in RAW264.7 and THP-1 cells. Pharmaceuticals 2024;17:1018.
33. Rahman M, Alam K, Zaki Ahmad M, Gupta G, Afzal M, Akhter S, et al. Classical to current approach for treatment of psoriasis: a review. Endocr, Metab & Immune Disord-Drug Targets. Formerly Curr Drug Targets-Immune, Endocr & Metabolic Disorders) 2012;12:287–302.
34. Mueller W, Herrmann B. Cyclosporin A for psoriasis. N Engl J Med 1979; 301:555.
35. Smith C, Jabbar-Lopez Z, Yiu Z, Bale T, Burden A, Coates L, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Br J Dermatol 2017;177:628–36.
36. Mariette X, Förger F, Abraham B, Flynn AD, Moltó A, Flipo R-M, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis 2018;77:228–33.
37. Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. J Am Acad Dermatol 2017;76:736–44.
38. Chorachoo Ontong J, Singh S, Nwabor OF, Chusri S, Kaewnam W, Kanokwiroon K, et al. Microwave-assisted extract of rhodomyrtone from rhodomyrtus tomentosa leaf: anti-inflammatory, antibacterial, antioxidant, and safety assessment of topical rhodomyrtone formulation. Separ Sci Technol 2023;58:929–43.
39. Singh S, Chidrawar VR, Hermawan D, Nwabor OF, Olatunde OO, Jayeoye TJ, et al. Solvent-assisted dechlorophyllization of Psidium guajava leaf extract: effects on the polyphenol content, cytocompatibility, antibacterial, anti-inflammatory, and anticancer activities. South Afr J Bot 2023;158:166–79.
40. Xie J, Huang S, Huang H, Deng X, Yue P, Lin J, et al. Advances in the application of natural products and the novel drug delivery systems for psoriasis. Front Pharmacol 2021;12. https://doi.org/10.3389/fphar.2021.644952.
41. Bonesi M, Loizzo MR, Menichini F, Tundis R. Flavonoids in treating psoriasis. In: Immunity and inflammation in health and disease. Salt Lake City: Elsevier; 2018:281–94 pp.
42. Comalada M, Ballester I, Bailón E, Sierra S, Xaus J, Gálvez J, et al. Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: analysis of the structure–activity relationship. Biochem Pharmacol 2006;72:1010–21.
43. Di T-T, Ruan Z-T, Zhao J-X, Wang Y, Liu X, Wang Y, et al. Astilbin inhibits Th17 cell differentiation and ameliorates imiquimod-induced psoriasis-like skin lesions in BALB/c mice via Jak3/Stat3 signaling pathway. Int Immunopharm 2016;32:32–8.
44. Wu J, Li H, Li M. Effects of baicalin cream in two mouse models: 2, 4-dinitrofluorobenzene-induced contact hypersensitivity and mouse tail test for psoriasis. Int J Clin Exp Med 2015;8:2128.
45. Chamcheu JC, Pal HC, Siddiqui IA, Adhami VM, Ayehunie S, Boylan BT, et al. Prodifferentiation, anti-inflammatory and antiproliferative effects of delphinidin, a dietary anthocyanidin, in a full-thickness three-dimensional reconstituted human skin model of psoriasis. Skin Pharmacol Physiol 2015;28:177–88.
46. Vijayalakshmi A, Ravichandiran V, Velraj M, Nirmala S, Jayakumari S. Screening of flavonoid "quercetin" from the rhizome of Smilax China Linn. for anti–psoriatic activity. Asian Pac J Trop Biomed 2012;2: 269–75.
47. Garg SS, Gupta J, Sharma S, Sahu D. An insight into the therapeutic applications of coumarin compounds and their mechanisms of action. Eur J Pharmaceut Sci 2020;152. https://doi.org/10.1016/j.ejps.2020.105424.
48. Lo H-Y, Li C-C, Cheng H-M, Liu I-C, Ho T-Y, Hsiang C-Y. Ferulic acid altered IL-17A/IL-17RA interaction and protected against imiquimod-

induced psoriasis-like skin injury in mice. Food Chem Toxicol 2019;129: 365–75.
49. May BH, Deng S, Zhang AL, Lu C, Xue CC. In silico database screening of potential targets and pathways of compounds contained in plants used for psoriasis vulgaris. Arch Dermatol Res 2015;307:645–57.
