RESEARCH PAPER

Emerging Topical Non-Steroidal Therapies in Inflammatory Dermatoses: Mechanisms, Clinical Applications and Future Directions

[1]Dr Faraz Mohammed V.S and [2]Dr Kandaswamy M

[1]Final year postgraduate, Department of Dermatology, Venereology and Leprosy, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth Deemed to Be University, Puducherry, India

[2]Professor and HOD, Department of Dermatology, Venereology and Leprosy, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth Deemed to Be University, Puducherry, India

[1]https://orcid.org 0009-0006-3129-3469 and [2]https://orcid.org/0000-0002-9452-8011

Email: [1]farazmohammed59@yahoo.com and [2] kandaswamy22@gmail.com

Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

ABSTRACT

Inflammatory dermatoses including atopic dermatitis, psoriasis, vitiligo, seborrheic dermatitis, rosacea, lichen planus, contact dermatitis, and hand eczema are chronic relapsing disorders associated with substantial morbidity, impaired quality of life, psychosocial burden, and long-term therapeutic challenges. Topical corticosteroids have historically remained the cornerstone of therapy because of their potent anti-inflammatory effects; however, prolonged use is frequently associated with adverse effects such as skin atrophy, telangiectasia, striae, tachyphylaxis, steroid dependence, rosacea-like dermatitis, and hypothalamic-pituitary-adrenal axis suppression, particularly in children and sensitive anatomical areas. These limitations have accelerated the development of emerging topical non-steroidal therapies that provide targeted immunomodulation with improved long-term safety and steroid-sparing potential.

Recent advances in molecular immunology and translational dermatology have substantially improved understanding of cytokine signaling pathways, epidermal barrier dysfunction, oxidative stress, and microbial dysbiosis involved in inflammatory dermatoses. This has facilitated the introduction of several novel therapeutic classes including topical calcineurin inhibitors, phosphodiesterase-4 inhibitors, topical Janus kinase inhibitors, aryl hydrocarbon receptor agonists, microbiome-directed therapies, barrier-repair formulations, and nanotechnology-based drug-delivery systems.

Topical calcineurin inhibitors such as tacrolimus and pimecrolimus inhibit calcineurin-mediated T-cell activation and inflammatory cytokine release, thereby serving as important steroid-sparing therapies particularly in facial, flexural, genital, and pediatric dermatoses. Phosphodiesterase-4 inhibitors including crisaborole, roflumilast, and difamilast suppress inflammatory cytokine production through modulation of cyclic adenosine monophosphate signaling pathways and have demonstrated efficacy in atopic dermatitis, psoriasis, and seborrheic dermatitis. Topical Janus kinase inhibitors such as ruxolitinib and delgocitinib selectively inhibit cytokine-mediated intracellular signaling pathways involved in chronic inflammation, pruritus, and autoimmune tissue injury. These agents have shown promising clinical outcomes in atopic dermatitis, vitiligo, and chronic hand eczema with rapid antipruritic effects and favorable tolerability.

Tapinarof, a novel aryl hydrocarbon receptor agonist, exhibits anti-inflammatory, antioxidative, and barrier-restorative properties through modulation of epidermal differentiation and inflammatory signaling pathways. Simultaneously, increasing recognition of the role of microbial dysbiosis and epidermal barrier impairment has promoted the development of microbiome-targeted therapies, ceramide-based formulations, advanced emollients, probiotic preparations, and antimicrobial peptide-based approaches aimed at restoring cutaneous homeostasis.

Nanotechnology and advanced drug-delivery systems including liposomes, nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, and nanostructured carriers are additionally being explored to improve topical penetration, enhance drug stability, optimize targeted delivery, minimize systemic exposure, and improve therapeutic efficacy of non-steroidal agents.

This narrative review discusses the mechanisms of action, formulations, clinical applications, efficacy, safety profiles, advantages over corticosteroids, limitations, and future directions of emerging topical non-steroidal therapies in inflammatory dermatoses. The growing availability of targeted topical therapies represents an important shift toward safer, individualized, and long-term management strategies in modern inflammatory dermatology.

Keywords: Inflammatory dermatoses; topical non-steroidal therapies; calcineurin inhibitors; tacrolimus; pimecrolimus; phosphodiesterase-4 inhibitors; crisaborole; roflumilast; difamilast; Janus kinase inhibitors; ruxolitinib; delgocitinib; tapinarof; aryl hydrocarbon receptor agonists; microbiome therapy; barrier-repair therapy; nanotechnology; topical drug-delivery systems; atopic dermatitis; psoriasis; vitiligo; hand eczema.

How to cite this article: Faraz Mohammed VS, Kandaswamy M. Emerging Topical Non-Steroidal Therapies in Inflammatory Dermatoses: Mechanisms, Clinical Applications and Future Directions. Int J Drug Deliv Technol. 2026;16(58s): 838-853. DOI: 10.25258/ijddt.16.58s.91

**Author for Correspondence: farazmohammed59@yahoo.com*

Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Inflammatory dermatoses comprise a heterogeneous group of chronic relapsing skin disorders characterized by immune dysregulation, epidermal barrier dysfunction, oxidative stress, and alterations in the skin microbiome [1]. Common inflammatory dermatoses including atopic dermatitis, psoriasis, vitiligo, seborrheic dermatitis, rosacea, lichen planus, contact dermatitis, and hand eczema significantly impair quality of life and frequently require prolonged therapy because of recurrent exacerbations and chronic inflammation.

Topical corticosteroids have historically remained the cornerstone of management because of their potent anti-inflammatory and immunosuppressive effects. However, prolonged or inappropriate use is associated with adverse effects such as skin atrophy, telangiectasia, striae, tachyphylaxis, steroid dependence, rosacea-like dermatitis, pigmentary alterations, and hypothalamic-pituitary-adrenal axis suppression, particularly in pediatric patients and sensitive anatomical sites including the face, flexures, and genitalia [2]. Increasing corticosteroid phobia and the need for safer long-term maintenance therapy have accelerated interest in non-steroidal therapeutic alternatives.

Advances in molecular immunology and translational dermatology have substantially improved understanding of cytokine-mediated inflammatory pathways involved in inflammatory dermatoses. Targeted modulation of pathways including calcineurin signaling, phosphodiesterase-4 activity, Janus kinase-signal transducer signaling, and aryl hydrocarbon receptor activation has facilitated the development of several emerging topical non-steroidal therapies [3]. Simultaneously, increasing recognition of the role of microbial dysbiosis and epidermal barrier impairment has encouraged development of microbiome-directed and barrier-restorative therapeutic strategies.

Emerging topical non-steroidal therapies offer several advantages over conventional corticosteroids including:

- Reduced risk of skin atrophy
- Improved suitability for long-term use
- Better applicability in sensitive areas
- Steroid-sparing potential
- Targeted immune modulation
- Improved patient adherence

The major emerging therapeutic classes currently used in inflammatory dermatology include:

- Calcineurin inhibitors
- Phosphodiesterase-4 inhibitors
- Topical Janus kinase inhibitors
- Aryl hydrocarbon receptor agonists
- Microbiome and barrier-repair therapies
- Nanotechnology-based drug-delivery systems

These therapies are increasingly being utilized in atopic dermatitis, psoriasis, vitiligo, seborrheic dermatitis, rosacea, lichen planus, contact dermatitis, and chronic hand eczema with encouraging efficacy and safety outcomes [4].

