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REVIEW ARTICLE

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# Advanced perspectives in the treatment of atopic dermatitis through nanotechnology

*Perspectivas avanzadas en el tratamiento de la dermatitis atópica mediante nanotecnología*

*Perspectivas avançadas no tratamento da dermatite atópica através de nanotecnologia*

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**Abstract**

This study aimed to explore the pathophysiology, current solutions, safety aspects, and future perspectives of nanoformulations for atopic dermatitis. An integrative review of the literature indexed in the Scientific Electronic Library Online, Medical Literature Analyses and Retrieval System Online, and Latin American and Caribbean Literature in Health Sciences was conducted. Eleven studies were selected. It was found that approaches have been employed to repair skin barrier function and control skin inflammation in patients with atopic dermatitis. With the help of ingenious nanocarriers, novel approaches can be demonstrated through combination with novel delivery routes to demonstrate the potential for successful optimization of skin-targeted nanoparticulate systems for the management of atopic dermatitis. It is concluded that nanomedicines, as drug carriers, appear to offer superior activity, including increased therapeutic efficacy with reduced toxicity at low doses, drug localization, and specific drug targeting.

**Descriptors:** Atopic Dermatitis; Treatments; Nanoformulations; Efficacy; Dermatology.

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**Resumén**

El objetivo de este estudio fue explorar la fisiopatología, las soluciones actuales, los aspectos de seguridad y las perspectivas futuras de las nanoformulaciones para la dermatitis atópica. Se realizó una revisión integrativa de la literatura indexada en Scientific Electronic Library Online, Medical Literature Analyses and Retrieval System Online y la Literatura Latinoamericana y del Caribe en Ciencias de la Salud. Se seleccionaron once estudios. Se encontró que se han empleado enfoques para reparar la función de barrera de la piel y controlar la inflamación de la piel en pacientes con dermatitis atópica. Con la ayuda de ingeniosos nanotransportadores, se pueden demostrar enfoques novedosos a través de la combinación con nuevas rutas de administración para demostrar el potencial de optimización exitosa de sistemas nanoparticulados dirigidos a la piel para el manejo de la dermatitis atópica. Se concluye que las nanomedicinas, como transportadores de fármacos, parecen ofrecer una actividad superior, incluyendo mayor eficacia terapéutica con menor toxicidad a dosis bajas, localización del fármaco y diana farmacológica específica.

**Descriptores:** Dermatitis Atópica; Tratamientos; Nanoformulaciones; Eficacia; Dermatología.

**Resumo**

Objetivou-se discutir a exploração da fisiopatologia, soluções atuais, aspectos de segurança e pontos de vista futuristas de nanoformulações para dermatite atópica. Procedeu-se com uma revisão integrativa da literatura indexada no portal de periódicos *Scientific Eletronic Library Online*, *Medical Literature Analyses and Retrieval System Online* e Literatura Latino-Americano e do Caribe em Ciências da Saúde. Foram selecionados 11 estudos. Verificou-se que abordagens têm sido empregadas para reparar a função de barreira cutânea e controlar a inflamação cutânea em pacientes com dermatite atópica. Com a ajuda de nanocarreadores engenhosos, novas abordagens podem ser demonstradas através da combinação com novas rotas de administração para o potencial de otimização bem-sucedido de sistemas nanoparticulados direcionados à pele para o manejo da dermatite atópica. Conclui-se que os nanomedicamentos, como transportadores de medicamentos, parecem oferecer atividade superior, incluindo aumento na eficácia terapêutica com menor toxicidade por pequenas doses, localização do medicamento e direcionamento específico do medicamento.

**Descritores:** Dermatite Atópica; Tratamentos; Nanoformulações; Eficácia; Dermatologia.

## Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by eczematous lesions, itching, redness, and scaling. It is a prevalent, long-term condition that affects a significant portion of the global population. Recent studies have shown a continued increase in the incidence of AD, particularly among urban children (15–30%) and adults (1–3%)[1].

The significant increase in prevalence over the past three decades has raised concerns, and there is evidence to suggest that environmental factors contribute to the development of AD. According to study[2], AD is not limited to a specific age group but can affect individuals of any age. It often begins in early childhood and can recur throughout the patient's life. There is a familial predisposition to AD, with a higher prevalence of atopic symptoms such as allergic rhinitis, bronchial asthma, and food allergies among affected individuals.

It is important to consider AD as a multifactorial disease characterized by non-contagious exudative eczema, primarily caused by a disruption of the stratum corneum barrier. This disruption leads to impaired skin function and increased transepidermal water loss (TEWL), resulting in dehydration. Furthermore, AD involves several inflammatory processes characterized by the release of cytokines, chemokines, and interleukins (ILs), such as IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, and IL-13[3].

However, a variety of pharmacological and non-pharmacological approaches, such as detecting and avoiding causative allergens, skin hydration (e.g., baths or moisturizers), topical anti-inflammatory or immunosuppressive treatments (tacrolimus and pimecrolimus), antipruritic medications (corticosteroids), and antibacterial agents (e.g., bleach baths, application of antiseptics or disinfectants) have been shown to be effective in treating AD with mild to severe symptoms, alone or in combination with other modalities[4,5].