50. Kang D, Li B, Luo L, Jiang W, Lu Q, Rong M, et al. Curcumin shows excellent therapeutic effect on psoriasis in mouse model. Biochimie 2016;123:73–80.
51. Patel R, Singh S, Singh S, Sheth N, Gendle R. Development and characterization of curcumin loaded transfersome for transdermal delivery. J Pharmaceut Sci Res 2009;1:71.
52. Bacakova L, Pajorova J, Bacakova M, Skogberg A, Kallio P, Kolarova K, et al. Versatile application of nanocellulose: from industry to skin tissue engineering and wound healing. Nanomaterials 2019;9:164.
53. Xie XJ, Di TT, Wang Y, Wang MX, Meng YJ, Lin Y, et al. Indirubin ameliorates imiquimod-induced psoriasis-like skin lesions in mice by inhibiting inflammatory responses mediated by IL-17A-producing γδ T cells. Mol Immunol 2018;101:386–95.
54. Huang ZZ, Xu Y, Xu M, Shi ZR, Mai SZ, Guo ZX, et al. Artesunate alleviates imiquimod-induced psoriasis-like dermatitis in BALB/c mice. Int Immunopharm 2019;75. https://doi.org/10.1016/j.intimp.2019.105817.
55. Wu S, Zhao M, Sun Y, Xie M, Le K, Xu M, et al. The potential of Diosgenin in treating psoriasis: studies from HaCaT keratinocytes and imiquimod-induced murine model. Life Sci 2020;241. https://doi.org/10.1016/j.lfs.2019.117115.
56. Torsekar R, Gautam MM. Topical therapies in psoriasis. Indian Dermatol Online J 2017;8:235–45.
57. Lebwohl M, Kircik L, Lacour J-P, Liljedahl M, Lynde C, Mørch MH, et al. Twice-weekly topical calcipotriene/betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO-LONG trial). J Am Acad Dermatol 2021;84:1269–77.
58. Wen J, Pei H, Wang X, Xie C, Li S, Huang L, et al. Gambogic acid exhibits anti-psoriatic efficacy through inhibition of angiogenesis and inflammation. J Dermatol Sci 2014;74:242–50.
59. Ali A, Ali S, Aqil M, Imam SS, Ahad A, Qadir A. Thymoquinone loaded dermal lipid nano particles: Box Behnken design optimization to preclinical psoriasis assessment. J Drug Deliv Sci Technol 2019;52: 713–21.
60. Uva L, Miguel D, Pinheiro C, Antunes J, Cruz D, Ferreira J, et al. Mechanisms of action of topical corticosteroids in psoriasis. Int J Endocrinol 2012;2012. https://doi.org/10.1155/2012/561018.
61. Huang TH, Lin CF, Alalaiwe A, Yang SC, Fang JY. Apoptotic or antiproliferative activity of natural products against keratinocytes for the treatment of psoriasis. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20102558.
62. Horn EJ, Domm S, Katz HI, Lebwohl M, Mrowietz U, Kragballe K. Topical corticosteroids in psoriasis: strategies for improving safety. J Eur Acad Dermatol Venereol 2010;24:119–24.
63. Lerche CM, Wulf HC. Photocarcinogenicity of selected topically applied dermatological drugs: calcineurin inhibitors, corticosteroids, and vitamin D analogs. Dermatol Rep 2010;2:e13.
64. Gudas LJ, Wagner JA. Retinoids regulate stem cell differentiation. J Cell Physiol 2011;226:322–30.
65. Amiri D, Schwarz CW, Gether L, Skov L. Safety and efficacy of topical calcineurin inhibitors in the treatment of facial and genital psoriasis: a systematic review. Acta Derm Venereol 2023;103:adv00890.
66. Lee C-H, Wu S-B, Hong C-H, Yu H-S, Wei Y-H. Molecular mechanisms of UV-induced apoptosis and its effects on skin residential cells: the implication in UV-based phototherapy. Int J Mol Sci 2013;14:6414–35.
67. Hemne P, Kunghatkar R, Dhoble S, Moharil S, Singh V. Phosphor for phototherapy: review on psoriasis. Luminescence 2017;32:260–70.