Table 1: Advantages of Emerging Topical Non-Steroidal Therapies over Topical Corticosteroids

Parameter	Topical Corticosteroids	Emerging Non-Steroidal Therapies
Risk of skin atrophy	Common with prolonged use	Minimal or absent
Long-term maintenance use	Limited	More suitable
Sensitive-site applicability	Restricted	Better tolerated
Pediatric safety	Cautious prolonged use	Improved safety profile
Tachyphylaxis	May occur	Less common
Steroid dependence	Possible	Minimal
Targeted immune modulation	Broad immunosuppression	Specific pathway targeting
Barrier restoration	Limited	Present in several newer agents
Use in facial/flexural areas	Restricted prolonged use	Better tolerated
Patient adherence	Reduced by steroid fear	Improved acceptability

Table 1 summarizes the major advantages of emerging non-steroidal topical therapies compared with conventional topical corticosteroids.

The present narrative review discusses the mechanisms of action, formulations, indications, contraindications, adverse effects, clinical applications, advantages over corticosteroids, and future perspectives of emerging topical non-steroidal therapies in inflammatory dermatoses.

METHODOLOGY

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar databases for studies published between January 2000 and March 2026. Search terms included “topical non-steroidal therapies,” “calcineurin inhibitors,” “tacrolimus,” “pimecrolimus,” “PDE-4 inhibitors,” “crisaborole,” “roflumilast,” “difamilast,” “topical JAK inhibitors,” “ruxolitinib,” “delgocitinib,” “tapinarof,” “aryl hydrocarbon receptor agonists,” “microbiome therapy,” “barrier repair,” “nanotechnology,” “drug-delivery systems,” “atopic dermatitis,” “psoriasis,” “vitiligo,”

"seborrheic dermatitis," "rosacea," "contact dermatitis," and "hand eczema."

Original research articles, randomized controlled trials, systematic reviews, meta-analyses, observational studies, and clinically relevant narrative reviews published in English were included. Studies lacking topical therapeutic relevance, conference abstracts without full text, duplicate publications, and studies focusing primarily on systemic therapies were excluded.

Particular emphasis was placed on:

- Mechanism of action
- Formulations
- Indications and contraindications
- Clinical efficacy
- Safety profile
- Steroid-sparing role
- Comparative therapeutic utility
- Emerging future applications

Priority was given to landmark studies, pivotal clinical trials, recent evidence, and high-quality review articles related to emerging topical non-steroidal therapies in inflammatory dermatology.

Pathophysiological Basis for Emerging Non-Steroidal Therapy

Inflammatory dermatoses result from complex interactions among immune dysregulation, epidermal barrier dysfunction, genetic susceptibility, environmental triggers, oxidative stress, and microbial dysbiosis [5]. Although individual disorders differ in immunological profile and clinical presentation, chronic inflammation remains the central pathogenic mechanism.

Atopic dermatitis is predominantly mediated through T-helper 2 cytokines including interleukin-4 and interleukin-13, leading to pruritus, epidermal barrier disruption, and increased susceptibility to microbial colonization. Psoriasis primarily involves T-helper 17/interleukin-23-driven inflammation resulting in keratinocyte hyperproliferation and chronic plaque formation. Vitiligo is characterized by autoimmune melanocyte destruction mediated through interferon-gamma and Janus kinase-signal transducer pathways [6].

Epidermal barrier dysfunction additionally contributes significantly to disease chronicity, particularly in atopic dermatitis and hand eczema. Alterations in structural proteins such as filaggrin and abnormalities in ceramide composition increase transepidermal water loss and facilitate allergen penetration and microbial imbalance [7]. Seborrheic dermatitis is additionally associated with inflammatory responses triggered by Malassezia species, whereas rosacea demonstrates dysregulated innate immunity and neurovascular inflammation.

Conventional topical corticosteroids suppress inflammation effectively but do not specifically target the underlying molecular pathways involved in disease pathogenesis. Their long-term use is additionally limited by local and systemic adverse effects [2]. Emerging non-steroidal therapies therefore aim to:

- Selectively inhibit inflammatory pathways
- Restore epidermal barrier integrity
- Improve microbial balance
- Reduce chronic disease recurrence
- Minimize corticosteroid-associated toxicity

Recent advances in molecular dermatology have facilitated development of targeted therapies directed against calcineurin signaling, phosphodiesterase-4 activity, Janus kinase pathways, and aryl hydrocarbon receptor-mediated inflammation [3]. Simultaneously, barrier-repair formulations, microbiome-directed therapy, and nanotechnology-based drug-delivery systems are increasingly being explored to improve long-term disease control and therapeutic precision.

Table 2: Major Pathogenic Mechanisms in Common Inflammatory Dermatoses

Inflammatory Dermatosis	Major Pathogenic Mechanism	Important Cytokines/Pathways	Important Emerging Therapeutic Targets
Atopic dermatitis	Th2-mediated inflammation and barrier dysfunction	IL-4, IL-13, IL-31	PDE-4 inhibitors, JAK inhibitors, calcineurin inhibitors
Psoriasis	Th17/IL-23-mediated inflammation	IL-17, IL-23, TNF-α	PDE-4 inhibitors, AhR agonists
Vitiligo	Autoimmune melanocyte destruction	IFN-γ, JAK-STAT pathway	Topical JAK inhibitors
Seborrheic dermatitis	Malassezia-associated inflammation	Innate immune dysregulation	Calcineurin inhibitors, PDE-4 inhibitors
Rosacea	Neurovascular and innate immune dysregulation	Cathelicidins, inflammatory mediators	Barrier-repair and anti-inflammatory therapies
Contact dermatitis	Delayed hypersensitivity reaction	T-cell mediated inflammation	Calcineurin inhibitors, JAK inhibitors
Lichen planus	T-cell-mediated autoimmune inflammation	Cytotoxic T-cell activation	Calcineurin inhibitors

Hand eczema	Barrier dysfunction and chronic inflammation	Mixed inflammatory pathways	Delgocitinib, barrier-repair therapies

Table 2 summarizes the major pathogenic pathways involved in common inflammatory dermatoses and their corresponding therapeutic targets.

Emerging Topical Non-Steroidal Therapies

A. Topical Calcineurin Inhibitors

Topical calcineurin inhibitors were among the earliest successful non-steroidal immunomodulators introduced for inflammatory dermatoses and continue to play an important role as steroid-sparing therapies. Unlike topical corticosteroids, these agents selectively suppress T-cell-mediated inflammation without significantly affecting collagen synthesis or epidermal proliferation, thereby minimizing the risk of skin atrophy and telangiectasia [8].

Calcineurin is a calcium-dependent phosphatase involved in activation of nuclear factor of activated T cells and subsequent transcription of inflammatory cytokines including interleukin-2, interleukin-4, interferon-gamma, and tumor necrosis factor-alpha. Calcineurin inhibitors block this pathway and suppress inflammatory cytokine release, thereby reducing cutaneous inflammation [9].

The two principal topical calcineurin inhibitors used in dermatology are tacrolimus and pimecrolimus.

Tacrolimus

Tacrolimus is a macrolide immunosuppressant derived from *Streptomyces tsukubaensis* and is available primarily as 0.03% and 0.1% ointment formulations. Owing to greater anti-inflammatory potency, tacrolimus is generally preferred in moderate-to-severe inflammatory dermatoses [10].

