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**Research Paper**

# Emerging Role of Phytoconstituents in the Treatment of Psoriasis: Mechanisms and Delivery Approaches

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***Abstract***
*Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by hyperproliferation of keratinocytes, aberrant differentiation, and infiltration of inflammatory cells. Emerging research highlights the therapeutic potential of phytoconstituents plant-derived bioactive secondary metabolites such as polyphenols, flavonoids, terpenoids, and alkaloids as safer, multi-targeted, low-toxicity alternatives for psoriasis management. This review explores the mechanisms of key phytoconstituents (e.g., curcumin, quercetin, resveratrol, boswellic acid, luteolin, hesperidin, kaempferol, ellagic acid, azadirachtin, and thymol) in modulating critical psoriasis pathways, including the IL-23/Th17 axis, NF-κB signaling, oxidative stress, and keratinocyte hyperproliferation. It also discusses innovative delivery approaches, such as nanocarriers (liposomes, ethosomes, nanoemulsions, solid lipid nanoparticles, transfersomes, and hyaluronic acid-modified systems), to overcome inherent challenges of poor bioavailability, low aqueous solubility, limited skin penetration, and rapid metabolism. Evidence from preclinical models (e.g., imiquimod-induced psoriasis), in vitro studies, and early clinical trials supports their potent anti-inflammatory, antioxidant, immunomodulatory, antiproliferative, and pro-apoptotic effects. Future perspectives emphasize optimized nanoformulations, standardization, and large-scale randomized controlled trials to facilitate clinical translation and integration into integrative dermatology.*

***Keywords***: *Psoriasis, phytoconstituents, curcumin, quercetin, resveratrol, IL-23/Th17 axis, NF-κB, nanocarriers.*

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## I. Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disorder that affects approximately 2–3% of the global population, equating to around 125 million people worldwide. Recent epidemiological data indicate that the total number of prevalent cases has nearly doubled from 1990 to 2021, reaching approximately 43 million, with projections suggesting a continued rise in disease burden through 2040–2050 due to population growth and environmental factors. The condition significantly impairs patients' quality of life through visible scaly plaques, intense itching, pain, and social stigma, often leading to psychological distress, reduced work productivity, and substantial economic burden **Boehncke et al [5]**.

**Figure 1**: Clinical presentation of chronic plaque psoriasis showing well-demarcated, erythematous plaques with silvery-white scales on the elbow, a common site of involvement.

Psoriasis arises from a complex interplay of **genetic predisposition** (e.g., strong association with HLA-C*06:02), environmental triggers (such as infections, stress, trauma, smoking, and obesity), and immunological dysregulation. This leads to aberrant activation of dendritic cells and T-helper (Th)1/Th17 cells, resulting in a **cytokine storm** involving key mediators like TNF-α, IL-12, IL-23, IL-17, and IL-22. These cytokines drive keratinocyte hyperproliferation, incomplete differentiation, and recruitment of inflammatory cells, manifesting as epidermal acanthosis and persistent plaques **Rendon et al [28]**.

The disease is increasingly recognized as systemic rather than purely cutaneous, with frequent comorbidities including psoriatic arthritis (affecting up to 30% of patients), cardiometabolic disorders (e.g., hypertension, dyslipidemia, diabetes, and increased cardiovascular risk), metabolic syndrome, inflammatory bowel disease, and psychiatric conditions such as depression and anxiety **Takeshita et al [33]**.