Researchers[6] highlight that topical formulations, including corticosteroids and calcineurin inhibitors for AD and other inflammatory conditions, act by inhibiting calcineurin activation in T cells and decreasing the secretion of pro-inflammatory cytokines and mediators involved in the AD process. However, the authors emphasize that they are associated with skin burns, heat, redness, and local allergic reactions. There is also a risk of secondary infections due to reduced immunity, and systemic absorption of these medications can cause respiratory difficulties, facial swelling, and systemic immunosuppressive effects, increasing the risk of infections and malignancies.

As authors point out[2], the absorption rates and therapeutic efficacy of ointments such as tacrolimus and pimecrolimus also vary. To address these concerns, nanotechnology can be used to specifically target inflamed

areas of the skin, thus avoiding risks to healthy skin and systemic circulation.

Nanotechnology, a rapidly expanding field with applications in health and disease, is being explored to develop safe and effective therapies to reduce AD symptoms after topical and systemic administration. New nanoparticle-based systems have shown promise for dermal delivery due to their ability to enhance drug permeation through the stratum corneum, which is naturally impermeable to some substances, as the skin acts as a natural physical barrier to particle penetration[3].

Nanocarrier-based topical formulations have the potential to improve skin targeting, increase drug efficacy, and decrease systemic side effects. While nanoparticle drug delivery has been hailed as a game-changer, its potential for treating localized cutaneous and systemic disorders has yet to be realized[1].

This article focuses on the fact that optimal management of AD requires a multifaceted strategy that aims to heal the diseased site and provide a shield across the skin barrier, in addition to addressing the complex immunopathogenesis. There is still no promising therapeutic regimen that can abrogate the pathological effects of AD, but nanotechnology-based topical formulations appear to have the potential to overcome the limitations as mentioned above.

The general objective of this article is to discuss the pathophysiology, current solutions, safety aspects, and future perspectives of nanoformulations for AD. The specific objective was to explore new approaches to AD treatment that may target the improvement of structural skin abnormalities and immune dysregulation, which are significant pathogenic events.

## Methodology

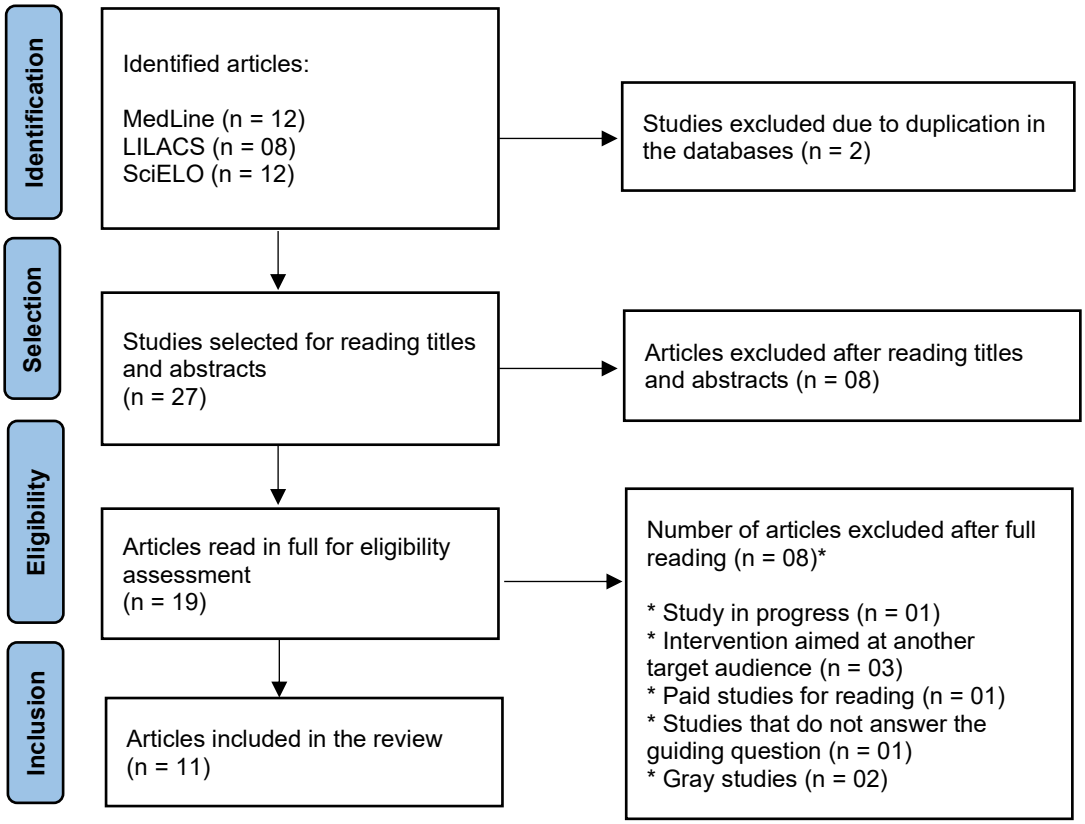
This is an integrative literature review of a descriptive and critical nature. The proposed research involved a survey of articles indexed in the Scientific Electronic Library Online (SciELO) and the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Latin American and Caribbean Health Sciences Literature (LILACS) databases. The following descriptors and their combinations in Portuguese and English were used to search for articles: "Atopic Dermatitis," "Treatments," and "Nanoformulations," with the help of the Boolean operator "AND".