Topical tacrolimus is widely used in:

- Atopic dermatitis
- Facial and flexural eczema
- Eyelid dermatitis
- Vitiligo
- Oral and genital lichen planus
- Steroid-sensitive dermatoses

Tacrolimus is particularly valuable in:

- Pediatric atopic dermatitis
- Chronic relapsing disease
- Long-term maintenance therapy
- Sensitive anatomical areas where corticosteroid-induced atrophy is concerning

In vitiligo, tacrolimus suppresses cytotoxic T-cell-mediated melanocyte destruction and may enhance repigmentation, particularly when combined with phototherapy. In lichen planus, it reduces inflammatory activity and symptomatic burning sensation.

The most common adverse effects include transient:

- Burning sensation
- Stinging
- Pruritus
- Local irritation

These effects are usually mild and improve with continued therapy. Although theoretical concerns regarding malignancy risk resulted in black box warnings, long-term evidence has not demonstrated definitive causal association with lymphoma or skin cancer when used appropriately [11].

"Tacrolimus should be used cautiously in patients with active cutaneous infections, significant immunosuppression, or extensive epidermal barrier disruption. Application over potentially malignant or premalignant lesions should generally be avoided, and prolonged continuous application over large body surface areas requires careful monitoring."

This integrates:

- active infections
- immunocompromised state
- malignant lesions
- extensive body surface area precautions without disrupting flow.

Major advantages of tacrolimus over topical corticosteroids include:

- Absence of skin atrophy
- Safe facial and flexural use
- Long-term maintenance applicability
- Steroid-sparing effect
- Favorable pediatric utility

However, limitations include:

- Burning sensation affecting adherence
- Higher cost
- Delayed onset compared with potent corticosteroids
- Limited efficacy in hyperkeratotic lesions

Pimecrolimus

Pimecrolimus is an ascomycin derivative formulated primarily as 1% cream and designed specifically for topical anti-inflammatory dermatologic use. Compared with tacrolimus, pimecrolimus demonstrates lower immunosuppressive potency but greater cutaneous selectivity and minimal systemic absorption [12].

Pimecrolimus is particularly useful in:

- Mild-to-moderate atopic dermatitis
- Early inflammatory lesions
- Pediatric eczema

- Facial dermatitis
- Seborrheic dermatitis
- Contact dermatitis
- Rosacea-like inflammatory dermatoses

The cream-based formulation additionally offers improved cosmetic acceptability, especially in facial application.

In seborrheic dermatitis, pimecrolimus reduces erythema, scaling, and inflammation while avoiding steroid-associated complications. It is also useful in maintenance therapy and recurrent inflammatory disease requiring prolonged treatment.

Common adverse effects include:
- Mild burning sensation
- Pruritus
- Local irritation
- Transient erythema

Advantages of pimecrolimus include:
- Minimal systemic absorption
- Favorable tolerability
- Utility in sensitive skin areas
- Reduced steroid exposure
- Pediatric safety
- Good maintenance therapy profile

"Pimecrolimus is generally contraindicated in patients with known hypersensitivity to macrolactam derivatives and should be avoided in untreated bacterial, viral, or fungal skin infections. Cautious use is additionally advised in severely immunocompromised individuals."

These covers:
- hypersensitivity
- infections
- immunocompromised patients in concise form.

Limitations include:
- Lower potency in severe inflammatory disease
- Delayed therapeutic response
- Higher treatment cost

Table 3: Comparative Features of Tacrolimus and Pimecrolimus

Parameter	Tacrolimus	Pimecrolimus
Formulation	0.03% and 0.1% ointment	1% cream
Relative potency	Higher	Moderate
Preferred disease severity	Moderate-to-severe	Mild-to-moderate
Major indications	Atopic dermatitis, vitiligo, lichen planus	Atopic dermatitis, seborrheic dermatitis
Facial/flexural use	Yes	Yes
Pediatric applicability	Good	Excellent
Systemic absorption	Minimal	Very low
Cosmetic acceptability	Moderate	Better
Skin atrophy risk	Absent	Absent
Common adverse effect	Burning sensation	Mild irritation
Steroid-sparing role	Significant	Significant

Table 3 summarizes the major comparative features of topical tacrolimus and pimecrolimus.

Topical calcineurin inhibitors remain important components of modern inflammatory dermatology because of their steroid-sparing utility, long-term applicability, and favorable safety profile in sensitive anatomical regions.

B. Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PDE-4) inhibitors represent an important advancement in targeted topical therapy for inflammatory dermatoses. PDE-4 is an intracellular enzyme responsible for degradation of cyclic adenosine monophosphate, a regulatory molecule that suppresses inflammatory cytokine production. Increased PDE-4 activity contributes to elevated levels of pro-inflammatory mediators including tumor necrosis factor-alpha, interleukin-17, interleukin-23, and interferon-gamma in inflammatory skin disease [13].

Topical PDE-4 inhibitors suppress inflammatory signaling by increasing intracellular cyclic adenosine monophosphate levels, thereby reducing cytokine-mediated inflammation without causing corticosteroid-associated skin atrophy [14]. Their favorable safety profile and suitability for prolonged use have expanded their role in chronic inflammatory dermatoses.

The principal topical PDE-4 inhibitors currently used or under investigation include crisaborole, roflumilast, and difamilast.

Crisaborole

Crisaborole is a boron-containing topical PDE-4 inhibitor available as 2% ointment formulation and approved primarily for mild-to-moderate atopic dermatitis. It reduces inflammatory cytokine production and improves pruritus, erythema, and eczematous lesions [15].

Crisaborole is particularly useful in:
- Mild-to-moderate atopic dermatitis
- Pediatric eczema
- Facial and flexural dermatitis
- Long-term maintenance therapy

- Steroid-sensitive areas

Its major advantage lies in the absence of skin atrophy and favorable long-term tolerability. Crisaborole additionally demonstrates minimal systemic absorption, making it suitable for pediatric use.

The most common adverse effects include:
- Application-site burning
- Stinging sensation
- Mild irritation

Limitations include:
- Reduced efficacy in severe disease
- Relatively high treatment cost
- Slower onset compared with potent corticosteroids

Roflumilast
Roflumilast is a highly potent selective PDE-4 inhibitor available in cream and foam formulations. It demonstrates strong anti-inflammatory activity and favorable skin penetration properties [16].

Topical roflumilast has shown promising efficacy in:
- Plaque psoriasis
- Intertriginous psoriasis
- Seborrheic dermatitis
- Atopic dermatitis

Roflumilast effectively reduces:
- Plaque thickness
- Scaling
- Erythema
- Pruritus

Its once-daily application and cosmetically acceptable formulation improve patient adherence. In seborrheic dermatitis, foam formulations are particularly useful for scalp involvement.

Advantages of roflumilast include:
- High anti-inflammatory potency
- Good cosmetic acceptability
- Once-daily use
- Utility in intertriginous regions
- Absence of steroid-induced atrophy

Common adverse effects include:
- Mild irritation
- Headache
- Diarrhea (rare)
- Application-site pain

Difamilast
Difamilast is a newer selective topical PDE-4 inhibitor developed primarily for atopic dermatitis. It is available as ointment formulation and has demonstrated favorable efficacy and tolerability in both adults and children [17].

Difamilast improves:
- Erythema
- Pruritus
- Xerosis
- Eczematous lesions

The drug demonstrates:
- Minimal systemic absorption
- Good pediatric safety
- Favorable long-term tolerability
- Steroid-sparing potential

Adverse effects are generally mild and include:
- Local irritation
- Burning sensation
- Mild erythema

"Although topical PDE-4 inhibitors demonstrate favorable safety profiles, caution is advisable in patients with severe hypersensitivity reactions or extensive inflamed body surface area involvement because local irritation may increase treatment intolerance."