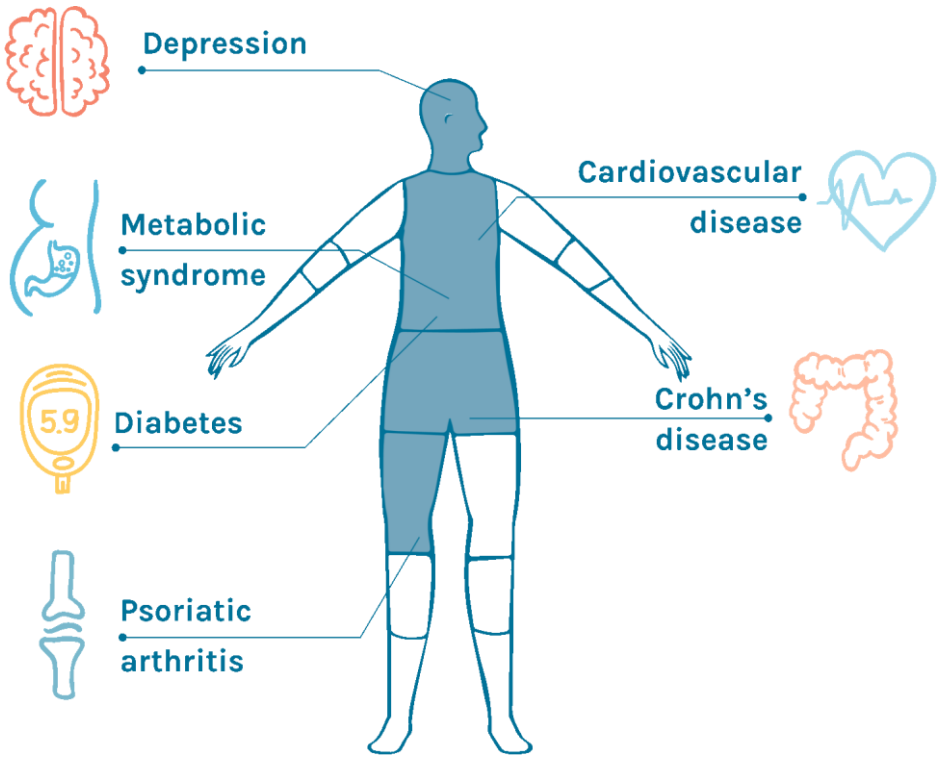


**Figure 2**: Schematic illustration highlighting major comorbidities associated with psoriasis, including psoriatic arthritis, cardiovascular disease, metabolic syndrome, diabetes, depression, and Crohn's disease.

While biologic agents targeting IL-17, IL-23, and TNF-α pathways have revolutionized psoriasis management by achieving high rates of skin clearance, they are limited by high cost, risk of immunosuppression and infections, potential loss of response over time, and restricted accessibility in many regions. These drawbacks have intensified the search for safer, more affordable, and multi-targeted natural alternatives **Rendon et al [28]**.

Phytoconstituents bioactive secondary metabolites from medicinal plants, including polyphenols (e.g., curcumin, resveratrol, quercetin), flavonoids (luteolin, kaempferol), terpenoids (boswellic acid), and others (e.g., ellagic acid, azadirachtin, thymol) offer promising multi-mechanistic actions. These compounds exhibit anti-inflammatory, antioxidant, immunomodulatory, and antiproliferative effects with generally lower toxicity profiles compared to conventional systemic therapies. Recent reviews underscore their potential in modulating the IL-23/Th17 axis and NF-κB signaling while improving patient compliance through topical or oral formulations **Afreen et al [1]**.

This growing interest in phytoconstituents reflects a broader shift toward integrative dermatology, where natural compounds may serve as adjunctive or standalone options, particularly for mild-to-moderate psoriasis or patients seeking fewer side effects. However, challenges such as poor bioavailability and limited large-scale clinical data must be addressed through advanced delivery systems.

## II. Pathophysiology of Psoriasis

Psoriasis pathogenesis involves activation of dendritic cells and T-helper (Th)1/Th17 cells, which release pro-inflammatory cytokines such as TNF-α, IL-12, IL-23, IL-17, and IL-22. These cytokines stimulate keratinocyte hyperproliferation, epidermal acanthosis, and immune cell recruitment, resulting in plaque formation. Environmental triggers and genetic susceptibility exacerbate the cytokine network, leading to chronic inflammation in the epidermis and dermis **Takeshita et al [33]**.

