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Review Article

Exploring the Anti-Inflammatory Mechanisms of Phytochemicals in Psoriasis: Molecular Insights and Translational Relevance

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Abstract

Psoriasis is a chronic inflammatory autoimmune skin condition characterized by rapid skin cell turnover, resulting in pain, inflammation, and scaling. Due to the side effects associated with conventional treatments, there is growing interest in alternative therapies that utilize natural phytochemicals sourced from plants, fruits, and herbs. This systematic review explores the potential of these compounds, including flavonoids, carotenoids, polyphenols, and essential oils, which exhibit anti-inflammatory, antioxidant, and immunomodulatory effects.

However, the clinical application of these natural compounds is often limited by issues like poor water solubility, chemical instability, and low bioavailability. Nanotechnology-based drug delivery systems, such as polymeric nanoparticles, ethosomes, and solid lipid nanoparticles, present effective strategies for overcoming these challenges. They enhance drug solubility, improve skin permeation, and allow for controlled, site-specific release.

The findings indicate that phytochemicals could serve as valuable complements or alternatives to existing psoriasis treatments. While further research is necessary to optimize their clinical application and establish standardized protocols, the integration of phytochemicals with nanotechnology represents a promising new approach in dermatology, offering safer and more effective long-term treatment options for psoriasis patients.

1. Introduction:

Psoriasis is an inflammatory autoimmune skin condition caused by T-cell activation, characterized by the formation of thick, silvery scales on peach-pink or dull-red skin areas. These lesions can cause severe discomfort, including abrasions, hyperkeratosis, dilated microvessels, aberrant keratinization, epidermal proliferation, and inflammatory cell infiltration. Additionally, psoriasis is linked to a higher risk of several comorbid diseases, such as dyslipidemia, type II diabetes, and cardiovascular disease(Aghmiuni and Khiavi, 2017).

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1.1. Psoriasis:

Psoriasis is an inflammatory autoimmune skin condition caused by T-cell activation, characterized by the formation of thick, silvery scales on peach-pink or dull-red skin areas. These lesions can cause severe discomfort, including abrasions, hyperkeratosis, dilated microvessels, aberrant keratinization, epidermal proliferation, and inflammatory cell infiltration. Additionally, psoriasis is linked to a higher risk of several comorbid diseases, such as dyslipidemia, type II diabetes, and cardiovascular disease. Individuals with psoriasis often experience secondary issues such as insomnia, arthritis-related pain, and depression. Although psoriasis can develop at any age, it most commonly appears between 15 and 22 years of age. It can affect any area of the body but typically occurs on the scalp, lower back, and extensor surfaces of the limbs, especially the knees and elbows. Around the 60-69 age range, psoriasis appears to reach a second peak. Women are slightly more likely than men to develop psoriasis at an earlier age, and family history also significantly affects the age of onset. With alternating periods of relapse and remission, the illness may endure for only a few weeks or for the rest of a person's life. There is a noticeable increase in the inflammatory cytokines IL-1, IL-6, and TNF-γ in patients with psoriasis. Metabolic syndrome is linked to psoriasis, a chronic systemic inflammatory condition. Individuals with metabolic syndrome also have cytokines, including IL-1, IL-4, IL-6, IL-8, IL-12, and TNF-α, which are involved in the development of psoriasis (Salihbegovic et al., 2015). Psoriasis is caused by several factors, in addition to chronic inflammation, including environmental factors, genetics, alcohol consumption, stress, and improper nutrition. Both genetic and environmental factors play a role in the development of psoriasis. Compared to those not affected by psoriasis, individuals with psoriasis have a higher incidence of metabolic syndrome. Pustular and non-pustular psoriasis can be broadly divided into two types, with other subtypes occurring in between. Psoriasis vulgaris is the most prevalent type of psoriasis. The subtypes that are typically grouped with plaque psoriasis include erythrodermic psoriasis, which affects 75% of the body surface, guttate psoriasis, and eruptive psoriasis, which typically affects young adults and children. Inverse psoriasis is associated with the flexural areas of the skin (Uppala et al., 2021). The first line of treatment is traditional topical therapy, which uses corticosteroids, Vitamin D, and its equivalents. The proliferation rate and epithelia are affected by several Vitamin A derivatives. These derivatives control keratin variation and its abnormalities in psoriasis, an autoimmune disease (Aghmiuni and Khiavi, 2017).