The acronym PICo (Population; Intervention; Co-context) was used, as seen in Chart 1. From this, the research question was structured to guide the study outlined here and to search recent reference literature.

**Chart 1.** Structure of the acronym PICo. Indaiatuba, SP, Brazil, 2023

| Acronym | Definition |
|---|---|
| P - Patient | Patients with atopic dermatitis |
| I - Intervention | Treatment with nanoformulations for atopic dermatitis |
| Co - Context | Health care |

**Figure 1.** Study search and selection flowchart. Indaiatuba, SP, Brazil, 2013-2023



The following guiding question was then defined: "What are the prospects for nanoformulation-based treatments for patients with atopic dermatitis?" The search and selection of studies took place in October 2023.

The inclusion criteria defined for selection were studies published in Portuguese and English, available in full text, that addressed the topic. The time frames considered were 2013 and 2023, that is, the last 10 years. Twenty-nine initial publications were found by combining the descriptors. Based on an exploratory reading of the titles and abstracts of these bibliographic materials, 11 publications were selected that were closely related to the study theme. The publications were read in full to confirm whether their topics addressed the question of interest, and were then selected as the final sample. The exclusion criteria for the initially selected studies included: unavailability or in full, inability to be translated into Portuguese, being outside the previously determined time frame, not addressing the proposed research objective, and being duplicated in the databases.

To select articles, a PRISMA checklist flowchart was used as a database search tool to facilitate the process. The initial selection included 29 studies, which were subsequently screened, and articles published before 2013 were excluded based on the nature of the study subject. Thus, of the articles initially found, after reading each in full to assess eligibility, 27 were found. Eight were subsequently excluded, leaving 19 articles for further screening. The following were excluded: one ongoing study; three for interventions aimed at a different target audience; one paid-for study; one study that did not answer the guiding question; and two gray studies. The flowchart followed for searching the electronic databases is presented in Figure 1.

For the analysis, Bardin's Thematic Content Analysis[7] was used, considering the benefit of using this methodological tool to better present the results based on thematic categories.

## Results and Discussion

Given the above, the sample for this review resulted in 11 studies, as can be seen in the synoptic chart below with their respective variables of interest.

**Chart 2.** Studies selected for review. Indaiatuba, SP, Brazil, 2013-2023

| Title | Year of Publication | Method | Objectives | Main Findings | Conclusion |
|---|---|---|---|---|---|
| Transporte de fármacos no tratamento da dermatite atópica | 2020 | SWOT analysis (Strengths, Weaknesses, Opportunities, Threats) followed by discussion of clinical cases related to the internship. | Addressing conventional AD treatment as well as the promising future of new nanotechnology-based drug delivery systems. | Increased drug permeation and accumulation at target sites, the ability to reduce erythema, TEWL, and adverse effects are the main advantages of these new therapies compared to conventional methods. | New therapeutic approaches using NP systems, such as nanoemulsions, SLNs, NLCs, liposomes, ethosomes and transferosomes, are currently being tested in AD models and show a promising future for the treatment of this disease. |
| Vehicles for drug delivery and cosmetic moisturizers: review and comparison | 2021 | Meta-analysis. | Examine common topical vehicles used for delivering medications and cosmetic moisturizers, including their formulation, advantages, disadvantages, and effects on the skin. | The same formulation technology used to improve the delivery and effectiveness of topical medications is also used to enhance the efficacy of cosmetic moisturizers to improve dry skin due to environmental insults, frequent exposure to harsh chemicals, use of certain medications, and aging. | The type of vehicle and nanotechnological property is generally related to the area of the body to be treated, the skin condition, and the patient's preference. |
| Hindrance of the proteolytic activity of neutrophil-derived serine proteases by serine protease inhibitors as a management of cardiovascular diseases and chronic inflammation | 2021 | Multiple case review. | Investigate current development and emerging nanomedicines for the effective treatment of AD. | Nanomedicines can minimize dosing frequency, achieve effective therapeutic concentration, reduce side effects, and improve patient compliance with targeted administration of many peptide and protein drugs. | Future studies are still needed to establish its safety and efficacy to ensure consumer health. |
| Pimecrolimus for the treatment of atopic dermatitis in infants: an Asian perspective | 2023 | Meta-analysis. | Encourage the use of pimecrolimus in children between 3 months and 2 years of age in the Asian population due to its safety profile. | The use of pimecrolimus has advantages such as reduced risk of flare-ups, average reduction in Eczema Area and Severity Index, long-term disease control, and early treatment success. | Based on the available evidence, the expert panel recommends pimecrolimus in children between 3 months and 2 years of age in the Asian population. |
| Nanotechnology meets atopic dermatitis: Current solutions, | 2019 | Systematic Review. | Review studies that address nanotechnology-based therapy in the | Nanotechnologies, taking these aspects into account, can pave the way for individualized treatment and management of patients with atopic | Future research should adopt this design to enable scholars to achieve robust findings and evidence. |

