World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Review Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 6
Page: 438-458

PHYTOCHEMICAL-LOADED NANOSTRUCTURED LIPID CARRIERS FOR TOPICAL TREATMENT OF PSORIASIS: A COMPREHENSIVE REVIEW

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Article Received: 11 April 2026 | | ***Article Revised: 02 May 2026*** | | ***Article Accepted: 22 May 2026***

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DOI: https://doi.org/10.5281/zenodo.20445353

How to cite this Article: Pooja Khatri, Preeti Singh (2026) PHYTOCHEMICAL-LOADED NANOSTRUCTURED LIPID CARRIERS FOR TOPICAL TREATMENT OF PSORIASIS: A COMPREHENSIVE REVIEW. World Journal of Pharmaceutical Science and Research, 5(6), 438-458.

ABSTRACT

Psoriasis is a chronic inflammatory immune-mediated skin disease that leads to hyperproliferation of keratinocytes, immune dysfunction, oxidative stress and a defective skin barrier. While topical treatment is still the preferred choice for mild-to-moderate psoriasis, conventional topical formulation vehicles, such as creams and ointments, suffer from poor penetration, short retention time, irritation, and poor patient compliance over extended use. Recently, phytochemicals, with their anti-inflammatory, antioxidant, antiproliferative and immunomodulatory properties, have attracted attention as potential therapeutic agents, as they can address several pathogenic mechanisms of psoriasis. But their therapeutic potential is limited due to limited water solubility, poor bioavailability, and insufficient penetration through the stratum corneum. Nanostructured lipid carriers (NLCs), as a novel generation of lipid-based nanocarriers, provide a promising solution for improving drug loading, stability, controlled release and skin penetration. Formulation of phytochemical-loaded NLCs into gel formulations enhances formulation acceptability, retention and efficacy. This review provides a detailed overview of psoriasis pathophysiology, important phytochemicals, approaches for NLC formulation and evaluation, and recent preclinical and clinical studies, demonstrating their potential as safer and more effective topical drug delivery systems.

KEYWORDS: Psoriasis; phytochemicals; nanostructured lipid carriers; topical delivery; NLC gel; skin penetration.

1. INTRODUCTION

Psoriasis is an inflammatory, immune mediated, persistent skin disease characterized by unregulated proliferation of keratinocytes, a dysregulated immunological response and chronic skin inflammation is a significant burden of dermatological and systemic disease of the world with an incidence of about 2 -3 per cent (Orzan et al., 2025).

Clinically, it is characterized by clearly defined erythematous plaques with silvery-white scales, which most commonly occur on the head, elbows, knees and lower back, and is now also a well-known disease not only as a skin disease but also as a systemic inflammatory disease with comorbid conditions, such as psoriatic arthritis, cardiovascular complications, metabolic syndrome and(MR et al., 2025). Pathogenesis It is a complex interplay between genetic predisposition and environmental stimuli and immune dysregulation, with particular emphasis on interleukin-23 (IL-23)/T helper 17 (Th17) pathway, where activated dendritic cells release cytokines, including IL-12 and IL-23, to differentiate native T cells into Th1 and Th17(MR et al., 2025; Prema & Shanmugamprema, 2025). This causes a tremendous retardation of the keratinocyte turnover cycle of approximately 28 days to a few days resulting in accumulation of immature cells and a thick and scaly plaque, as illustrated pictorially in Figure 1, which compares structural and pathological differences between normal and psoriatic skin. (Giorgio et al., 2026). Although conventional therapies, especially topical ones, such as corticosteroids, vitamin D analogues, retinoids and calcineurin inhibitors, are available, there are however some limitations, including side effects such as skin atrophy, irritation, telangiectasia and reduced response rate with prolonged use, and poor drug penetration through the skin, as the stratum corneum is hyperkerat to these(Garg et al., 2026). Over the past few years, interest has been drawn towards phytochemicals as potential therapeutic agents because of their anti-inflammatory, antioxidant and immunomodulatory effects. Bioactive compounds such as curcumin (Curcuma longa) and thymoquinone (Nigella sativa) have been demonstrated to modulate the inflammatory processes, NF-kB and prevent oxidative stress and therefore act on multiple pathogenesis mechanisms of psoriasis(Majumdar et al., 2026). They, however, have poor bioavailability at the target site because their applicability in clinical use is poor, as is their aqueous solubility, stability and poor skin permeability. To overcome these shortcomings, drug delivery technologies based on nanotechnology have emerged as potential remedies towards enhancement of dermal drug delivery. Among them, lipid-based nanocarriers and nanostructured lipid carriers (NLCs) in particular have a significant number of advantages, including improved drug solubilization, stability, release control at the site, epidermal skin hydration by occlusivity, and retention of drugs in the epidermis (Gupta & Singh).

The unique mixture of solid lipids and liquid lipids in NLCs forms a less ordered matrix that can absorb increased amounts of drugs with little drug expulsion(Meng et al., 2025). Moreover, the inclusion of NLCs in gel preparations increases patient adherence as the particles are not greasy and oily, simple to apply, and spread better, and they also increase the time of action of the drug at the target site (Gupta & Singh). Thus, the idea of a combination of phytochemicals and nanotechnology-based delivery systems should be seen as a rational and innovative solution to the shortcomings of the conventional therapies and an increase in treatment benefits of psoriasis since Figure 1 supports this conceptual idea through the use of the structural difference.(Liu et al., 2026).

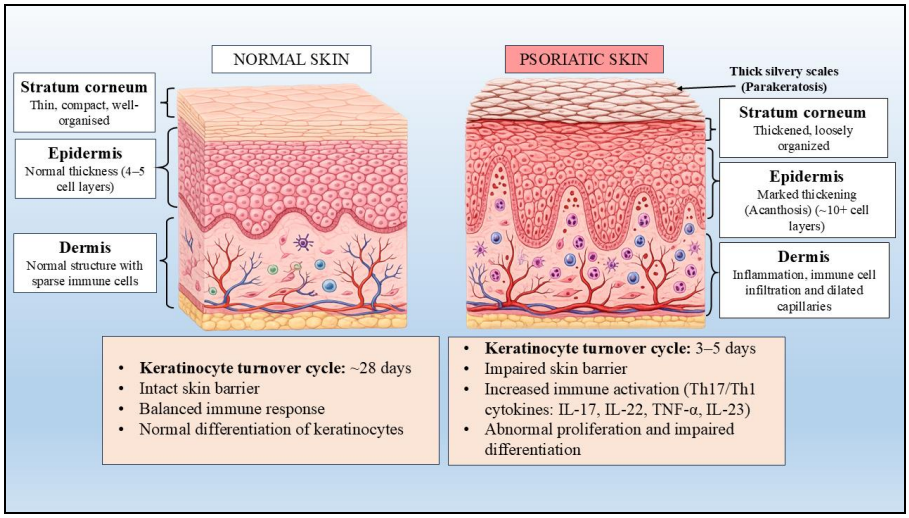

Figure 1: Comparative illustration of normal skin and psoriatic skin.

