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Atopic dermatitis: Comprehensive and extended Epidemiology, Management and Treatment schema- newer insights.

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ABSTRACT: -

In a chronic inflammatory skin condition Atopic dermatitis (AD) has a detrimental effect on patients' general quality of life and financial resources for medical care. With numerous clinical presentations and symptom clusters, it is a complex illness. According to recent research, the prevalence of AD is still increasing, especially in low-income countries, where it may impact up to 20.1% of children and 4.9% of adults. Usually, AD onset is in the early years of life, and it frequently happens before other allergy diseases like asthma or allergic rhinitis. The appearance and geography of the rash are normally thoroughly examined, together with information regarding the particular patient, before a diagnosis is generally reached. Conditions that occasionally mirror AD include Scabies, Seborrheic Dermatitis, and Contact Dermatitis.Risk factors for AD are frequently immune system or skin barrier dysfunction that are genetically determined. Clinical signs of AD may not be due to genetic defects alone, but rather to a dysfunctional epidermal barrier in genetically predisposed individuals mixed with the adverse effects of environmental toxins. Despite the fact that AD has always been referred to be an allergic skin disease, current research disputes the contribution of allergic reactions to the onset of the disease and contends that in those with AD and an underlying atopic constitution, allergy manifests as a side consequence.

To stop the disease from spreading, people apply creams on a daily basis to encourage the regeneration of the epidermal barrier. One of the conventional treatments is topical corticosteroids, although alternative possibilities for those with more severe AD include Calcineurin Inhibitors, Antihistaminic, Antibiotics, Photo-therapy, and Immunosuppressant medications. Drugs administered topically to skin layers that are deep is cumbersome because of its nature as an anatomical barrier, that inhibits drugs from going deeper into the skin. Due to the potential of nanoparticles (NPs), innovative medication delivery strategies have attracted a lot of interest having the capability to: - enhance the solubility,bioavailability,diffusion,target particular cell type, andminimise any side-effects of those drugs used to treat AD.

Keywords: - Epidermal barrier, Atopic Dermatitis, Allergic, Topical corticosteroids ,Nanoparticle.

I. INTRODUCTION: -

1.1 What is Atopic Dermatitis?

The most prevalent chronic inflammatory skin condition is Atopic Dermatitis (AD) [1, 2]. The majority of disease presentations—nearly 80%—typically begin in infancy or youth, with the remaining 20% appearing in maturity. While the prevalence varies between 2.1% and 4.9% in adults, it varies between 2.7% and 20.1% in children across all geographic regions [3, 4]. The disease presents an elevated heterogeneity in its natural presentation, and individual tangents are improbable.

AD is one of the major diseases in the wide spectrum of atopic disorder class involving food allergies,asthma and/or Allergic Rhinoconjunctivitis, that are pertinent comorbid associations [5]. Immunoglobulin-E (IgE)-associated allergic reactions caused by environmental allergens constitute the most prevailing aspect of atopic disorders. In recent times, cardio-vascular, and neurological, psychiatric diseases have also been noted to be associated illness with AD, notwithstanding the fact that the mechanisms influencing these coalitions remain elusive [6-8].

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2. CAUSATIVES: -

2.1 General: -

The skin assists as the bodily surface that connects to the outside world.Because of this,skin is very responsive to a variety of factors that could cause inflammation, including allergens as well as irritants. The resultant of these elements is scratching, which both starts and keeps the inflammatory cascade going since atopic keratinocytes secrete pro-inflammatory cytokines. Stress has been shown to affect the immune system and, when combined with scratching, has been shown to exacerbate AD.

2.2 Allergens: -

Inover 40% of children with moderate to severe AD, food allergies can result in eczematoid skin rashes, according to placebo-controlled food challenge studies.

In a subordinate group of these people, urticarial responses, or non-cutaneous sensations, can set off the cycle of itching and scratching that worsens the condition of the skin.

