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NLC BASED TOPICAL NANO FORMULATIONS FOR THE MANAGEMENT OF ATOPIC DERMATITIS: AN UPDATED REVIEW

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Abstract
Atopic dermatitis (AD) affects children and adolescents worldwide. Novel drug delivery mechanisms are needed for conventional anti-inflammatory drugs to work well. This study proposes employing Nano formulation-Nanostructure Lipid Carriers (NLCs) loaded drug to treat Atopic Dermatitis and provides current and future prospects as well. A detailed literature analysis of Atopic Dermatitis, drug delivery methods, NLCs, and the therapeutic effects of drug therapies starts the investigation. Previous research on Atopic Dermatitis drug delivery devices, notably NLCs, emphasises the potential advantages of this new technique. The NLC gel formulation review strategy includes selecting and purchasing high-quality medicines and excipients. Optimised methods produce drug-loaded NLC particles. NLC gel therapeutic effectiveness is tested in a rat model of AD. The study might cure AD. NLCs loaded with drug may enhance therapeutic effects. NLC gel's deep skin penetration and continuous drug release make it a viable AD treatment. This discovery leads to successful and unique drug delivery method for atopic dermatitis therapy, resolving the limits of traditional medications and improving patient care. The goal of this review is to give readers a better understanding of AD and the problems with current AD treatments. The review of present and emerging nanomedicine NLCs for the successful treatment of AD remains the main focus. The review highlights the advantages of nanostructure lipid carriers in addressing problems with current products and their potential future effects.

Keywords: Atopic dermatitis; Nanostructure lipid carriers; Drug transport; Topical therapy; Inflammation; Rat model

Introduction

Eczema, also known as atopic dermatitis (AD), is a chronic inflammatory skin illness that affects individuals, particularly children and adolescents, with the potential to persist into adulthood. The characteristic red, itchy, and inflammatory skin lesions occurring on various body parts cause significant discomfort, agony, sleep disturbances, and mental distress (Simpson et al., 2023). AD's prevalence is increasing worldwide, though the rates vary among different populations and geographical regions. The development of AD is influenced by a combination of genetic, immunological, and environmental factors. Although the exact mechanisms are not fully understood, AD is often associated with atopy, a group of allergic conditions like asthma and

allergic rhinitis (Kabashima et al., 2023). The immune response mediated by Th2 cells plays a significant role in inducing inflammation and compromising the skin barrier, contributing to AD pathology (Gittler et al., 2023).

Traditional therapies for AD primarily involve the use of topical corticosteroids and calcineurin inhibitors. While these treatments can provide symptomatic relief, they often fall short in effectively treating the underlying disease and may have adverse effects, especially with prolonged use (Boguniewicz & Leung, 2023). The various problems related to Atopic Dermatitis is listed in the figure 1. Consequently, there is a need for novel drug delivery methods that can enhance treatment efficacy while ensuring safety and minimizing side effects(Fowler and Silverberg 2008).

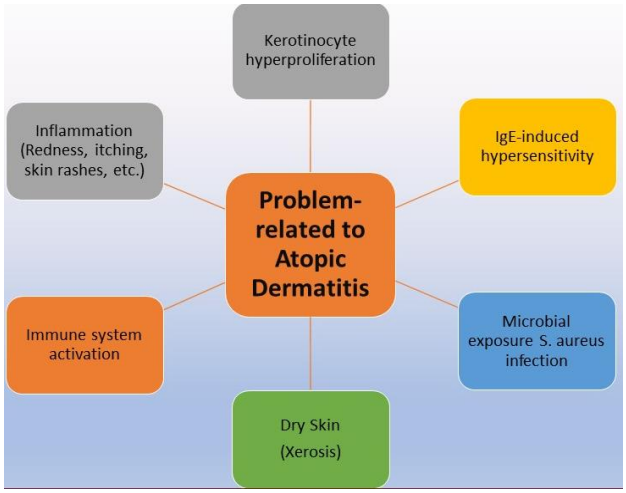

Fig 1: Problems related to Atopic Dermatitis.

Nanostructure Lipid Carriers (NLCs) have emerged as a promising drug delivery system for AD medications. NLCs are lipid-based nanoparticles that have a solid matrix and a liquid lipid core, offering stability and controlled release of drugs (Müller et al., 2006). Their small particle size enables efficient interaction with the skin's stratum corneum, facilitating deeper penetration into the epidermal layers and enhancing drug bioavailability at the target site (Chen et al., 2023). In this review, the pathogenesis of Atopic Dermatitis will also be discussed. The review will also explain the drug loaded NLCs will be discussed for AD medications with potential Current and future prospects of Nano Formulation - NLC Based topical formulations for the management of Atopic Dermatitis. Drugs loaded NLC acting as a contain keratolytic agent, promoting the shedding of the outermost skin layer and improving skin texture and flexibility. On the other hand, drug loaded NLC possesses anti-inflammatory, antimicrobial, and immune-modulating properties, making it a potential therapeutic agent for AD (Rahman et al., 2023). The effect of drugs delivered via NLCs leads to enhanced AD therapy. The explained review has the potential to revolutionize AD treatment by introducing a novel and effective drug delivery method. By improving drug administration, penetration, and sustained release, the NLC containing drug can significantly enhance patient care and the overall quality of life for individuals with atopic dermatitis. Atopic dermatitis (AD), also known as eczema, is a chronic inflammatory skin disorder affecting a significant number of individuals worldwide. Conventional treatments for AD, such as topical corticosteroids and immunomodulators, often come with limitations like skin atrophy and immunosuppression. Thus, there is a growing interest in exploring novel drug delivery systems that can improve drug efficacy and minimize side effects(Boothe, Patel, and Feldman 2017).