2. Pathophysiology of Psoriasis

Psoriasis is a persistent inflammatory skin condition characterized by an inadequate immune response, excessive keratinocyte growth, and unresolved inflammatory signalling in the epidermis and dermis(Deng et al., 2016). Psoriatic lesions are formed as a multifactorial process that includes genetic predisposition, environmental stimuli, and immune-mediated processes. The understanding of the pathogenesis of psoriasis has been immensely advanced by immunology and molecular biology, as it has revealed that due to the complex interaction of innate and adaptive immunity, prolonged cytokine signalling and aberrant epidermal differentiation occurs(Orsmond et al., 2021). The IL-23/Th17 axis mediates this process and leads to chronic inflammation and normal psoriatic plaque.

2.1 Genetic Susceptibility

People who have first-degree relatives affected have a very high risk of developing the disease. Over sixty genetic loci associated with psoriasis susceptibility have been discovered through genome-wide association studies, often known as psoriasis susceptibility(Rahman & Elder, 2005). The most important genetic determinant of these is PSORS1 which is found in the major histocompatibility complex on chromosome 6p21. HLA-Cw6 allele in this region is associated with the longest effect on the onset of psoriasis in early life and is commonly correlated with the severity of the disease and specific clinical phenotypes(Holm, 2005). Carriers of this allele often develop psoriasis earlier and have a more extensive skin involvement. Other genes including IL23R, IL12B, STAT3, TNFAIP3, and CARD14 are part of the pathways that control immune cell activation and the inflammatory reaction in addition to HLA-Cw6(Sukhov et al., 2016). Genetic factors play an important role, but as a rule, they are not enough on their own to cause psoriasis in the absence of environmental or immunological triggers. These genetic effects are tightly connected with the mechanisms of immune activation, especially with the IL-23/Th17 axis shown in Figure 2 that is very important in the development and progression of the disease.

2.2 Immune System Dysregulation

The dysregulation of the immune system is the key pathogenic mechanism of psoriasis, especially the interplay between the innate immune system and adaptive T-cell responses(Orzan et al., 2025). It is thought that the disease process starts with the environmental stimuli triggering immune cells that are located in the skin, such as dendritic cells, macrophages, and keratinocytes. The response to the stimulation of these cells includes the release of

antimicrobial peptides and pro-inflammatory mediators that trigger the recruitment of immune cells and activation of inflammatory signalling pathways(Prema & Shanmugamprema, 2025). Dendritic cells are one of the different immune cells that are important in the initiation of the psoriatic inflammatory cascade. Cytokines produced by activated dendritic cells include interleukin-12 (IL-12) and interleukin-23 (IL-23) that facilitate differentiation of naive T cells into T helper type 1 (Th1) and T helper type 17 (Th17) lymphocytes(Wen et al., 2026). The Th17 cell type generates proinflammatory cytokines such as IL-17A, IL-17F, IL-21, and IL-22. The IL-23/ Th17 signalling axis depicted in Figure 2 is the most well-known central immunological pathway that supports the survival and proliferation of Th17 cells with IL-17 having a direct effect on the keratinocytes. Also neutrophils, macrophages and natural killer cells accumulate in lesions and neutrophils develop Munro microabscesses, increasing inflammation(Jawale et al., 2025).

2.3 Cytokine Network and Inflammatory Signalling

The psoriasis is linked to a very complicated network of cytokines that controls the immune response and the behavior of keratinocytes. Some of the pro-inflammatory cytokines have been found to play a major role such as tumor necrosis factor-alpha (TNF- 2), interleukin-17(IL-17), interleukin- 22 (IL-22), and interferon-gamma (IFN- 2)(Man et al., 2023) TNF-a is one of these and is pivotal in sustaining the inflammatory microenvironment through dendritic cell maturation, leukocyte recruitment, and encouraging the manufacture of other inflammatory mediators (Rodríguez-Montaño et al., 2025). Likewise, IL-17 has direct action on keratinocytes that causes the generation of antimicrobial peptides, chemokines, and inflammatory cytokines that aid in recruitment of immune cells and inflammation. IL-22 stimulates the growth of keratinocytes and inhibits normal epidermal differentiation resulting in epidermal thickening. All these cytokines create a long-lasting inflammatory milieu based on the IL-23/Th17 axis as shown in Figure 2 and enhances inflammatory signaling and disease persistence (Zhang et al., 2025).

2.4 Keratinocyte Hyperproliferation and Epidermal Alterations

The abnormal growth and differentiation of keratinocytes is a hallmark of psoriasis. In normal physiological conditions there is a highly controlled maturation process of keratinocytes which leads to epidermal renewal of about 28 days.

However, this process is significantly accelerated in psoriatic skin, and the turnover is only 3-5 days(Al-Dhubaibi et al., 2025). The excessive proliferation results in epidermal thickening (acanthosis) and deposition of immature keratinocytes on the skin surface, which causes typical silvery scales. Besides structural changes, keratinocytes also play an active role in the inflammation process by the secretion of chemokines including CXCL8 (IL-8) and CCL20, which attract neutrophils and T cells(Pan et al., 2025). The persistent exchange between the immune cells and the keratinocytes creates a vicious circle of an inflammatory process. The IL-23/Th17 axis-produced cytokines (Figure 2) also promote proliferation and differentiation disruption of keratinocytes, which supports disease progression(Wei et al., 2025).

2.5 Angiogenesis and Vascular Alterations

Psoriatic lesions are associated with severe vascular alterations of the dermis. The formation of new blood vessels in the psoriatic skin is enhanced by an increased expression of angiogenic factors including vascular endothelial growth factor (VEGF)(Kim et al., 2025). They are normally swollen, smooth and long in shape, a phenomenon that contributes to the erythematous character of psoriatic plaques. Enhanced vascularization facilitates vascular infiltration of immune cells to the targeted skin that sustains inflammatory mechanisms(Liu et al., 2026). The cytokine-vascular cross-interaction is also important, with IL-23/Th17 axis mediators (Figure 2) capable of further promoting angiogenesis. The

endothelial cells are also active in that they express adhesion molecules that facilitate leukocyte migration. These vascular changes are a contributive factor to clinical characteristics and maintenance of psoriasis(Elton, 2025).