Rapid skin tests or serum IgE are frequently positive for several foods in children with food allergies, explicitly:

1. Eggs
2. Milk
3. Wheat
4. Soy
5. Peanuts.

Importantly, T-cells that are distinct to immunological irritant associated with food have been cloned from the skin lesions of patients suffering from AD, delivering conclusive proof that food may cause inflammation of skin. In AD mouse models, oral food sensitization causes eczematous skin lesions to appear in response to subsequent oral food challenges.

Children usually outgrow food allergies by the time they are three, but they could develop a sensitivity to inhalant allergens instead.In patients with sensitised AD, intranasal or bronchial inhalation challenges with aerial allergens can result in pruritus and skin lesions.30–50% of the individuals who undergo Atopy patch testing utilising aeroallergens such HDMs, weeds, animal dander, and moulds on the unaffected skin of patients suffering from AD experience eczematoid reactions. It has been found that a combination of successful HDM-reduction strategies can improve AD.The level of severity of AD is directly coincides with the level of Ig-E sensitivity to the aero-allergens.

The isolation of the T-cells which particularly reacts to Dermatophagoides pteronyssinus and other aero-allergens fromskin lesions of AD andthe notion that environmental allergens may be able to cause the immunological response in AD skin is supported by the locations of the allergen patch tests.

2.3 Auto-allergens: -

It has been noted that patients with severe AD produce IgE antibodies against human proteins. IgE immune complexes in AD sera contain the intracellular proteins that have been revealed to be auto-allergens thus far. According to these findings,inflammation due to allergy can be sustained in chronic AD due to theproteins produced by the injuredhuman skin, as opposed to external allergens that cause IgE immune responses.

2.4 Microorganisms: -

A majority of patients with AD have Staphylococcus aureus colonisation, as this bacterium overgrows, it causes relapse of their skin illness [9]. The observation that treating patients suffering from AD with secondary infections by using topical corticosteroids and anti-staphylococcal medications results in more significant improvements in clinical symptoms than does treating AD patients using topical corticosteroids by itself underscores the importance of S. aureus. One way that S. aureus worsens AD is by releasing toxins called super-antigens, which cause macrophages and T-lymphocytes to become more active. The majority of patients suffering from AD produce a particular type of Ig-E antibodies in response toStaphylococcal Super-Antigens [10], and/or the level of severity of skin illness is in return correlated with these Immunoglobin-E Anti-Super-Antigens. Additionally, super-antigens cause corticosteroid resistance, indicating that super-antigens may worsen AD through a variety of routes. The underlying skin inflammation caused by AD is what causes S. aureus to adhere to skin more frequently. Studies showing that tacrolimus or topical corticosteroids lower S. aureusextents on atopic skin sites provide clinical support for this. S. aureus bindingat atopic skin sites in experimental animal models with Th-2 in opposed to Th1-mediated inflammation of skin was notably higher because IL-4 stimulated the synthesis of

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fibronectin. It was also discovered that the AD skin lacks peptides from antimicrobialsthat are necessary for defences of host against bacteria, viruses,and fungus [11, 12]. Due to this, once the S. aureus attaches to AD infected skin, insufficient to defences of the hostit enables bacterial colonisation and growth.

These patients may be more prone to viral and fungal infections because ofthe absence of innate immune responses in the skin.The patients suffering from AD have a higher chance to have widespread Herpes Simplex or Vaccinia Virus Infections. In light of this, smallpox immunisation is not advised for AD patients unless there is a serious risk of contracting the disease.

3. PATHOPHYSIOLOGY: -

For the purpose of explaining inflammatory lesions in atopic dermatitis, two main theories have been put forth. The main idea is that the adaptive immune system is out of balance, and the secondary idea is that the skin barrier is not working properly. These two theories may not be mutually exclusive, but they may also work well together.

They are: -

3.1 Immunological Hypothesis: -According to the immunological imbalance idea, the disproportion of T-cells, specifically T-helper cell types 1, 2, 17, and 22, as well as regulatory T-cells, is what causes Atopic Dermatitis [13]. Particularly in the cases of Acute Eczema, the Th-2 differentiation of naive CD4+ T-cells is predominant in an allergic (atopic dermatitis) state. As a result, there is an elevatedproduction of interleukins, especially IL-4, IL-5, and IL-13, thatraises Ig-E levels and inhibits Th-1 differentiation.