1.2. Epidemiology:

According to a worldwide epidemiological study, psoriasis is common in many nations and affects people of all ages in certain places. In children, the prevalence was 0% in Taiwan, 0.71% in Germany, and 2.1% in Italy. In France, adults accounted for 5.20% of cases. Although not as common in India as in Western nations, there are still some reported cases. Psoriasis is a significant condition in its own right, but it can also be worsened by other conditions, such as heart attacks, diabetes, and arthritis. The National Health Services places more emphasis on educating and empowering patients to reduce the negative effects of illness. On May 24, 2014, the 67th World Health Assembly of the WHO passed a resolution on psoriasis treatment. Every member state has committed to making the necessary efforts to reduce the number of patients with psoriasis. Members were aware of the worldwide psoriasis sufferers due to insufficient care, delayed or inaccurate diagnoses, and issues with access to treatment. The petition requested the WHO to organize a worldwide report on psoriasis and be involved in spreading awareness about the condition to draw attention to its effects on public health. Policymakers aim to enhance the health and social inclusion of people with psoriasis. Health services research must enhance the effectiveness and quality of care so that psoriasis therapy can serve as a paradigm for other chronic skin disorders. Different triggering events that cause the disease to appear or chronic diseases to flare-up have been identified. Understanding and reducing these triggers is crucial

for managing psoriasis. Many studies from several countries have demonstrated a link between obesity or weight gain and the development of psoriasis. Smoking tobacco is a significant risk factor. Psoriasis can also be caused by specific types of infections such as streptococcal throat infections. The risk of psoriasis is elevated in patients with periodontitis. Stress is the primary triggering factor for psoriasis in both adults and children.

1.3. Classification Of Psoriasis

a) Plaque psoriasis: Plaque psoriasis is the most prevalent type of psoriasis, and patients may have plaques that are nummular (coin-sized), circular, or oval in shape. The lesions may start out as erythematous papules that are flat and 1 cm in diameter, spread outward, and then combine to create plaques that range in diameter from 1 cm to several centimeters. Ninety percent of plaque psoriasis cases are chronic.

b) Guttate psoriasis: The term "guttate psoriasis" refers to the sudden appearance of numerous tiny psoriatic lesions with diameters of 2 to 10 mm. Although they can also affect the head and limbs, guttate lesions are typically spread in a centripetal manner. It accounts for 2% of all psoriasis cases.

c) Inverse or flexural psoriasis: Specifically, perineal, inframammary, and axillary psoriasis differ morphologically from conventional plaques in different locations on the limbs and trunk. Flexural lesions are red, lustrous, well-defined plaques that lack scales and can resemble candidal, intertrigo, and dermatophyte diseases.

d) Erythroderma: Erythroderma is the term for entire or partial skin involvement caused by active psoriasis, and it can appear in one of two ways. First, when plaques enlarge and become confluent, chronic plaque psoriasis may gradually worsen. Second, erythroderma can be a symptom of unstable psoriasis caused by infection, exposure to tar, medications, or discontinuation of corticosteroids.

e) Generalized pustular psoriasis: This is uncommon and indicates an aggressive and unstable illness. The patient has monomorphic, sterile pustules that may merge into sheets and has pyrexial skin that is red, uncomfortable, inflammatory, and studded with these lesions.

f) Palmoplantar pustulosis: The symptoms of palmoplantar pustulosis include sterile yellow pustules on the palms and/or soles, along with erythema and scaling.

g) Psoriatic nail infection: Shallow depths in the nail plate, caused by improper nail development in the proximal region of the nail matrix, are the most frequent observation. Approximately 50% of patients with psoriasis develop psoriatic nail disease.

2. Pathophysiology of Psoriasis: Myeloid cells are triggered early in the pathogenesis of psoriasis by cytokines released by keratinocytes, natural killer T cells, plasmacytoid dendritic cells, and macrophages. Sharply delineated, erythematous, and flaky plaques are the clinical markers of psoriatic lesions, which are caused by the interplay of dendritic cells (DCs), keratinocytes (KCs), and T lymphocytes. According to research, the condition appears to affect the skin's outermost layer, which is composed of keratinocyte-type cells. Inflammation caused by psoriatic plaques is not restricted to the epidermis; rather, it spreads to the dermis owing to the interaction between keratinocytes and adaptive immune cells. Psoriasis pathogenesis can be categorized into two stages: the initial stage, which may be brought on by the Koebner phenomenon, medications, or infection, and the subsequent maintenance stage, which exhibits persistent clinical expansion. Dendritic cells play a vital role in the initial stages of the disease. Specialized antigen-presenting cells include dendritic cells. However, the exact mechanism underlying their stimulation in psoriasis remains unknown. One suggested process is the release of antimicrobial peptides (AMPs), which are frequently overexpressed in psoriatic skin and generated by keratinocytes in response to injury.

The three AMPs that specifically cause psoriasis are defensins, LL37, and S100 proteins. Interferon alpha (IFN-α), released by plasmacytoid dendritic cells stimulated by DNA-LL37, activates myeloid dendritic cells. IL-23 and IL-12 are released once the myeloid dendritic cells are activated. IL-12 induces basic T cells to differentiate into TH1 cells. IL-23 sustains the existence and growth of TH17 and TH22 cells, respectively. TNF-Y and Interferon gamma (IFN-y) are produced by TH1 cells, IL-22 is produced by TH22 cells, and IL-17, IL-22, and TNF-Y are produced by TH17 cells. Different T cells that trigger an adaptive immune response can cause psoriatic inflammation. TH17 cytokines, including IL-17, IL-22, and IL-21, promote keratinocyte growth in the epidermis. TNF-Y, IL-17, and IFN-y, as well as keratinocyte activation by LL37 and DNA, which considerably boosts the creation of type I IFNs-α, are all induced by psoriatic inflammation. Moreover, they actively contribute to the inflammatory cascade through the production of cytokines, chemokines, and AMP. The Tyk2-Jak2 and STAT3 pathways are intracellular intermediates in the IL-23 signaling process that trigger the transcription of the main