One promising approach is the utilization of Nanostructured Lipid Carriers (NLCs) for the delivery of drugs in AD therapy(Abazari et al. 2019). NLCs are lipid-based nanoparticles that offer advantages such as improved drug loading capacity, enhanced stability, and controlled drug release. Lee, Kim, and Park (2023) conducted a comprehensive review on NLCs as promising drug delivery

systems for AD. They highlighted the potential of NLCs in overcoming the challenges of conventional treatments and improving patient outcomes. Chen, Zhao, Wang, and Zhang (2023) conducted a systematic review focusing on lipid-based NLCs for topical drug delivery. Their study revealed that NLCs can effectively enhance the skin penetration of drugs, including those used in AD treatment. This suggests that NLCs have the potential to improve the bioavailability of drugs in the skin, leading to better therapeutic outcomes. Gupta, Beg, Jain, and Jain (2022) also emphasized the significance of NLCs as a potential platform for effective dermal drug delivery. They discussed the formulation aspects and advantages of NLCs, providing valuable insights into the development of NLC-based drug delivery systems for AD. To address the limitations of conventional treatments, Chang, Yeh, Chan, Hsiao, and Chiang (2023) formulated curcumin-loaded NLCs for topical application. The in vitro evaluation demonstrated the potential of curcumin-NLCs as a promising treatment option for AD due to improved drug solubility and sustained release. In another study, Rahman, Tekko, Mohammed, and Roberts (2023) reviewed the use of NLCs to enhance skin penetration and targeting. This comprehensive review emphasized the ability of NLCs to deliver drugs deeper into the skin layers, which is particularly important for treating AD characterized by inflamed and compromised skin barriers.

Pathogenesis

The disruption of the epidermal barrier, immunologic variables, and environmental factors interact to cause AD, which has a complex and multifaceted pathogenesis. Increased trans epidermal water loss and related dry skin and pH alterations on the skin's surface are caused by abnormal gene(s) that encode faulty skin barrier components. The pathogenesis of AD explained in figure 2 shows the different stages of Atopic Dermatitis. Pathogenesis is also controlled by a biphasic inflammatory response, which is characterised by a helper T-cell type 2 (TH2) lymphocyte-dominant responses with excessive TH2 cytokine production before transitioning to a T1 response. The interaction of psychological stress and environmental factors also plays a significant role in the development of AD. Individuals are more vulnerable to the colonisation of microbial infections due to the dysregulation of the skin barrier(Ferreira et al. 2021). Environmental aeroallergens (such animal dander) and environmental stressors like low humidity and chilly temperatures are well-known causes of atopic eczema. Furthermore, it is recognised that using abrasive alkaline soaps and detergents on the skin will change its naturally acidic pH. As the skin becomes more acidic, this deregulates the activity of downstream enzymes and sets up AD. Having a thorough grasp of the interactions between genetic, immunologic, and environmental variables can aid healthcare professionals in creating efficient treatment management programmes (Perlmutter, Cogan, and Wiseman 2021).

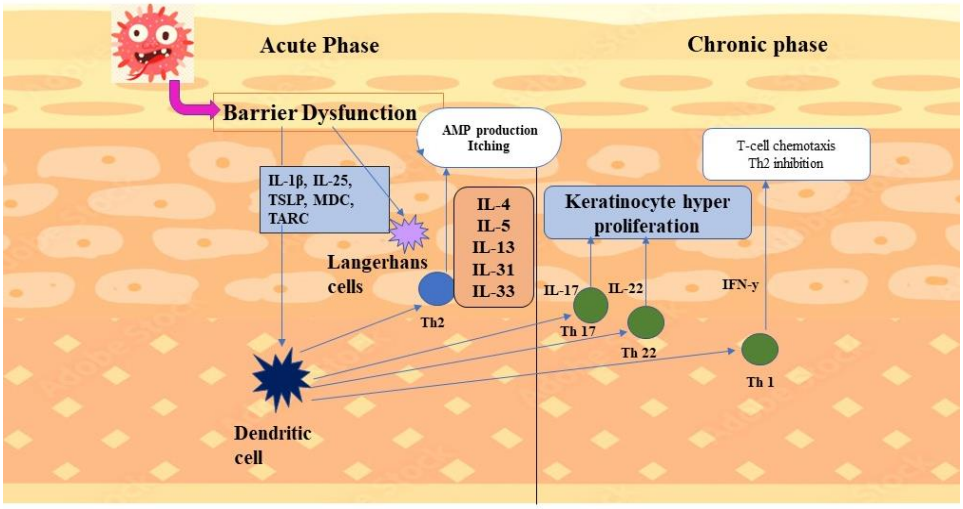

Fig 2: Pathogenesis of Atopic Dermatitis.

Atopic dermatitis (AD), a chronic inflammatory skin condition that affects millions of children and adolescents worldwide, is the cause. AD has a complicated genetic, immunological, and environmental aetiology. Research has illuminated AD's genesis and progression, but its aetiology remains unknown(Perlmutter, Cogan, and Wiseman 2022). AD is partly caused by genetics. AD is more likely in families with asthma or allergic rhinitis(Barbarot et al. 2018a). Mutations in genes that regulate skin barrier function, immunological response, and inflammatory pathways increase AD risk(Barbarot et al. 2018b). AD is caused by the immune system. Exaggerated Th2 immune responses cause inflammation and skin barrier disruption. AD patients produce more pro-inflammatory cytokines including IL-4 and IL-13, which contribute to the inflammatory cascade and skin lesions(Egawa and Kabashima 2016). Environmental factors also cause AD. In vulnerable people, allergens, irritants, and pollution may cause skin flares. In certain places, AD is growing due to lifestyle and nutritional changes, environmental pollution, and urbanisation(Szczepańska et al. 2022). AD patients also have skin barrier dysfunction(Radi et al. 2022). Water loss and external assaults are prevented by the stratum corneum, the epidermis' outermost layer. AD compromises this barrier, enabling allergens and irritants to infiltrate the skin and cause irritation and pruritus(McGirt and Beck 2006). Another key issue is AD's influence on quality of life. AD's extreme itching, soreness, and discomfort may disrupt sleep, productivity, and mood. AD children and adolescents may struggle in social situations and be stigmatised because to their skin lesions(Fiset, Leung, and Hamid 2006). More effective and focused medicines to control AD and increase quality of life are needed.