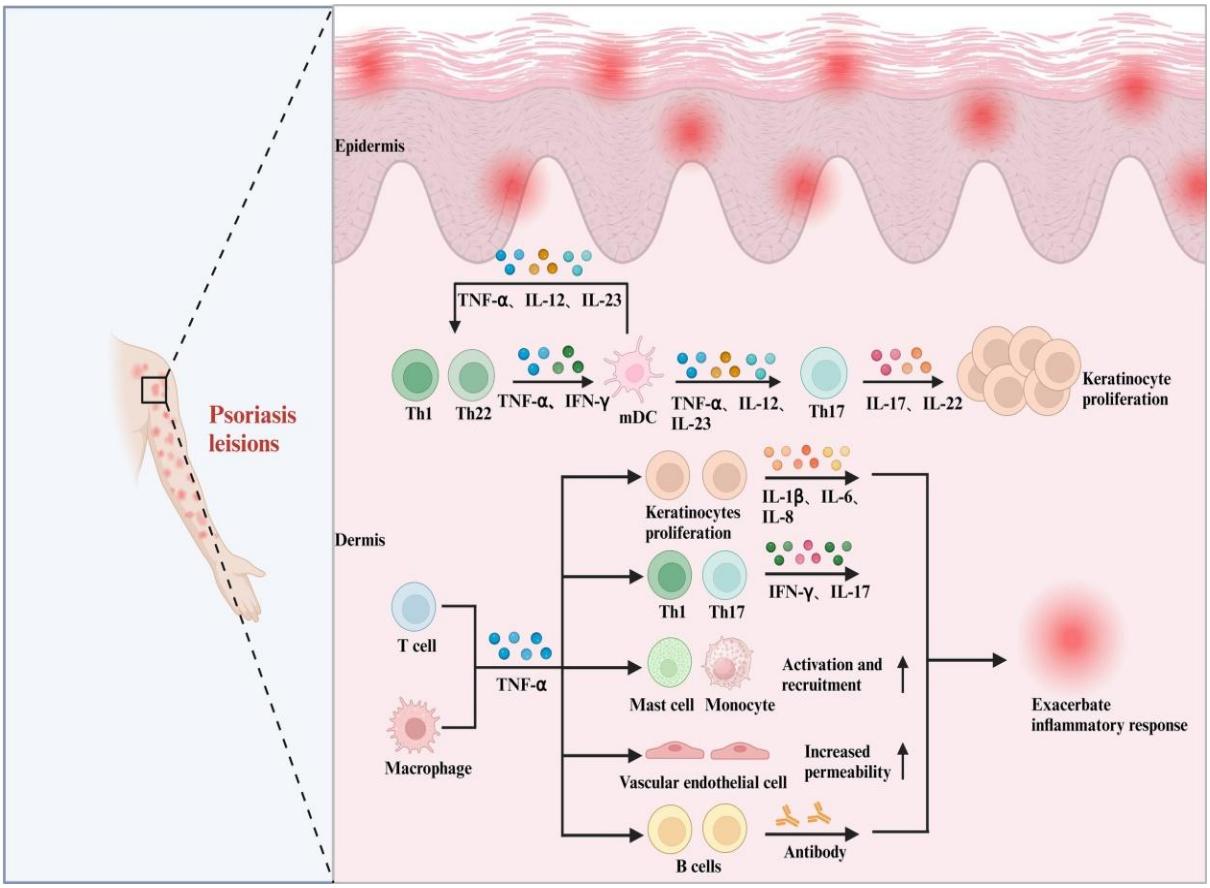


Figure 3: Schematic diagram illustrating psoriasis pathogenesis, highlighting key cytokines (TNF-α, IL-12, IL-23, IL-17, IL-22) and cellular interactions between Th1/Th17 cells, keratinocytes, and immune infiltrates in the epidermis and dermis.