68. Sedger LM, McDermott MF. TNF and TNF-receptors: from mediators of cell death and inflammation to therapeutic giants–past, present and future. Cytokine Growth Factor Rev 2014;25:453–72.
69. P De Miguel M, Fuentes-Julian S, Blazquez-Martinez A, Y Pascual C, A Aller M, Arias J, et al. Immunosuppressive properties of mesenchymal stem cells: advances and applications. Curr Mol Med 2012;12:574–91.
70. Ferreira R, Napoli J, Enver T, Bernardino L, Ferreira L. Advances and challenges in retinoid delivery systems in regenerative and therapeutic medicine. Nat Commun 2020;11:4265.
71. Raut AS, Prabhu RH, Patravale VB. Psoriasis clinical implications and treatment: a review. Crit Rev Ther Drug Carrier Syst 2013;30. https://doi.org/10.1615/critrevtherdrugcarriersyst.2013005268.
72. Miroddi M, Navarra M, Calapai F, Mancari F, Giofrè SV, Gangemi S, et al. Review of clinical pharmacology of Aloe vera L. in the treatment of psoriasis. Phytother Res 2015;29:648–55.
73. Dujic J, Kippenberger S, Hoffmann S, Ramirez-Bosca A, Miquel J, Diaz-Alperi J, et al. Low concentrations of curcumin induce growth arrest and apoptosis in skin keratinocytes only in combination with UVA or visible light. J Invest Dermatol 2007;127:1992–2000.
74. Boonyagul S, Banlunara W, Sangvanich P, Thunyakitpisal P. Effect of acemannan, an extracted polysaccharide from Aloe vera, on BMSCs proliferation, differentiation, extracellular matrix synthesis, mineralization, and bone formation in a tooth extraction model. Odontology 2014;102:310–7.
75. Zhang Q, Xie J, Li G, Wang F, Lin J, Yang M, et al. Psoriasis treatment using indigo naturalis: progress and strategy. J Ethnopharmacol 2022; 297. https://doi.org/10.1016/j.jep.2022.115522.
76. Janeczek M, Moy L, Lake EP, Swan J. Review of the efficacy and safety of topical Mahonia aquifolium for the treatment of psoriasis and atopic dermatitis. J Clin Aesthet Dermatol 2018;11:42–7.
77. Waller JM, Dreher F, Behnam S, Ford C, Lee C, Tiet T, et al. 'Keratolytic' properties of benzoyl peroxide and retinoic acid resemble salicylic acid in man. Skin Pharmacol Physiol 2006;19:283–9.
78. Qiong H, Han L, Zhang N, Chen H, Yan K, Zhang Z, et al. Glycyrrhizin improves the pathogenesis of psoriasis partially through IL-17A and the SIRT1-STAT3 axis. BMC Immunol 2021;22:34.
79. Pandey S, Jha A, Kaur V. Aqueous extract of neem leaves in treatment of Psoriasis vulgaris. Indian J Dermatol, Venereol Leprol 1994;60:63.
80. Pazyar N, Yaghoobi R, Kazerouni A, Feily A. Oatmeal in dermatology: a brief review. Indian J Dermatol Venereol Leprol 2012;78:142.
81. Kolahdooz S, Karimi M, Esmaili N, Zargaran A, Kordafshari G, Mozafari N, et al. Evaluation of the efficacy of a topical chamomile-pumpkin oleogel for the treatment of plaque psoriasis: an intra-patient, double-blind, randomized clinical trial. Biomedical Res Therapy 2018;5:2811–9.
82. Pazyar N, Yaghoobi R. Tea tree oil as a novel antipsoriasis weapon. Skin Pharmacol Physiol 2012;25:162–3.
83. Timoszuk M, Bielawska K, Skrzydlewska E. Evening primrose (oenothera biennis) biological activity dependent on chemical composition. Antioxidants (Basel) 2018;7. https://doi.org/10.3390/antiox7080108.
84. Singh S, Supaweera N, Nwabor OF, Chaichompoo W, Suksamrarn A, Chittasupho C, et al. Poly (vinyl alcohol)-gelatin-sericin copolymerized film fortified with vesicle-entrapped demethoxycurcumin/

bisdemethoxycurcumin for improved stability, antibacterial, anti-inflammatory, and skin tissue regeneration. Int J Biol Macromol 2024; 258. https://doi.org/10.1016/j.ijbiomac.2023.129071.