inflammatory mediators. These cytokines trigger downstream keratinocyte development, enhance endothelial cell and angiogenic mediator interactions, and promote immune cell penetration into lesional skin. Drugs that target TNF-Y-, IL-23, and IL-17, as well as JAK/STAT signaling pathways, are effective in treating plaque psoriasis. Other inflammatory pathways also function well for psoriatic variations. Topical medicines such as corticosteroids, keratolytics, calcineurin inhibitors, targeted phototherapy, and Vitamin D analogs are used to treat mild psoriasis. Biologics, oral medicines, and ultraviolet-B (UV-B)/PUVA phototherapy are helpful for treating moderate-to-severe psoriasis.

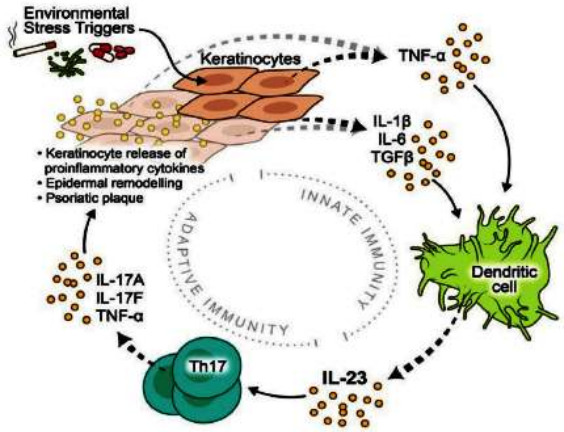

Figure 1 Pathopysiology of Psoriasis

2. Plants acting against psoriasis: Many plants, including Centella asiatica, Aloe Vera, Panax ginseng, Saccharum officinarum, and Rubia cordifolia, have been found to have antipsoriatic action, according to a thorough review of the literature. The information covered includes the biological source (family, common name, and plant's botanical name), the extract or isolate of the plant portion employed, the bioactive dose, the path of administration, the humans or animals, the experimental model or scientific research, and the way of action (if reported). The negative effects of current psoriasis treatments have caused researchers to turn their attention to safer natural remedies. The psoralen active component in PUVA therapy, which is extensively used to treat psoriasis, is derived from the plant Psoralea corylifolia. Herbal medicines appear to be a potential way to investigate better, safer, and more effective antipsoriatic pharmaceuticals, keeping in mind the significant adverse effects related to synthetic treatments accessible for psoriasis treatment. There is scientific evidence supporting the traditional use of plants such as Aloe vera, Curcuma longa, and Thespesia populnea for treating skin conditions such as psoriasis. The addition of such plant medicines to the arsenal of contemporary treatments has restored researchers' confidence in natural resources (Lei et al., 2013). In this review, plant-derived chemical components with anti-psoriatic activity have been described (Table 1).

Table 1: Various plant components that have been identified and shown to have antipsoriatic action

S. No.	Active Constituent	Plant Source	Dose	Animals \Human being	Mode of Action	Reference
1.	Artesunate	Artemisia annua L.(Sweet Wormwood).	0.01-00.5mg/mL	Cell line of Keratinocyte HaCaT	Controlling the expression of CXCR2 and boosting TGF 1 secretions in vitro to have an antiproliferative effect	**(Doke et al., 2024)**
2.	Comptothecin	Camptotheca acuminate Decaisne (Heaven wood tree).	0.5mg/mL	Albino mice	Limiting proliferation and promoting differentiation.	**(Balasubramanian and Eckert, 2007)**
3.	Colchicine	Colchicum autumale L. (Autumn crocus) 0	0.02mg/kg per day,	Human patients	AntichemotactiC	**(Wahba and Cohen, 1980)**
4.	Curcumin	Curcuma longa L. (Turmeric).	Gel,2-5 weeks	Human patients	NFKB is inhibited with a selective phosphoryalase kinase inhibitor, which lowers inflammation.	**(Traub and Marshall, 2007)**

5.	Hypericine	Hpericum perforatum L. (St john's Wort). Topical Hairless mice	Topical	Hairless mice	Alleviated erythema, desquamation, and erosions by penetrating the skin with a photoactive concentration.	(Hamuhalbwa et al., 1999)
6.	Iso-Comptothecin	Camptotheca acuminate Decaisne (Heaven wood tree).	51µg/mL for 24 hr, 48 hr	Human Keratinocyte cell line HaCaT	Inhibits the growth of keratinocyte and triggers apoptosis	(Lin et al., 2008)
7.	Podophyllotoxin	Podophyllum peltatum L. (Mayapple).	0.1%,0.25%or 0.5% in an ointment base	Human patients		(Larsson and Rosén, 1986)