**Limitations of Conventional Therapies and Rationale for Phytoconstituents.** Conventional topical agents (e.g., corticosteroids, vitamin D analogs) and systemic drugs often cause skin atrophy, organ toxicity, or broad immunosuppression. Phytoconstituents address these gaps by targeting multiple pathways simultaneously—anti-inflammatory, antioxidant, and antiproliferative—while exhibiting favorable safety profiles in preclinical models. Recent reviews emphasize their role in downregulating key psoriasis cytokines without the systemic risks of biologics **Akhtar et al [2]**.

**4. Key Phytoconstituents and Their Sources.**

Promising phytoconstituents include polyphenols (curcumin from *Curcuma longa*, quercetin and resveratrol from various plants), flavonoids (luteolin, kaempferol, hesperidin), terpenoids (boswellic acid, azadirachtin), and others like ellagic acid and thymol. These compounds are derived from traditional medicinal plants used historically for skin ailments **Almutairi et al [3]**.

**Table 1: Summary of Selected Phytoconstituents, Sources, Mechanisms, and Potential Delivery Approaches in Psoriasis**

| Phytoconstituent | Plant Source | Key Mechanisms | Delivery Approaches |
|---|---|---|---|
| Curcumin | *Curcuma longa* (Turmeric) | Inhibits NF-κB, IL-17/IL-23, TNF-α; antioxidant; antiproliferative | Liposomes, nanoparticles, ethosomes |
| Quercetin | Onions, apples, capers | Antioxidant; inhibits cytokine production; immunomodulatory | Nanoemulsions, polymeric NPs |
| Resveratrol | Grapes, berries | Modulates SIRT1; anti-inflammatory via NF-κB suppression | Lipid-based carriers |
| Boswellic acid | *Boswellia serrata* | Inhibits 5-LOX; reduces leukocyte infiltration | Topical creams, nanoformulations |
| Luteolin | Celery, parsley | Suppresses Th17 cytokines; antioxidant | Liposomal systems |
| Aloe vera polysaccharides | *Aloe vera* | Anti-inflammatory; cytokine downregulation | Gels, transferosomes |

Table 1: Overview of major phytoconstituents with evidence-based mechanisms and advanced delivery strategies.

**5. Mechanisms of Action of Phytoconstituents.**

Phytoconstituents primarily act by inhibiting pro-inflammatory signaling pathways. Curcumin, for instance, suppresses NF-κB activation, reducing downstream cytokines (IL-17A, IL-17F, TNF-α) and keratinocyte proliferation. Quercetin and luteolin exert antioxidant effects, scavenging reactive oxygen species (ROS) and modulating immune cell responses. Boswellic acid targets leukotriene pathways, while resveratrol influences SIRT1-mediated anti-inflammatory effects. Collectively, these mechanisms restore epidermal homeostasis and dampen the IL-23/Th17 axis central to psoriasis **Bahramian et al [4]**.