85. Singh S, Supaweera N, Nwabor OF, Yusakul G, Chaichompoo W, Suksamrarn A, et al. Polymeric scaffold integrated with nanovesicle-entrapped curcuminoids for enhanced therapeutic efficacy. Nanomedicine. 2024:1–17. https://doi.org/10.1080/17435889.2024.2347823.
86. Singh S, Dodiya TR, Dodiya R, Ushir YV, Widodo S. Lipid nanoparticulate drug delivery systems: a revolution in dosage form design and development. Rijeka: Drug Carriers: IntechOpen; 2022.
87. Kapoor DU, Gaur M, Parihar A, Prajapati BG, Singh S, Patel RJ. Phosphatidylcholine (PCL) fortified nano-phytopharmaceuticals for improvement of therapeutic efficacy. EXCLI J 2023;22:880–903.
88. Mohite P, Singh S, Pawar A, Sangale A, Prajapati BG. Lipid-based oral formulation in capsules to improve the delivery of poorly water-soluble drugs. Front Drug Deliv 2023;3. https://doi.org/10.3389/fddev.2023.1232012.
89. Shah Sunny CH, Hardik M, Dhaval M, Moinuddin S, Sudarshan S, Bhupendra P. Lipids fortified nano phytopharmaceuticals: a breakthrough approach in delivering bio-actives for improved therapeutic efficacy. Pharm Nanotechnol 2024;12.
90. Patel P, Garala K, Singh S, Prajapati BG, Chittasupho C. Lipid-based nanoparticles in delivering bioactive compounds for improving therapeutic efficacy. Pharmaceuticals 2024;17:329.
91. Bahadur S, Sharma M. Liposome based drug delivery for the management of psoriasis-A comprehensive review. Curr Pharmaceut Biotechnol 2023;24:1383–96.
92. Antimisiaris S, Marazioti A, Kannavou M, Natsaridis E, Gkartziou F, Kogkos G, et al. Overcoming barriers by local drug delivery with liposomes. Adv Drug Deliv Rev 2021;174:53–86.
93. Jain H, Geetanjali D, Dalvi H, Bhat A, Godugu C, Srivastava S. Liposome mediated topical delivery of Ibrutinib and Curcumin as a synergistic approach to combat imiquimod induced psoriasis. J Drug Deliv Sci Technol 2022;68. https://doi.org/10.1016/j.jddst.2022.103103.
94. Wadhwa S, Singh B, Sharma G, Raza K, Katare OP. Liposomal fusidic acid as a potential delivery system: a new paradigm in the treatment of chronic plaque psoriasis. Drug Deliv 2016;23:1204–13.
95. Wunnoo S, Bilhman S, Amnuaikit T, Ontong JC, Singh S, Auepemkiate S, et al. Rhodomyrtone as a new natural antibiotic isolated from Rhodomyrtus tomentosa leaf extract: a clinical application in the management of acne vulgaris. Antibiotics 2021;10:108.
96. Nwabor OF, Singh S. A systematic review on Rhodomyrtus tomentosa (Aiton) Hassk: a potential source of pharmacological relevant bioactive compounds with prospects as alternative remedies in varied medical conditions. Int J Pharm Sci Nanotechnol (IJPSN) 2022;15:5875–91.
97. Nordin UUM, Ahmad N, Salim N, Yusof NSM. Lipid-based nanoparticles for psoriasis treatment: a review on conventional treatments, recent works, and future prospects. RSC Adv 2021;11:29080–101.
98. Md S, Haque S, Madheswaran T, Zeeshan F, Meka VS, Radhakrishnan AK, et al. Lipid based nanocarriers system for topical delivery of photosensitizers. Drug Discov Today 2017;22:1274–83.
99. Sindhu RK, Gupta R, Wadhera G, Kumar P. Modern herbal nanogels: formulation, delivery methods, and applications. Gels 2022;8:97.
100. Pleguezuelos-Villa M, Diez-Sales O, Manca ML, Manconi M, Sauri AR, Escribano-Ferrer E, et al. Mangiferin glycethosomes as a new potential adjuvant for the treatment of psoriasis. Int J Pharm 2020;573. https://doi.org/10.1016/j.ijpharm.2019.118844.