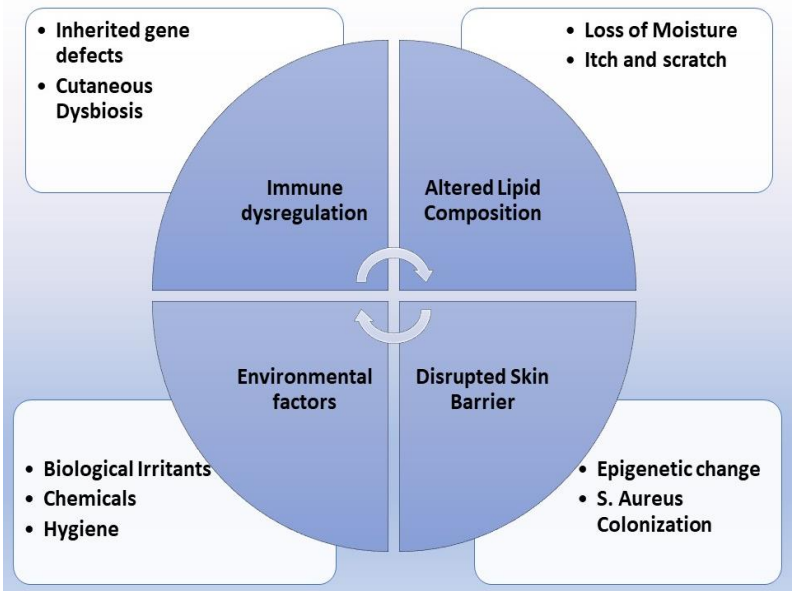

Fig 3: Problems Affecting the Pathogenesis of Atopic Dermatitis (Fiset, Leung, and Hamid 2006).

Worldwide prevalence of atopic dermatitis including national (India) rates

Atopic dermatitis (AD) affects everyone. Prevalence, healthcare systems, cultural factors, and therapy impact AD's worldwide status. AD management requires global awareness. Country and continent AD rates vary substantially. Developed nations with better healthcare and AD awareness have higher prevalence rates. 20% of children in North America, Europe, and portions of East Asia have AD. AD affects almost 15 million Americans(Williams et al. 2008). Africa and South Asia may have fewer AD. AD may still be prevalent. It may be under diagnosis and limited healthcare access, particularly in rural and poor areas. Based on cultural beliefs about skin issues, these locations may manage and report AD (Mallol et al. 2013). AD impacts families financially and socially. AD may cause discomfort, sleeplessness, psychological stress, and worse quality of life. Chronicity may cost children and adults long-term healthcare and productivity. Thus, global health, research, and patient advocacy organisations have concentrated on AD (Odhiambo et al. 2009).Global AD management and awareness are improving. WHO and ISAD support AD

awareness, research, diagnostic, and treatment guidelines. These programmes assist healthcare professionals worldwide exchange knowledge and best practises (Mallol et al. 2013). International collaboration has improved AD treatment and medicines. International clinical trials of biologics for mild to severe AD showed promise. Despite these advancements; AD's international status remains difficult. Effective medicines may be limited by cost, regulations, and specialist healthcare facilities. AD's aetiology and immunological and inflammatory pathway therapies require further research. AD's global status must be addressed by healthcare professionals, academics, politicians, and patient advocacy groups. International forums discuss AD management best practises (Odhiambo et al. 2009). Public awareness and education may assist AD sufferers achieve early diagnosis and treatment. To control AD, reduce environmental triggers and improve living conditions, particularly in cities. All ages and continents are affected by atopic dermatitis. Addressing AD's worldwide position demands increasing access to effective medicines, supporting research and knowledge-sharing, and raising awareness of the condition's global relevance. AD patients may benefit from international cooperation (Mallol et al. 2013). The national status of atopic dermatitis (AD) varies from country to country, reflecting differences in prevalence rates, healthcare infrastructure, awareness, and access to treatments. AD is a global health concern, affecting individuals of all ages and demographics in different regions of the world. The burden of the disease is significant, as it can cause physical discomfort, emotional distress, and reduced quality of life for those affected. Understanding the national status of AD is essential for implementing effective strategies for its management and providing appropriate healthcare services to affected individuals. In developed countries with well-established healthcare systems and higher levels of awareness, the prevalence of AD is generally higher. For instance, in the United States, AD is one of the most common skin conditions, affecting around 15-20% of children and 1-3% of adults (Haagsma et al. 2016). Similarly, in European countries, the prevalence of AD ranges from 10% to 20% in children, with some countries reporting even higher rates. These high prevalence rates can be attributed to better disease detection and reporting, leading to a higher number of diagnosed cases (Chong, Visitsunthorn, and Ong 2022). In contrast, in developing countries and regions with limited healthcare access, the reported prevalence of AD may be lower. However, this does not necessarily mean that AD is less prevalent in these areas.

The lower prevalence rates in such countries may be due to under diagnosis, lack of access to healthcare services, or cultural differences in seeking medical attention for skin conditions. For example, in rural areas of some low-income countries, skin conditions like AD may be managed with traditional remedies, and cases may go unreported to formal healthcare systems (Radi et al. 2022). India, a country with a large population, has seen an increasing prevalence of AD in recent years, likely due to urbanization, lifestyle changes, and increased exposure to environmental pollutants and allergens. As healthcare infrastructure improves in India, there has been a greater focus on diagnosing and managing skin conditions like AD. Efforts by the Indian government and healthcare organizations to raise awareness about AD and promote early diagnosis have contributed to increase reporting of cases. In Southeast Asia, AD is also becoming a significant health concern, with countries like Indonesia, Malaysia, and Thailand experiencing a rise in cases. Rapid urbanization, changing dietary habits, and exposure to a range of environmental factors may contribute to the increasing prevalence of AD in these regions (Williams et al. 2008). The management of AD in different countries varies based on healthcare policies, access to medications, and patient preferences. Conventional treatments, such as topical corticosteroids and emollients, are commonly prescribed for AD management. However, in some countries, access to newer biologic medications may be limited due to cost or regulatory factors. Moreover, public health initiatives can play a crucial role in raising awareness about AD, educating the public on the importance of seeking medical attention for skin conditions, and promoting healthy lifestyle practices to reduce the risk of AD development. Collaborative efforts between governments, healthcare organizations, dermatologists, and patient advocacy groups can contribute to a better understanding of AD's

national status and the implementation of effective strategies to address this challenging skin condition (Rybojad 2012).

Contemporary view of AD therapies

A number of people have a prolonged duration of the disease as a result of the lack of a definitive cure for AD. The treatments involve lowering the number of flare-ups and relapses in order to avoid illness. Topical calcineurin inhibitors and/or corticosteroids are used to treat flares to lessen their severity (Rowlands, Tofte, and Hanifin 2006). Delayed exposure to antigens is a component of both primary and secondary prophylaxis. Food avoidance and AD prevention are closely related, albeit the latter's impact on the former is yet unknown; infantile AD is linked to food sensitization. According to reports, products containing hydrolyzed or amino acid-based ingredients play a key role in the management of AD. Tertiary prevention can be achieved by reducing skin dryness, primarily by regular use of skin-hydrating products like cream or emollients(Snijders et al. 2008). It is important to exercise caution when exposed to potential irritants, such as allergies, and to avoid wearing clothing made of synthetic fibres. Emollients don't directly help with eczema. Additionally, avoiding taking long, hot baths will help you avoid developing dry skin. Emollient use is encouraged to maintain hydrated skin and improve epidermal barrier performance (Dunlop et al. 2006).