3. Overview of Herbal Nanomedicines in psoriasis management: Topical administration of capsaicin demonstrates potential therapeutic use in the prevention of cutaneous vasodilatation and blocking of axon reflex vasodilatation caused by a number of substances. Capsaicin regulates (HIF-1) Hypoxia-Induced Factor-1 translation through transient receptor potential, causing proper differentiation and preventing hyperproliferation of the psoriatic epidermis. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) with and without capsaicin were synthesized using the solvent diffusion method for high drug retention in the afflicted skin. Comparing NLCs and SLNs to plain capsaicin solution, a high flux was observed. The skin of albino rats exhibits more capsaicin penetration according to capsaicin NLCs (capsaicin delivery) (Cevc and Blume, 2004). The stratum corneum drug retention in SLNs and NLCs was much higher than that in capsaicin solution alone, being 3.13 times for SLNs and 4.5 times for NLCs, respectively. Lipid formulations of SLNs and NLCs resulted in greater capsaicin penetration compared to the capsaicin solution. The NLC formulation of capsaicin has a great chance of regulated and sustained medication delivery at an effective dosage. To effectively treat skin conditions, a localized depot and subsequent extended residency of capsaicin are maintained. In the case of psoriasis, NLCs exhibited greater skin permeation through deep and hyperproliferative skin than SLNs, suggesting that NLCs may be a better choice than SLNs for such diseases. The NLCs were small in size, exhibited high drug entrapment, superior skin permeation with good drug retention, and no signs of skin irritation. Therefore, NLCs may be investigated as a medication carrier for topical drug delivery (Fesq et al., 2003) (Lei et al., 2013). Capsaicin (CAP), which blocks TNF-ϒ, is promising for the management of psoriasis. By suppressing TNF-ϒ, the mediator of psoriasis, in psoriatic cells of the stratum corneum, it prevents the development of NF-kB. Furthermore, capsaicin prevents axon reflex vasodilatation induced by several erythematogenic substances. CAP also inhibits cutaneous vasodilatation. Capsaicin reduces substance P, which is a crucial aspect of psoriasis etiology. The drug accumulation in various skin layers was enhanced with the CAP-loaded emulsomal gel, demonstrating maximum therapeutic efficacy and few negative effects. Emulsomal gels loaded with capsaicin have a local effect and may be used to treat psoriatic infections (Gupta et al., 2014). Curcumin and caffeine combined in a topical gel formulation on a nanosponge demonstrated efficacy in psoriasis treatment. Compared to curcumin alone, the combination with caffeine shortened the time required to treat psoriasis. The results of the histological analysis support the positive antipsoriatic activity of the nanogel mixture of curcumin and caffeine. Nanogels demonstrated continuous drug release over 12 h. Coffee inhibits phosphodiesterase, whereas methyl xanthine raises AMP levels inside cells, which blocks inflammatory pathways and slows psoriasis evolution. Cyclodextrin Nano-sponges offer the maximum drug loading and regulated release of drug, as well as bioavailability and stability for a spectrum of therapeutic molecules. The gel was translucent, clear, uniform, and free of lumps and aggregates. Topical gels with a nanosponges foundation have good spreading capabilities. The formulations displayed a primary drug burst release during the early hours, which may have been caused by the unentrapped drug content of the gel matrix. This early burst was followed by persistent drug release from the Nano-core sponges over a longer period (Iriventi et al., 2020). In a Nano-emulsion formulation, tacrolimus and kalonji oil (functional excipient) were combined to deliver two antipsoriatic medications topically at the same time. Kalonji oil is a natural excipient with effective antipsoriatic properties. Tacrolimus, a calcineurin inhibitor and successful treatment for autoimmune illnesses, has an immunosuppressive effect. Based on tacrolimus' solubility and possible psoriasis-related activity,

kalonji oil was used. The solubility of tacrolimus is supported by the increased hydrophobicity of kalonji oil compared to other synthetic oils. Nano-emulsions were created using the spontaneous emulsification method. To optimize the therapeutic effect, treatments are often combined. Nano-emulsions are particularly effective for the topical delivery of several therapeutic drugs. The nano-emulsion gel containing tacrolimus and kalonji oil reduced the severity of psoriatic lesions, demonstrating its ability to reduce inflammation. The intrinsic properties of kalonji oil, as opposed to other oils used in amalgamation with tacrolimus for double action, in the formulation of nano-emulsion. The anti-inflammatory properties of kalonji oil aid in the inhibition of several inflammatory cytokines. The Nano-emulsion created using tacrolimus and kalonji oil had a noticeable impact on cytokine levels (Sahu et al., 2018) (Sathe et al., 2019). Psoriasis-related skin inflammation reveals an overexpressed protein that could be the target of new nanocarriers to increase medication absorption by the skin. As a new drug delivery system for curcumin, ethosomes made from modified propylene glycol and hyaluronic acid were joined through covalent bonding. Due to air, temperature, and light, babchi oil (Psoralea corylifolia) is susceptible to oxidation and deterioration.