| | | | | | |
|---|---|---|---|---|---|
| challenges, and future prospects. Insights and implications from a systematic review of the literature | | | prevention of atopic dermatitis. | dermatitis, such as drug delivery, controlled release, dosage, and skin permeation/ retention, which play a fundamental role. | |
| Therapeutic effects of topically administered guar gum nanoparticles in oxazolone-induced atopic dermatitis in mice | 2019 | Experimental study. | Determine the therapeutic effect of guar gum nanoparticles (GN) in vitro and in vivo in AD. | The populations of helper T cells and macrophages, when examined by flow cytometry, showed a percentage increase when treated with Oxa; the percentage was reduced after application of GN. | Guar gum nanoparticles, GN, when administered topically, were successful in relieving dermatitis caused by oxazolone, Oxa. |
| Treatment resistant atopic dermatitis: challenges and solutions | 2019 | Cohort study. | Present an exploration of the pathophysiology, current solutions, safety aspects, and futuristic viewpoints of nanoformulations for AD. | In vitro/ in vivo correlations for topically applied nanosystems and regulatory guidelines to evaluate their technological and biopharmaceutical properties would aid in clinical translation and marketing authorizations of these products in the future. | It is important to emphasize the modification of the physicochemical properties of nanoparticles, with size being a particularly significant aspect, during nanoparticle development. This modification must be made in a way that does not compromise the safety of the nanoparticles. |
| Dermatite atópica: dos tratamentos farmacológicos clássicos aos novos sistemas de libertação de fármacos | 2019 | Systematic Review. | Summarize recent solutions based on nanoformulations loaded with natural ingredients, specifically for the treatment of AD. | Available data on the clinical efficacy of such nanosystems loaded with natural ingredients are scarce or even non-existent in most cases, since most studies remain in the preclinical research phase and are fundamentally based on single-animal models. | It is suggested that future studies focus on robust clinical trials that can confirm the safety and efficacy of such naturally based nanosystems, thus paving the way for more reliable treatments for AD. |
| Guidelines on management of atopic dermatitis in India: an evidence-based review and an expert consensus | 2019 | Preparação das diretrizes. | Provide an evidence-based consensus statement for the management of AD with special reference to the Indian context. | Nanocarriers allow for better skin penetration and retention of active ingredients and promote controlled release and targeted delivery of active ingredients. | It is of utmost importance to consider the severity of the disease, socioeconomic factors, psychological status, and the patient's desire for treatment before choosing an appropriate treatment for each patient with AD. |
| Material engineering for atopic dermatitis treatment | 2020 | Meta-analysis. | Discuss new methods of treating AD and the use of hydrogels and nanotechnology. | Despite the various innovative formulations, research into nanotechnology-based carriers should address specific aspects such as the use of moisturizers associated with pharmacological therapies, toxicity studies, scale-up production processes, and the influence of nanocarriers on the immune response. | New approaches to scale-up production, cost-effectiveness, toxicity, and randomized controlled clinical investigations should address the most appropriate nanocarrier systems for the treatment of AD. |
| Nanotecnologia aplicada no desenvolvimento de formulações despigmentantes | 2021 | Systematic Review. | Address the main depigmenting agents used in the market and the advantages associated with the use of nanostructured systems employed to deliver these active substances. | Nanointerventions encompass a wide range of delivery aids, including lipid and polymeric nanoparticles, liposomes, silica nanoparticles, hydrogels, and various other delivery systems. These interventions are primarily designed to achieve enhanced drug encapsulation, increased stability, and enhanced skin permeation. | Nanotechnology can increase the delivery of depigmenting agents incorporated into topical formulations to the skin. It may represent an alternative to increasing the efficacy and safety of depigmenting formulations already on the market. |

The synoptic chart considered variables such as the title, year of publication, and method used in each selected publication, considering the main findings and conclusions of each. The selection corresponded to the objective proposed in this review, in that all studies mentioned nanotechnology-based therapy for atopic dermatitis. Five studies published in 2019 were selected, two studies published in 2020 were selected, only one publication was selected from 2023, and three selected studies were published in 2021, demonstrating the current relevance of this review.

Regarding the method adopted in the studies, a heterogeneous aspect is observed in the methodology adopted by each of them, in which there is a predominance of systematic review, in 4 of the 11 selected studies, followed by three studies that adopted meta-analysis, one study adopted the preparation and elaboration of

guidelines, one experimental study, one study was of the cohort type and a SWOT Analysis.

Regarding the objectives, none of the selected studies focused on the treatment of atopic dermatitis. The correlation with nanotechnology, as well as most of the results, pointed to advantages in the formulation used in nanotechnology-based atopic dermatitis treatments compared to conventional drugs. However, there is concern about the type of vehicle and nanotechnological properties, as well as a consensus that future studies are needed to establish the safety and efficacy of nanotechnology-based drugs for the treatment of atopic dermatitis.

Regarding the results found, the discussion takes place in categories considering the objective proposed for this review, with the discrimination of information related to the answer to the guiding question, such as: Barrier function in the pathogenesis of atopic dermatitis, The stratum corneum, Relative involvement of permeation pathways, Current approaches and challenges during the treatment of atopic dermatitis, Systemic therapy, Roles of multidisciplinary healthcare providers in the treatment of atopic dermatitis and Nanotechnological approaches for effective treatment of atopic dermatitis.

**Barrier function in the pathogenesis of atopic dermatitis**

The skin barrier plays a vital role in protecting the body from external threats such as pathogens, chemicals, irritants, and allergens. It acts as a defense mechanism, preventing these substances from penetrating the deeper layers of the skin, including the epidermis and dermis, where they could potentially trigger an immune response[8].