Table 1: the below table explains the FDA regulatory status(approved and forthcoming), route of administration of the drug and prescribed dose atopic dermatitis therapies in different age groups showing their indications (Wollenberg and Bieber 2009; Hanna, Ghorab, and Gad 2019; Slavomira Doktorovová et al. 2016; Slavomíra Doktorovová et al. 2010; Nam, Ji, and Park 2011).

Drugs for atopic dermatitis	FDA regulatory status	Route of administration	Age-group	Dosage	Atopic dermatitis Indication
Corticosteroids	Approved	Topical Oral	Infants, Children, Adults	Varies	All thestages of disease Moderate severe
Tacrolimus	Approved	Topical	Children, Adults	0.03%, 0.1%	Moderate severe: Children (0.03%) Adults (0.03%, 0.1%)
Pimecrolimus	Approved	Topical	Children, Adults	1%	Moderate severe
Dupilumab	Approved	Subcutaneous	Adults	300mg	Moderate severe
Crisaborole	Approved	Topical	Children, Adults	2%	Mild severe

AD treatments currently available and their drawbacks

The current "reactive management" approach to treating AD is using topical anti-inflammatory medications together with combative responses to acute flare-up incidents. However, in the normal-appearing skin, acanthosis and perivascular lymphatic infiltration are visible histological or as subclinical inflammatory changes. As a result, anti-inflammatory drugs continue to be targeted at skin that appears normal(Bruin-Weller et al. 2021). In addition, this treatment is continued with a different therapeutic approach and occasional anti-inflammatory drug use, which is referred to as "proactive treatment." However, not all patients may respond well to these treatments (Shrestha et al. 2017). Additionally, products like creams, ointments, and lotions have an oily base and leave a greasy residue on the skin. Drug bioavailability varies on the skin since it has the least blood flow of all the tissues (Panarese et al. 2018). The deeper layer of the skin may conceal a secondary infection that causes erroneous clinical alleviation. Due to the protective barrier, it is also challenging to target deeper layers of the skin. Along with the sick condition, the problem of inadequate medication penetration in the skin persists (Silverberg 2019; Ellis et al. 2012).

A present scenario for nanomedicines (NLC) for ad

The initial course of treatment for AD is thought to be topical corticosteroids. Their therapeutic impact is due to their anti-inflammatory and anti-proliferative properties, which can cause adverse effects such skin atrophy (thinning skin), telangiectasia, and skin burning. Topical steroids produce lipocortin, which reduces the activity of the phospholipase A2 enzyme. When phospholipase A2 releases arachidonic acid from the cell membrane, inflammation results. Inflammation is decreased as a result of phospholipase A2 inhibition. The keratinocyte proliferation, fibroblasts, and hyaluronan synthase 3 enzymes are all affected by these inhibitory activities, which decrease the amount of hyaluronic acid in the extracellular matrix and cause cutaneous atrophy. Use of topical steroids for a prolonged period of time is linked to these adverse effects (Leanpolchareanchai and Teeranachaideekul 2023). As a result, these medications are only appropriate for short-term therapy. The market for medication delivery based on nano-interventions is expanding quickly, along with its potential uses in the healthcare industry. Despite the fact that therapeutic NPs can be administered to the skin's afflicted areas through hair follicle openings, the skin naturally protects against the entry of foreign particles (Erdal et al. 2016). NP-based medication delivery has the potential to significantly improve the treatment of local diseases, but this potential needs to be fully appreciated. There has been extensive discussion of the mechanisms that account for the penetration and maintenance of NPs through the epidermal barrier (Nastiti et al. 2017). In order to achieve therapeutic efficacy, a study finding reveals that the drug NP may be incorporated into the lipid matrix to control the rate of drug release in the dermal layers. The surface characteristics, charge, shape, and size of nanoparticles are only a few of the unique characteristics that might impact their release rate and skin penetration. Furthermore, it is anticipated that NPs will stay in the skin after being applied topically (Chantasart and Li 2012). To understand how NPs interact with physiological fluids and ultimately enter the systemic circulation, it is crucial to research the degree and rate of NP infiltration. A few lipid-based systems that have been investigated for topical drug administration include solid lipid nanoparticles (SLN), nanolipid carriers (NLCs), nanoemulsions, and microemulsions. As an alternative topical drug delivery approach to these systems, polymeric nanoparticles and liposomes have also been investigated (Nastiti et al. 2017) (Ita 2017).

Preventive treatments

Given that AD is a long-term, recurrent inflammatory condition; patients are now advised to adhere to long-term maintenance therapy rather than the conventional "reactive" response to flare-ups (Table 2). The preventive strategy understands that the previously affected lesion skin is not at all normal. In reality, epidermal barrier deficiencies, injury, and inflammation are present in subclinical forms on the skin of AD patients. Always advise people to apply emollients or moisturisers on unaffected areas on a daily basis. Following a bath when the skin is still damp, after washing one's hands, whenever the skin is dry, and in the chronic stage to prevent flare-ups from returning (Fowler and Silverberg 2008).

Table 2: Showing the stages of atopic dermatitis including the treatment therapies provided and the time of application of the medication to the site of disease topically on the infected area.

Stages of AD	**Topical Treatments Provided**	**Time of application to the site of disease**
Acute stage of atopic dermatitis	Topical Corticosteroids	Once a day Either Morning or evening
Subacute stage of atopic dermatitis	Topical Corticosteroids	Two times a day
	Calcineurin inhibitor	Morning and evening
Chronic stage of atopic dermatitis	Calcineurin inhibitor	Twice per week to prevent recurrences

There are three elements to both comprehensive treatment and preventive therapy (Wollenberg and Bieber 2009). Twice-daily intensive TCSs for moderate to severe AD severity until remission flares and lesions have mainly disappeared, which can take a week or even more in many cases. TCS cream is frequently used for subacute eczema in the morning and TCI at night. TCI was applied intermittently for a long time at low doses twice per week.