3.2

3.3 The Skin-Barrier Hypothesis: -The fact that people having mutationin the filaggrin gene haveconsiderably higher likelihood of acquiring AD is the ground for the more recent idea of skin barrier abnormalities [14]. In the Stratum Corneum and Stratum Granulosum, the Filaggrin gene encodes structural proteins that aid in the adhesion of the keratinocytes. This keeps the stratum corneum moist and the skin barrier maintained. Less filaggrin is created due to gene abnormalities, which causes trans-epidermal water loss and skin barrier malfunction, which results in eczema. There is evidence to support the theory that dry skin caused by a weakened skin barrier allows allergens to penetrate the skin more easily, causing Allergic Sensitization, Asthma, and Hay Fever [15].

Emollient application may be an important strategy for halting the development of eczema into allergic airways disease. Early in life, dry skin and aggressive eczema can be avoided.

4. HISTOPATHOLOGY: -

Intercellular oedema, lymphocyte-dominated Perivascular Infiltrates, and/or parakeratosis—the retention of keratinocyte nuclei as they go upwards into the stratum corneum—are all seen in the skin sample taken from a site with severe atopic dermatitis. Chronic eczema can be recognised by the lack of lymphocytic infiltration, thicker stratum corneum (Hyperkeratosis), and a Thickened Stratum Spinosum (Acanthosis).

5. DIAGNOSIS AND CLINICALPRESENTATION: -

Distinctive skin lesions resulting from atopic dermatitis mimic other eczemas, for instance, contact eczema. The subacute and chronic varieties of eczema are characterised by lichenification, excoriations, papules, and nodules. The acute form of eczema can be recognised by a bright red infiltration with oedema, vesicle, leaking, and the formation of crusting. This results in the diagnostic approachto build on the other traits that includes the eczema's spread and its related characteristic traits of the patient.

The typical patient suffering from AD exhibits an early-onset of itchy eczema that is restricted to typical locations, such as kneesand flexures of the elbows, or they have family history of the condition. Hanifin and Rajka created the most popular diagnostic standards for AD in 1980, and the American Academy of Dermatology subsequently updated them.[Table 1] [16].

The UK Working Party produced a new set of diagnostic questions that are often utilised in epidemiological research in 1994, despite the fact that the majority of these set of criteria are beneficial in clinical practise [Table 2] [17].

The level of severity of eczema can be categorised using a number of scoring systems, including SCORAD [18] and EASI [19].

5.1 General Manifestations: -This description of the disease matches many cases, although the clinical presentation of AD is

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frequently more complex, with a wide range in the morphology and distribution of the eczema mixed with a number of additional symptoms. But manypatients suffering from ADhas a prevalent propensity to characterised by dry skin (Xerosis), perhaps as a result of the stunted water content & considerable loss of water through the epidermis.Skin tone became paler as a result of decreased perspiration and elevated cutaneous capillary tension. The condition known as white dermographism, also referred to as skin-writing, is an intensified cholinergic response to scratching that causes hives to form in the area where the scratching occurred. The people's hair is dry and fragile, and the palms of their hands and feet could exhibit hyper-linearity. The **Dennie-Morgan fold**, a double skinfold that frequently enlarges during periods of heightened disease activity, is located behind the inferior eyelid. Due to post-inflammatory hyperpigmentation, the area around the eyes may become darker. Three clinical stages of atopic dermatitis can be distinguished, albeit it may be challenging to replicate each stage in a given patient [20].

5.1.1 Atopic Dermatitis occurrence in Infancy: Infants develop eczema, which can be widespread or restricted to the extensor surfaces of the arms, legs, scalp, and face. Erythema, papules, vesicles, excoriations, leaking, and crust formation are the lesions' defining features.

