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Nanoemulsion-Mediated Dermal Delivery of Herbal Anti-Inflammatory Agents: A comprehensive review on Mechanistic Insights and Clinical Relevance

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KEYWORDS

Inflammatory skin diseases; Herbal nanoemulsion; Topical drug delivery; Acalypha indica; Anti-inflammatory activity..

ABSTRACT:

Introduction: Multiple internal and external variables interact to cause skin illnesses that are marked by inflammatory responses. Psoriasis, contact dermatitis, acne vulgaris, and atopic dermatitis are common inflammatory skin conditions. These disorders are mostly linked to dysregulation of the immune system, oxidative stress brought on by environmental stressors, and compromised epidermal barrier function. Because of its anti-inflammatory, antioxidant, and antibacterial qualities, herbal products have drawn a lot of interest in dermatological therapy. However, low bioavailability and inadequate stratum corneum penetration frequently restrict the clinical use of herbal medications, decreasing their therapeutic efficacy.

Objectives: This review aims to assess the potential of herbal nanoemulsion-based delivery systems as innovative topical treatment methods and to examine the pathophysiology of common inflammatory skin conditions. Acalypha indica, a medicinal plant with anti-inflammatory and wound-healing qualities that has long been utilized in herbal therapy, is given special attention.

Methods: To examine previously published research on herbal nanoemulsion formulations, inflammatory skin disease processes, and the pharmacological characteristics of Acalypha indica, a literature-based review methodology was used. The role of polyphenols, flavonoids, and nanoemulsion-based topical administration methods in improving medication distribution and therapeutic efficacy was investigated.

Results: Recent pre-clinical research indicates that the solubilization, stability, and skin penetration of herbal bioactive substances are greatly improved by oil-in-water herbal nanoemulsions. Acalypha indica extracts, which are high in polyphenols and flavonoids, have been shown to have significant anti-inflammatory and wound-healing properties in nanoemulsion formulations. Compared to standard formulations, these formulations reduce pro-inflammatory cytokine levels by improving dermal absorption and modulating inflammatory signaling pathways, including NF-κB pathways.

Conclusion: A promising approach to enhancing the therapeutic potential of herbal medications in dermatology is the use of herbal nanoemulsion-based delivery systems. Even though recent research shows improved skin penetration and anti-inflammatory effects, there are still a number of translational issues. To determine the safety and effectiveness of herbal nanoemulsions for the treatment of inflammatory skin conditions, future studies should concentrate on formulation standardization, long-term stability, pharmacokinetic assessment, and clinical validation.

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1. Introduction

Herbal medicines are receiving increasing attention in modern therapeutics, particularly in the field of dermatology. In recent years, several advanced technologies have been explored to improve the delivery and effectiveness of herbal drugs. Among the various routes of administration, dermal application of herbal extracts has gained its attention in pharmacology because of its eco-friendly nature and minimal side effects. Herbal medicines are widely available and are known to be effective in treating skin disorders according to recent studies because they contain bioactive phytochemicals such as flavonoids, terpenoids, alkaloids and saponins. These compounds exhibit anti-inflammatory, antibacterial, antifungal and moisturizing properties, which contribute to skin soothing and healing (Aswan, P. A., *et al., 2025).* Compared with synthetic ointments, herbal formulations are generally considered eco-friendly, less cytotoxic, making them suitable for long-term topical use (Schafer, N., *et al* 2023). However, despite their high therapeutic potential, the dermal bioavailability of herbal drugs remains low. This limitation is mainly due to the stratum corneum, the outermost layer of the skin, which acts as a strong barrier and restricts the penetration of many phytoconstituents. As a result, conventional topical formulations often fail to deliver adequate amounts of the active compounds to the target site (Xin, Y., *et al* 2021). There are several plants which has been researched to have skin soothing properties for wound healing and anti-inflammation, this study specifically focuses on *Acalypha indica* which belongs to the family Euphorbiaceae, consists of several phytoconstituents in its leaves and roots that exhibit anti-inflammatory, antimicrobial, anti-diuretic, wound healing properties which had been used in ayurveda and siddha medicine (Senthilkumar and Kiruba Rani 2024). The major limitation of current herbal dermal therapies therefore lies not in the efficacy of the drug itself, but in the formulation strategies employed. Recent advances in nanotechnology-based delivery systems have shown promising results in improving skin penetration, protecting unstable herbal actives and enhancing therapeutic outcomes (Aswan, P. A., *et al., 2025,* Chen, R.-P., *et al* 2022 *and* Najafi, F., *et al*., 2025). This review focuses on pathophysiology of common skin inflammatory conditions such as atopic dermatitis, psoriasis, acne vulgaris, contact dermatitis, need for herbal based solution, the challenges associated with dermal delivery systems of herbal medicines, emphasizing skin-barrier limitations, and discussing advanced nanoemulsion based formulation approaches that can improve their bioavailability and clinical performance (Marques, M. P., *et al* 2023 and Gugleva, V., *et al* 2021).

2. Common skin inflammatory conditions

Skin inflammation is one of the pathological mechanisms which occurs due to wide spectrum of dermatological conditions, which includes common dermatological conditions like atopic dermatitis, psoriasis, acne vulgaris, contact dermatitis and more. As highlighted by (Tampa *et al.,* 2022), skin inflammatory cascades are initiated when the cutaneous barrier and immune response system are disrupted by external or internal stimuli. The growing prevalence of skin inflammation in recent years are closely associated with modern lifestyle and environmental changes. Increased exposure to pollution, excessive usage of cosmetics, diet practices, stress, climate factors, and skin microbiome has significantly affected skin barrier integrity, and immune-mediated hypersensitivity reactions disrupting skin inflammation as a growing dermatological concern.