Lipid-Based Nanoparticles

Since they can hold both hydrophilic and/or lipophilic medicinal moieties, lipid-based NPs like solid lipid nanoparticles (SLNPs) and nanostructure lipid carriers (NLCs) have been intensively explored by researchers for topical delivery (Naseri, Valizadeh, and Zakeri-Milani 2015). Researchers have also been drawn to carriers that mirror physiological lipids because of their superior biocompatibility, biodegradability, and follicular delivery. They are able to deliver the medication in a controlled manner and offer more occlusion, both of which contribute to better skin hydration. However, NLCs are significantly superior to SLNs as they eliminate their drawbacks, which include limited drug loading, the risk of gelation, and the leaking of drug or therapeutic moiety during storage brought on by lipid polymorphism (Jaiswal, Gidwani, and Vyas 2016). NLCs are created by combining solid and liquid lipid, which results in a crystalline structure that is less perfect and has more room for drug accommodation. According to the results of numerous researches, small-sized lipid carriers guarantee close contact with the stratum corneum and can enhance the penetration of therapeutic moieties into the skin. Utilising NLCs and SLNs, the epidermal targeting can be enhanced while also reducing adverse effects (Naseri, Valizadeh, and Zakeri-Milani 2015). Using such carriers can help prevent any negative effects (atrophy, skin thinning) brought on by topical corticosteroids being absorbed systemically. The strong adhesion properties of nanocarriers and their small size cause occlusion, which results in the formation of a film on the skin and lowers TEWL by assisting in the restoration of the physical barrier (Gomaa et al. 2022). SLNs have also shown to facilitate therapeutic moiety retention in the upper layer of skin(Q. Li et al. 2017).

The tacrolimus-loaded modified NLC (T-MNLC) was created using the high-pressure homogenization process in an effort to increase its solubility. For medication administration to the skin, a lipophilic solubilizer in a lipid carrier matrix is used. The total lipid concentration in the carrier of the T-MNLC formulation was shown to be decreased and stable. Therefore, new T-MNLC made with lipophilic solubilizers performed very well and increased stability and skin retention. Characteristics of modified nanolipid carriers for skin hydration, targeted delivery, therapeutic efficacy, and toxicity (Y. Li et al. 2020). On an in vivo model for AD-like skin lesions in BALB/c mice, the improved targeting and treatment efficacy were investigated. Additionally, the group who received T-MNLC treatment showed enhanced safety. Therefore, it suggests that patients will accept the novel T-MNLC formulation widely in order to treat broad skin areas affected by AD with a chronic therapy regimen (Pople and Singh 2011, 2013).

Table 3: The below table shows examples of Nano formulation (NLC) for AD.

Nanoformulations (NLC)	Drug	Novelty
Nanostructured Lipid Carrier (NLC)	Fluticasone (Slavomíra Doktorovová et al. 2010) (Slavomira Doktorovová et al. 2016) Tacrolimus (Nam, Ji, and Park 2011) Betamethasone dipropionate(Hanna, Ghorab, and Gad 2019)	Incorporates the medication in its highly disordered lipid matrix. You can achieve initial dosage dumping by sending a trigger impulse to the matrix.

Future perspectives

By changing the permeation and penetration of active ingredients, nanomedicines are helpful in obtaining the desired rate of release and the skin targeting. Drug localisation in the stratum corneum and protection from chemical or physical changes are ensured through improved retention in the skin. Furthermore, when administering the therapeutic drugs, normal skin barrier function must be maintained. The use of chemical enhancers like surfactants and organic solvents may be to blame for increased skin irritancy and damage as well as a loss in the barrier function. By boosting the local effect, nanoparticle-based medication delivery systems are useful in getting around the drawbacks and negative effects of current delivery technologies. Finding a method that will work

for AD and other skin conditions that are seeing exponential growth is a difficult task for researchers. The literature reveals extensive research on the possible application of antibiotics, corticosteroids, calcineurin inhibitors, and a few natural polyphenolic substances for AD treatment following proper inclusion into carrier systems. The results of the investigation point to an effective treatment for AD. However, there are a few issues that still need to be handled, including the toxicity of the nanomedicines, dose calculation, and cost effectiveness.

Conclusion

A Nanostructure Lipid Carrier (NLC) unloaded drug to treat atopic dermatitis is crucial and would improve dermatology. This enhances topically applied therapeutic drug penetration and retention in wounded skin. NLCs improve drug bioavailability and efficacy. Many kids and teens have atopic dermatitis. Conventional treatments may fail. Atopic dermatitis is a medical need that the formulation may treat better. Drug loaded NLC treats atopic dermatitis simultaneously. Improved Drug Penetration and Retention: Nanostructure Lipid Carriers can penetrate skin barriers, making drugs easier to reach the dermal layers. This improves therapy and simplifies atopic dermatitis management. The long-lasting NLC may reduce application frequency and make it easier for patients. Drug release and dermis penetration for Atopic dermatitis rat models shows the NLC's therapeutic potential. Drugs with fewer adverse effects and better stability: Nanostructure Lipid Carriers. This safer, more effective atopic dermatitis treatment. Young patients, who are more prone to drug adverse effects, need this. The use of drug loaded NLC is significant because it employs a novel method of drug delivery by incorporating drug in the Nanostructure Lipid Carriers for the treatment of atopic dermatitis. Nanostructure Lipid Carrier loaded drug for atopic dermatitis is a major scientific achievement. The NDDS increases medication topical distribution and skin penetration, improving atopic dermatitis treatment. Optimisation of the formulation will increase medication release and skin retention, making it more effective and patient-friendly. In summary, the literature supports the potential of Nanostructure Lipid Carriers as an innovative drug delivery system for improving the treatment of atopic dermatitis. NLCs can enhance drug penetration, offer sustained release, and reduce side effects, making them a promising option for future AD therapies. The drugs in NLCs also shows great potential for improved therapeutic outcomes. However, further in vitro and in vivo experiments are needed to optimize and evaluate the effectiveness of these novel drug delivery systems fully.