2.6 Environmental Triggers

Environmental factors play an important role in initiating or exacerbating psoriasis in genetically susceptible individuals (Singh & Schikowski, 2025) . A number of triggers have been identified such as infections, psychological stress, mechanical injury, smoking, obesity, and some medications. Streptococcal infections are closely linked with guttate psoriasis, especially in children and young adults(Orzan et al., 2025). The other phenomenon that is well known is the Koebner response where new psoriatic lesions form on the areas of skin trauma like cuts, burns or surgical wounds. This underscores the importance of local inflammatory reactions and immune stimulation to the disease(J. Yang et al., 2025). Psoriatic inflammation is triggered and maintained by the interplay of environmental factors with genetic susceptibility and immune responses, with the IL-23/Th17 axis (as indicated in Figure 2) being one of the key pathways, and highlights the polygenic character of the disease (Prema & Shanmugamprema, 2025).

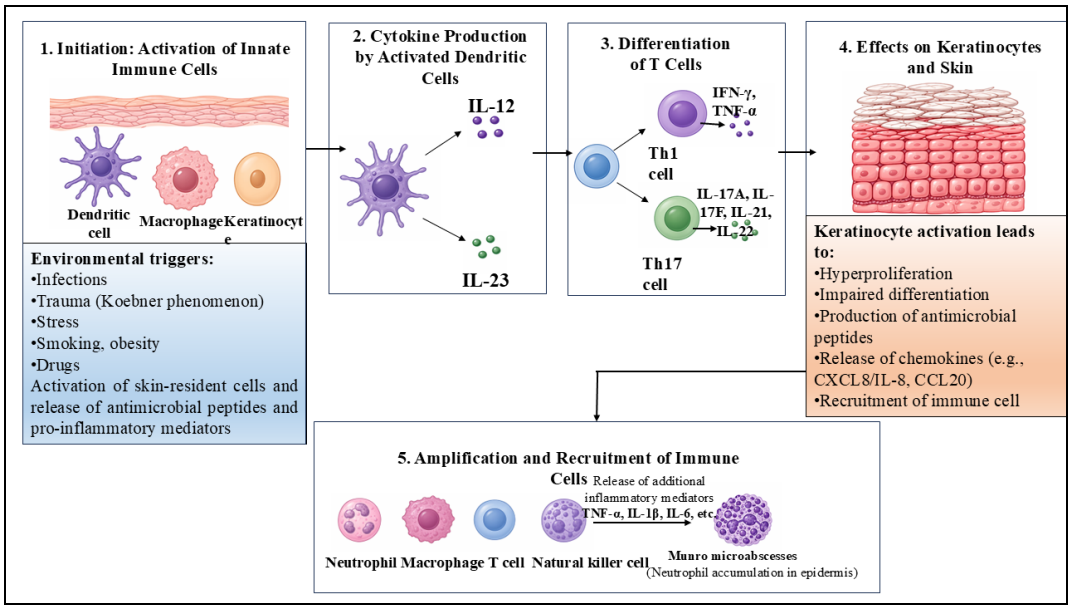

Figure 2: IL-23/Th17 Axis and Cytokine Signalling Pathway in Psoriasis.

3. Role of Phytochemicals in Psoriasis Management

The increasing worries about the long-term negative side effects of traditional ant psoriatic medicines have triggered the need to consider plant-based bioactive substances as alternative medicines(Radu et al., 2025). Phytochemicals have a wide range of pharmacological action such as anti-inflammatory, antioxidant, and immunomodulatory effects, which could be used to control various molecular pathways that contribute to psoriasis pathogenesis(Patel et al., 2025). The natural compounds have the potential to regulate the production of cytokines, prevent oxidative stress, and avoid abnormal proliferation of keratinocytes, and thus play a role in the treatment of inflammatory skin diseases. Various phytochemicals have been identified to block nuclear factor-kappa B (NF- κB), mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT) signalling pathways, which are significant in the immune response and inflammatory reactions. Phytochemicals suppress pro-inflammatory cytokines, including TNF-a, IL-17, and IL-23, by modulating these pathways (Mustafa et al., 2025).

Table 1: Selected phytochemicals and their mechanisms in psoriasis.

Phytochemical	Source	Mechanism of Action	Pharmacological Effects
Curcumin	*Curcuma longa* (Turmeric)	Inhibits NF-κB, STAT3, MAPK pathways	Reduces TNF-α, IL-17, IL-23; inhibits keratinocyte proliferation; antioxidant; restores epidermal homeostasis
Thymoquinone	*Nigella sativa* (Black seed)	Inhibits NF-κB; enhances antioxidant enzyme activity	Reduces inflammatory cytokines (TNF-α, IL-6); decreases oxidative stress; improves skin structure
Resveratrol	Grapes, berries	Modulates NF-κB and STAT pathways	Anti-inflammatory; inhibits keratinocyte proliferation; reduces cytokine production
Quercetin	Fruits, vegetables	Inhibits inflammatory mediators; antioxidant activity	Reduces oxidative stress; suppresses cytokine release; regulates immune response
EGCG (Epigallocatechin gallate)	Green tea	Inhibits MAPK and NF-κB pathways	Reduces inflammation; controls keratinocyte growth; antioxidant

3.1 Curcumin

Curcumin is a polyphenolic compound, which is extracted whole of the rhizome of Curcuma longa and has been widely researched on because of its anti-inflammatory and anti-oxidant properties (Boudou et al., 2025). Presence of several experimental researches has demonstrated that curcumin is capable of modulating several molecular targets in pathogenesis of psoriasis (Edokpiawe et al.). One of its major mechanisms is the inhibition of the NF-KB signalling pathway leading to the down-regulation of pro-inflammatory cytokines such as TNF-a, IL-1-b and IL-6. It is also reported that curcumin regulates proliferation and differentiation of keratinocytes hence helping in normal epidermal homeostasis. In vitro and in vivo experience has suggested curcumin inhibits activation of the STAT3 and MAPK cascade, which have been implicated in abnormal growth of keratinocytes in lesions of psoriasis (Rashad, 2025).