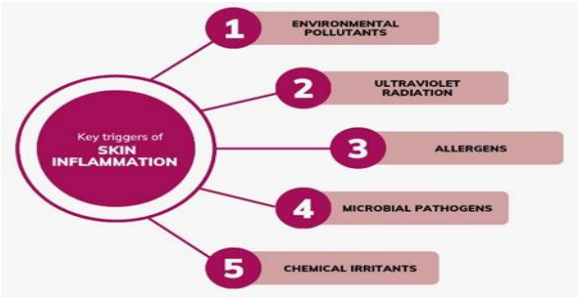

Figure 1 Key triggers of skin inflammation

Key trigger factors in Figure 1 trigger the keratinocytes, Langerhans cells, and resident immune cells activating inflammatory pathways, especially nuclear factor-kB (NF-kB) and mitogen-activated protein kinases (MAPKs). This activation leads to abundant release of pro-inflammatory cytokines which includes TNF-alpha, IL-1beta, IL-6, IL-17, chemokines, and reactive oxygen species, resulting in chronic inflammation and tissue damage (Tampa *et al.,* 2022).

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2.1. Pathophysiology of Atopic dermatitis

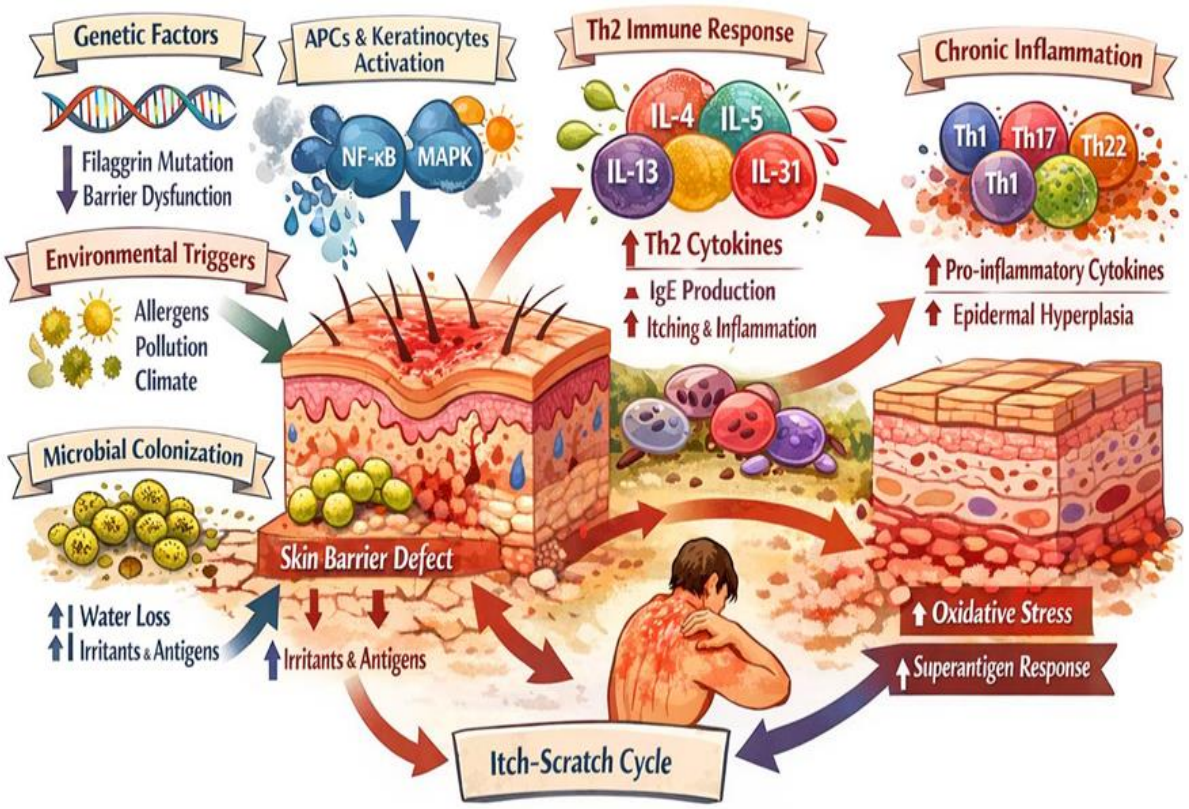

Figure 2 Pathophysiology of Atopic dermititis

Atopic dermatitis is a chronic inflammatory skin condition resulted from epidermal barrier dysfunction, immune dysregulations, genetic susceptibility, and external environmental factors which leads to impairment of the skin barrier. This is due to the reduced expression or mutation of structural proteins such as filaggrin which results in increased water loss and enhanced susceptibility to allergens, irritants, and microbial antigens. This barrier defect represents an initiating event in AD pathogenesis. (Lyons *et al.,* 2015). Immune dysregulation involves dominance of T helper 2 (Th2) response, particularly in the acute phase of the disease. Activation of antigen-presenting cells and keratinocytes triggers downstream signalling pathways, including NF-κB and MAPKs, resulting in excess production of Th2-associated cytokines such as IL-4, IL-5, IL-13, and IL-31 as represented in figure 2. These cytokines suppress epidermal differentiation, induce leakage of the barrier, and promote IgE class switching, and contribute itching and inflammation. In stages, a mixed Th1/Th17/Th22 cytokine response takes place, sustaining inflammation and epidermal hyperplasia (Kim J *et al.,* 2019). Oxidative stress and microbial colonization, particularly by *Staphylococcus aureus*, further amplify inflammatory signalling through superantigen-mediated T-cell activation and enhanced cytokine release. According to (Dhar and Banerjee 2010) environmental allergens, climate, recurrent infections, and early-life immune immaturity significantly modulate disease severity and persistence in pediatric and Indian population. The ongoing interaction between cytokine-driven immune responses and barrier dysfunction establishes a self-perpetuating inflammatory cycle central to atopic dermatitis.