Table.02: A summary of some selected plants and their parts having antipsoriatic activity

Common Name	Botanical Name	Part used	Results	Ref.
Babchi	Psoralea carylifolia	Seeds	Babichi Oil Furocoumarins, the primary ingredients of babichi oil, which likewise inhibit DNA synthesis and cause cell proliferation to slow down, have been shown to have anti-psoriatic properties.	**(Kumar et al., 2019a)**
Bell pepper	Capsicum annuum	Fruits	Capsaicin In the case of psoriasis, NLCs exhibit high skin permeation through deep and hyper-proliferative skin than SLNs, suggesting that NLCs may be a much better choice than SLNs for such diseases.	**(Agrawal et al., 2015)**
Kalonji	Nigella sativa	Seeds	Ethosomal vesicular system could be use as delivery medium to increase drug solubility, trapping, and penetration.	**(Negi et al., 2019)**
China root	Smilax china	Roots	The created NLC formulation serves as a practical drug delivery system for the management of psoriasis.	**(Qadir et al., 2020)**
Turmeric	Curcuma longa	Rhizome	HA-ES system designed to boost the skin's absorption of the medication curcumin by targeted drug delivery.	**(Zhang et al., 2019)**
Aloe	Aloe barbadensis miller	Leaves	Stem less, leaves fleshy green, thick and green or grey colour.	**(Aghmiuni and Khiavi, 2017)**
Cayenne red Paper	Capsicum annuum Fruits	Fruits	Flower purplish or off white colour. Stem thickly branched Fruit yellow, green, or red when ripe.	**(Sanati et al., 2018)**
Winter green	Gaultheria procumbens	Leave	Flowers pink or white, bell-sheped corolla fruits red colour.	**(Michalek et al., 2017)**
Chamomile	Matricaria recutita	Flowers	Leaves-narrow bipinnate or tripinnate. Flowers-paniculate flower heads.	**(Dos Santos et al., 2019)**
Christmas berry	Psoropermum febrifugum	Stem bark	Small scrub flowers, white or creamy colour	**(Asogwa et al., 2020)**

However, there are still more issues with babchi oil that need to be researched, such as its skin irritation and toxicity. Despite its effective antipsoriatic properties, these shortcomings prevent the routine use of BO. Furocoumarins, which are the major components of babchi oil, slow down DNA synthesis and cell proliferation and have antipsoriatic properties. The use of phytoconstituents as nanocarriers for drug delivery has garnered considerable interest from scientists because it has been demonstrated to be a successful strategy for treating skin problems. Moreover, cyclodextrins have been scientifically proven to enhance local irritancy and aid in drug delivery, which is very important in psoriasis treatment. Babchi oil nanostructure gel based on cyclodextrin can be used to treat psoriasis and has been investigated in human clinical studies for potential future commercial exploitation (Kumar et al., 2019b). Thymoquinone (TQ), a lipid-soluble benzoquinone with specific expertise in therapeutic antagonistic effects on skin diseases, such as

pigmentation, hypersensitivity, vitiligo, and early skin tumor stages, including psoriasis, has been credited with the significant antipsoriatic action of Nigella sativa seeds. Despite its significant therapeutic potential, thymoquinone has several drawbacks, including low hydrosolubility, high hydrophobicity, chemical instability, low bioavailability, and limited penetration. Ethosomal vesicular systems are potential delivery vehicles for bypassing these restrictions, as they increase drug solubility, trapping, and penetration. The ethosomal gel with TQ loading demonstrated promising results for the treatment of psoriasis (Kaur et al., 2017). The full relationship between serum total bilirubin levels and psoriasis improvement in patients suggests that bilirubin has therapeutic potential for psoriasis. When applied topically, bilirubin nanoparticles are an effective nanomedicine for treating psoriasis. BRNPs effectively halted tumor growth in vivo. Previous studies have shown that BRNPs can enter the stratum corneum, a skin layer that is disrupted in psoriatic skin, and integrate into activated keratinocytes. Therefore, bilirubin nanoparticles hold considerable promise for the topical management of psoriasis. Moreover, (Bilirbilirubin nanoparticles (have a significant clinical effect and have been used to treat additional diseases caused by Reactive Oxygen Species (ROS) because they have antioxidant properties and are biodegradable when oxidized in response to ROS (Aggarwal, 2018). A summary of some selected plants with antipsoriatic activity is presented in Table 2. The negative effects of current psoriasis treatments have caused experts to turn their attention to safer natural remedies. The active ingredient in PUVA therapy, which is extensively used to treat psoriasis, is psoralen, derived from the plant Psoralea corylifolia. Herbal medicines appear to be a potential strategy for investigating better, safer, and more helpful antipsoriatic treatments, considering the significant side effects associated with synthetic drugs used to manage psoriasis. There is scientific proof to support the traditional use of plants such as Curcuma longa, Thespesia populnea, and Aloe vera for treating skin conditions such as psoriasis. The addition of such plant medicines to the arsenal of contemporary treatments has restored researchers' faith in natural resources. Herbal remedies are still considered a significant source of many cutting-edge drugs and are seen as a precious gift of nature for the management of many disorders. Natural medicines have, up to this point, continually attracted attention due to their eco-friendliness and remarkably low side effects.