Besides, curcumin is an effective antioxidant, and it inhibits the destruction of skin cells by oxidative stress. Using a variety of experimental models, topical or systemic intake of curcumin has been found to be able to reduce the amount of erythema, scaling and inflammatory cytokines (Jikah & Edo, 2025). However, its application in clinical practice has been thwarted by low aqueous solubility, low stability, and rapid degradation at physiological conditions because of these encouraging effects. Table 1 gives these pharmacological activities and limitations, and Table 2 compares them even more (Feng, 2025).

3.2 Thymoquinone

The main bioactive extract of Nigella sativa seeds is thymoquinone which is of particular interest due to its anti-inflammatory, antioxidant and immunomodulatory effects (Chatterjee et al., 2025). Studies have demonstrated that thymoquinone can inhibit the production of several inflammatory mediators, including TNF-α, IL-6, and prostaglandins, which play important roles in inflammatory skin diseases. The therapeutic effects of thymoquinone are largely attributed to its ability to suppress oxidative stress and modulate immune responses (Fareid et al., 2026). It has been demonstrated to promote antioxidant defence mechanisms by augmenting the actions of enzymes like superoxide dismutase and catalase, and thus lowering the quantity of reactive oxygen species in inflamed tissues. Furthermore, thymoquinone has been also known to suppress the process of NF-KB which has been linked to suppressed production of inflammatory cytokines (Pandey et al., 2025). It has been shown in experimental studies that thymoquinone has the potential to decrease epidermal hyperplasia and cell infiltration in psoriasis models. But like most phytochemicals, it

has poor aqueous solubility and stability and this limits its therapeutic use. Table 1 summarises these aspects and Table 2 discusses them comparatively (Arshad et al., 2025).

3.3 Other Phytochemicals (Resveratrol, Quercetin, EGCG)

Besides curcumin and thymoquinone, a number of other phytochemicals also showed a potential therapeutic effect in the treatment of psoriasis. Resveratrol is a polyphenolic compound present in grapes and berries, which has been reported to suppress the growth of keratinocytes and inflammatory cytokines by regulating the activity of NF-B and STAT signalling (Mustafa et al., 2025). Likewise, quercetin is a flavonoid commonly found in vegetables and fruits and has anti-inflammatory and antioxidative properties that can be used to control immune responses in psoriatic skin. Research has revealed that quercetin has the potential to inhibit the release of inflammatory mediators and oxidative stress in keratinocytes (Koycheva et al., 2025). Another compound of interest is epigallocatechin-3-gallate (EGCG), a major polyphenol found in green tea, which inhibits keratinocyte proliferation and reduces inflammatory signalling by modulating MAPK and NF-κB pathways (Alalwan et al., 2025). Despite the promising pharmacological effects of these phytochemicals in the topical preparations, they have not been clinically effectual because of solubility limitations, chemical instability, and insufficient stratum corneum penetration. Table 1 shows these mechanisms and limitations and compares them further in Table 2, which justifies the necessity of more advanced nanocarrier-based delivery systems (Kantasa et al., 2025).

Table 2: Comparative pharmacological activities and limitations of major phytochemicals.

Phytochemical	Key Pharmacological Activities	Advantages	Limitations
Curcumin	Anti-inflammatory, antioxidant, immunomodulatory; inhibits NF-κB, STAT3, MAPK	Multi-target action; reduces cytokines; regulates keratinocytes	Poor water solubility; low stability; rapid degradation; poor bioavailability
Thymoquinone	Anti-inflammatory, antioxidant; inhibits NF-κB; enhances antioxidant enzymes	Reduces oxidative stress; improves immune balance; decreases epidermal hyperplasia	Poor solubility; instability; limited skin penetration
Resveratrol	Anti-inflammatory; modulates NF-κB, STAT pathways	Inhibits keratinocyte proliferation; antioxidant benefits	Low bioavailability; instability; rapid metabolism
Quercetin	Anti-inflammatory; antioxidant; inhibits cytokine release	Strong ROS scavenger; regulates immune response	Poor solubility; limited permeability
EGCG	Anti-inflammatory; inhibits MAPK and NF-κB pathways	Controls keratinocyte growth; antioxidant	Low stability; poor skin penetration; degradation issues

4. Nanostructured Lipid Carriers in Dermal Drug Delivery

Drug delivery systems driven by nanotechnology have made tremendous changes in topical therapeutics by overcoming constraints revolving around the use of conventional dosage forms like creams, ointments and lotions; limited penetration of active pharmaceutical compounds and their rapid breakdown as well as their inability to maintain concentration at point of application (Ullah et al., 2025). These constraints decrease therapeutic effectiveness, particularly in chronic dermatological diseases like psoriasis. The interest in lipid-based nanocarriers is because they are biocompatible, less toxic, and can mimic the natural lipid structure of the skin, thus improving dermal drug delivery (Khan et al., 2025). Of these, nanostructured lipid carriers (NLCs) are second-generation lipid nanoparticles that address shortcomings of solid lipid nanoparticles, providing better drug loading, less drug expulsion, and stability.

Their structure and drug incorporation process are shown in Figure 3 (1* et al., 2025).

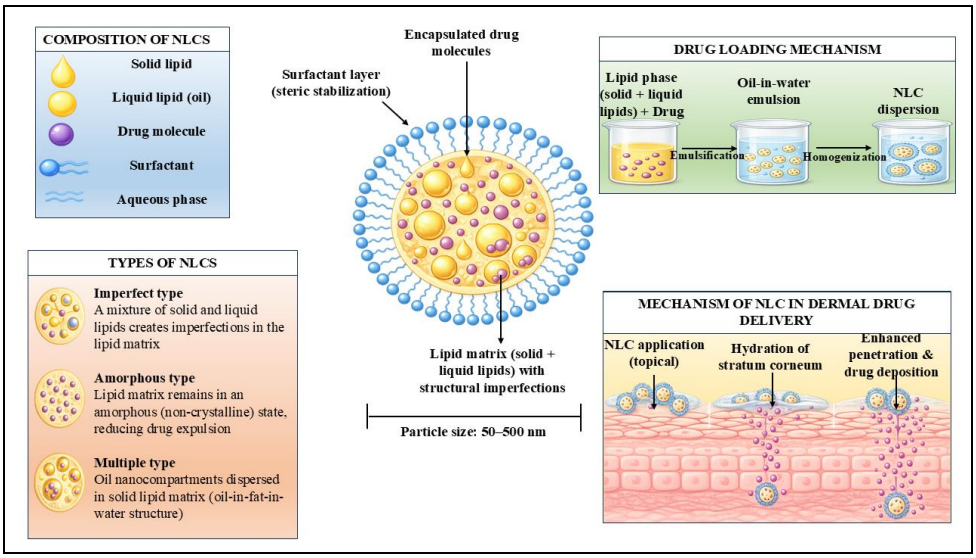

Figure 3: Structural representation and drug loading mechanism of NLCs.