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2.2. Pathophysiology of Psoriasis

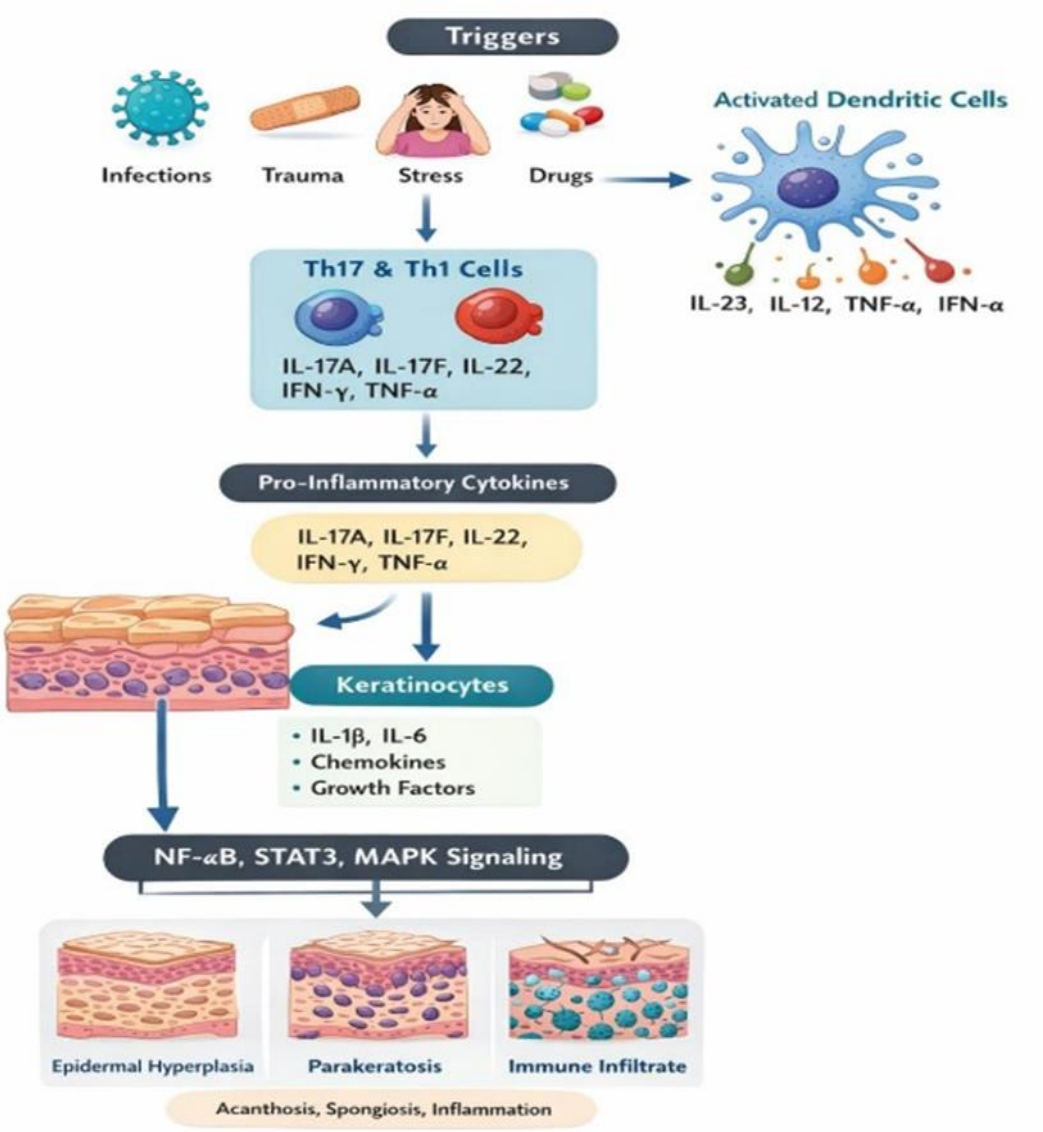

Figure 3 Immunopathogenesis of Psoriasis

Psoriasis is an immunologically mediated, hyper-proliferative disease of the skin, associated with exaggerated keratinization, immunologically altered epidermal cell turnover, and inflammation of the skin. As shown in the figure 3 the immune system is activated in the skin due to various factors like infections, trauma, psychological stress, and certain medications. The triggering of the immune response in the skin sets off the cascade of events leading to psoriasis. At the molecular level, psoriasis is mainly mediated through the IL-23/Th17 axis. Upon activation, dendritic cells secrete factors such as IL-23, IL-12, TNF-α, and interferon-α, all of which stimulate Th1 and Th17 lymphocyte differentiation and expansion. The immune cells release pro-inflammatory cytokines such as IL-17A, IL-17F, IL-22, IFN-γ, and TNF-α, which target keratinocytes and cause their hyperplasia, incomplete differentiation, and overproduction of antimicrobial peptides and chemokines, respectively. Keratinocytes also contribute to the promotion of the inflammatory response through

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the production of IL-1β, IL-6, chemokines, and growth factors. The activation of intracellular signalling pathways, especially NF-κB, STAT-3, and MAPK, is also sustained and contributes to the constant production of cytokines and the thickening of the epidermis (Rahman *et al*., 2022 and Raharja *et al*., 2021).

2.3. Pathophysiology of Acne vulgaris

Acne vulgaris is an inflammatory disease of the pilosebaceous unit, with four key pathogenic processes: sebaceous hypersecretion, follicular hyperkeratinisation, microbial colonization, and inflammation. There is an increased androgen activity that acts upon the stimulus for sebaceous glands, leading to the overproduction of sebum. The focal points of altered keratinocyte differentiation within the follicular infundibulum establish the development of hyperkeratinisation and comedones, thus offering a suitable microenvironment for microbial proliferation (Suva *et al*., 2023). This shifts the follicular ecosystem to a predominance of Propionibacterium acnes Cuti bacterium acnes, which metabolizes sebum triglycerides into pro-inflammatory free fatty acids, stimulates TLRs on keratinocytes and immune cells, and activates downstream signalling cascades including NF-κB and MAPKs that result in the induction of pro-inflammatory cytokines IL-1β, IL-8, TNF-α, and chemokines, which attract neutrophils and other leukocytes into the lesion. This inflammation follows a sequence in the development of papules, pustules, nodules, and cysts through the induction of oxidative stress, activation of various immune cells, and matrix-degrading enzymes as represented in the figure 4. Collectively, sebum excess, follicular occlusion, microbial factors, and cytokine-mediated inflammation establish a self-amplifying cycle central to acne pathogenesis (Suva *et al*., 2023 and Vasam *et al*., 2023).