Furthermore, the skin barrier serves to retain moisture and prevent excessive water loss through the epidermal layer. Skin barrier function can be assessed by measuring the percentage of transepidermal water loss (%TEWL), which is inversely related to the length of the diffusional permeation path through the stratum corneum[9].

According to study[10], several methods can be used to assess skin barrier function. These include measuring skin surface pH, assessing tracer permeation, and assessing stratum corneum cohesion and hydration. These techniques provide valuable information about the integrity and effectiveness of the skin barrier.

Damage to the skin barrier can facilitate the transport of allergens or haptens (molecules that only cause an allergic effect after binding to proteins) into the skin structure, resulting in inflammation after stimulating the production of pro-inflammatory cytokines. Simultaneously, Th2 cytokines, namely IL-4, IL-13, and IL-22, downregulate FLG expression, causing further impairment of the skin barrier[6].

According to study[2], pathogenic and commensal bacteria, fungi, and viruses make up the cutaneous microbiome that inhabits the skin and helps maintain epidermal homeostasis. When the stratum corneum layer is structurally proficient with a well-ordered lipid matrix, it prevents the colonization of pathogens, such as Staphylococcus aureus (S. aureus), which can adversely affect barrier function. In AD, the skin is colonized by S. aureus in over 90% of patients.

S. aureus surface proteins decrease the production of free fatty acids in the epidermis, which promotes permeability through the skin. In AD patients, S. aureus exotoxins with superantigenic activity stimulate IgE production and produce pruritus symptoms. Subsequent excoriations (skin abrasions) due to scratching further damage to the skin's barrier functions[3].

**The stratum corneum**

The uppermost layer, known as the "brick and mortar" of the epidermis, is the SC. It is composed of a highly organized intercellular lipid matrix that acts as mortar and corneocytes (keratinocytes without nuclei and cytoplasmic organelles) as the building blocks. SC homeostasis is altered in AD patients with both lesional and non-lesional skin. This results in increased water loss and increased access to allergens[9].

According to research[11], the structure and composition of the SC in AD condition can be influenced in the following ways: loss or decrease of filaggrin (FLG) protein function; enhanced serine protease activity; impaired lipid processing.

The FLG protein plays an important role in the structural integrity of the SC. FLG accumulates keratin filaments within corneocytes and then facilitates the formation of a cornified cell envelope adjacent to the corneocytes. FLG also provides the SC with water retention capacity and an acidic pH. FLG mutations are associated with a history of AD onset, disease severity, and disease persistence. Approximately 50% of AD cases with moderate to severe symptoms can be attributed to FLG mutations[9].

Regarding kallikrein (KLK) 5 and 7, authors[6] explain are serine proteases, and their activity is regulated by the pH of the stratum corneum. Both proteases KLK5 and KLK7 break down the extracellular corneodesmosomal proteins that simultaneously connect corneocytes. Their elevated activity is shown to decrease corneocyte adhesion and desquamation. The skin pH is normally acidic and limits the activity of the protease (more active in a basic environment). In AD, the skin pH is increased, consequently reflecting increased serine protease activity[1].

Another enzyme involved in AD is neutrophil elastase (NE), a broad-spectrum serine protease released by neutrophils and macrophages. It can degrade several extracellular matrix proteins, acting as a potent pro-inflammatory agent and generating chemotactic factors. After matrix degradation and loss of intercellular contacts, NE appears to contribute to the inflammatory characteristics of eczematous diseases, resulting in spongiosis and desquamation[12].

In particular, it has been shown that NE activity is absent in the skin of healthy individuals. At the same time, a massive increase in its action has been demonstrated in the skin of patients with allergic contact (average 55-fold) and atopic dermatitis (35-fold), the most common form of eczema[4].

Cholesterol, free fatty acids, and ceramides are the three main types of lipids present in the SC. This lipid matrix forms a highly ordered structure of compact lipid layers. This is the most important pathway for substances that cross the intercellular lipid matrix through the skin barrier. In AD, a decrease in total lipids and changes in their composition have been observed. As a result of this impaired skin barrier function, increased drug penetration through the stratum corneum has been observed[8].

**Relative involvements of permeation pathways**

The primary route for compounds to penetrate the skin is the transepidermal route, with the movement of substances through the EC layer serving as the rate-limiting step, influencing the overall permeant flux under sink conditions. Previous research has shown that permeant flux through the skin does not correlate with the density of appendages on the skin surface[9].

Although the transappendicular route, which utilizes appendages such as hair follicles, sweat ducts, and sebaceous glands, constitutes only about 0.1% of the skin surface area (although this percentage may be higher in specific regions such as the forehead), its contribution to percutaneous transport is generally considered secondary[3].

However, the relative importance of these pathways may vary depending on the physicochemical properties of the permeant and the specific formulation being studied, as the authors point out[10]. Lipophilic drugs tend to accumulate in the SC, which can hinder their partitioning into the more hydrophilic viable epidermis. As a result, SC clearance, rather than diffusion through it, can become the limiting factor for highly lipophilic drugs[1].

On the other hand, for highly hydrophilic compounds such as caffeine and electrolytes, as well as large molecules with low diffusion coefficients, the transappendicular pathway may play a more significant role. Such compounds are effectively excluded from the transepidermal pathway and rely on the path through the appendageal structures for penetration. Numerous studies have shown that the transappendicular pathway transiently dominates in the early stages but eventually gives way to the predominance of the transepidermal path at a steady state[12].