4.1 Advantages of NLCs in Topical Delivery

Nanostructured lipid carriers offer numerous advantages over conventional topical drug delivery systems, making them particularly suitable for chronic skin disorders (Rajak et al., 2025). Among the main advantages is enhanced solubility of drugs, particularly of lipophilic drugs like phytochemicals, since the lipid matrix offers a good hydrophobic condition. The other significant benefit is that they have increased penetration of the skin since they are small in the form of nanoparticles and have a lipid structure that allows them to interact with the stratum corneum lipid layers and the diffusion of the drug to deeper layers (S. Sharma et al., 2025). The sealing effect that NLCs have reduces the loss of trans epidermal water and enhances stratum corneum hydration, which further enhances drug permeation. Moreover, NLCs enhance the retention of drugs in the epidermis where the therapeutic effect is localized, and the exposure to the body is reduced. These carriers also ensure that encapsulated drugs are not degraded by light, oxygen, and enzymatic action, thus increasing stability (Shivgotra et al., 2025). Moreover, NLCs allow the release of drugs in a controlled and sustained rate, which decreases the rate of dosing and increases patient compliance. They are biocompatible and biodegradable, which makes them highly tolerable, and thus best used in long-term therapy, as shown conceptually in Figure 3 (Tran et al., 2025).

4.2 Types of Nanostructured Lipid Carriers

The types of nanostructured lipid carriers are categorized in terms of the internal arrangement of solid and liquid lipids in the nanoparticle framework, which directly affects the drug loading capability, release characteristics, and stability (Alloush & Demiralp, 2025). The imperfect type NLCs are developed through blending solid lipids and liquid lipids resulting in structural defects that provide more space to accommodate drugs and less expulsion of drugs. It is a common type of lipophilic drug encapsulate because of the high encapsulation efficiency and sustained release (Nurohman et al., 2026). The amorphous type NLCs are designed to prevent crystallization of the lipid matrix, maintaining a non-crystalline structure that enhances stability and ensures uniform drug distribution (Rahman et al., 2026). The multi-type NLCs have a more complicated structure, in which the oil nano compartments are dispersed in a solid lipid matrix, which enables the solubilization of more drugs and controlled release. These structural differences are important in maximizing formulation activity and therapeutic results as shown in Figure 3 (Tamer & Kassab, 2025).

4.3 Methods of Preparation of NLCs

Nanostructured lipid carriers preparation entails a number of methods used to form nanoparticles with a defined size, stability and effective drug encapsulation(Alloush & Demiralp, 2025). High-pressure homogenization in which a lipid melt is mixed with an aqueous surfactant solution followed by high-pressure homogenization, in which a uniform particle size and reproducibility is obtained is one of the most common methods. However, high temperatures may not favour thermolabile drugs(Kushwaha et al., 2025). Other methods are cold homogenization that reduces thermal degradation caused by solidification and grinding of the lipid phase, before homogenization, although it may result in slightly larger particles. Melt emulsification is a simple and less costly method that involves the mixing of a heated layer of water and a layer of melted lipids, and cooling to form nanoparticles (Taha et al., 2025). At the laboratory scale, ultrasonication is typically utilized and involves the use of ultrasonic energy to decrease the size of the particles, though too much exposure can result in degradation of sensitive compounds. These methods of preparation affect the ultimate structure and performance of NLCs, as shown in Figure 3(Dev & Chandel, 2025).

4.4 NLC-Based Gel Systems

Nanostructured lipid carriers are usually incorporated in gel preparations to facilitate dermal delivery to enhance usability, stability, and compliance in patients. The advantages of gel systems are increased spreadability, easy application, and prolonged retention in the administration site(Pula, 2025). NLCs incorporated into hydrogels make aggregation of nanoparticles undesirable, stabilizing the formulations. The Carbopol-based gels are also dependable because of their superior rheology, biocompatibility, and the capability to create stable formulations (Behera et al., 2025). Such gels preserve the integrity of the nanoparticle and allow drugs to be released under control. Also, NLC-based gels increase the drug delivery in the skin and enhance therapeutic effects in inflammatory diseases like psoriasis (Parga et al., 2025). The nanocarrier systems to gel formulations are associated with better bioavailability, prolonged drug release, and patient acceptability relative to traditional formulations. Figure 3 demonstrates the structural interaction and drug delivery mechanism of NLC-based systems and Table 3 summarizes their comparative advantages (V. Singh et al., 2026).

Table 3: Comparison of SLNs vs NLCs vs Conventional Topical System.

Parameter	Conventional Topical Systems (Creams/Ointments/Gels)	SLNs (Solid Lipid Nanoparticles)	NLCs (Nanostructured Lipid Carriers)
Drug Penetration	Poor penetration across stratum corneum	Improved penetration	Significantly enhanced penetration
Drug Loading Capacity	Low	Moderate (limited by crystalline structure)	High (due to imperfect lipid matrix)
Drug Expulsion	Not applicable but unstable retention	Possible during storage due to recrystallization	Minimal due to structural imperfections
Stability	Limited (drug degradation likely)	Good stability	Excellent stability
Lipid Structure	No lipid nanoparticle system	Highly ordered crystalline lipid matrix	Disordered matrix (solid + liquid lipids)
Controlled Drug Release	Limited and uncontrolled	Controlled release possible	Sustained and controlled release
Occlusive Effect	Low	Moderate	High (reduces TEWL, increases hydration)
Skin Hydration	Minimal	Improved	Significantly enhanced
Drug Protection	Poor (prone to degradation)	Protects drug to some extent	Strong protection against light, oxygen, enzymes
Suitability for Phytochemicals	Limited due to poor solubility	Moderate	Highly suitable (enhanced solubilization)

Bioavailability	Low	Improved	Significantly improved
Patient Compliance	Moderate	Good	High (non-greasy, better spreadability)

5. Phytochemical-Loaded NLCs for Psoriasis Treatment

Over the past few years, much focus has been given to the development of plant-derived bioactive compounds into the next-generation nanocarrier systems in dermatological therapy, specifically nanostructured lipid carriers (NLCs), which has become a promising system to enhance the therapeutic efficacy of phytochemicals in the treatment of psoriasis (Hashempur et al., 2025). Phytochemicals (polyphenols, flavonoids, alkaloids and quinones) have anti-inflammatory, antioxidant and immunomodulatory properties, which allow them to control the production of cytokines, oxidative stress, and abnormal growth of keratinocytes (D. D. Singh et al., 2026). But they have a low clinical use due to the poor aqueous solubility, low permeability, instability and fast degradation. NLCs circumvent these shortcomings with their imperfect lipid matrix, which improves the loading, stability, and controlled release of drugs. Their nanoscales make it easier to penetrate and be retained by the skin, and the occlusive effect enhances the hydration and permeability, as shown in Figure 4 (Alsaikhan & Farhood, 2026).