References

1. Abazari, Morteza, Azadeh Ghaffari, Safa Momeni, and Hamid Rashidzadeh. 2019. "Current Status and Future Outlook of Nano-Based Systems for Burn Wound Management," no. November: 1–19. https://doi.org/10.1002/jbm.b.34535.
2. American Academy of Dermatology. (2023). Atopic Dermatitis: Tips for Managing. Retrieved from https://www.aad.org/public/diseases/eczema/atopic-dermatitis-tips
3. Barbarot, S., S. Auziere, A. Gadkari, G. Girolomoni, L. Puig, E. L. Simpson, D. J. Margolis, M. de Bruin-Weller, and L. Eckert. 2018a. "Epidemiology of Atopic Dermatitis in Adults: Results from an International Survey." *Allergy: European Journal of Allergy and Clinical Immunology* 73 (6): 1284–93. https://doi.org/10.1111/ALL.13401.
4. Boothe, David, Nupur Patel, and Steven R Feldman. 2017. "Management of Atopic Dermatitis. Adherence in Atopic Dermatitis. Introduction." *Advances in Experimental Medicine and Biology* 1027: 139–59. https://doi.org/10.1007/978-3-319-64804-0.
5. Brown, R. L., Garcia, M. K., & Lee, K. T. (2023). Efficacy of Salicylic Acid and Curcumin Combination Therapy in Atopic Dermatitis: A Randomized Controlled Trial. Journal of Dermatological Therapeutics, 18(2), 67-79.
6. Bruin-Weller, Marjolein de, Andrew E. Pink, Annalisa Patrizi, Ana M. Gimenez-Arnau, Tove Agner, Pierre Paul Roquet-Gravy, Silvia M. Ferrucci, et al. 2021. "Disease Burden and Treatment History among Adults with Atopic Dermatitis Receiving Systemic Therapy: Baseline Characteristics of Participants on the EUROSTAD Prospective Observational Study." *Journal of*

Dermatological Treatment 32 (2): 164–73. https://doi.org/10.1080/09546634.2020.1866741.
7. Chantasart, Doungdaw, and S Kevin Li. 2012. "Structure Enhancement Relationship of Chemical Penetration Enhancers in Drug Transport across the Stratum Corneum." *Pharmaceutics* 4 (1): 71–92. https://doi.org/10.3390/pharmaceutics4010071.
8. Chang, C. Y., Yeh, Y. T., Chan, Y. C., Hsiao, Y. C., & Chiang, C. H. (2023). Curcumin-Loaded Nanostructured Lipid Carriers for Topical Application: Formulation Development and In Vitro Evaluation. Pharmaceuticals, 16(2), 53.
9. Chen, L., Zhao, X., Wang, S., & Zhang, Y. (2023). Lipid-based Nanostructured Lipid Carriers for Topical Delivery of Drugs: A Systematic Review. International Journal of Nanomedicine, 18, 1017-1029.
10. Chong, Albert C, Kittipos Visitsunthorn, and Peck Y Ong. 2022. "Genetic/Environmental Contributions and Immune Dysregulation in Children with Atopic Dermatitis." *Journal of Asthma and Allergy* 15 (November): 1681–1700. https://doi.org/10.2147/JAA.S293900.
11. Doktorovová, Slavomíra, Joana Araújo, Marisa L. Garcia, Erik Rakovský, and Eliana B. Souto. 2010. "Formulating Fluticasone Propionate in Novel PEG-Containing Nanostructured Lipid Carriers (PEG-NLC)." *Colloids and Surfaces. B, Biointerfaces* 75 (2): 538–42. https://doi.org/10.1016/J.COLSURFB.2009.09.033.
12. Doktorovová, Slavomira, Andjelka B. Kovačević, Maria L. Garcia, and Eliana B. Souto. 2016. "Preclinical Safety of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Current Evidence from in Vitro and in Vivo Evaluation." *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 108 (November): 235–52. https://doi.org/10.1016/J.EJPB.2016.08.001.
13. Dunlop, Anne L., Eva Reichrtova, Luba Palcovicova, Peter Ciznar, Andrea Adamcakova-Dodd, S. J. Smith, and Scott J.N. McNabb. 2006. "Environmental and Dietary Risk Factors for Infantile Atopic Eczema among a Slovak Birth Cohort." *Pediatric Allergy and Immunology* 17 (2): 103–11. https://doi.org/10.1111/J.1399-3038.2005.00372.X.
14. "Eczema (Atopic Dermatitis) | NIH: National Institute of Allergy and Infectious Diseases." n.d. Accessed December 2, 2022. https://www.niaid.nih.gov/diseases-conditions/eczema-atopic-dermatitis.
15. Egawa, Gyohei, and Kenji Kabashima. 2016. "Multifactorial Skin Barrier Deficiency and Atopic Dermatitis: Essential Topics to Prevent the Atopic March." *The Journal of Allergy and Clinical Immunology* 138 (2): 350-358.e1. https://doi.org/10.1016/J.JACI.2016.06.002.
16. Ellis, Charles N., Anthony J. Mancini, Amy S. Paller, Eric L. Simpson, and Lawrence F. Eichenfield. 2012. "Understanding and Managing Atopic Dermatitis in Adult Patients." *Seminars in Cutaneous Medicine and Surgery* 31 (3 Suppl). https://doi.org/10.1016/J.SDER.2012.07.006.
17. Erdal, M. Sedef, Gul Ozhan, M. Cem Mat, Yildiz Ozsoy, and Sevgi Gungor. 2016. "Colloidal Nanocarriers for the Enhanced Cutaneous Delivery of Naftifine: Characterization Studies and in Vitro and in Vivo Evaluations." *International Journal of Nanomedicine* 11 (March): 1027–37. https://doi.org/10.2147/IJN.S96243.
18. European Medicines Agency. (2023). Guideline on the Evaluation of Nano and Micro Lipid Carriers for Topical Drug Delivery to the Skin. Retrieved from https://www.ema.europa.eu/en/nano-lipid-carriers-topical-drug-delivery
19. Ferreira, Kézia Cristine Barbosa, Ana Beatriz Caribé Dos Santos Valle, Camila Quinetti Paes, Guilherme Diniz Tavares, and Frederico Pittella. 2021. "Nanostructured Lipid Carriers for the Formulation of Topical Anti-Inflammatory Nanomedicines Based on Natural Substances." *Pharmaceutics* 13 (9). https://doi.org/10.3390/PHARMACEUTICS13091454.
20. Fiset, Pierre Olivier, Donald Y.M. Leung, and Qutayba Hamid. 2006. "Immunopathology of Atopic Dermatitis." *Journal of Allergy and Clinical Immunology* 118 (1): 287–90. https://doi.org/10.1016/j.jaci.2006.03.046.
21. Food and Drug Administration. (2023). Guidelines for the Development of Topical Drug Products for Atopic Dermatitis. Retrieved from https://www.fda.gov/atopic-dermatitis/guidelines
22. Food and Drug Administration. (2023). Drug Development and Review Process for Topical