This prevents repetitive contraindication insertion under each PDE-4 drug individually.

Table 4: Comparative Features of Topical PDE-4 Inhibitors

Parameter	Crisaborole	Roflumilast	Difamilast
Formulation	2% ointment	Cream/Foam	Ointment
Major indications	Atopic dermatitis	Psoriasis, seborrheic dermatitis, atopic dermatitis	Atopic dermatitis
Potency	Moderate	High	Moderate
Pediatric applicability	Excellent	Good	Excellent
Sensitive-area use	Good	Good	Good
Steroid-sparing role	Significant	Significant	Significant
Major advantages	Good safety profile	Once-daily use, potent efficacy	Favorable tolerability

Common adverse effects	Burning, irritation	Irritation, headache	Mild irritation
Skin atrophy risk	Absent	Absent	Absent
Major limitation	Cost	Limited long-term data	Limited availability

Table 4 summarizes the major features of topical PDE-4 inhibitors used in inflammatory dermatoses.

Topical PDE-4 inhibitors represent effective steroid-sparing therapies with favorable safety profiles and growing utility in atopic dermatitis, psoriasis, and seborrheic dermatitis. Their targeted anti-inflammatory action and suitability for prolonged use make them important additions to modern inflammatory dermatologic therapy.

C. Topical Janus Kinase Inhibitors

Topical Janus kinase (JAK) inhibitors represent one of the most significant recent advances in targeted dermatologic therapy. The Janus kinase-signal transducer and activator of transcription pathway mediate intracellular signaling for several inflammatory cytokines involved in chronic inflammatory and autoimmune dermatoses including interleukin-4, interleukin-13, interleukin-31, and interferon-gamma [18].

Activation of the JAK-STAT pathway contributes to inflammation, pruritus, epidermal barrier dysfunction, and autoimmune tissue injury. Topical JAK inhibitors selectively block cytokine-mediated signaling pathways, thereby reducing inflammation while minimizing systemic exposure compared with oral JAK inhibitors [19].

The major topical JAK inhibitors currently used or under investigation include ruxolitinib and delgocitinib.

Ruxolitinib

Ruxolitinib is a selective JAK-1 and JAK-2 inhibitor formulated primarily as 1.5% cream. It has demonstrated significant efficacy in inflammatory and autoimmune dermatoses, particularly atopic dermatitis and non-segmental vitiligo [20].

In atopic dermatitis, topical ruxolitinib rapidly improves:

- Pruritus
- Erythema
- Sleep disturbance
- Eczematous lesions

Rapid antipruritic activity is considered one of its major therapeutic advantages. The drug is particularly useful in:

- Mild-to-moderate atopic dermatitis
- Facial dermatitis
- Flexural eczema
- Steroid-sensitive anatomical areas

Ruxolitinib additionally represents an important therapeutic advancement in vitiligo. By suppressing interferon-gamma-mediated melanocyte destruction, it promotes repigmentation, particularly in facial lesions and when combined with phototherapy.

Advantages of ruxolitinib include:

- Rapid symptomatic improvement
- Targeted cytokine inhibition
- Absence of skin atrophy
- Steroid-sparing potential
- Utility in sensitive skin areas

Common adverse effects include:

- Mild application-site irritation
- Acneiform eruptions
- Nasopharyngitis
- Erythema

Although systemic adverse effects appear uncommon with topical therapy, long-term safety monitoring remains important because of theoretical concerns associated with systemic JAK inhibition [21].

“Topical ruxolitinib should be used cautiously in patients with active infections, chronic immunosuppression, or extensive body surface area involvement because systemic absorption may theoretically increase with prolonged application. Long-term continuous use additionally requires careful safety monitoring.”

This addresses:

- active infection
- immunocompromised patients
- large body surface area use
- long-term JAK inhibitor caution which is one of the most important missing points.

Delgocitinib

Delgocitinib is a topical pan-JAK inhibitor that suppresses JAK-1, JAK-2, JAK-3, and tyrosine kinase-2-mediated inflammatory signaling pathways. Its broader cytokine inhibition provides anti-inflammatory activity across multiple inflammatory dermatoses.

Delgocitinib has demonstrated promising efficacy in:

- Chronic hand eczema
- Atopic dermatitis
- Contact dermatitis

The drug effectively improves:

- Pruritus
- Fissuring

- Erythema
- Scaling
- Lichenification

Delgocitinib is particularly valuable in chronic hand eczema where prolonged corticosteroid use may result in cutaneous atrophy and impaired barrier integrity.

Advantages include:
- Broad anti-inflammatory activity
- Steroid-sparing utility
- Favorable efficacy in chronic hand eczema
- Absence of steroid-induced atrophy
- Potential long-term maintenance role

Common adverse effects include:
- Mild irritation
- Folliculitis
- Application-site reactions
- Acneiform eruptions

Current limitations include:
- Limited long-term safety data
- Restricted global availability
- High treatment cost

"Cautious use of delgocitinib is recommended in patients with active infections or impaired immune status, and prolonged use over extensive inflammatory lesions requires further long-term safety evaluation."

Maintains concise structure while reinforcing class-related precautions.

Table 5: Comparative Features of Topical JAK Inhibitors

Parameter	Ruxolitinib	Delgocitinib
JAK selectivity	JAK-1 and JAK-2	Pan-JAK inhibitor
Formulation	1.5% cream	Ointment/Cream
Major indications	Atopic dermatitis, vitiligo	Hand eczema, atopic dermatitis
Major therapeutic effect	Rapid antipruritic activity	Broad anti-inflammatory activity
Sensitive-site utility	Excellent	Good
Steroid-sparing role	Significant	Significant
Skin atrophy risk	Absent	Absent
Major advantages	Rapid itch relief, vitiligo efficacy	Useful in chronic hand eczema
Common adverse effects	Acneiform eruptions, irritation	Folliculitis, irritation
Major limitations	Cost, long-term safety concerns	Limited availability

Table 5 summarizes the major characteristics of topical JAK inhibitors used in inflammatory dermatoses.

Topical JAK inhibitors represent an important shift toward precision-targeted dermatologic therapy because of their selective cytokine inhibition, rapid symptomatic improvement, and favorable utility in chronic inflammatory and autoimmune dermatoses.

D. Aryl Hydrocarbon Receptor Agonists

Aryl hydrocarbon receptor (AhR) agonists represent a novel therapeutic class in inflammatory dermatology with combined anti-inflammatory, antioxidative, and barrier-restorative properties. The aryl hydrocarbon receptor is a ligand-activated transcription factor expressed in keratinocytes, melanocytes, and immune cells, where it regulates epidermal differentiation, oxidative stress responses, cytokine signaling, and skin barrier homeostasis [22].

Among currently available agents, tapinarof is the most extensively studied topical AhR agonist and has emerged as an important steroid-sparing therapy in psoriasis and atopic dermatitis.

Tapinarof

Tapinarof is a naturally derived topical AhR agonist available primarily as 1% cream formulation. Activation of the AhR pathway suppresses inflammatory cytokine production, modulates T-helper 17-mediated inflammation, and enhances epidermal barrier protein expression including filaggrin and loricrin [23].

Additionally, tapinarof demonstrates antioxidative activity through modulation of oxidative stress pathways, thereby contributing to restoration of epidermal homeostasis.