5.1 Curcumin-Loaded NLCs

Curcumin is a hydrophobic polyphenolic derivative of Curcuma longa that has been widely studied due to its therapeutic potential in inflammatory skin diseases, such as psoriasis (Kantasa et al., 2025). Its pharmacological effect is mainly explained by the fact that it has the capacity to inhibit several signalling pathways, including NF-KB, MAPK and STAT3 leading to the inhibition of production of pro-inflammatory cytokines, including TNF-A, IL-17, and IL-23.

Moreover, curcumin has a powerful antioxidant property, which decreases oxidative stress and shields the damage of keratinocytes (Alalwan et al., 2025). Although it has these advantages, it is not used in clinical practice due to its low aqueous solubility, low bioavailability, rapid metabolism, and instability. Its solubilization is greatly increased, and it is better protected against degradation by incorporation into nanostructured lipid carriers, increasing its stability and therapeutic efficacy (Mustafa et al., 2025). Nanoscale size of NLCs facilitates the increased contact with the skin barrier and results in the increased penetration and retention of NLCs in epidermal layers. Preclinical trials have shown that curcumin-impregnated NLCs decrease erythema, scaling, and epidermal thickening and suppress inflammatory cytokines and recover normal skin structure. The sustained drug release also improves the therapeutic effects, which is conceptually illustrated in Figure 4 (Gutiérrez-Ruiz et al., 2026).

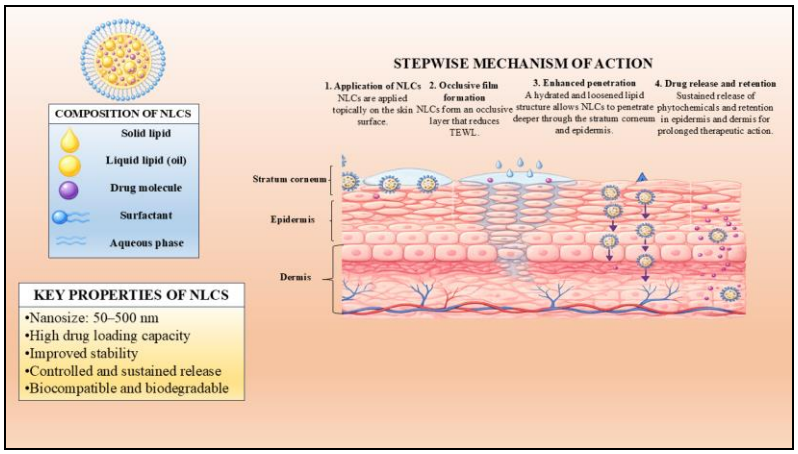

Figure 4: Mechanism of Enhanced Skin Penetration and Drug Retention by NLCs.

5.2 Thymoquinone-Loaded NLCs

The main bioactive compound of Nigella sativa is thymoquinone, which has attracted interest because of its powerful anti-inflammatory, antioxidant, and immunomodulatory effects. It not only suppresses the activity of inflammatory mediators like TNF- 0, IL-6 and prostaglandins, which play a major role in the pathogenesis of psoriasis, but also increases antioxidant defense mechanisms through the enhancement of the activity of enzymes like superoxide dismutase and catalase (Fareid et al., 2026). However, its therapeutic application is limited by poor aqueous solubility and chemical instability. Incorporation into nanostructured lipid carriers improves solubility, enhances stability, and enables controlled drug release (Chatterjee et al., 2025). The lipid matrix preserves thymoquinone by inhibiting its degradation and enhances its penetration across the stratum corneum and retention in the layers of the skin. It has been experimentally demonstrated that thymoquinone-impregnated NLCs cause epidermal hyperplasia, inflammatory cell infiltration, oxidative damage, and inflammatory cell infiltration to be reduced, resulting in improved skin structure and a lowered severity of the disease. These effects show better therapeutic performance than conventional formulations and have a mechanistic explanation in Figure 4 (Pandey et al., 2025).

5.3 Other Phytochemical-Loaded NLC Systems

Besides curcumin and thymoquinone, some other phytochemicals have also been explored to be incorporated in nanostructured lipid carrier system in managing psoriasis (Alam et al., 2025). Polyphenols including resveratrol, a compound in grapes and berries, have high antioxidant and anti-inflammatory actions and have been demonstrated to enhance stability, skin penetration, and dermal retention upon delivery using NLCs (Patel et al., 2025). Quercetin is a flavonoid available in fruits and vegetables that has anti-inflammatory and antioxidant effects, including the inhibition of cytokine synthesis and the reduction of oxidative stress, and the solubility and dermal delivery of quercetin is improved by NLC formulations (Suddikattu et al., 2025). Likewise, one of the main polyphenols in the green tea, epigallocatechin-3-gallate (EGCG) suppresses the growth of keratinocytes and has anti-inflammatory effects on NF-KB and MAPK pathways. Integration into NLC systems contributes to better stability and allows better penetration across the stratum corneum, leading to enhanced therapeutic efficacy. In general, the phytochemical-loaded NLCs enhance solubility, stability, penetration and controlled release which largely improves the performance of therapeutic in psoriasis management as seen in Figure 4 (Tahvilian et al., 2025).

6. Evaluation and Characterization of NLC Systems

To achieve successful development of nanostructured lipid carrier (NLC) formulations, physicochemical and performance analysis is essential to guarantee stability, safety and therapeutic efficacy (Alloush & Demiralp, 2025).

The studies of characterization furnish key data on the structure of nanoparticles, the effectiveness of their incorporation, and the interaction with the biological system which is obligatory to predict the in vivo practice and provide the reproducible results. Various techniques of analysis are used such as particle size analysis, polydispersity index (PDI), zeta potential, entrapment efficiency, drug release, and skin permeation (Nurohman et al., 2026). These parameters directly influence the drug penetration through stratum corneum, retention at epidermal layers, and the overall therapeutic responses. It can also be analysed properly to achieve maximum formulation variables such as lipid composition, surfactant concentration and processing conditions. The presence of a well-defined NLC system ensures a consistent delivery of drugs, enhanced bioavailability and increased patient compliance as a summary in Table 4 (Nadeem et al., 2025).