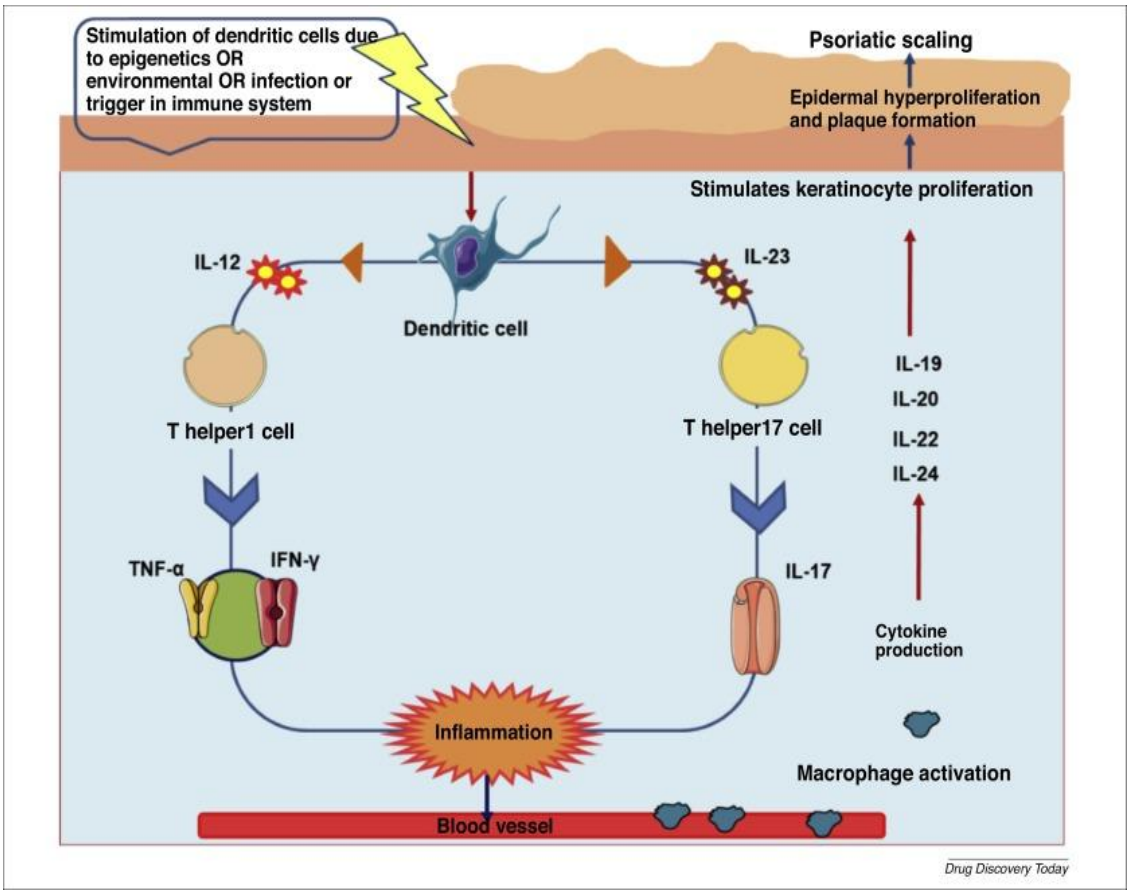


**Figure 4**: Representative diagram of psoriasis cytokine signaling pathways (IL-12, IL-23, IL-17, TNF-α) that phytoconstituents target to reduce inflammation and hyperproliferation.

**6. Specific Example: Curcumin in Psoriasis.**

Curcumin stands out due to its potent inhibition of IL-17 and IL-23 pathways in imiquimod-induced psoriasis models. It also promotes keratinocyte apoptosis and reduces oxidative stress. Clinical observations support its efficacy in reducing PASI scores when formulated appropriately**Chandrasekaran et al [6]**.

**7. Delivery Approaches for Enhanced Efficacy.**

Poor aqueous solubility and low skin permeability limit phytoconstituent bioavailability. Advanced delivery systems liposomes, ethosomes, nanoemulsions, solid lipid nanoparticles, and hyaluronic acid-modified transfersomes improve dermal retention, controlled release, and targeted delivery to inflamed skin. These nanocarriers enhance penetration through the stratum corneum barrier in psoriatic lesions while minimizing systemic absorption **Dai et al [7]**.

**7.1 Conventional Systems**

Traditional topical formulations such as creams, ointments, and gels remain the first-line approach for psoriasis management due to their ease of application and patient familiarity. These systems primarily act on the superficial layers of the skin and are suitable for mild to moderate psoriasis. However, their effectiveness is often limited by poor penetration across the stratum corneum, frequent reapplication requirements, and inadequate drug retention at the target site. Additionally, issues such as greasiness, instability of active compounds, and low bioavailability reduce patient adherence and therapeutic outcomes. These limitations necessitate the development of more advanced delivery strategies **Dubey et al [8]**.