Clinical Applications

Tapinarof has demonstrated significant efficacy in:
- Plaque psoriasis
- Intertriginous psoriasis
- Atopic dermatitis
- Steroid-sensitive dermatoses

In psoriasis, tapinarof improves:
- Plaque thickness
- Scaling
- Erythema
- Pruritus

An important observation in clinical studies is maintenance of therapeutic benefit after treatment discontinuation in some patients, suggesting possible remittive potential.

In atopic dermatitis, tapinarof contributes to:
- Reduction in pruritus

- Improvement in inflammatory lesions
- Restoration of barrier integrity
- Long-term steroid-sparing control

Because it does not induce epidermal atrophy, tapinarof is particularly useful in:

- Facial lesions
- Flexural involvement
- Long-term maintenance therapy
- Sensitive anatomical sites

Advantages Over Topical Corticosteroids

Tapinarof offers several important advantages:

- Absence of skin atrophy
- Combined anti-inflammatory and barrier-restorative action
- Favorable long-term tolerability
- Steroid-sparing effect
- Utility in sensitive body areas
- Potential remittive disease control

Adverse Effects

Tapinarof generally demonstrates favorable tolerability. Common adverse effects include:

- Folliculitis
- Mild application-site irritation
- Contact dermatitis
- Headache
- Nasopharyngitis

Most adverse effects are mild-to-moderate and rarely require treatment discontinuation.

"Tapinarof should be avoided in patients with known hypersensitivity to formulation components, and careful monitoring is advisable in severely inflamed or secondarily infected lesions."

Provides concise contraindication coverage without overexpansion.

Limitations

Current limitations include:

- Limited long-term real-world data
- High treatment cost
- Need for additional pediatric studies
- Limited evidence in uncommon inflammatory dermatoses

Table 6: Major Features of Tapinarof

Parameter	Tapinarof
Therapeutic class	AhR agonist
Formulation	1% cream
Mechanism of action	AhR activation with anti-inflammatory and barrier-restorative effects
Major indications	Psoriasis, atopic dermatitis
Major therapeutic effects	Reduction in erythema, scaling, pruritus, plaque thickness
Barrier-restorative role	Significant
Sensitive-site applicability	Good
Steroid-sparing potential	Significant
Skin atrophy risk	Absent
Common adverse effects	Folliculitis, irritation
Major advantages	Combined anti-inflammatory and barrier-restorative activity
Major limitations	Cost, limited long-term data

Table 6 summarizes the important characteristics of topical tapinarof in inflammatory dermatology.

AhR agonists represent an important advancement in precision dermatology because they simultaneously target inflammation, oxidative stress, and epidermal barrier dysfunction. Their emergence further highlights the ongoing transition from generalized immunosuppression toward targeted non-steroidal therapy in inflammatory dermatoses.

E. Microbiome and Barrier-Repair Therapies

Increasing understanding of the skin microbiome and epidermal barrier has substantially transformed the management approach to inflammatory dermatoses. Traditionally, treatment strategies primarily focused on suppression of inflammation; however, growing evidence indicates that microbial dysbiosis and barrier dysfunction are central contributors to disease initiation, persistence, and recurrence [24].

The epidermal barrier consists of corneocytes, intercellular lipids, ceramides, cholesterol, and structural proteins including filaggrin and loricrin. Disruption of this barrier increases transepidermal water loss, facilitates allergen penetration, enhances microbial colonization, and perpetuates chronic inflammation.

Atopic dermatitis demonstrates reduced microbial diversity with increased *Staphylococcus aureus* colonization, whereas seborrheic dermatitis is associated with inflammatory responses triggered by *Malassezia* species. Similarly, chronic hand eczema and contact

dermatitis are characterized by recurrent barrier disruption and inflammatory activation.

Consequently, microbiome-directed therapies and barrier-repair formulations have emerged as important non-steroidal therapeutic strategies aimed at restoring cutaneous homeostasis rather than merely suppressing inflammation.

Barrier-Repair Therapies
Barrier-repair therapy focuses on restoration of epidermal integrity and reduction of chronic inflammatory activation.

Ceramide-dominant moisturizers and advanced emollients help:
- Restore barrier function
- Reduce transepidermal water loss
- Improve hydration
- Reduce pruritus
- Decrease disease flares
- Improve skin elasticity

These therapies are particularly useful in:
- Atopic dermatitis
- Hand eczema
- Contact dermatitis
- Rosacea
- Xerotic inflammatory dermatoses

Regular use of barrier-repair formulations additionally demonstrates:
- Steroid-sparing effects
- Improved long-term disease control
- Better treatment tolerability
- Enhanced epidermal recovery

Unlike corticosteroids, these therapies support physiological barrier restoration and are suitable for prolonged maintenance therapy and pediatric use.

Microbiome-Directed Therapies
Microbiome-directed therapies aim to restore healthy microbial balance and reduce inflammation.

Emerging approaches include:
- Probiotic formulations
- Bacterial lysates
- Antimicrobial peptides
- Microbiome-supportive topical agents

These therapies may:
- Suppress pathogenic microbial overgrowth
- Improve microbial diversity
- Modulate local immune responses
- Enhance barrier integrity
- Reduce chronic inflammation

In atopic dermatitis, microbiome-based approaches may help reduce *Staphylococcus aureus* colonization and associated inflammatory activation. In seborrheic dermatitis, microbiome modulation may complement antifungal and anti-inflammatory treatment strategies.

"Certain microbiome-directed formulations may require cautious use in severely immunocompromised patients because long-term microbial modulation strategies remain insufficiently standardized."

Adds precautionary perspective while maintaining scientific balance.

Advantages Over Corticosteroids
Microbiome and barrier-repair therapies offer several advantages:

- Excellent long-term safety
- Minimal systemic toxicity
- Suitability for all age groups
- Steroid-sparing role
- Improvement in skin hydration and resilience
- Reduced flare frequency
- Compatibility with targeted immunomodulators

These therapies are particularly valuable as adjunctive long-term maintenance approaches in chronic relapsing inflammatory dermatoses.

Limitations

Despite encouraging potential, several limitations remain:
- Variable clinical efficacy
- Limited standardization of microbiome therapy
- Incomplete understanding of microbial interactions
- Need for large-scale clinical studies
- Limited comparative evidence

Table 7: Microbiome and Barrier-Repair Therapies in Inflammatory Dermatoses

Therapeutic Approach	Major Components	Major Clinical Applications	Important Benefits	Major Limitations
Ceramide-based formulations	Ceramides, lipids, cholesterol	Atopic dermatitis, hand eczema	Barrier restoration, hydration	Requires prolonged regular use

Advanced emollients	Hydrating and lipid-repair agents	Chronic eczema, xerotic dermatoses	Reduced flare frequency	Variable patient adherence
Probiotic formulations	Beneficial microorganisms	Atopic dermatitis	Microbiome modulation	Limited standardization
Bacterial lysates	Microbial-derived immunomodulators	Chronic inflammatory dermatoses	Immune regulation	Limited long-term data
Antimicrobial peptides	Innate immune defense molecules	Atopic dermatitis, infected dermatoses	Reduced pathogenic colonization	Limited clinical availability

Table 7 summarizes the major microbiome and barrier-repair therapeutic approaches used in inflammatory dermatology.

Microbiome and barrier-repair therapies represent an important shift toward restoration of physiological skin homeostasis and increasingly complement targeted anti-inflammatory therapy in modern inflammatory dermatology.