101. Zhang Y-T, Shen L-N, Wu Z-H, Zhao J-H, Feng N-P. Comparison of ethosomes and liposomes for skin delivery of psoralen for psoriasis therapy. Int J Pharm 2014;471:449–52.
102. Singh S, Ushir YV, Prajapati BG. Phytosomes and herbosomes: a vesicular drug delivery system for improving the bioavailability of natural products. In: Prajapati BPJ, editor. Lipid-Based Drug Delivery Systems: Principles and Applications. London: Jenny Stanford Publishing; 2023.
103. Yeo PL, Lim CL, Chye SM, Ling APK, Koh RY. Niosomes: a review of their structure, properties, methods of preparation, and medical applications. Asian Biomed 2017;11:301–14.
104. Venkatesha SH, Moudgil KD. Celastrol and its role in controlling chronic diseases. Adv Exp Med Biol. 2016;928:267–89.
105. Meng S, Sun L, Wang L, Lin Z, Liu Z, Xi L, et al. Loading of water-insoluble celastrol into niosome hydrogels for improved topical permeation and anti-psoriasis activity. Colloids Surf B Biointerfaces 2019;182. https://doi.org/10.1016/j.colsurfb.2019.110352.
106. Abu HII, Abo El-Magd NF, El-Sheakh AR, Hamed MF, Abd El-Gawad AEH. Pivotal role of Acitretin nanovesicular gel for effective treatment of psoriasis: ex vivo-in vivo evaluation study. Int J Nanomed 2018;13:1059–79.
107. Ontong JC, Singh S, Siriyong T, Voravuthikunchai SP. Transferosomes stabilized hydrogel incorporated rhodomyrtone-rich extract from Rhodomyrtus tomentosa leaf fortified with phosphatidylcholine for the management of skin and soft-tissue infections. Biotechnol Lett 2024;46:127–42.
108. Biswasroy P, Pradhan D, Kar B, Ghosh G, Rath G. Recent advancement in topical nanocarriers for the treatment of psoriasis. AAPS PharmSciTech 2021;22:164.
109. Pleguezuelos Villa M. Advances in antioxidant phytochemical for inflammatory skin diseases: mangiferin and naringin nanocarriers based lipids. 2020.
110. Yadav K, Singh D, Singh MR. Novel archetype in psoriasis management bridging molecular dynamics in exploring novel therapies. Eur J Pharmacol 2021;907https://doi.org/10.1016/j.ejphar.2021.174254.
111. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: a novel technique for transdermal drug delivery. J Drug Deliv Therapeut 2019;9:279–85.
112. Scognamiglio I, De Stefano D, Campani V, Mayol L, Carnuccio R, Fabbrocini G, et al. Nanocarriers for topical administration of resveratrol: a comparative study. Int J Pharm 2013;440:179–87.
113. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Adv Pharmaceut Bull 2015;5:305.
114. Salvi VR, Pawar P. Nanostructured lipid carriers (NLC) system: a novel drug targeting carrier. J Drug Deliv Sci Technol 2019;51:255–67.
115. Silva AC, González-Mira E, García M, Egea M, Fonseca J, Silva R, et al. Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. Colloids Surf B Biointerfaces 2011;86:158–65.
116. Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, et al. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. RSC Adv 2020;10:26777–91.
117. Mohite P, Rajput T, Pandhare R, Sangale A, Singh S, Prajapati BG. Nanoemulsion in management of colorectal cancer: challenges and future prospects. Nanomanufacturing 2023;3:139–66.

118. Alam MS, Ali MS, Alam N, Siddiqui MR, Shamim M, Safhi MM. In vivo study of clobetasol propionate loaded nanoemulsion for topical application in psoriasis and atopic dermatitis. Drug Invent Today 2013; 5:8–12.
119. Yousefiasl S, Manoochehri H, Makvandi P, Afshar S, Salahinejad E, Khosraviyan P, et al. Chitosan/alginate bionanocomposites adorned with mesoporous silica nanoparticles for bone tissue engineering. J Nanostruct Chem 2023;13:389–403.
120. Sánchez-López E, Guerra M, Dias-Ferreira J, Lopez-Machado A, Ettcheto M, Cano A, et al. Current applications of nanoemulsions in cancer therapeutics. Nanomaterials 2019;9:821.