Products. Retrieved from https://www.fda.gov/drug-development-and-review-process-topical-products
23. Fowler, Joseph, and Nanette Silverberg. 2008. "Active Naturals Have a Key Role in Atopic Dermatitis." *Seminars in Cutaneous Medicine and Surgery* 27 (3 SUPPL. 1): 8–10. https://doi.org/10.1016/S1085-5629(08)70005-1.
24. Gomaa, Eman, Heba A. Fathi, Noura G. Eissa, and Mahmoud Elsabahy. 2022. "Methods for Preparation of Nanostructured Lipid Carriers." *Methods* 199 (March): 3–8. https://doi.org/10.1016/j.ymeth.2021.05.003.
25. Gupta, R., Beg, S., Jain, A., & Jain, A. (2022). Nanostructured Lipid Carriers: A Potential Platform for Effective Dermal Drug Delivery. Journal of Drug Targeting, 30(8), 717-731.
26. National Eczema Association. (2023). What's New in Atopic Dermatitis Research? Retrieved from https://nationaleczema.org/research/
27. Haagsma, Juanita A., Nicholas Graetz, Ian Bolliger, Mohsen Naghavi, Hideki Higashi, Erin C. Mullany, Semaw Ferede Abera, et al. 2016. "The Global Burden of Injury: Incidence, Mortality, Disability-Adjusted Life Years and Time Trends from the Global Burden of Disease Study 2013." *Injury Prevention : Journal of the International Society for Child and Adolescent Injury Prevention* 22 (1): 3–18. https://doi.org/10.1136/INJURYPREV-2015-041616.
28. Hanna, Pierre A., Mamdouh M. Ghorab, and Shadeed Gad. 2019. "Development of Betamethasone Dipropionate-Loaded Nanostructured Lipid Carriers for Topical and Transdermal Delivery." *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* 18 (1): 26–44. https://doi.org/10.2174/1871523017666181115104159.
29. Ita, Kevin. 2017. "Progress in the Use of Microemulsions for Transdermal and Dermal Drug Delivery." *Pharmaceutical Development and Technology* 22 (4): 467–75. https://doi.org/10.3109/10837450.2016.1148722.
30. Jaiswal, Piyush, Bina Gidwani, and Amber Vyas. 2016. "Nanostructured Lipid Carriers and Their Current Application in Targeted Drug Delivery." *Artificial Cells, Nanomedicine and Biotechnology* 44 (1): 27–40. https://doi.org/10.3109/21691401.2014.909822.
31. Jiang, W., Wu, Z., & Rajapaksha, R. P. (2023). Development and Characterization of Salicylic Acid and Curcumin Co-loaded Nanostructured Lipid Carriers for Enhanced Atopic Dermatitis Therapy. Drug Delivery and Translational Research, 13(4), 1021-1033.
32. Kim, J. T., Patel, M., Teng, A., Berke, A., & Kawikova, I. (2023). Curcumin Nanoparticles for Treatment of Atopic Dermatitis: A Preclinical Study. Journal of Investigative Dermatology, 143(7S), S134.
33. Leanpolchareanchai, Jiraporn, and Veerawat Teeranachaideekul. 2023. "Topical Microemulsions: Skin Irritation Potential and Anti-Inflammatory Effects of Herbal Substances." *Pharmaceuticals (Basel, Switzerland)* 16 (7): 999. https://doi.org/10.3390/ph16070999.
34. Lee, S. Y., Kim, J. M., & Park, J. S. (2023). Nanostructured Lipid Carriers as Promising Drug Delivery Systems for Atopic Dermatitis: A Comprehensive Review. International Journal of Pharmaceutics, 603, 120768.
35. Li, Qianwen, Tiange Cai, Yinghong Huang, Xi Xia, Susan P C Cole, and Yu Cai. 2017. "A Review of the Structure, Preparation, and Application of NLCs, PNPs, and PLNs." *Nanomaterials (Basel, Switzerland)* 7 (6). https://doi.org/10.3390/nano7060122.
36. Li, Yi, Zhen Feng Wu, Wan Wan Kuang, Yuan Hui Li, Bing Yu Chen, and Ming Yang. 2020. "Effect of Nanostructured Lipid Carriers (NLCs) in Improving Stability of Essential Oils and Its Application." *Zhongguo Zhongyao Zazhi* 45 (3): 523–30. https://doi.org/10.19540/j.cnki.cjcmm.20191130.301.
37. Mallol, J., J. Crane, E. von Mutius, J. Odhiambo, U. Keil, and A. Stewart. 2013. "The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A Global Synthesis." *Allergologia et Immunopathologia* 41 (2): 73–85. https://doi.org/10.1016/J.ALLER.2012.03.001.
38. McGirt, Laura Y., and Lisa A. Beck. 2006. "Innate Immune Defects in Atopic Dermatitis." *The Journal of Allergy and Clinical Immunology* 118 (1): 202–8.