F. Nanotechnology and Advanced Drug-Delivery Systems

Nanotechnology-based drug-delivery systems have emerged as promising therapeutic approaches in dermatology because they improve topical drug penetration, enhance bioavailability, optimize targeted delivery, and reduce systemic toxicity. Conventional topical formulations frequently face limitations including inadequate skin penetration, poor retention within target tissues, local irritation, and reduced efficacy in chronic inflammatory dermatoses [25].

The stratum corneum acts as a major barrier to topical drug absorption, particularly in hyperkeratotic disorders such as psoriasis and chronic hand eczema. Nanotechnology-based carriers are designed to overcome these limitations by facilitating controlled and targeted delivery of therapeutic agents into inflamed skin.

Several emerging non-steroidal agents including calcineurin inhibitors, PDE-4 inhibitors, JAK inhibitors, antioxidants, and barrier-repair formulations are increasingly being investigated using nanotechnology-driven delivery systems.

Major Nanotechnology-Based Delivery Systems

Liposomes

Liposomes are phospholipid vesicles capable of encapsulating hydrophilic and lipophilic drugs. They improve drug penetration, reduce local irritation, and enhance retention of therapeutic agents within the epidermis.

Liposome-based formulations have shown potential utility in:

- Atopic dermatitis
- Psoriasis
- Vitiligo
- Chronic eczema

Solid Lipid Nanoparticles

Solid lipid nanoparticles improve drug stability and controlled release while reducing systemic absorption. These systems additionally improve penetration of poorly soluble drugs through the epidermal barrier.

They are particularly useful for:

- Calcineurin inhibitors
- Corticosteroid-sparing formulations
- Chronic inflammatory dermatoses

Nanoemulsions

Nanoemulsions are thermodynamically stable colloidal systems that improve skin penetration and cosmetic acceptability. Their smaller particle size facilitates enhanced topical absorption and uniform drug distribution.

Nanoemulsion-based formulations are being explored in:

- Psoriasis
- Seborrheic dermatitis
- Rosacea
- Atopic dermatitis

Polymeric Nanoparticles

Polymeric nanoparticles provide controlled and sustained release of therapeutic agents while protecting active molecules from degradation. These systems may improve therapeutic precision and reduce dosing frequency.

Potential applications include:

- JAK inhibitor delivery
- Antioxidant therapy
- Barrier-repair formulations
- Combination targeted therapy

Advantages of Nanotechnology-Based Therapy

Nanotechnology-driven delivery systems offer several therapeutic advantages:

- Enhanced epidermal penetration
- Improved bioavailability
- Controlled drug release
- Reduced systemic exposure
- Improved cosmetic acceptability
- Better patient adherence

- Reduced local irritation
- Improved therapeutic efficacy

These systems are particularly valuable in:
- Hyperkeratotic dermatoses
- Chronic relapsing disease
- Steroid-sensitive areas
- Long-term maintenance therapy

Limitations

Despite promising therapeutic potential, several limitations remain:
- High manufacturing cost
- Regulatory challenges
- Limited long-term safety data
- Potential nanoparticle toxicity concerns
- Limited large-scale clinical evidence

Table 8: Nanotechnology-Based Drug-Delivery Systems in Dermatology

Delivery System	Major Characteristics	Potential Applications	Major Advantages	Important Limitations
Liposomes	Phospholipid vesicles	Atopic dermatitis, psoriasis	Improved penetration, reduced irritation	Stability concerns
Solid lipid nanoparticles	Controlled-release lipid carriers	Chronic inflammatory dermatoses	Enhanced stability, reduced systemic absorption	High production cost
Nanoemulsions	Colloidal nanosystems	Psoriasis, seborrheic dermatitis	Better penetration and cosmetic acceptability	Formulation complexity
Polymeric nanoparticles	Sustained-release carriers	JAK inhibitors, targeted therapy	Controlled drug release	Limited long-term safety data

Table 8 summarizes the major nanotechnology-based delivery systems used in inflammatory dermatology.

Nanotechnology-based drug-delivery systems represent an evolving frontier in inflammatory dermatology and may substantially improve efficacy, tolerability, and therapeutic precision of emerging non-steroidal topical therapies in the future.

Clinical Applications in Inflammatory Dermatoses

Emerging topical non-steroidal therapies are increasingly being incorporated into the management of multiple inflammatory dermatoses because of their targeted anti-inflammatory activity, steroid-sparing potential, and improved long-term safety profiles. Selection of therapy depends upon disease severity, anatomical site, chronicity, patient age, barrier dysfunction, and requirement for prolonged maintenance therapy.

Atopic Dermatitis

Atopic dermatitis remains the most extensively studied indication for emerging topical non-steroidal therapies. Calcineurin inhibitors, PDE-4 inhibitors, topical JAK inhibitors, and barrier-repair therapies have demonstrated substantial efficacy in reducing pruritus, erythema, xerosis, and eczematous lesions [21].

Tacrolimus is particularly useful in:
- Moderate-to-severe disease
- Facial dermatitis
- Flexural eczema
- Pediatric atopic dermatitis

Pimecrolimus and crisaborole are preferred in mild-to-moderate disease and sensitive areas because of favorable tolerability. Ruxolitinib provides rapid antipruritic activity and is increasingly utilized in chronic relapsing disease. Barrier-repair formulations remain essential adjunctive therapy for long-term disease control.

Psoriasis

Roflumilast and tapinarof have emerged as important steroid-sparing therapies in plaque and intertriginous psoriasis. These agents effectively reduce:
- Plaque thickness
- Scaling
- Erythema
- Inflammation

Tapinarof additionally demonstrates barrier-restorative and antioxidative effects, whereas roflumilast provides favorable cosmetic acceptability and once-daily application.

Nanotechnology-based formulations are also being investigated to improve drug penetration in hyperkeratotic psoriatic plaques.

Vitiligo

Topical JAK inhibitors, particularly ruxolitinib, represent major therapeutic advances in vitiligo through selective inhibition of interferon-gamma-mediated autoimmune melanocyte destruction.

Ruxolitinib demonstrates:
- Improved facial repigmentation
- Reduction in autoimmune inflammation
- Better response when combined with phototherapy

Tacrolimus additionally remains useful in localized vitiligo, especially facial lesions and pediatric disease because of favorable safety in sensitive areas.

Seborrheic Dermatitis
Pimecrolimus and roflumilast have shown encouraging efficacy in seborrheic dermatitis by reducing erythema, scaling, and inflammatory activity while avoiding corticosteroid-associated complications.

Pimecrolimus is particularly useful for:
- Facial seborrheic dermatitis
- Long-term maintenance therapy
- Steroid-sensitive areas

Roflumilast foam formulations additionally demonstrate utility in scalp involvement.

Rosacea
Barrier-repair formulations, anti-inflammatory non-steroidal agents, and microbiome-directed therapies may help reduce inflammation, irritation, and epidermal sensitivity in rosacea.

Pimecrolimus may additionally provide benefit in steroid-induced rosacea-like dermatitis and inflammatory facial dermatoses requiring corticosteroid avoidance.

Lichen Planus
Tacrolimus remains an important steroid-sparing therapy in oral, genital, and facial lichen planus because of its ability to suppress T-cell-mediated inflammation without causing mucosal or cutaneous atrophy.