121. Lu Y, Zhang E, Yang J, Cao Z. Strategies to improve micelle stability for drug delivery. Nano Res 2018;11:4985–98.
122. Rashid SA, Bashir S, Naseem F, Farid A, Rather IA, Hakeem KR. Olive oil based methotrexate loaded topical nanoemulsion gel for the treatment of imiquimod induced psoriasis-like skin inflammation in an animal model. Biology 2021;10:1121.
123. Sahu S, Katiyar SS, Kushwah V, Jain S. Active natural oil-based nanoemulsion containing tacrolimus for synergistic antipsoriatic efficacy. Nanomedicine 2018;13:1985–98.
124. Ghatage MM, Mane PA, Gambhir RP, Parkhe VS, Kamble PA, Lokhande CD, et al. Green synthesis of silver nanoparticles via Aloe barbadensis miller leaves: anticancer, antioxidative, antimicrobial and photocatalytic properties. Appl Surf Sci Adv 2023;16. https://doi.org/10.1016/j.apsadv.2023.100426.
125. Ramanunny AK, Wadhwa S, Singh SK, Kumar B, Gulati M, Kumar A, et al. Topical non-aqueous nanoemulsion of Alpinia galanga extract for effective treatment in psoriasis: in vitro and in vivo evaluation. Int J Pharm 2022;624. https://doi.org/10.1016/j.ijpharm.2022.121882.
126. Feldman SR, Ravis SM, Fleischer AB, McMichael A, Jones E, Kaplan R, et al. Betamethasone valerate in foam vehicle is effective with both daily and twice a day dosing: a single-blind, open-label study in the treatment of scalp psoriasis. J Cutan Med Surg: Incorporat Med Surgical Dermatol 2001;5:386–9.
127. Mirtič J, Papathanasiou F, Rakuša ŽT, GosencaMatjaž M, Roškar R, Kristl J. Development of medicated foams that combine incompatible hydrophilic and lipophilic drugs for psoriasis treatment. Int J Pharm 2017;524:65–76.
128. Müller R, Junghanns. Junghanns. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomed 2008:295. https://doi.org/10.2147/ijn.s595.
129. Raj SJS, Sumod US, Sabitha M. Nanotechnology in cosmetics: opportunities and challenges. J Pharm BioAllied Sci 2012;4:186–93.
130. Döge NHS, Schumacher F, Balzus B, Colombo M, Hadam S, Rancan F, et al. Ethyl cellulose nanocarriers and nanocrystals differentially deliver dexamethasone into intact, tape-stripped or sodium lauryl sulfate-exposed ex vivo human skin - assessment by intradermal microdialysis and extraction from the different skin layers. J Contr Release 2016;28:25–34.
131. Singh S, Sharma N, Behl T, Sarkar BC, Saha HR, Garg K, et al. Promising strategies of colloidal drug delivery-based approaches in psoriasis management. Pharmaceutics 2021;13:1978.
132. Amrutiya N, Bajaj A, Madan M. Development of microsponges for topical delivery of mupirocin. AAPS PharmSciTech 2009;10:402–9.
133. Mohite P, Patel M, Puri A, Pawar A, Singh S, Prajapati B. Revisiting the advancement with painless microneedles for the diagnosis and treatment of dermal infections: a review. Nanofabrication 2023;8. https://doi.org/10.37819/nanofab.8.332.
134. Berl V, Hurd YL, Lipshutz BH, Roggen M, Mathur EJ, Evans M. A randomized, triple-blind, comparator-controlled parallel study investigating the pharmacokinetics of cannabidiol and tetrahydrocannabinol in a novel delivery system, solutech, in association with cannabis use history. Cannabis and Cannabinoid Res 2022;7:777–89.
135. Khorshidian A, Sharifi N, Choupani Kheirabadi F, Rezaei F, Sheikholeslami SA, Ariyannejad A, et al. In vitro release of Glycyrrhiza glabra extract by a gel-based microneedle patch for psoriasis treatment. Gels 2024;10:87.
136. Pradhan MAA, Singh MR, Singh D, Saraf S, Saraf S, Ajazuddin, et al. Understanding the prospective of nano-formulations towards the treatment of psoriasis. Biomed Pharmacother 2018;107:447–63.