6.1 Particle Size and PDI

Particle size is among the most crucial parameters that influence the performance of NLCs in dermal drug delivery because it determines the surface area on which the surface can interact with the skin, which directly correlates with the drug penetration and deposition(Ch et al., 2025). Smaller nanoparticles present a higher surface area, which leads to a higher adhesion of the skin surface and the stratum corneum can be permeated. Normally, NLC preparations range in particle size between 50-500 nm, although smaller sizes of less than 200 nm are believed to be especially effective in promoting dermal penetration and epidermal layer build up of drugs (Di et al., 2025). Dynamic light scattering (DLS) is a method that is often used to measure particle size, and it measures the hydrodynamic diameter of particles in suspension. The polydispersity index (PDI) is the measure of the uniformity of the particle distribution size with the values below 0.3 representing the homogeneous and stable system, whereas the values greater than that indicate aggregation or instability (Mohan et al., 2025). The optimization of formulation parameters including the homogenization speed, concentration of surfactants, and lipid composition are important in attaining desirable particle size and distribution, as summarized in Table 4 (Bakhrushina et al., 2025).

6.2 Zeta Potential

Zeta potential is a critical measure, which determines the surface charge and stability of nanoparticle dispersions, through the electrical potential at the particle interface (Tamboli & Tade, 2025). It defines the level of electrostatic repulsion between particles that is crucial in preventing aggregation and stability of formulations. Zeta potential values in NLCs are usually between ±20 mV and ±40 mV with various combinations of lipids and surfactants (Frangenberg et al., 2025). A value of over +30 mV or -30 mV is usually regarded as a sign of good physical stability as it has high electrostatic repulsion. Though in systems that are stabilized by non-ionic surfactants, steric stabilization can also play a role in stabilizing the system even at lower zeta potential values (Z. Yang et al., 2025). In addition to stability, zeta potential determines the 6interaction with biological membranes. The positively charged or neutral nanoparticles can have increased adhesion and penetration due to the slight negative charge of the skin surface, which can enhance drug retention and local delivery in topical applications. These attributes are significant in maximizing NLC performance, as they are summarized in Table 4 (Khanum et al., 2026).

6.3 Entrapment Efficiency and Drug Loading

One of the most important parameters, which dictate the percentage of drug that was effectively embedded into the lipid matrix of NLCs, is the entrapment efficiency (EE) that is essential to guarantee the adequate amount of drug being available to be released and act as a therapeutic agent (Baltz et al., 2026). Drug loading capacity indicates the amount of drug present relative to the total formulation weight and is important for dose optimization (Alloush & Demiralp, 2025). EE is usually determined by centrifugation or ultrafiltration to isolate free drug and nanoparticle dispersion and then quantifying this with an analytical technique such as UV-visible spectrophotometry or high-performance liquid chromatography (HPLC) (Baltz & Scherließ, 2025). The lipid matrix composition has a strong effect on entrapment efficiency since the inclusion of liquid lipids in solid lipid matrix develops structural defects that enable more drugs to fit and less drug to be released during storage. Optimized lipid mixtures increase EE and stability of the formulations, and thus this parameter is critical in assessing the performance of NLC, as presented in Table 4 (Rahman et al., 2026).

6.4 In Vitro Drug Release Studies

In vitro drug release is necessary to know the kinetics of drug release of NLC systems and gives some knowledge of the mechanism of drug diffusion. These studies aid in predicting in vivo behaviour and are especially crucial in the case of psoriasis treatment where the action of drugs should be prolonged. A commonly used method of measuring drug release is by dialysis membranes or Franz diffusion cells, under controlled conditions and the sample was collected at regular intervals of time to measure cumulative drug release. The majority of NLC formulations are biphasic in release, i.e. a burst release phase in the initial stages of release is caused by the presence of the drug molecules closer to the nanoparticle surface, and then a sustained release is observed, which is caused by a progressive diffusion of the lipid core. This prolonged release aids in the maintenance of therapeutic levels of drugs over longer periods of time, causing a decrease in the frequency of dosing and enhancing patient compliance. These release properties are essential towards assessment of formulation performance and are recapped in Table 4.

6.5 Ex Vivo Skin Permeation Studies

Ex vivo skin permeation studies are widely used to evaluate the ability of NLC formulations to deliver drugs across the skin barrier under simulated physiological conditions (Ashfaq et al., 2026). They are normally performed by placing excised animal or human skin on Franz diffusion cells where the permeation of drugs can be measured with time.

Besides permeation, skin deposition experiments are also conducted to determine drug retention in various layers of the skin, which is of special interest in topical treatments (Hemnani & Suresh, 2025). NLC systems enhance dermal delivery, since they are nanoscale in size and structure and have the capacity to associate intimately with the stratum corneum. The nanoparticles can be deposited in hair follicle that is depository of sustained release of drugs to enhance drug retention and prolong therapeutic activities(Rozas et al., 2025). This follicular targeting can play a role in enhancing the efficacy of NLC-based preparations in chronic diseases such as psoriasis. These evaluation parameters are summarised in table 4 (Malode et al., 2025).

6.6 Stability Studies

Stability testing plays a vital role in assessing long-term stability and shelf life of NLC formulas under various storage conditions(Sipos et al., 2025). Such studies include observing the parameters like particle size, PDI, zeta potential, drug content, and physical appearance with time. Pharmaceutical guidelines recommend that formulations be kept at a controlled temperature and humidity and assessed at fixed time intervals to identify physicochemical changes (Attar et al., 2025). Growth of particle size or zeta potential: This could be a sign of aggregation, whereas decreased drug content can be a sign of degradation or leakage. NLC systems can be affected by the lipid composition, type of surfactant, and mode of preparation (Behera et al., 2025). These parameters should be optimised appropriately to avoid crystallisation, aggregation and expulsion of the drug. The development of new strategies in formulations has increased the stability and improved the commercial viability of systems based on NLC. Table 4 summarises these stability parameters and methods of analysis (Hidayat et al., 2025).

Table 4: Key Characterisation Parameters and Analytical Techniques for NLCs.