**7.2 Advanced Drug Delivery Systems**

To overcome the shortcomings of conventional formulations, advanced drug delivery systems have been developed to enhance drug solubility, stability, penetration, and controlled release, particularly for phytoconstituents **El-Setouhy et al [9]**.

**7.2.1 Emulgel**

Emulgels are hybrid systems combining the properties of emulsions and gels, making them especially suitable for delivering both hydrophilic and lipophilic drugs **Fathalla et al [10]**.

**Advantages:**

- Enhance drug penetration through dual release mechanisms

- Improve spreadability, stability, and patient compliance
- Provide controlled and sustained drug release
- Reduce greasiness compared to ointments
- Suitable for incorporating phytoconstituents like curcumin and essential oils

**Significance in Psoriasis:**
Emulgels facilitate deeper penetration into inflamed skin layers, improving therapeutic efficacy while maintaining cosmetic acceptability **Goindi et al [12]**.

**7.2.2 Liposomes**
Liposomes are spherical vesicles composed of phospholipid bilayers capable of encapsulating both hydrophilic and lipophilic drugs **Gupta et al [13]**.

**Advantages:**

- Enhance drug encapsulation efficiency
- Provide targeted delivery to epidermal and dermal layers
- Improve skin hydration and drug retention
- Reduce systemic toxicity

**Role in Psoriasis:**
Liposomes can localize anti-inflammatory agents at the site of lesions, improving efficacy while minimizing adverse effects **Hamdan et al [15]**.

**7.2.3 Nanoemulsions**
Nanoemulsions are thermodynamically stable dispersions with droplet sizes typically in the range of 20–200 nm **Jamal et al [16]**.

**Advantages[20]:**

- Increase drug solubility and bioavailability
- Enhance skin permeation due to small droplet size
- Provide rapid onset and controlled release
- Improve stability of phytoconstituents.

**Application in Psoriasis:**
They facilitate efficient delivery of poorly soluble compounds like flavonoids and terpenoids into deeper skin layers **Joshi et al [17]**.

**7.2.4 Solid Lipid Nanoparticles (SLN)**
SLNs are submicron-sized lipid-based carriers composed of solid lipids stabilized by surfactants **Kaur et al [18]**.

**Advantages:**

- Provide sustained and controlled drug release
- Enhance drug stability against degradation
- Offer occlusive effect, improving skin hydration
- Reduce irritation potential

**Role in Psoriasis:**
SLNs improve retention of anti-psoriatic agents in the epidermis, enhancing therapeutic efficiency **Kumari et al [20]**.

**7.2.5 Nanostructured Lipid Carriers (NLC)**
NLCs are second-generation lipid nanoparticles composed of a mixture of solid and liquid lipids**Lohani et al [21]**.

**Advantages[27]:**

- Higher drug loading capacity compared to SLNs
- Improved drug entrapment efficiency
- Enhanced long-term stability
- Reduced drug expulsion during storage
- Better controlled release profiles

**Application in Psoriasis:**
NLCs are particularly effective for delivering phytoconstituents with poor solubility, ensuring prolonged therapeutic action and improved patient compliance **Lohani et al [21]**.

**8. Clinical Evidence**
Preclinical investigations and early-stage clinical studies provide encouraging evidence regarding the therapeutic potential of phytoconstituent-based formulations. Various in vitro and in vivo studies have

demonstrated that plant-derived bioactive compounds possess significant anti-inflammatory, antioxidant, and immunomodulatory properties, which contribute to symptom improvement in chronic diseases such as psoriasis and other inflammatory disorders **Nast et al [23]**.

Limited clinical trials have reported measurable improvements in disease severity scores, reduction in erythema, scaling, and lesion thickness, along with enhanced patient quality of life. These studies indicate that phytoconstituents can modulate multiple molecular targets, offering a multi-mechanistic approach compared to conventional single-target therapies. However, most available clinical data are preliminary, involving small sample sizes and short durations, which restricts the generalizability of the findings **Paller et al [24]**.