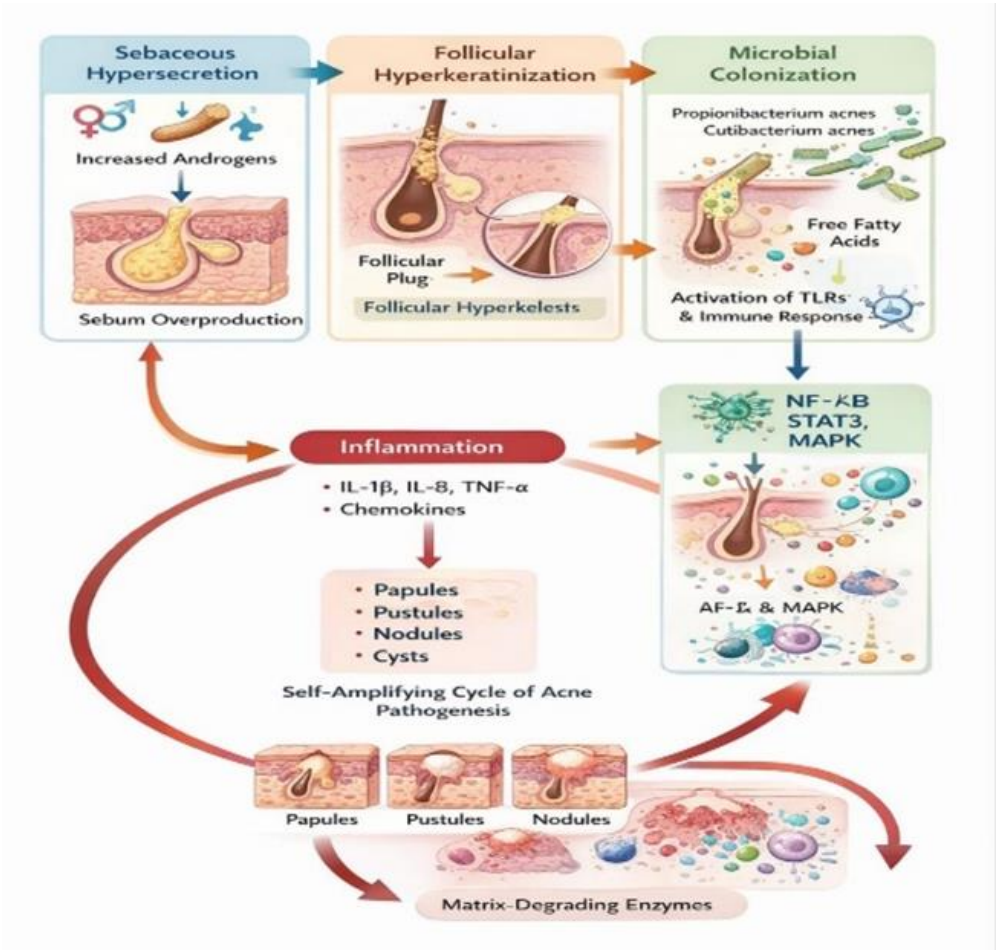

Figure 4 Pathogenesis of Acne vulgaris

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2.4. Pathophysiology of Contact dermatitis

There are two types of contact dermatitis: allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). Both forms of contact dermatitis cause inflammation on the skin, but they have different immunological pathways. ACD is an example of a delayed type IV hypersensitivity reaction that occurs when haptens (low molecular weight chemicals) are absorbed by the skin, enter the skin barrier and combine with endogenous proteins to make a complex that stimulates an immunogenic response. Once these haptens form complexes in the skin, they are taken up by Langerhans cells or dermal dendritic cells, which then travel to regional lymph nodes where they activate T lymphocytes. This produces a hapten-specific CD4+ or CD8+ T-cell effector and memory response. When an individual is re-exposed to the same allergen, these sensitized T-cells quickly enter the skin and release inflammatory cytokines and chemokines such as IL-17, IFN-γ, TNF-α, which activate the keratinocytes and cause keratinocyte activation, spongiosis, erythema, swelling and vesiculation. The peak inflammatory response is typically seen 48–72 hours after allergen exposure, which is consistent with the delayed immunological response in ACD (Johansen *et al*., 2022).

On the contrary, the development of irritant contact dermatitis is due to the direct cytotoxic effects of irritants (either physical or chemical) on the keratinocytes. The irritants cause the keratinocytes to release inflammatory mediators (alarmins) and other initial inflammatory mediators, and do not require prior immune sensitization. Repeated exposure to irritants can induce a chronic low-grade inflammatory state and disruption of the epidermal barrier. Together, irritant and allergic contact dermatitis are two forms of dermatitis, but ACD is distinguished by antigen specific T-cell memory and cytokine driven adaptive immunity (Kimber *et a*l., 2002) and Brar *et al*., 2021).