4. Novel nanotechnology-based approaches for the topical treatment of psoriasis

Topical treatment is the cornerstone of psoriasis management. New developments and recent advancements have improved drug therapy and patient satisfaction. Recent advances, such as nanoparticles, ethosomes, and niosomes, are strategies to improve the efficacy, safety, and comfort of topical treatment in the management of psoriasis. Recently, various technologies have been developed to increase the effectiveness of topical drug therapy for the management of psoriasis. Several new drug carriers provide the opportunity to introduce new molecules into topical therapy for psoriasis. Vesicular drug delivery systems, such as liposomes, niosomes, proniosomes, and transferosomes. Non-vesicular drug delivery system including foams, gels & nanoparticles are the approaches developed to achieve better & enhanced topical treatment

a. Polymeric Nanoparticles

Polymeric nanoparticles are solid particulate dispersions comprising drugs that can be encapsulated, dispersed, or adsorbed within a suitable polymer matrix. These nanoparticles are categorized into non-self-assembled and self-assembled types. Non-self-assembled polymeric nanoparticles include microspheres and nanospheres of the matrix type, where drugs are entrapped within the polymer matrix, and microcapsules/nanocapsules, which have a core-shell structure with the core acting as a reservoir for the active substance in solid, liquid, or molecularly dispersed forms. Self-assembled polymeric nanoparticles primarily refer to hydrogels, which are crosslinked polymeric networks formed by the self-assembly of one or more monomers. Drug entrapment within hydrogels can be achieved via post-loading or in situ loading approaches. The particle sizes typically range between 10 and 1000 nm. Polymeric nanoparticles can encapsulate hydrophilic drugs and serve as potential carriers for delivering therapeutics across the skin for psoriasis management.

Specifically, polycaprolactone (PCL) nanoparticles loaded with hydrocortisone have demonstrated enhanced control of drug release, higher permeation into skin layers, and reduced drug toxicity during psoriasis treatment. PLGA nanoparticles encapsulating cyclosporine displayed increased permeation into the dermal and epidermal layers, resulting in greater drug accumulation in the skin, reduced systemic absorption, and overall improvement in psoriasis symptoms. In vitro studies showed drug permeation rates into the dermis and epidermis as 4.58 and 6.6, respectively, compared to

free drugs, indicating greater efficacy of polymeric nanoparticle formulations. Furthermore, clobetasol 17-propionate loaded PLGA nanoparticles provide delayed drug release into the skin for psoriasis treatment, enhancing drug stability and significantly reducing side effects compared to conventional formulations. Betamethasone-loaded PLGA/PLA nanoparticles carrying zinc have demonstrated improved drug efficacy, enhanced entrapment efficiency, and sustained drug release for up to eight days during psoriasis treatment (Sala et al., 2016).

b. Polymersomes

Polymersomes are polymeric vesicles composed of amphiphilic polymers that self-assemble in aqueous environments to form thick bilayer membranes. The bilayer contains cationic lipids internally and fusogenic lipids coated with polyethylene glycol on its exterior. Electrostatic interactions link nucleic acids via their negative charge to cationic lipid head groups, facilitating their encapsulation within the core. Polymersomes provide enhanced drug stability compared with conventional formulations. Novel fusogenic nucleic acid lipid particles (F-NALPs), considered polymersomes, incorporate two distinct nucleic acids—anti-STAT3 siRNA and anti-TNF-α siRNA— and demonstrate synergistic activity in psoriasis treatment. These particles efficiently deliver nucleic acid segments into skin layers, significantly lowering the expression of STAT3 and TNF-α mRNAs as well as Ki-67 protein compared to marketed formulations, resulting in reduced psoriasis symptoms (Sala et al., 2016).

Additionally, studies have shown that transferosomes designed for psoriasis therapy and loaded with betamethasone dipropionate can deliver medication deep into the dermal tissue, improving patient tolerability for those with psoriasis plaques. Compared to conventional formulations, transferosomes also enhance antipsoriatic activity and improve drug stability. In another report, transferosomes loaded with tacrolimus gel exhibited higher drug accumulation in both the dermis and epidermis—3.8 and 4.2 times more, respectively, than conventional ointments—resulting in better therapeutic efficacy and enhanced topical delivery. Transferosomes containing dexamethasone provided a fourfold increase in the duration of action, improved the risk-benefit ratio, and reduced the frequency of application compared to conventional treatments. Triamcinolone-loaded niosomes enabled a tenfold reduction in dose and showed marked suppression of skin erythema, along with a 12.1% reduction in skin thickness (Thapa and Yoo, 2014).

c. Ethosomes:

These are third-generation elastic deformable lipid vesicles made up of phospholipids, water, and ethanol (high concentration), which function as permeation enhancers. Ethanol was used to enhance the fluidity of the vesicles, and the ethanol concentration varied from 20 to 45%. A study reported the effects of linking hyaluronic acid to curcumin-loaded propylene glycol-based ethosomes in psoriasis treatment, which provided various advantages, such as reduction in drug leakage, enhanced permeation, and enhanced retention, which was 2.3 folds for plain ethosomes and 4 folds for propylene solution. Ethosomal gel loaded with clobetasol provides high entrapment efficiency and improved drug release pattern compared to marketed formulations in the treatment of psoriasis (Li et al., 2012). Topical administration of psoralen in the form of ethosomes enhances permeation and deposition of drug in skin layers, exhibiting higher permeation of drug, that is, 6.5 folds as compared to conventional tincture. In comparison to conventional tinctures, ethosomes showed increased peak concentration and AUC, that is, up to 3.37 and 2.34 higher, respectively. Ethosomes loaded with tacrolimus showed significantly higher penetration in the epidermal layer than conventional formulations, along with better epidermal accumulation during psoriasis treatment. Methotrexate in the form of ethosomes, when applied topically for the treatment of psoriasis, showed enhanced transdermal flux and lowered lag time compared to conventional liposomes, drug solutions, and hydroethanolic solutions, which exhibited lower flux values. The ethosomal gel formulation provides high skin deposition due to the integrated effects of ethanol and phospholipids, which eventually enhance the efficacy of the formulation, that is, its antipsoriatic effect.

d. Liquid crystalline nanoparticles

These nanoparticles have been reported to encapsulate drugs such as tacrolimus and cyclosporine. They interact with cell-penetrating peptides (CPPs); hence, this strategy is utilized to encourage uptake by skin cells across the plasma membrane. Liquid crystalline nanoparticles are built using liquid crystals (LC) with the combined effects of solid crystals and isotropic liquids. Phase transition is displayed by lyotropic LCs, which depend on the temperature and concentration of the liquid crystal molecules that are often amphiphilic in the aqueous phase. For topical drug delivery, such as in the treatment of psoriasis, liquid crystalline nanoparticles are a potential drug delivery system for the delivery of pharmaceuticals. Tacrolimus, a highly

hydrophobic drug, can be incorporated into the hydrophobic core of the LCN, as it is capable of incorporating hydrophobic drugs. Drugs in gel form cause less irritation. Psoriatic lesions heal with combination drug therapy, and the topical drug concentration is improved. The safety profile of this combination therapy is satisfactory. In addition, it can be used for long-term treatment because of its lack of irritation and can be used for future applications (Kumar et al., 2019a).

e. SLN (Solid Lipid Nanoparticle):

The lipid-based vesicular system is the class to which SLN belong and has a great advantage due to the release of the drug in a controlled and site-specific manner. The SLN keeps the skin hydrated owing to its ability to form a lipid layer. In addition, deeper penetration is due to the lipid vesicles present in the formulation. A study reported that tri-amcinolone formulated as an SLN showed deeper penetration in the skin, and the release profile of the drug was prolonged when applied topically for the treatment of psoriasis. The growth of keratinocytes and the thickness of the epidermis decreased. One advantage over conventional creams is the decrease in skin irritation, and the distribution of the dermis and epidermis is constrained. Another study reported that mometasone-loaded SLNs improved skin penetration. The penetration was enhanced by 15.21 times, and the release pattern of the drug was sustained for treating psoriasis, which is an advantage over conventional dosage forms. Another study reported that encapsulation of betamethasone into solid lipid nanoparticles resulted in the accumulation of the drug in the epidermis of the skin, which develops into a reservoir that is used for targeting the superficial layers of the skin. They also stated that the nanoparticles showed an outstanding release profile of the drug and reduced side effects in the treatment of psoriasis. Systemic absorption was also minimized by the topical use of the drug (Negi et al., 2019).

f. Liposomes:

Liposomes are used to treat dermatological conditions such as psoriasis and dermatitis. Liposomes are spherical vesicles composed of phospholipids that can encapsulate both hydrophilic and lipophilic drugs. They also have the ability for site-specific delivery because of their small size and lipidic nature. A study reported that cyclosporine-loaded cationic liposomes are used in the treatment of psoriasis in an imiquimod-induced plaque psoriasis model. The symptoms of psoriasis were reduced by the topical application of the reported cyclosporine-loaded cationic liposomes, that is, the levels of cytokines such as IL-17, IL-23, and TNF-α were reduced, which is advantageous over the conventional formulations. Another study revealed that liposomes made from a steroidal antibiotic known as fusidic acid were used to treat psoriasis. The amalgamation of drugs into liposomes showed better and improved efficacy. A study reported that cyclosporine-loaded liposomes were prepared by entrapment of the drug, that is, cyclo-sporine in multilamellar liposomes, for the treatment of limited chronic plaque psoriasis. The clinical performance of cyclosporine-loaded liposomal nanocarriers (li-pogel) was better than that of cyclosporine incorporated in conventional cream. The drug release profile from the lipogel was also slow, forming microreservoirs to accumulate the drug locally on psoriatic sites. The elevation of plaque was also reduced by the topical application of cyclosporine-induced lipogel (Wadhwa et al., 2016). Another study reported the preparation of pegylated calcipotriol liposomes for the treatment of psoriasis. These liposomes showed better penetration of the drug, and drug accumulation in the stratum corneum of the skin was improved. Pegylation is important for the stability of liposomes, which does not affect the ability of the drug to penetrate the skin.

g. Niosomes:

A study reported the preparation of niosomes loaded with celastrol. Celastrol nanosomesshowed improved in vitro permeation ability compared to the raw drug. The cytokine levels of IL-22, IL-23, and IL-17 were reduced, which showed better therapeutic activity. The celastrol niosomes also improved the permeation of the drug into the skin, indicating a better potential for the treatment of psoriasis. Another study reported the preparation of acitretin-loaded niosomal gels. Niosomal gels have been shown to reduce the thickness of the epidermis (Meng et al., 2019). It also overcomes problems such as skin irritation and higher orthokeratosis compared to the control and other formulations. The niosomal gel also showed deep penetration into the skin layers, which improved the efficacy and reduced systemic absorption compared to conventional gels.