**Current approaches and challenges during the treatment of atopic dermatitis**

*Corticosteroids*

Topical corticosteroids (TCs) are considered the first-line treatment for AD in adults and children. They effectively address the inflammatory signs, symptoms, flare-ups, and itching associated with the disease. The efficacy of TCs in reducing acute and chronic AD symptoms has been well established, supported by over 100 randomized clinical trials[8]. According to study[2], when selecting TCs for infants and young children, it is important to choose formulations with low systemic bioavailability and a well-established therapeutic index. The choice of TC potency considers factors such as patient age, disease severity, and skin thickness/relative area of absorption.

However, it's important to be aware of the potential side effects associated with TCs. These side effects can include skin atrophy, perioral dermatitis, adrenal suppression, acne rosacea, and the progression of striae. Once AD lesions improve, patients are advised to gradually reduce the frequency of TC application, transitioning to maintenance therapy with less frequent use[3].

For individuals, both adults and children, with moderate to severe AD, long-term use of medium-potency TCs in combination with proactive twice-weekly treatment with emollients may help minimize the risk of relapse. It is crucial to exercise caution and avoid regular use of high-potency TCs (such as those containing >3% hydrocortisone) on thin-skinned areas such as the face, body folds, or groin to mitigate the potential risk of skin atrophy. For a 2-week treatment, approximately 0.5 g of the currently available cream or ointment can be applied, which corresponds to the size of two adult hands, using adult fingertip units as a reference[1].

*Topical calcineurin inhibitors*

Topical nonsteroidal calcineurin inhibitors (TCIs), including tacrolimus and pimecrolimus, are beneficial in the treatment of acute flares and maintenance therapy for AD in adults and children over two years of age. TCIs exert their anti-inflammatory effects by suppressing the activation of calcineurin-dependent T cells, thus preventing the release of cytokines and pro-inflammatory mediators. Although tacrolimus ointment 0.1% is indicated only for adults, tacrolimus ointment 0.03% and pimecrolimus cream 1% are recommended for patients two years of age and older with AD[9].

According to a research[13], however, the latest guidelines published in the reference literature suggest off-label use of these TCIs in children under two years of age with mild or severe AD. The most common side effects of TCIs include temporary local burning or itching at the application site. Unlike topical steroids, TCIs do not cause skin atrophy with prolonged use and help preserve the weakened epidermal barrier.

TCIs are primarily recommended for the target treatment of AD in specific areas, such as the eyelids, face, and intertriginous regions. They offer a valuable alternative for patients with multiple flare-ups or chronic AD who would otherwise require high doses of topical steroids. In cases where patients experience moderate to severe symptoms, tacrolimus ointment (0.1%) is often used in combination with topical steroids. For individuals with mild to moderate symptoms, pimecrolimus cream (1%) is typically recommended[8].

Although concerns have been raised about the potential risk of malignancies associated with long-term TCI use, current evidence does not indicate an increased risk of lymphoma in AD patients who used TCI for short- to medium-term periods (more than 10 years) when compared to the general population. Researchers[10] point out that patients with AD who receive maintenance therapy with tacrolimus three times a week have fewer attacks and longer

intervals between relapses, providing further support for the effectiveness of TCIs in the management of AD.

*Wet wrap therapy*

A combined approach to treating AD flare-ups is wet wrap therapy with topical medications. Topical agents are often applied to the skin, followed by a layer of wet viscose tubular dressing and a secondary layer of dry dressing[4].

By providing a smooth texture to the skin and preventing water loss, this treatment enhances its moisturizing effects. Authors[11] cited that a bleach bath combined with twice-weekly intranasal mupirocin treatment was more effective than a placebo in one trial. Bleach baths have been recommended as a technique to reduce S. aureus colonization on the skin and thus prevent recurrent skin infections.

Study[2] reinforces that antiseptics, including triclosan, potassium permanganate, and chlorhexidine gluconate, as well as bleach or sodium hypochlorite, are used to treat infected skin and prevent AD. Antiseptic bathing has been shown to reduce the bacterial load on the skin of AD patients. Consequently, antibiotics mixed with antiseptics have been shown to be particularly effective in treating clinically infected skin in AD.

For the past two decades, wet dressing has been advocated as a relatively safe and effective treatment modality for children with severe and/or refractory AD. Despite numerous publications from various research groups, there are still many unresolved questions regarding the use of wet dressings in the treatment of AD. Wet dressing with cream or ointment and a double layer of cotton bandages, with a moist first layer and a dry second layer, is an effective short-term intervention treatment for children with severe and/or refractory AD[6].

**Systemic therapy**

*Phototherapy*

According to study[13], the technical and scientific recommendation is that phototherapy be a topical therapy option for AD. Among the available phototherapy treatments, narrowband ultraviolet B (UVB) is particularly advantageous due to its low-risk profile, high efficacy, accessibility, and comfort. The Joint Task Force (JTF) guidelines also suggest the use of ultraviolet A (UVA) for acute exacerbations, UVB modalities for chronic AD, and photochemotherapy involving psoralen and UVA for AD patients with severe and generalized symptoms.