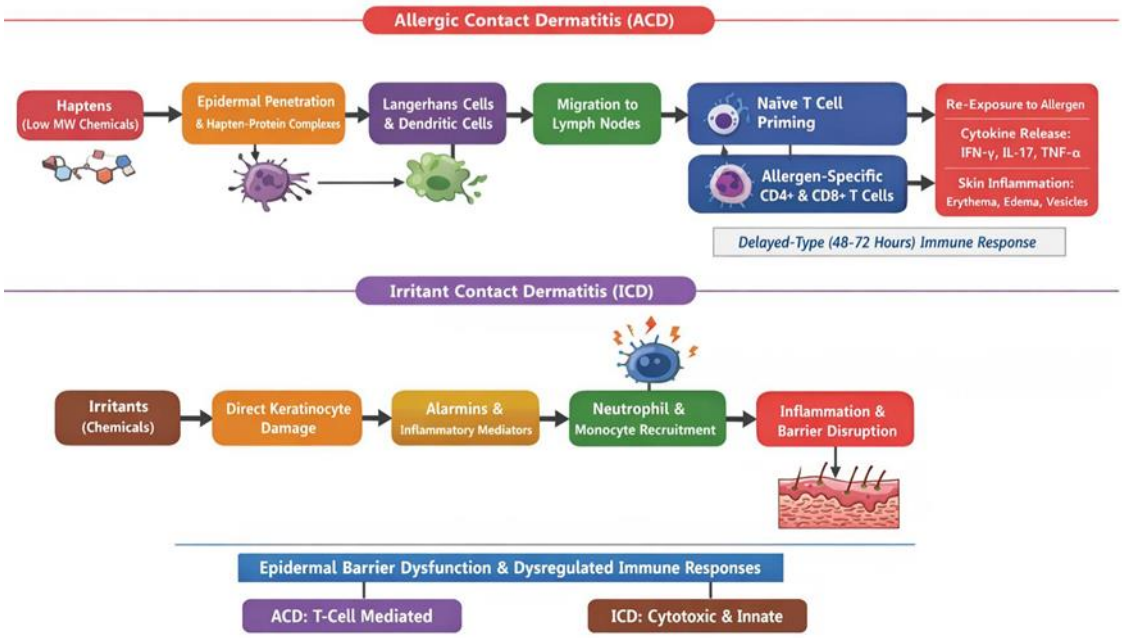

Figure 5 Flow chart representation of pathophysiology of ACD and ICD

3. Why Herbal medicine preferred for skin inflammation?

Millions of people are suffering from skin conditions such as atopic dermatitis, psoriasis, allergies which are often treated with conventional corticosteroid which is frequently complicated by irritation, skin atrophy, or systemic symptoms (Iraji *et al*., 2024). Topical herbal remedies have been found to have anti-inflammatory, barrier-supporting, moisturizing and antimicrobial properties and are commonly perceived as being natural,

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as it improving patient compliance (Janeczek *et al*., 2018). Clinical trials have demonstrated significant lower SCORAD values for multi-herb cream combinations (*Calendula officinalis, Glycyrrhiza glabra, Curcuma longa, Fumaria parviflora*) in comparison to mometasone cream after 8 weeks and 16 weeks of treatment, thus proving equal effectiveness with reduced risks for steroid-induced side effects (Iraji *et al*., 2024). Comparable success has been demonstrated by oil in water emulsions with active components being ginger extracts and cannabidiol (BNO 3731/3732) in reducing itch, redness, and dry skin for up to 12 weeks (Herrmann *et al*., 2025). Tea tree oil (a plant-derived essential oil) significantly reduced allergic contact dermatitis by about 40.5% in experimental models ($p = 0.003$) compared to zinc oxide and clobetasone butyrate in reducing some aspects of dermatitis (Wallengren *et al.,* 2011). The studies by (Nazri *et al.,* 2015) reviews several ayurvedic herbal formulations that are clinically proven to manage skin conditions like acne vulgaris, significantly reducing inflammatory lesions, and comedones. These studies provide evidential proof that herbal formulations can be an effective solution for the negative dermal conditions with proper standardizations. This supports the use of herbal formulations as safe alternative to conventional treatments, particularly for patients who experience irritation, antibiotic resistance, or poor tolerance with standard topical or systemic drugs.

4. Phytoconstituents *Acalypha indica* in skin inflammation

A.indica is an annual herb which is abundantly available in locals of India, Sri Lanka, Southeast Asia and parts of Africa. Leaves and roots of *A.indica* are employed as a traditional medicine for any skin related diseases over decades in ayurveda and siddha. As advanced analytical technologies have developed over years for phytochemical screening in plants such as High-Resolution Liquid Chromatography Mass Spectrometry (HR-LC-MS), and Gas Chromatography Mass Spectrometry (HR-LC-MS) *A.indica* has also gained its platform of interest for its phytoconstituents (Vijayalakshmi *et al*., 2025 and Ravi *et al*., 2022). Several studies, research and reviews have established confirmation of wide range of phytochemical compounds like phenolics, flavonoids, alkaloids, tannins, saponins, coumarins, terpenoids, sterols, glycosides, and some volatile compounds in *A.indica* with significant pharmacological accordance, which helps in inflammation, wound healing, oxidative stress and microbial infection. Traditionally *A.india* has been used as laxatives, anthelmintic, and diuretics. Leaves and roots of *A.indica* has been made as pastes and topically applied to skin to manage skin conditions like atopic dermatitis, psoriasis, acne vulgaris, contact dermatitis, eczema, scabies, and wounds. It is also employed as decoctions for asthma, bronchitis, and gastrointestinal disorders. Several studies have also confirmed the antimicrobial antioxidant, anti-inflammatory, anti-ulcer, hepatoprotective activities of *A.indica*. Although *A.indica* was traditionally used widely, standardized formulations, dosage limitations, and validated therapeutics indices remain absent limiting its clinical applications (Senthilkumar & Rani, 2025).

Table 1: Anti-inflammatory Phytochemistry of *Acalypha indica*

Plant part used	**Phyto -chemicals**	**Specific compounds**	**Function**	**Mechanism of anti-inflammatory action**	**Reference**
Roots	Phenolic acids, flavonoids	Gallic acid, caffeic acid, catechin	Anti-inflammatory, antioxidant	Inhibition of NO and COX-2 expression; suppression of NF-κB signaling	Sahukari et al., 2021