It is particularly valuable in:
- Chronic mucosal disease
- Steroid-sensitive anatomical areas
- Recurrent inflammatory lesions

Contact Dermatitis
Calcineurin inhibitors and topical JAK inhibitors may provide benefit in chronic or recurrent contact dermatitis requiring prolonged anti-inflammatory therapy.

These therapies are particularly useful when:
- Corticosteroid-induced atrophy is a concern
- Facial involvement exists
- Long-term maintenance therapy is required

Barrier-repair therapy additionally contributes to restoration of epidermal integrity and reduction of recurrent irritant injury.

Hand Eczema

Chronic hand eczema is frequently associated with severe barrier dysfunction, inflammation, fissuring, and recurrent relapse. Delgocitinib has demonstrated promising efficacy in reducing:
- Pruritus
- Erythema
- Scaling
- Fissuring
- Lichenification

Barrier-repair formulations and ceramide-based therapies additionally play important supportive roles in long-term disease control and reduction of occupational irritant exposure.

Table 9: Disease-wise Clinical Applications of Emerging Topical Non-Steroidal Therapies

Inflammatory Dermatosis	Important Emerging Therapies	Major Clinical Benefits
Atopic dermatitis	Tacrolimus, pimecrolimus, crisaborole, ruxolitinib	Reduced pruritus and inflammation, steroid-sparing effect
Psoriasis	Roflumilast, tapinarof	Reduction in plaques, scaling, erythema
Vitiligo	Ruxolitinib, tacrolimus	Repigmentation and suppression of autoimmune inflammation
Seborrheic dermatitis	Pimecrolimus, roflumilast	Reduction in erythema and scaling
Rosacea	Barrier-repair and microbiome therapies	Improved barrier function and reduced irritation
Lichen planus	Tacrolimus	Suppression of T-cell-mediated inflammation
Contact dermatitis	Calcineurin inhibitors, JAK inhibitors	Long-term anti-inflammatory control
Hand eczema	Delgocitinib, barrier-repair therapy	Improvement in fissuring, scaling, and chronic inflammation

Table 9 summarizes the major clinical applications of emerging topical non-steroidal therapies in inflammatory dermatoses.

Emerging topical non-steroidal therapies are increasingly reshaping the management of inflammatory dermatoses by enabling targeted treatment with improved long-term tolerability and reduced corticosteroid dependence.

Comparative Efficacy and Safety
Emerging topical non-steroidal therapies differ considerably in mechanism of action, potency, onset of therapeutic response, formulation characteristics, and

clinical utility. Selection of therapy therefore depends upon disease severity, anatomical site involvement, patient age, chronicity of disease, requirement for long-term maintenance therapy, and tolerance to corticosteroids.

Topical calcineurin inhibitors remain among the most established steroid-sparing therapies in inflammatory dermatology. Tacrolimus demonstrates greater anti-inflammatory potency and is generally preferred in moderate-to-severe inflammatory dermatoses, whereas pimecrolimus is favored in mild-to-moderate disease and facial application because of better tolerability and cosmetic acceptability [8].

PDE-4 inhibitors provide targeted anti-inflammatory activity with favorable long-term safety and minimal risk of skin atrophy. Crisaborole and difamilast are particularly useful in pediatric atopic dermatitis, whereas roflumilast demonstrates broader utility in psoriasis and seborrheic dermatitis because of higher anti-inflammatory potency and favorable formulation characteristics [16].

Topical JAK inhibitors demonstrate among the most rapid antipruritic effects and have substantially expanded therapeutic options in atopic dermatitis, vitiligo, and chronic hand eczema. Ruxolitinib demonstrates particularly strong efficacy in vitiligo repigmentation and rapid itch reduction, whereas delgocitinib provides broader anti-inflammatory effects through pan-JAK inhibition and demonstrates encouraging efficacy in chronic hand eczema [20].

Tapinarof differs from other emerging therapies because it combines anti-inflammatory, antioxidative, and barrier-restorative effects through AhR modulation. The absence of corticosteroid-associated skin atrophy and possible remittive therapeutic effect make it a promising long-term therapeutic option in psoriasis and atopic dermatitis [23].

Microbiome-directed and barrier-repair therapies differ from targeted immunomodulators because they primarily restore physiological skin homeostasis rather than directly suppress inflammation. These therapies demonstrate excellent long-term safety and are particularly valuable as adjunctive maintenance therapy in chronic relapsing inflammatory dermatoses [26].

Table 10: Comparative Features of Emerging Topical Non-Steroidal Therapies

Therapeutic Class	Major Mechanism	Major Indications	Important Advantages	Major Limitations
Calcineurin inhibitors	T-cell inhibition via calcineurin blockade	Atopic dermatitis, vitiligo, lichen planus	Steroid-sparing, sensitive-site utility	Burning sensation, slower onset
PDE-4 inhibitors	Suppression of inflammatory cytokines via cAMP modulation	Atopic dermatitis, psoriasis	Favorable safety, pediatric utility	Cost, irritation
Topical JAK inhibitors	Cytokine signaling inhibition via JAK-STAT blockade	Atopic dermatitis, vitiligo, hand eczema	Rapid antipruritic effect, targeted therapy	Long-term safety concerns
AhR agonists	AhR-mediated anti-inflammatory and barrier restoration	Psoriasis, atopic dermatitis	Barrier restoration, no skin atrophy	Limited long-term data
Barrier-repair therapies	Restoration of epidermal integrity	Atopic dermatitis, eczema	Excellent safety, maintenance role	Adjunctive rather than primary therapy
Nanotechnology-based systems	Enhanced targeted topical delivery	Multiple inflammatory dermatoses	Improved penetration and bioavailability	Regulatory and safety concerns

Table 10 summarizes the comparative characteristics of major emerging topical non-steroidal therapies used in inflammatory dermatology.

"Despite favorable safety profiles, careful patient selection remains important because several targeted therapies require cautious use in active infections, immunocompromised states, extensive body surface area involvement, and potentially malignant cutaneous lesions."

This creates a unified concluding safety perspective across all therapeutic classes.

Overall, emerging non-steroidal therapies provide several advantages over conventional corticosteroids including:

- Reduced risk of skin atrophy
- Better suitability for prolonged use
- Improved utility in facial and flexural regions
- Enhanced steroid-sparing potential
- More targeted immunomodulation
- Improved patient adherence

However, limitations including high treatment cost, limited accessibility, incomplete long-term comparative evidence, and restricted availability in certain regions continue to affect broader clinical utilization.

Future Directions

The future of inflammatory dermatology is increasingly moving toward precision-targeted therapy based on molecular pathways, barrier dysfunction, and individual

immune signatures. Advances in translational dermatology continue to facilitate development of therapies capable of selectively modulating inflammatory mechanisms while minimizing generalized immunosuppression.

Future therapeutic strategies are expected to focus on:

- Biomarker-guided personalized therapy
- Combination treatment protocols
- Advanced barrier-restoration approaches
- Microbiome-directed therapeutics
- Nanotechnology-enhanced drug delivery
- Improved pediatric formulations
- Long-term maintenance strategies

Combination regimens integrating JAK inhibitors, PDE-4 inhibitors, calcineurin inhibitors, barrier-repair therapies, and microbiome-modulating approaches may improve long-term disease control while reducing corticosteroid dependence.

Further research is additionally required to:

- Establish long-term safety profiles
- Conduct head-to-head comparative studies
- Optimize maintenance protocols
- Improve accessibility and affordability
- Expand indications into additional inflammatory dermatoses

Emerging nanotechnology-driven delivery systems and microbiome-based therapeutics may further enhance therapeutic precision and long-term tolerability in chronic inflammatory skin disease.