Phototherapy can also be used as maintenance therapy for individuals in the chronic phase of AD. The dosage and frequency of phototherapy depend on factors such as the minimum erythema dose, Fitzpatrick skin type, or both. Data on the use of phototherapy in children with AD is limited, and therefore, caution should be exercised when using this technique in children[1].

*Systemic antihistamines*

Scratching the skin triggers the release of histamine and other mediators, which intensifies itching and can lead to frustrating conditions for patients, including sleep disruptions. To address this issue, sedative and non-sedating oral antihistamines are commonly recommended. However, non-sedating antihistamines have not been found to be very effective in controlling pruritus (itching), while sedative antihistamines, such as hydroxyzine, diphenhydramine, and doxepin, have shown some benefit in helping AD patients sleep better[12].

It is important to note that there is currently a lack of evidence to fully support the usefulness of antihistamines specifically for patients with AD. Antihistamines are an important therapeutic class of medications in children. Because the pediatric population encompasses a wide age range, drug therapy in children should be evidence-based[13].

With many new antihistamines now being introduced with additional properties and improved safety profiles, it is imperative to raise concerns that prevent the routine use of first-generation antihistamines in children. More research is needed on newer antihistamines, focusing on specific pediatric age groups[3].

**Roles of multidisciplinary healthcare providers in the treatment of atopic dermatitis**

*Psychological support*

Psychologists play a vital role in providing support to AD patients and their families. They help identify the behavioral and emotional triggers that contribute to itching and scratching, helping patients understand and break this cycle. Psychological interventions have shown promise, although controlled trials in this area are limited[8].

These interventions include relaxation training, diversion techniques, addressing habit problems (identifying situations that worsen symptoms, such as scratching, and replacing them with healthier responses), and stress management[9].

For children with AD, methods such as diversion and redirection to hands-on activities (such as squeezing a stress ball, coloring, or applying moisturizer) can be helpful. Several child-friendly apps for relaxation and sleep therapy are also available to help improve AD treatment[2].

It is important to emphasize that psychological involvement also improves children's attitudes toward adopting various approaches to reduce anxiety about the bite, such as baths and the use of creams. Psychologists can be of great help to patients with AD, as they help build confidence and acceptance of the changes that may occur due to AD. It is important to note that the effectiveness of these psychological interventions may vary from person to person, and more research is needed to fully establish their impact on AD management[10].

*Nutritional assessment and management*

In the multidisciplinary management of infants and children with AD, a licensed dietitian plays a vital role, especially when the AD patient has concomitant food allergies, which occur in approximately 35% of newborns and children with moderate to severe eczema symptoms[1].

Long-term avoidance of various dietary allergens can have adverse effects, including failure to thrive, below-

average height, weight loss, inadequate nutrient intake, and nutritional deficiencies. The author also mentions that short stature is associated with insufficient sleep-in children with AD. Dietary counseling has been shown to help children with food allergies improve their overall energy intake, weight, length/height, and micronutrient intake[13].

**Nanotechnological approaches for the effective treatment of atopic dermatitis**

Nanotechnology offers a safer and more effective therapeutic approach for various dermatological conditions, such as AD, psoriasis, eczema, and cancer. While nanocosmetics are commercially available and readily available to end users, their therapeutic potential for skin diseases remains to be explored[12].

Targeted delivery to the skin is enabled by nanotechnology-based drug delivery systems, which utilize a regulated release and diffusion profile. Due to their site-specific targeting, further reductions in off-target side effects have also been achieved. The authors cite that the use of nanoparticles has been suggested as a potential drug delivery strategy to circumvent poor permeability and poor solubility[11].

Nanoparticles, such as solid lipid nanoparticles (SLNs), nanolipid carriers (NLCs), polymeric nanoparticles (PNPs), nanogels, nanoemulsions (NEs), and other nanocarriers, have been shown to be effective delivery options for AD. Traditionally, topical delivery systems include ointments, creams, and gels of some form. Different carrier systems have been suggested to improve drug penetration into the skin, facilitating drug retention and, in some cases, enabling controlled release mechanisms[9].

Skin permeation is important for a variety of issues, including bacterial and chemical contamination, drug delivery to the skin (dermatological management), and skin care and safety (cosmetics). The physicochemical characteristics of nanocarrier systems, including nanoparticle composition, structural design, size, shape, surface charge, and any associated molecules on the surface, determine the interaction with biological systems and the internalization of nanocarrier cells[2].

Polymeric nanoparticles offer a versatile approach for delivering therapeutic compounds in dermatological applications. These nanoparticles can encapsulate therapeutic agents within their polymeric core or have them adsorbed onto their surface. Nanocapsules and nanospheres are two distinct morphological structures commonly used. The use of polymeric nanoparticles has demonstrated significant potential for topical drug delivery[13].

For example, study[14] cited tacrolimus-loaded chitosan nanoparticles decorated with hyaluronic acid (HA) and demonstrated that the HA coating improved dermal targeting and resulted in superior anti-dermatitis efficacy.

Authors[1] described research involving skin-sensitive chitosan nanoparticles that delivered ceramide and C-phycocyanin to provide anti-inflammatory effects without causing cytotoxicity. They evaluated the impact of these nanoparticles on EC in a mouse model of AD. The study found that the effect of ceramide-containing poly (lactic-co-glycolic acid) nanoparticles on EC formation, as determined by the production of keratinization factors, was like or superior to that of free ceramide.