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Roots	Polyphenols	Catechin, epicatechin	Reduction of inflammatory damage	Free-radical scavenging and cytokine suppression	Ravi et al., 2021
Leaves	Flavonoids, phenolics, tannins, alkaloids	Quercetin, rutin, gallic acid	Anti-inflammatory in skin disorders	Inhibition of protein denaturation and membrane stabilization	Kumar et al., 2023
Leaves	Phenolics, flavonoids	Gallic acid, ferulic acid	Anti-inflammatory, antimicrobial	ROS scavenging and oxidative stress attenuation	Thamil Priya et al., 2020
Leaves	Flavonoids, tannins, steroids	B-sitosterol, quercetin-like flavonoids	Significant anti-inflammatory effect	Reduction of edema and stabilization of lysosomal membranes	Senthilkumar & Rani, 2025
Leaves	Polyphenols, flavonoids	Quercetin, kaempferol	Systemic anti-inflammatory activity	Down-regulation of TLR9 and NF-κB signaling	Supriatna et al., 2022
Leaves	Flavonoids, phenolics	Quercetin, rutin	Anti-inflammatory in metabolic inflammation	Suppression of TNF-α in macrophages and hepatocytes	Supriatna et al., 2022
Leaves	Alkaloids, flavonoids	Acalyphin	Anti-inflammatory, immunomodulatory	Modulation of inflammatory mediators via antioxidant action	Godipurge et al., 2014
Whole plant	Flavonoids, phenolics, saponins	Quercetin-type flavonoids	Anti-inflammatory	Inhibition of protein denaturation and inflammatory cell damage	Ravi et al., 2022
Leaves	Polyphenols, flavonoids	Not specified	Anti-inflammatory	NF-κB pathway inhibition	Sharma et al., 2025

The compiled evidence in Table 1 underlines the fact that Acalypha indica is a good source of phyto-compounds possessing anti-inflammatory properties, where the leaves and root are the most cited parts for extensive studies. Polyphenols, flavonoids, such as gallic acid, catechin, quercetin, rutin, and kaempferol, are identified as the key pharmacologically active compounds contributing towards the inflammation-related pharmacological properties. Mechanistically, the compounds have been shown to possess anti-inflammatory properties through the predominantly antioxidant-mediated pathways, such as the scavenging of Reactive Oxygen Species (ROS) followed by the modulation of the oxidative-stress induced-inflammatory responses. Some studies have shown the regulation of the key signaling pathways involved in the mediation of the inflammatory responses, such as the suppression of the NF-κB signaling. The ethanolic fraction of the leaves possesses consistent anti-inflammatory properties, being effective in the stabilization of the cell membrane, through the inhibition of lysosomes, thereby justifying the traditional uses of the leaves in related skin complaints associated with inflammation. The root, being the most cited part, offers better molecular clarity, particularly regarding the modulation of the Cytokines & the redox-signaling. Therefore, this data forms a strong pharmacological foundation to substantiate the anti-inflammatory potency of *A. indica*, which can therefore be developed further, possibly through advanced topical or nano-formulations to improve bioavailability.

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5. Limitations of herbal formulations in crossing skin barrier

5.1. Skin anatomy

The skin is known to be the body's largest organ and serves as the primary protective barrier against external mechanical injury, harmful pathogens, UV radiation, and fluid loss from the body. It is composed of three major layers: the epidermis, the dermis, and the hypodermis (subcutaneous tissue) as represented in figure 6 (Agarwal *et al.,* 2023) .

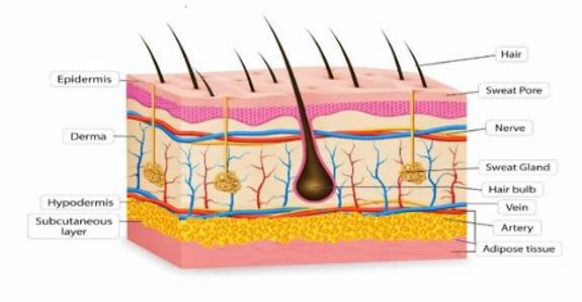

Figure 6 Skin and its layers (Epidermis, dermis, and hypodermic)

5.1.1. Epidermis

A stratified, keratinized squamous epithelium that is avascular which lacks blood vessels and continuously renewed from epidermal stem cells in stratum basale. The new cells from stratum basale are pushed up across the layers to form new epidermal cells while the old cells die eventually and shed itself. Vital role of epidermis is to provide a waterproof barrier, contains melanocytes for pigment production, and houses immune cells such as Langerhans cells (Yousef *et al.,* 2024).

5.1.2. Dermis

A dense connective-tissue layer, which lies in middle of epidermis and hypodermis that is rich in collagen and elastin, supplying strength and elasticity. It contains blood vessels to supply nutrients, lymphatic vessels to fight pathogens, nerves to enable sensation, hair follicles, sweat glands keep skin moist, sebaceous glands fights toxins and prevent excess water adsorption, and supports the epidermis (Yung *et al.,*2007).

5.1.3. Hypodermis

The deepest layer, which cushions the muscles, which is also called as subcutaneous layer. They are composed mainly of adipose tissue and loose connective tissue, which regulates body temperature, and serves as an energy reserve by storing fats (Yung *et al.,*2007).

5.2. Transdermal adsorption pathway of drugs

As reviewed by (Aswan *et al*.,2025) the process of transdermal absorption of drug components is mainly by diffusion through the epidermis, with the stratum corneum being the major barrier to permeation. The ordered lipoprotein complex of the outermost layer is responsible for the low permeability of foreign substances. Based on the mechanism, there are three main routes of drug transport across the skin: Appendageal pathway, intercellular pathway, and transcellular pathway, which is clearly represented in figure 7.

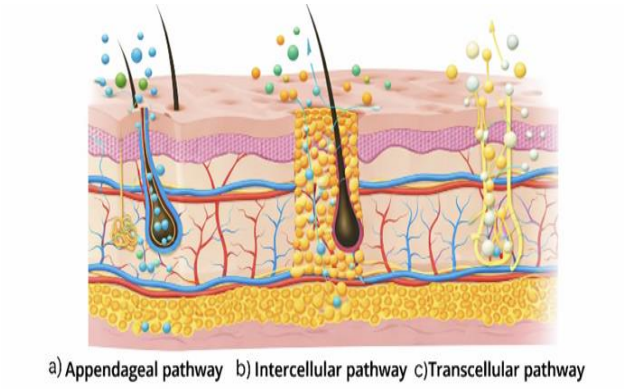

Figure 7 Diagrammatic representation of transdermal drug adsorption pathways a) Appendageal pathway: via hair follicles and sweat glands b) Intercellular pathway: via lipid rich spaces between corneocytes and c) Transcellular pathway: Across corneocytes and cell membrane

5.2.1. Appendageal pathway

This mechanism works by allowing the entry of the drug through hair follicles and sweat glands. There is growing evidence that hair follicles can act as drug reservoirs, which can improve targeted drug delivery in dermatology.