137. Mascarenhas-Melo F, Carvalho A, Gonçalves MBS, Paiva-Santos AC, Veiga F. Nanocarriers for the topical treatment of psoriasis-pathophysiology, conventional treatments, nanotechnology, regulatory and toxicology. Eur J Pharm Biopharm 2022;176:95–107.
138. Lee H-J, Kim M. Challenges and future trends in the treatment of psoriasis. Int J Mol Sci 2023;24:13313.
139. Elmets CA, Lim HW, Stoff B, Connor C, Cordoro KM, Lebwohl M, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. J Am Acad Dermatol 2019;81:775–804.
140. Kang J-H, Chon J, Kim Y-I, Lee H-J, Oh D-W, Lee H-G, et al. Preparation and evaluation of tacrolimus-loaded thermosensitive solid lipid nanoparticles for improved dermal distribution. Int J Nanomed 2019; 14:5381–96.
141. Sathe P, Saka R, Kommineni N, Raza K, Khan W. Dithranol-loaded nanostructured lipid carrier-based gel ameliorate psoriasis in imiquimod-induced mice psoriatic plaque model. Drug Dev Ind Pharm 2019;45:826–38.
142. Doppalapudi S, Jain A, Chopra DK, Khan W. Psoralen loaded liposomal nanocarriers for improved skin penetration and efficacy of topical PUVA in psoriasis. Eur J Pharmaceut Sci 2017;96:515–29.
143. Fathalla D, Youssef EMK, Soliman GM. Liposomal and ethosomal gels for the topical delivery of anthralin: preparation, comparative evaluation and clinical assessment in psoriatic patients. Pharmaceutics 2020;12:446.
144. Mobini N, Toussaint S, Kamino H, Elder D, Elenitsas R, Johnson B, et al. Lever's histopathology of the skin. Noninfectious Erythematous, Papular, and Squamous Dis 2005;10:185–90.
145. Kim BY, Choi JW, Kim BR, Youn SW. Histopathological findings are associated with the clinical types of psoriasis but not with the corresponding lesional psoriasis severity index. Ann Dermatol 2015; 27:26.
146. Nissinen L, Kähäri V-M. Matrix metalloproteinases in inflammation. Biochim Biophys Acta Gen Subj 2014;1840:2571–80.
147. Keijsers R, Hendriks AGM, van Erp PEJ, van Cranenbroek B, van de Kerkhof PCM, Koenen H, et al. In vivo induction of cutaneous inflammation results in the accumulation of extracellular trap-forming neutrophils expressing RORγt and IL-17. J Invest Dermatol 2014;134:1276–84.
148. Jiang M, Fang H, Shao S, Dang E, Zhang J, Qiao P, et al. Keratinocyte exosomes activate neutrophils and enhance skin inflammation in psoriasis. Faseb J 2019;33:13241–53.
149. Mihu C, Neag MA, Bocşan IC, Melincovici CS, Vesa ŞC, Ionescu C, et al. Novel concepts in psoriasis: histopathology and markers related to modern treatment approaches. Rom J Morphol Embryol 2022;62: 897–906.
150. Reich K, Papp KA, Matheson RT, Tu JH, Bissonnette R, Bourcier M, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol 2015;24:529–35.

151. Moorchung N, Khullar J, Mani N, Chatterjee M, Vasudevan B, Tripathi T. A study of various histopathological features and their relevance in pathogenesis of psoriasis. Indian J Dermatol 2013;58: 294–8.
152. Kk MK. Psoriasis and significance of clinicopathological correlation in a tertiary care hospital. Archive Cytol Histopathol Res 2017;2:23–6.
153. Singh K, Tripathy S. Natural treatment alternative for psoriasis: a review on herbal resources. J Appl Pharmaceut Sci 2014;4:114–21.
154. Bosetti R, Jones SL. Cost-effectiveness of nanomedicine: estimating the real size of nano-costs. Nanomedicine (Lond). 2019;14:1367–70.
155. Richardson JJ, Caruso F. Nanomedicine toward 2040. Nano Lett 2020; 20:1481–2.
156. Saleem S, Iqubal MK, Garg S, Ali J, Baboota S. Trends in nanotechnology-based delivery systems for dermal targeting of drugs: an enticing approach to offset psoriasis. Expet Opin Drug Deliv 2020;17:817–38.