**9. Challenges**

Despite promising outcomes, several challenges hinder the clinical translation of phytoconstituent-based therapies. One of the major limitations is the lack of standardization in herbal formulations. Variability in plant sources, cultivation conditions, extraction methods, and phytochemical composition often leads to inconsistency in therapeutic efficacy**Parisi et al [25]**.

Batch-to-batch variability further complicates quality control and reproducibility of results. Additionally, the complexity of phytoconstituents, which often contain multiple active compounds, makes it difficult to identify precise mechanisms of action and pharmacokinetic profiles**Puig et al [26]**.

Another critical challenge is the limited availability of large-scale, well-designed clinical trials. Regulatory hurdles, insufficient funding, and lack of harmonized guidelines for herbal medicines also contribute to the slow progress in clinical validation. Moreover, issues related to bioavailability, stability, and targeted delivery remain significant concerns**Rachakonda et al [27]**.

**10. Future Perspectives**

Future research should focus on overcoming the current limitations through advanced formulation strategies and robust clinical evaluation. The development of hybrid nano-formulations integrating phytoconstituents with conventional drugs holds great promise for enhancing therapeutic efficacy, bioavailability, and targeted delivery **Sawant et al [29]**.

Personalized medicine approaches, including patient-specific drug delivery systems and biomarker-based therapy optimization, are emerging as potential strategies to improve treatment outcomes. Advances in nanotechnology, such as liposomes, nanoparticles, and nanoemulgels, can further facilitate controlled and sustained drug release **Sharma et al [30]**.

Importantly, conducting rigorous, large-scale randomized controlled trials is essential to establish long-term safety, efficacy, and clinical applicability. Standardization protocols, quality assurance measures, and regulatory frameworks must also be strengthened to ensure consistency and reproducibility **Singh et al [31]**.

Overall, the integration of traditional phytotherapy with modern pharmaceutical technologies represents a promising direction for the development of safer and more effective therapeutic interventions **Stern et al [32]**.

## III. Conclusion

Phytoconstituents represent a promising and evolving frontier in the management of psoriasis, primarily due to their ability to act on multiple molecular targets involved in disease pathogenesis. Unlike conventional therapies that often focus on single pathways, plant-derived bioactive compounds exhibit a broad spectrum of pharmacological activities, including anti-inflammatory, antioxidant, immunomodulatory, and antiproliferative effects. These properties collectively contribute to the reduction of keratinocyte hyperproliferation, modulation of immune responses, and improvement in clinical symptoms such as erythema, scaling, and plaque formation. Additionally, phytoconstituents are generally associated with a more favorable safety profile, making them suitable candidates for long-term management of chronic dermatological conditions like psoriasis.

The integration of phytoconstituents with advanced drug delivery systems, particularly nanotechnology-based platforms such as liposomes, nanoparticles, nanoemulgels, and solid lipid nanoparticles, has further strengthened their therapeutic potential. These innovative delivery systems address key limitations such as poor solubility, low bioavailability, and inadequate skin penetration, thereby enhancing drug stability, controlled release, and site-specific targeting. As a result, the clinical translation of phytoconstituent-based therapies becomes more feasible and effective.

Despite these advantages, challenges related to standardization, quality control, regulatory approval, and limited large-scale clinical evidence must be addressed to fully realize their potential. Future research should focus on well-designed randomized controlled trials, identification of active phytochemical markers, and development of reproducible formulations. Moreover, the incorporation of personalized medicine approaches and biomarker-based therapies may further optimize treatment outcomes.

In conclusion, the convergence of traditional phytotherapy with modern pharmaceutical and nanotechnological advancements holds significant promise for the development of safer, more effective, and patient-friendly therapeutic strategies. With continued scientific validation and technological innovation, phytoconstituents are likely to become an integral part of mainstream dermatological practice in the near future.

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