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5.2.2. Intercellular pathway

This route is marked by diffusion along the lipid-rich intercellular regions between corneocytes in the stratum corneum. The presence of flexible hydrophobic domains and non-lamellar structures makes diffusion easier along the intercellular lipid regions, and hence this route is the major route for most lipophilic drugs.

5.2.3. Transcellular pathway

In the transcellular route, drug molecules move through layers of corneocytes and cell membranes. Transporters include passive diffusion, active transport, endocytosis, and transcytosis, depending on the physicochemical properties of the permeant. This route is especially important for small molecules and some polar or ionic compounds.

5.3. Why do herbal formulations fail in transdermal applications?

Herbal medicines from plant extracts face challenges to diffuse through the stratum corneum because of the presence of large proportions of phytoconstituents with molecular weight greater than the approximate 500 Da threshold. Moreover, they are largely hydrophilic or lipophilic to be partitioned from the lipids of the epidermis successfully (Abhijeet *et al*., 2024). In addition to this property, insolubility of herbal medicines restricts their diffusion to reach therapeutic levels when topically administered (Aswan *et al*., 2025). Technical challenges are entailed by the absence of standardized purity tests as well as lack of information on standardized safety. Furthermore, irritation or sensitization to dermatological irritation can be perceived as hazardous (Pulipati *et al*., 2025). Lastly, the skin barrier itself forces drugs to meet stringent requirements for diffusion because only small to moderately lipophilic drugs can be metabolized through diffusional processes, even so, they are not likely to diffuse because of the skin layers. Even modern carriers like phytosomes are seeking to increase bioavailability, although their effectiveness is currently challenged by requirements for high dosage and long-term delivery to successfully reconstruct epigenetic boundaries in skin cells. Analogously, nanosystems (such as niosomes and liposomes) show enhanced delivery capacity but are associated with instability and poor drug loading capacity (Aswan *et al.*, 2025). Incompatibilities in solubility between herbal drugs and matrix materials for carriers further increase the difficulty level of designing effective delivery systems, thus limiting the dosage of the drugs that can be incorporated (Fathima Shana *et al*., 2024). Chemical absorption promoters like DMSO and NMP show enhanced delivery capability but tend to generate skin irritation and system toxicity, thus limiting their acceptability (Junyaprasert *et al*., 2013). According to (Schäfer *et al*., 2023) natural absorption promoters are non-toxic and safer, in some cases only cannot provide enough delivery support without damaging the skin barrier.

6. Nanoemulsion - A solution for skin barrier bypassing

Nanoemulsions are colloidal systems which are formulated by combining two immiscible fluids, most commonly oil and water, in which one fluid is dispersed to droplets of a about 20-200 nm using suitable surfactants and co-surfactants for complete emulsification (Ravi *et al.,* 2025). Because of the very small droplet size, nanoemulsions have a large interfacial area, improved kinetic stability, increased optical clarity, and a remarkably high solubilizing ability of both hydrophilic and lipophilic drugs (Malik *et al.,* 2024). According to the internal phase, nanoemulsions can be classified into three types: oil-in-water O/W, water-in-oil W/O, or nano-multiple emulsions, which can be O/W/O, W/O/W, respectively as represented in figure 8 (S. Yang et al., 2020). Nanoemulsions in transdermal drug delivery have been shown to greatly improve the permeation of drugs across the skin by overcoming the diffusion barrier offered by the stratum corneum, causing increased drug flux level compared to conventional emulsions (Rai *et al.,* 2018). Their fluid nature, as well as the presence of surfactants in their interfaces, makes them amenable to skin components, enhancing drug solubility, penetration, and stability, also preventing degradation via oxidation or hydrolysis reactions (Hiranphinyophat *et al*.,2021). Compared to conventional semisolid drug delivery systems, nanoemulsions have several advantages, such as increased rates of absorption, less intraindividual variability, better bioavailability of lipophilic compounds (Koli *et al.,* 2025). Moreover, nanoemulsions can be developed into nanoemulgels or combined with other

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nanocarriers to increase their viscosities and patient compliance for topical and transdermal drug delivery routes. Nanoemulsions serve as a versatile and effective drug delivery vehicle for poorly water-soluble compounds through the transdermal route, proving their importance in current advanced dermatologic and pharmaceutical therapies.

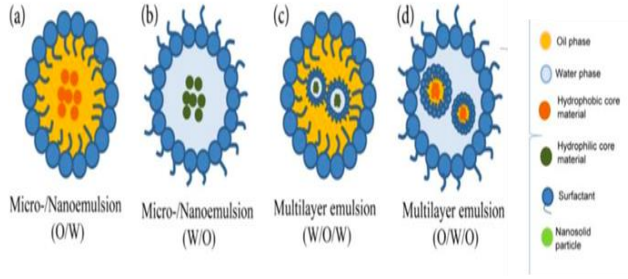

Figure 8 Types of Nanoemulsion represented by (S.Yang et al., 2020)

Formulation of Nanoemulsion

The herbal nanoemulsion was prepared by incorporating the herbal extract (aqueous phase) with a suitable oil phase, followed by the addition of appropriate emulsifiers and stabilizers. The mixture was initially homogenized using a high-speed stirrer to form a coarse emulsion. Subsequently, the emulsion was subjected to ultrasonication for 10 minutes to reduce droplet size and obtain a stable nanoemulsion. The prepared nanoemulsion was then characterized for physicochemical properties such as droplet size, polydispersity index, zeta potential, and stability. Based on satisfactory characterization results, the formulation may be further evaluated in preclinical and clinical studies (Qureshi et al., 2022).