5.1.2 Atopic Dermatitis occurrence in Childhood: Although it can happen anywhere, eczema lesions frequently restrict themselves to the elbows, knees, wrists, and ankles in toddlers and older kids due to their propensity to move around. In general, excoriations, papules, and nodules appear together with a drier, lichenified eczema.

5.1.3 Atopic Dermatitis occurrence in Adolescence and Adulthood: Adult patients usually develop head-and-neck dermatitis, where the face and neck are the frequent sites for the lesions to localise. Around 30% of patients also develop atopic hand eczema, which can be disruptive at work.

5.2 Distinctive Manifestations: -Other common, benign skin conditions like keratosis pilaris and pityriasis alba, which create small, rough keratotic papules on the upper arms and thighs and dry, pale patches on the face and upper arms, respectively, may also be present in some patients.**Dermatitis plantaris sicca**, another name for the condition known as Atopic winter feet, is characterised by symmetrical eczema on the foot soles that bear weight.Eczemas around the mouth's edges (Cheilitis), on the earlobe, and on the nipple can be extremely bothersome and frequently entail staphylococcal infection. AD can occasionally be made worse by Keratoconus and Cataracts.

5.3 Differential Diagnoses: -A skin rash that resembles AD may be present as a symptom of several disorders. The appearance and geography of the rash are normally thoroughly examined, together with information regarding the particular patient, before a diagnosis is generally reached. Occasionally, disorders like AD can also look likeSeborrheic Dermatitis, Scabies,&Contact Dermatitis.

Crucial features	Salient features	Connected features
Itch	early age of onset	Atypical vascular response (i.e., facial pallor, white dermographism)

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Eczema with typical morphology and age-specific pattern	Atopy (personal or family history)	Keratosis pilaris, palmar hyper-linearity, ichthyosis
	Dry skin	Ocular and periorbital changes
		Other regional findings (e.g., perioral, and periauricular lesions)
		Perifollicular accentuation, lichenification, and excoriations

Table 1: - Diagnostic criteria used for atopic dermatitis. (Adapted from American Academy of Dermatology) [16]

Topical treatments	Phototherapy	Systemic treatments
Corticosteroids	Ultraviolet light-A (UV-A)	Oral corticosteroids
Calcineurin inhibitors	Ultraviolet light-B (UV-B)	Azathioprine
	Ultraviolet light A+ Psoralene (PUV-A)	Cyclosporine
		Methotrexate

Table 2: - Therapeutic approaches used for atopic dermatitis.

6. AGGRAVATING FACTORS: -

Atopic dermatitis typically progresses in persons in a chronic, relapsing fashion when it is tough to forecast peak activity times or identify aggravating factors. However, there are several exposures that have been shown to aggravate eczema and should therefore be avoided. Wool apparel irritates many patients, rendering their skin itchier and more unpleasant. Longer baths should be avoided since hot water may aggravate itchy skin. Infections that are particularly staphylococci, along with particular meals, especially if a patient is sensitised to the food, frequently serve as exacerbation triggers.

Food abstinence only be stipulated if patient have a diagnosed allergic response to a putative food, rather than simply because of an asymptomatic sensitivities. Contact Urticaria, a reaction caused by skin contact with a specific type of food, for example; tomatoes or fruits rich in vitamin-C, may trigger eczema. This sort of reaction frequently affects the skin around the mouth. Finally, numerous individuals claim that leading a stressful lifestyle worsens their eczema.

7. EPIDEMIOLOGY: -

Atopic dermatitis impacts approximately one fifth of the population at some stage in their lives, however prevalence rates vary considerably across the globe [21]. Between 1950 and 2000, the rate of allergic reactions escalated substantially in a number of so-called industrialised nations, resulting in what has grown to be known as the **"Allergic Epidemic."** Current evidence implies, however, that eczema symptoms have become less frequent or even levelled off in certain nations with historically elevated prevalence rates, among which are the United Kingdom &New Zealand. It demonstrates that an outbreak of allergic conditions

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is not expanding rapidly over the entirety of the globe. However, atopic dermatitis continues to be a significant threat to public health and is on upward trajectory in various nations, especially those in countries that are developing.