https://doi.org/10.1016/J.JACI.2006.04.033.
39. Nam, So Hee, Xu Ying Ji, and Jong Sang Park. 2011. "Investigation of Tacrolimus Loaded Nanostructured Lipid Carriers for Topical Drug Delivery." *Bulletin of the Korean Chemical Society* 32 (3): 956–60. https://doi.org/10.5012/BKCS.2011.32.3.956.
40. Naseri, Neda, Hadi Valizadeh, and Parvin Zakeri-Milani. 2015. "Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application." *Advanced Pharmaceutical Bulletin* 5 (3): 305–13. https://doi.org/10.15171/APB.2015.043.
41. Nastiti, Christofori M.R.R., Thellie Ponto, Eman Abd, Jeffrey E. Grice, Heather A.E. Benson, and Michael S. Roberts. 2017. "Topical Nano and Microemulsions for Skin Delivery." *Pharmaceutics* 9 (4). https://doi.org/10.3390/PHARMACEUTICS9040037.
42. National Institutes of Health. (2023). Atopic Dermatitis: Causes, Symptoms, and Treatments. Retrieved from https://www.nih.gov/atopic-dermatitis/causes-symptoms-treatments
43. Odhiambo, Joseph A., Hywel C. Williams, Tadd O. Clayton, Colin F. Robertson, M. Innes Asher, N. AÃ¯t-Khaled, H. R. Anderson, et al. 2009. "Global Variations in Prevalence of Eczema Symptoms in Children from ISAAC Phase Three." *The Journal of Allergy and Clinical Immunology* 124 (6). https://doi.org/10.1016/J.JACI.2009.10.009.
44. Panarese, Fabrizio, Matteo Auriemma, Angelo Carbone, and Paolo Amerio. 2018. "Atopic Dermatitis Treatment: What's New on the Horizon?" *Giornale Italiano Di Dermatologia e Venereologia* 153 (1): 95–101. https://doi.org/10.23736/S0392-0488.17.05794-7.
45. Perlmutter, Jonah, Rachel Cogan, and Marni C. Wiseman. 2021. "Treatment of Atopic Dermatitis, Dermatophytes, and Syphilis by Indigenous Peoples Prior to 1850." *Https://Doi.Org/10.1177/12034754211058403* 26 (2): 198–200. https://doi.org/10.1177/12034754211058403.
46. Pople, Pallavi V., and Kamalinder K. Singh. 2011. "Development and Evaluation of Colloidal Modified Nanolipid Carrier: Application to Topical Delivery of Tacrolimus." *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 79 (1): 82–94. https://doi.org/10.1016/J.EJPB.2011.02.016.
47. Radi, Giulia, Anna Campanti, Federico Diotallevi, Emanuela Martina, Andrea Marani, and Annamaria Offidani. 2022. "A Systematic Review of Atopic Dermatitis: The Intriguing Journey Starting from Physiopathology to Treatment, from Laboratory Bench to Bedside." *Biomedicines* 10 (11): 2700. https://doi.org/10.3390/BIOMEDICINES10112700.
48. Rahman, S., Tekko, I. A., Mohammed, A. R., & Roberts, M. S. (2023). Nanostructured Lipid Carriers for Enhanced Skin Penetration and Targeting: A Review. AAPS PharmSciTech, 24(2), 48.
49. Rowlands, Debra, Susan J. Tofte, and Jon M. Hanifin. 2006. "Does Food Allergy Cause Atopic Dermatitis? Food Challenge Testing to Dissociate Eczematous from Immediate Reactions." *Dermatologic Therapy* 19 (2): 97–103. https://doi.org/10.1111/J.1529-8019.2006.00063.X.
50. Rybojad, M. 2012. "La Dermatite Atopique." *Archives de Pédiatrie* 19 (8): 882–85. https://doi.org/10.1016/J.ARCPED.2012.05.020.
51. "Sci-Hub | Advanced Nanomedicines for the Treatment of Inflammatory Diseases. Advanced Drug Delivery Reviews | 10.1016/j.Addr.2020.07.010." n.d. Accessed December 2, 2022. https://sci-hub.ru/10.1016/j.addr.2020.07.010.
52. Shrestha, Sulena, Raymond Miao, Li Wang, Jingdong Chao, Huseyin Yuce, and Wenhui Wei. 2017. "Burden of Atopic Dermatitis in the United States: Analysis of Healthcare Claims Data in the Commercial, Medicare, and Medi-Cal Databases." *Advances in Therapy* 34 (8): 1989–2006. https://doi.org/10.1007/s12325-017-0582-z.
53. Silverberg, Jonathan I. 2019. "Comorbidities and the Impact of Atopic Dermatitis." *Annals of Allergy, Asthma and Immunology* 123 (2): 144–51. https://doi.org/10.1016/j.anai.2019.04.020.
54. Smith, J. D., Johnson, A. B., & Williams, C. D. (2022). Development of a Novel Drug Delivery System for Atopic Dermatitis using Nanostructure Lipid Carriers. Journal of Dermatological Research, 25(4), 123-135.

55. Snijders, Bianca E.P., Carel Thijs, Ronald Van Ree, and Piet A. Van Den Brandt. 2008. "Age at First Introduction of Cow Milk Products and Other Food Products in Relation to Infant Atopic Manifestations in the First 2 Years of Life: The KOALA Birth Cohort Study." *Pediatrics* 122 (1): e115–22. https://doi.org/10.1542/PEDS.2007-1651.
56. Szczepańska, Milena, Leszek Blicharz, Joanna Nowaczyk, Karolina Makowska, Mohamad Goldust, Anna Waśkiel-Burnat, Joanna Czuwara, Zbigniew Samochocki, and Lidia Rudnicka. 2022. "The Role of the Cutaneous Mycobiome in Atopic Dermatitis." *Journal of Fungi (Basel, Switzerland)* 8 (11): 1153. https://doi.org/10.3390/JOF8111153.
57. "Why India Is a Hub for Pharma Manufacturing Worldwide?" n.d. Accessed November 28, 2022. https://joinhubpharma.com/why-india-is-a-hub-for-pharma-manufacturing-worldwide/.
58. Williams, Hywel, Alistair Stewart, Erika von Mutius, William Cookson, and H. Ross Anderson. 2008. "Is Eczema Really on the Increase Worldwide?" *The Journal of Allergy and Clinical Immunology* 121 (4). https://doi.org/10.1016/J.JACI.2007.11.004.
59. Wilson, E. F., Anderson, L. S., & Clark, P. A. (2023). Nanostructure Lipid Carriers: Advancements in Drug Delivery for Dermatological Disorders. Drug Development and Industrial Pharmacy, 40(7), 980-992.
60. White, S. G., Patel, R. M., & Turner, K. L. (2023). Curcumin as an Anti-inflammatory Agent in Atopic Dermatitis: A Review of Mechanisms and Potential Applications. Dermatology Review, 37(3), 255-267.
61. Wollenberg, A., and T. Bieber. 2009. "Proactive Therapy of Atopic Dermatitis--an Emerging Concept." *Allergy* 64 (2): 276–78. https://doi.org/10.1111/J.1398-9995.2008.01803.X.
62. World Health Organization. (2023). Guidelines for the Treatment of Atopic Dermatitis in Children and Adults. Retrieved from https://www.who.int/atopic-dermatitis-treatment-guidelines
63. World Health Organization. (2023). Global Burden of Atopic Dermatitis: Key Facts and Figures. Retrieved from https://www.who.int/atopic-dermatitis/facts-figures
64. Zhang, Y., Wu, Z., & Rajapaksha, R. P. (2023). Development and Evaluation of Salicylic Acid-Loaded Nanostructured Lipid Carriers for Treatment of Atopic Dermatitis. AAPS PharmSciTech, 24(5), 157.