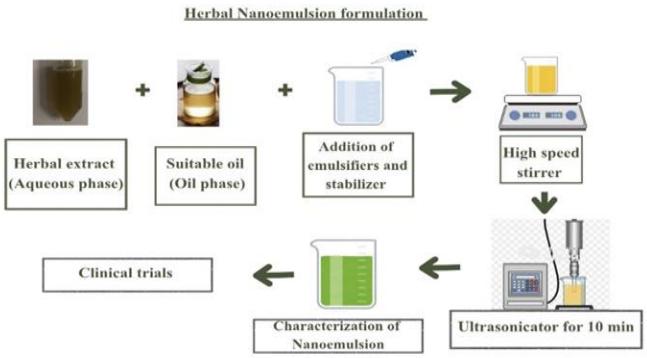

Figure 9 Formulation of Nanoemulsion

6.1. Herbal based nanoemulsions for inflammatory conditions:

Table 2 Herbal based nanoemulsions for inflammatory conditions

Herbal source	Disease	Major bioactive constituent(s)	Clinical implication	Key limitations	Reference
Mixed herbal extracts	Inflammatory bowel disease	Polyphenols, flavonoids	Improved oral bioavailability and reduced inflammatory burden in IBD	Absence of human clinical validation	Alshahrani & Ali, 2022
Curcuma longa L.	Acute inflammation (paw edema)	Curcumin	Rapid anti-inflammatory response in acute inflammation models	Limited translational relevance of injectable delivery	Marwa et al., 2023
Nigella *sativa* L.	LPS-induced hepatic inflammation	Thymoquinone	Hepatoprotective and systemic anti-inflammatory effects	Restricted to preclinical animal models	Haffez et al., 2024
Allium sativum L. & Zingiber officinale Roscoe	Wound inflammation and healing	Allicin, gingerols	Accelerated wound closure and reduced microbial load	Risk of irritation due to essential oil concentration	Ibrar et al., 2022
Cinnamomum spp.	Burn wound inflammation	Cinnamaldehyde	Enhanced burn wound healing with antioxidant protection	Surfactant-associated	Qureshi et al., 2022

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				toxicity concerns	
Eugenia sulcata	Inflammatory signaling (P2X7R)	Essential oil terpenoids	Modulation of inflammatory receptor signaling in vivo	Challenges in formulation scalability	Magalhães et al., 2022
Blumea balsamifera (L.)	Trauma repair	Borneol-rich essential oil	Improved trauma repair and inflammatory control	Lack of pharmacokinetic and human safety data	Liu et al., 2023

The table 2 summarizes that there has been a considerable increase in the number of research and studies regarding the use of herbal-based nanoemulsion systems as potential anti-inflammatory therapy. Within these studies, all of the nanoemulsions containing plant-derived bioactive ingredients such as essential oils, polyphenols, flavonoids, and terpenoids have been shown to have an enhanced level of anti-inflammatory activity when compared to their respective standard herbal formulations. The differences in the degree of activity are primarily due to the small droplet sizes/high surface area/ and greater physicochemical stability that result in an increase in skin penetration and increased bioavailability of poorly-soluble/limitedly-soluble phytoconstituents. All the nanoemulsion in the table 2 are oil-in-water o/w nanoemulsions and are primarily used for topical anti-inflammatory therapies for its anti-inflammatory properties and compatibility with the skin. Most of the formulations contain biocompatible surfactants and co-surfactants which contribute to their feasibility over a long-term duration in dermatological applications. The results from in vitro and in vivo testing of the formulations indicate that there was a significant decrease in the levels of several pro-inflammatory mediators TNF-α, IL-6, COX-2 and nitric oxide, which demonstrate the mechanism for nanoemulsions modulating inflammatory pathways. tables present a compelling picture for nanoemulsion-based delivery systems, showing that they may provide the better therapeutic benefit with lower doses which may help to decrease toxicity and side effects from the use of synthetic non-steroidal anti-inflammatory agents. These formulations also show a greater stability in formulation and prolonged drug release in several studies. Thus, the data provide strong support that herbal sources of nanoemulsions represent a viable, dual-action option for the treatment of inflammatory diseases, taking advantage of both the anti-inflammatory properties of natural herbs and the advantages afforded by using nanoparticles as drug delivery systems. Although the studies still lack of clinical validation through clinical trials and standard formulation guidelines for this type of pharmaceutical product, which is still being a research gap and the standardization for well-designed clinical trials and the development of regulatory standards are needed to support such applications.

7. Conclusion

Inflammatory skin diseases are complex conditions that are driven by immune system dysregulation, oxidative injury, and impaired cutaneous barrier function and require an effective and safe treatment approach. Inflammation in skin conditions can be effectively controlled and modified by anti-inflammatory and antioxidant phytoagents present in herbal remedies, however, their efficacy is still observed to be low because of poor skin permeability and lack of formulation standardization, stability and poor skin permeability. The data accumulated in this review makes it abundantly clear that herbal agents can be effectively and safely delivered into the dermatologically applicable nanoemulsion formulation with increased skin bioavailability and improved pharmacological activity by overcoming the limitations imposed by the stratum corneum and managing NF-κB and MAPK signalling pathways in inflammatory skin diseases. Among the assessed herbal agents, *Acalypha indica* has shown potential as an anti-inflammatory drug because of the various phytochemicals and extensive traditional and scientific evidence. However, there is limited potential in the use of this compound as a drug because there is no standardized formulation in the nano-scale and a defined dose, in addition to the lack of safety information in humans. Although the preclinical studies involving the

use of herbal nanoemulsions provide evidence for improved efficacies, such as reduced cytokines and improved wound healing and antioxidant activity, this has been restricted to in vitro and animal studies. In this way, herbal nanoemulsions may prove to be a practically feasible newer strategy for the treatment of inflammatory skin disorders, and the therapeutic benefits provided by natural products with technological advancements afforded by nanocarriers. Scalable formulation strategies, long-term stability assessment, pharmacokinetic profiling, and well-designed clinical trials should be the main focus of future studies to ensure translational outcomes.

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