Due to their wide acceptance as safe, biocompatible, and easy-to-scale lipid nanocarriers, a wide range of therapeutic agents, from biotechnology products to small pharmacological molecules, are increasingly being transported and delivered using these carriers[8].

NLCs incorporate small amounts of liquid lipids into their structure to produce a rearrangement of the lipid matrix, preventing drug expulsion and increasing drug-loading capacity and long-term stability of the nanoparticles. Solid lipid nanoparticles (SLNs) consist of lipids that are solid at room temperature with crystalline lipid matrices[6].

Researchers[10] describe a study in which they prepared SLNs loaded with cyclosporine A using a hot homogenization method. This formulation showed improved skin dispersion, resulting in a twofold increase and decrease in the release of inflammatory markers, such as IL-4 and IL-5, by TH2 cells when tested in a mouse model of AD. In another study, authors demonstrated improved drug transport of tacrolimus-loaded thermosensitive SLNs (TCR-SLNs) compared to a commercial formulation (0.1% Protopic®) in a murine model. TCR-SLNs allowed deeper penetration of tacrolimus into the skin layers.

Due to the destruction of the skin barrier, AD patients with stratum spinosum and stratum granulosum appear to have an abundance of lamellar, ovoid, and membrane-coating granules, which are composed of extruded, parallel discs that aid in the creation of continuous lamellae[14].

Liposomes can be used to treat AD due to their comparable structure, which has a hydrating impact on the EC, as well as the ability to transport bioactive chemicals.

Authors[11] mentioned a study that investigated the antiseptic and anti-inflammatory efficacy of a polyvinylpyrrolidone (PVP)-iodine (3%) liposomal hydrogel applied topically for 4 weeks in a prospective, single-arm (uncontrolled), open-label, phase II pilot clinical trial involving 20 patients with AD. The treatment resulted in significant improvements in Global Clinical Severity (GCS) scores, pain levels, quality of life, and Eczema Area and Severity Index (EASI) scores. The product exhibited mild adverse reactions and was well tolerated.

Another potential agent for the treatment of AD is glycyrrhizin, an antioxidant and antimicrobial compound extracted from licorice. Glycyrrhizin, specifically its active component 18β-glycyrrhetinic acid (GA), was loaded into liposomes and examined for efficacy. In vivo research using a mouse model confirmed the efficacy of GA in preventing itch in chronic dermatitis[12].

Nanoemulsions are emulsions characterized by the presence of nanosized oil globules dispersed in an aqueous phase. The oil phase can be formulated using various lipids and oils, such as triglycerides and essential oils, resulting in nanoemulsions with diverse physicochemical and biological properties. The aqueous portion of nanoemulsion can also be modified by incorporating different water-soluble components. An important distinction between

nanoemulsions and microemulsions is that the former require energy during production, while the latter form spontaneously[6].

Authors[1] cited a study on positively charged O/W nanoemulsions (O/W) containing ceramide-3B, ceramide-3, cholesterol, and palmitic acid (O/W). The efficacy of the O/W cream was compared with that of O/W, negatively charged o/w nanoemulsion (O/W), and stratum corneum lipids stabilized with Carbopol-940 (carbomer), and a commercially available cream (Physiogel®). Fourteen healthy female participants aged 25 to 50 years were involved in the trials. All formulations exhibited improvements in skin hydration and elasticity, with O/W demonstrating significantly greater efficacy than O/W and O/W. This result highlighted the importance of phytosphingosine, lipids, and ceramides in the formulation.

Despite growing interest in developing nanoparticulate formulations to improve the permeation and bioavailability of drugs administered through the skin, there are currently no specific guidelines for topical application. The existing regulatory framework for nanomedicine products focuses primarily on parenteral formulations. However, aspects of this framework can be considered when identifying and investigating the critical quality attributes of nanoformulations in general, including their physical, chemical, and microbiological characteristics during pharmaceutical development.

## Conclusion

Numerous factors, consisting of epidermal genetic mutations, skin barrier dysfunction, immune dysregulation, inflammation of nervous tissues, altered lipid composition, and microbial imbalance, are aspects involved in the development of AD.

Various approaches have been employed to repair skin barrier function and control cutaneous inflammation in patients with AD. To overcome the disadvantages of topically applied anti-inflammatory agents and systemic immunosuppressants, extensive efforts have been made to develop new therapeutic options, namely biologics and microbiome transplantation.

With the help of ingenious nanocarriers, novel approaches can be demonstrated through a combination of novel delivery routes to demonstrate the potential for successful optimization of skin-targeted nanoparticle systems for the management of AD. Nanotechnology applications in skin diseases have offered a promising answer and potential to solve the problems of inflammatory skin diseases. New nanomedicine-based techniques are anticipated to revolutionize aspects of clinical dermatology. Nanomedicines as drug carriers offer superior activity, including increased therapeutic efficacy with reduced toxicity at low doses, drug localization, and specific drug targeting.

However, most existing studies lack clinical data on AD; hence, the need for clinically oriented research to explore the potential benefits of nanoparticles as a future nanocultured anti-AD therapy. Ensuring that nanoformulations comply with current safety regulations is crucial to mitigating potential toxicity risks. Nanotechnology-based drug delivery systems would ultimately be a significant advance in accessible treatments for AD patients shortly.

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