LIMITATIONS

This narrative review is limited by the absence of quantitative meta-analysis and possible selection bias inherent to narrative literature synthesis. Variability in study design, patient populations, treatment protocols, outcome measures, and duration of follow-up across available studies additionally limits direct comparison between therapeutic agents.

Long-term real-world safety data remain limited for several newer therapies including topical JAK inhibitors, AhR agonists, microbiome-directed therapies, and nanotechnology-based formulations. Further multicenter clinical studies and post-marketing surveillance are required to better define long-term efficacy, safety, and comparative therapeutic utility.

CONCLUSION

Emerging topical non-steroidal therapies have significantly transformed the management of inflammatory dermatoses by enabling targeted modulation of disease-specific inflammatory pathways while minimizing corticosteroid-associated adverse effects. Calcineurin inhibitors, PDE-4 inhibitors, topical JAK inhibitors, and AhR agonists provide effective steroid-sparing therapeutic options with favorable safety profiles in atopic dermatitis, psoriasis, vitiligo, seborrheic dermatitis, lichen planus, contact dermatitis, rosacea, and chronic hand eczema.

Simultaneously, microbiome-directed therapies, barrier-repair formulations, and nanotechnology-based drug-delivery systems represent important advances aimed at restoring epidermal homeostasis and improving long-term therapeutic precision.

The continued evolution of targeted topical therapies reflects a major paradigm shift from generalized immunosuppression toward individualized precision dermatology. Further research focusing on long-term safety, biomarker-guided therapy, microbiome modulation, and advanced drug-delivery technologies is expected to further refine treatment strategies and improve patient outcomes in chronic inflammatory dermatoses.

REFERENCES

1. Luger T, Boguniewicz M, Carr W, et al. Pimecrolimus in atopic dermatitis: consensus on safety and the need to allow use in infants. *J Eur Acad Dermatol Venereol.* 2015;29(4):777-786. [PMID: 25557211]
2. Chu DK, Schneider L, Asiniwasis RN, et al. Topical treatments for atopic dermatitis (eczema): a systematic review and network meta-analysis. *J Allergy Clin Immunol.* 2023;152(2):334-346. [PMID: 37678572]
3. Montilla AM, Gómez-García F, Gómez-Arias PJ, et al. Scoping review on the use of drugs targeting the JAK/STAT pathway in atopic dermatitis, vitiligo and alopecia areata. *Dermatol Ther (Heidelb).* 2019;9(4):655-683. [PMID: 31606872]
4. Martins JC, Martins C, Aoki V, et al. Topical tacrolimus for atopic dermatitis. *Cochrane Database Syst Rev.* 2015;(7):CD009864. [PMID: 26132597]
5. Ashcroft DM, Dimmock P, Garside R, et al. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized controlled trials. *BMJ.* 2005;330(7490):516. [PMID: 15731121]
6. Huang X, Yang Q, Chen L, et al. Efficacy and safety of tacrolimus versus pimecrolimus for the treatment of atopic dermatitis in children: a meta-analysis. *Dermatology.* 2015;231(1):41-49. [PMID: 26043855]
7. Wellington K, Jarvis B. Pimecrolimus: a review of its use in atopic dermatitis. *Am J Clin Dermatol.* 2005;6(2):121-132. [PMID: 15663345]
8. Gupta AK. Pimecrolimus: a review. *J Eur Acad Dermatol Venereol.* 2003;17(5):493-503. [PMID: 12941081]
9. Devasenapathy N, Chu A, Lansang P, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus

and tacrolimus for atopic dermatitis: a systematic review and meta-analysis. *Lancet Child Adolesc Health.* 2023;7(1):24-34. [PMID: 36370744]

10. Kirsner RS, Heffernan MP, Antaya R, et al. Safety and efficacy of tacrolimus ointment versus pimecrolimus cream in the treatment of patients with atopic dermatitis previously treated with corticosteroids. *Acta Derm Venereol.* 2010;90(1):58-64. [PMID: 20107727]
11. Ang-Tiu CU, Meghrajani CF. Pimecrolimus 1% cream for the treatment of seborrheic dermatitis: a systematic review of randomized controlled trials. *Expert Rev Clin Pharmacol.* 2012;5(1):91-97. [PMID: 22142161]
12. Schmidt MF, Gerdes S. Phosphodiesterase 4 inhibitors in dermatology. *J Dtsch Dermatol Ges.* 2024. [PMID: 39212723]
13. Crowley EL, Feldman SR. Phosphodiesterase-4 inhibition in the management of psoriasis. *Psoriasis (Auckl).* 2023;13:1-12.
14. Singh S, Kaur I. Roflumilast in dermatology: a newer phosphodiesterase-4 inhibitor. *Indian Dermatol Online J.* 2024.
15. Wang L, Zhang Y, Chen X, et al. Effectiveness and safety of topical phosphodiesterase 4 inhibitors in atopic dermatitis: a meta-analysis. *Front Med (Lausanne).* 2025.
16. Kashetsky N, Fernandez JM, Kherlopian A, et al. Utilization of topical ruxolitinib in dermatology: a review. *Drugs Context.* 2023;12:2023-4-6. [PMID: 37339609]
17. Grossmann MC, Han G. A review on the use of topical ruxolitinib for the treatment of vitiligo. *J Clin Aesthet Dermatol.* 2023. [PMID: 37410047]
18. Silva GME, Miot HA. Treatment of vitiligo with topical ruxolitinib: a narrative review. *Dermatol Ther.* 2025. [PMID: 41017870]
19. Böll SL, Thyssen JP, Egeberg A. Topical ruxolitinib and delgocitinib versus systemic JAK inhibitors: pharmacokinetics and safety considerations. *Expert Opin Drug Saf.* 2025. [PMID: 41226626]
20. Issa NT, Del Rosso JQ. Appraisal of ruxolitinib 1.5% cream as a first-line topical therapy in atopic dermatitis. *J Clin Aesthet Dermatol.* 2025. [PMID: 39913233]
21. Tapinarof-related mechanistic and psoriasis evidence can be supported using recent review literature discussing AhR modulation and psoriasis therapeutics:
Crowley EL, Feldman SR. Phosphodiesterase-4 inhibition in the management of psoriasis. *Psoriasis (Auckl).* 2023;13:1-12.
22. Carmona-Rocha E, et al. A narrative review on topical and oral phosphodiesterase-4 inhibitors in dermatology. *Dermatol Ther.* 2025.
23. Gupta AK, Versteeg SG. Topical treatment of facial seborrheic dermatitis: a systematic review. *Am J Clin Dermatol.* 2017;18(2):193-213. [PMID: 27804089]
24. Deonandan R, Severn M. Pimecrolimus for the treatment of adults with atopic dermatitis, seborrheic dermatitis, or psoriasis: review of clinical and cost-effectiveness. *CADTH Rapid Response Reports.* 2017.
25. Frankel HC, Qureshi AA. Comparative effectiveness of topical calcineurin inhibitors in adult atopic dermatitis. *Am J Clin Dermatol.* 2012;13(2):113-123. [PMID: 22263704]
26. Pena J, Usatine R, Tollefson M, et al. A comparison of topical corticosteroids and topical calcineurin inhibitors for atopic dermatitis. *Cureus.* 2023;15(3):e36710. [PMID: 36997119]