6. Advantages of phytoconstituent-based nanomedicine in the management of psoriasis

Nanotechnology in combination with phytoconstituents (plant science) is a green approach that has beneficial therapeutic effects and fewer therapeutic side effects. Na-nomedicines are very efficient in drug delivery, disease diagnosis, and therapeutic result monitoring. The finest therapeutic activity can be attained by formulating a theranostic nanomedicine, which is a rapidly growing field. Phytoconstituents can be loaded into theranostic

nanomedicines and are useful for therapeutic functions as well as imaging. Therapy with liposomal drug delivery can be the first choice because of its low side effects. In the treatment of diseases such as inflammatory diseases, liposomal drug therapy can be used for the optimal delivery of therapeutic agents. Liposome-based nanomedicines improve the therapeutic effect of drugs and are effective against various diseases, such as psoriasis and inflammatory bowel disease. Various nanocarriers, including solid lipid NPs, liposomes, and polymeric NPs, have been discovered and are highly useful in the treatment of psoriasis. (Gilani et al., 2020b). The efficacy and bioavailability of phytoconstituent-based nanomedicine are improved. Toxicity and side effects are also reduced by using nanophytomedicine. The solubility of phytomolecules is enhanced by the use of nanopharmaceuticals. Solubility is enhanced by the formation of particles and droplets, which can be encapsulated or emulsified, thereby modifying the physicochemical properties. These nanoparticles increase the solubility of phytoconstituents; for example, curcumin nanoparticles have solubility increased by several folds. The bioavailability of phytomedicine is increased, which is also followed by an increase in drug absorption. In a report, the solubility of silymarin was increased by making a nanoformulation, which eventually increased the bioavailability of the phytoconstituents. Nanotechnology has also shown great increase in biological activity by combining with phytoconstituents; for example, nanogels of phytoconstituents acitretin and aloe-emodin have shown antipsoriatic activity. Recently, various nanocarriers, such as liposomes, silver nanomaterials, nanoemulsions, and microspheres, in combination with herbal drugs, have been discovered. The nano delivery system selected for the delivery of herbal remedies, as the effective molecules of plants, soluble in various solvents such as chloroform and methanol, is not suitable for delivery as such. Nano delivery is a capable approach for well-organized herbal drug delivery for the treatment of many chronic diseases, such as psoriasis. Nano-structured systems constituting phytoconstituents may have the potential to enhance the action of extracts obtained from plants and also reduce the dose required as well as side effects, and hence improve the activity. Nanotechnology in the formulation of nano-emulsions, lipid nanocarriers, nano liposomes, and phytosomes is beneficial as it increases the absorption rate and bioavailability, resulting in enhanced effects of herbal drugs. Nanophytomedicine has the potential to improve the viability of plant-based medicines by addressing issues related to different types of plant medications. Despite the fact that bioavailability investigations of plant medications are still in their early stages, this section provides an updated status of the bioavailability of nanophytomedicine.

7. Conclusion:

In conclusion, the growing body of research on the use of natural photochemicals for the treatment and prevention of psoriasis underscores their potential as effective adjuncts or alternatives to conventional therapies. Photochemicals derived from natural sources, such as flavonoids, polyphenols, and terpenoids, have demonstrated a wide range of therapeutic properties, including anti-inflammatory, antioxidant, and immunomodulatory effects, which are essential in managing psoriasis. Furthermore, these compounds often exhibit fewer side effects than traditional pharmacological treatments, making them attractive options for long-term management. While promising results have been reported from both in vitro and in vivo studies, as well as some clinical trials, it is important to note that further rigorous research is needed to better understand their mechanisms of action, optimal dosing, and potential interactions with other treatments. Additionally, the standardization and quality control of natural photo-chemical preparations remain key challenges in translating these findings into clinical practice. Future studies should focus on large-scale, well-designed clinical trials to confirm the efficacy and safety of these natural compounds for psoriasis treatment. With ongoing advancements in phytotherapy and photomedicine, natural photochemicals hold significant promise for offering safer and more sustainable therapeutic options for patients with psoriasis.

Ethical Approval

NA

Informed Consent

Not Applicable.

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Conflict of Interest

The authors declare that there are no apparent conflicts of interest between the authors' personal relationships or financial interests that may have affected the results of this study. The authors declare no conflicts of interest. All ideas and opinions expressed in this article are those of the authors.

Financial Interests

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