Parameter	Description	Analytical Technique
Particle Size	Determines penetration and surface interaction	Dynamic Light Scattering (DLS)
PDI	Indicates size distribution uniformity	DLS
Zeta Potential	Measures surface charge and stability	Electrophoretic light scattering
Entrapment Efficiency	Drug incorporation into lipid matrix	Centrifugation + UV/HPLC

Drug Loading	Amount of drug in formulation	UV/HPLC
In Vitro Release	Drug release kinetics	Dialysis membrane / Franz diffusion cell
Skin Permeation	Drug penetration through skin	Franz diffusion cell
Stability Studies	Long-term formulation stability	Physicochemical analysis

7. Preclinical and Clinical Evidence

Nanotechnology-based formulations have revolutionized treatment approaches to inflammatory skin diseases like psoriasis, and nanostructured lipid carriers (NLCs) are a particularly promising drug delivery system for improving skin penetration and therapeutic outcomes of poorly soluble phytochemicals(Parveen et al., 2022) .Numerous preclinical studies have shown that NLC systems loaded with phytochemicals enhance penetration of drugs across the stratum corneum, increase drug retention in the epidermal compartment, and significantly alleviate the inflammatory responses of psoriatic skin(Shahrulidzafa, 2024). The imiquimod-induced psoriasis-like mouse model has gained widespread acceptance because of its close resemblance to the human disease pathology, by activating the IL-23/Th17 pathway(Gugleva et al., 2021). Research using this model has demonstrated that NLC formulations consistently alleviate redness, scaling, hyperproliferation and immune cell infiltration more effectively than traditional formulations.

Specifically, curcumin-loaded NLCs have shown improved stability and solubility, leading to significant reductions in keratinocyte proliferation and various inflammatory cytokines due to sustained drug release and improved drug penetration into the epidermis(Elkhateeb et al., 2023). Likewise, thymoquinone-loaded NLCs have shown significant anti-inflammatory and antioxidant properties by downregulating crucial cytokines, including the tumour necrosis factor (TNF-α) and interleukin-6 (IL-6), in addition to decreasing oxidative stress and normalising skin structure. Other phytochemicals such as resveratrol and epigallocatechin gallate (EGCG) have also exhibited enhanced stability, skin permeation and immunomodulatory effects when delivered via NLCs(Al-Gabri et al., 2021). A key benefit of NLCs is their capacity to create an occlusive layer on the skin surface, which not only minimises transepidermal water loss, but also increases stratum corneum hydration and improves drug penetration into deeper skin layers(Pal et al., 2023).

Moreover, their nano dimensions facilitate follicle targeting, enabling them to accumulate in hair follicles, and function as drug depots for sustained release, thereby extending the duration of action and minimising the frequency of administration. While promising preclinical data are available, clinical data are scarce, yet initial studies on phytochemical-loaded topical formulations have shown reduction in erythema, scaling, and inflammatory cytokines, indicating potential therapeutic efficacy(Singh Patel et al., 2024). In summary, phytochemical-based NLCs provide a novel and effective approach for treating psoriasis, with improved stability, solubility, targeted delivery and sustained release, but additional well-conducted clinical research is needed to validate their clinical potential.

8. Future Perspectives and Challenges

While significant progress has been made in designing phytochemical-encapsulated nanostructured lipid carriers (NLCs) for the treatment of psoriasis, there are key scientific and translational gaps that limit their translational potential(G. Sharma et al., 2025). While detailed studies have been performed on formulation development, physicochemical properties, and animal studies, there is a critical need for rigorous clinical investigations evaluating long-term safety, pharmacokinetics and efficacy in humans(Neervannan, 2006). Natural phytochemicals like curcumin, resveratrol and thymoquinone have inherent drawbacks, such as limited water solubility, poor permeability, and chemical instability, which limit their bioavailability and efficacy(Aljabali et al., 2025). Although NLC formulations improve the solubility, stability and transdermal penetration of drugs via a liquid matrix, formulation design is crucial

for avoiding problems such as particle aggregation, polymorphic changes, and drug leakage upon storage(Javed et al., 2022). Additionally, production scalability is a significant challenge due to the difficulty and expense in maintaining nanoparticle size, drug loading and consistency across batches for mass production. Lack of regulatory consensus also hampers clinical translation as there are no published guidelines for nanocarrier-based drug formulations. Future studies should explore multifunctional and responsive nanocarrier systems to enhance drug targeting and efficacy(Garg et al., 2022). In conclusion, phytochemicals encapsulated in NLCs hold great promise; however, rigorous clinical evaluation and regulatory harmonisation are essential for clinical translation.

9. CONCLUSION

Psoriasis is a chronic inflammatory immune-mediated skin disease that is associated with hyperproliferation of keratinocytes, immune dysfunction and inflammation, with a profound impact on the quality of life of patients and posing a significant challenge for treatment. While there are many traditional approaches for psoriasis treatment, such as topical steroids, vitamin D analogues, phototherapy and systemic immunosuppressants, these are often hindered by poor skin penetration, high dosing frequency and side effects associated with prolonged use. These drawbacks suggest there's a pressing need for safer and more effective treatment strategies that offer prolonged relief with reduced systemic adverse effects. In this regard, phytochemicals have attracted attention as potential substitutes, owing to their multiple biological properties such as anti-inflammatory, antioxidant and immunomodulatory activity. Biologically active phytochemicals like curcumin, resveratrol and thymoquinone have been shown to modulate various molecular pathways, suppress the hyperproliferation of keratinocytes and reduce inflammation in psoriasis. Yet, their therapeutic use is greatly limited by physicochemical issues such as low aqueous solubility, instability, short half-life and low bioavailability that prevent effective delivery to the site of action. To improve their therapeutic potential, nanostructured lipid carriers (NLCs) have been employed as a novel drug delivery system. NLCs are composed of a mixture of solid and liquid lipids, which form an imperfect crystal lattice and allow effective drug encapsulation, stability, drug loading and reduction in drug expulsion during storage. NLCs' small size and lipid-based composition allow them to engage with the skin's outermost layer - the stratum corneum - enhancing drug permeation and retention into the epidermal and dermal layers. Moreover, the occlusive effect of lipid nanoparticles boosts skin hydration, improving drug absorption. NLCs also offer sustained drug release that can be advantageous in long-term chronic diseases such as psoriasis, thereby increasing patient compliance. In recent years, formulations incorporating phytochemicals in NLCs have been shown to improve drug solubility, stability and efficacy, effectively alleviating psoriasis symptoms, including erythema, scaling and epidermal thickness, and normalising the skin structure. Hence, the use of phytochemicals in NLC formulations offers a novel and effective approach to manage psoriasis and address the challenges associated with the current therapies.

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