7.1 Natural History: -Up to 95% of those diagnosed with atopic dermatitis possess symptoms before the age of five, with roughly fifty percent of these symptoms developing within their very first year of their lives [22].A spontaneous remission occurs in around 75% of cases of eczema with childhood beginnings before puberty; the rest of the 25% either suffer from eczema throughout their adulthood or sometimes following a period of years without symptoms, put up with a reappearance of symptoms.Hand eczema is a common primary feature of adult-onset AD or adult-onset AD that recurs. For some patients, this creates an enormous obstacle because it might affect how they choose a job or workplace, and in some cases, it might even cause them to leave the workforce sooner.Unlike individuals with AD that develops later in life, between 50 and 75 % of kids with an early-onset AD are sensitised to only one or additional allergenic substances, which include the ones found in food, household allergens such as dust mites, or pet animals[23]. However, eating certain foods or being exposed to airborne allergens seldom causes atopic dermatitis exacerbations; many patients have food sensitivities without these sensitivities contributing to the severity of their eczema. When it affects a child severely, AD signals the onset of additional atopic illnesses. Up to 50% of children with moderate to severe AD may go on to acquire asthma, and 75% may go on to get hay fever [24].

7.2 Risk Factors: -People with affected family members have a substantially increased risk of having atopic dermatitis themselves.As an illustration, the concurrence rate of AD in twins who are monozygotic is approximately 75%, implying that if the cotwin is afflicted, the risk of the ailment in the twin sibling is 75% [25]. In comparison, just 30% of dizygotic twins are at danger. This demonstrates that AD susceptibility is influenced by genetic variables. However, because monozygotic twins, who share all of their genes, do not have perfect concordance, environmental and developmental factors also need to be taken into consideration. As a result, AD is a complicated genetic illness caused by a number of interactions between genes and their environments.

7.3 Genetics: -Numerous genes, especially those that code for structural proteins found in the epidermis and those that code for important components of the immune system, have been linked to atopic dermatitis. The proven high correlation between AD and mutations in the Filaggrin gene, located on chromosome 1, is a recent and intriguing genetic discovery [26].

The Filaggrin gene is among the most significant genetic risk factor for AD. The mutations in this gene are present in 10% of western populations but they are present in 50% of all AD sufferers. Filaggrin protein functional defects result from its genomic mutations, disrupting the skin barrier. An increased incidence of eczema and dry skin with fissures are the clinical manifestations of such deficits. Other genetic variations have also been implicated, and not all atopic dermatitis sufferers have these mutations [27]. The interplay of all of these variants in genes alongside environmental risk factors as well as developmental risk factors brings about atopic dermatitis.

7.4 Environment: -Only a small number of environmental risk factors are generally recognised, despite the fact that many distinct ones have been thought to be potential causes of AD. For instance, there has been significant proof to suggest that the western way of life contributes to some of the recent increase in eczema cases, despite the fact this has not been explicitly connected to any particular risk factors related to the environment or functional preventive strategies [28]. When attempting to explain the sharp rise in eczema prevalence, the hygiene theory is frequently cited [29]. According to this theory, atopic disorders are more likely to develop as a result of decreased exposure to archetypal infections in early childhood, such as hepatitis A and tuberculosis [30].The evidence showing that kids who grew up on a traditional farming lifestyle and were subjected to an array of microflora, including that exists in unpasteurized cow's milk, livestock, and their living spaces, weresafeguarded against contracting the illness and allergy conditions which broadly supports the hypothesis [31]. The youngestsiblings had the lowest risk of AD.

The length of breastfeeding is most likely connected with illness progression [32],meanwhile numerous studies have associated a child's likelihood of developing atopic dermatitis to the social status of the parents[33].

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Although difficult to interpret, such results could support the hygiene relatedthe hypothesis or else at the very least, the widely acknowledged notion that the eczema develops through genetics in predisposed individuals exposed to a particular unfavourable surroundings.

8. CLINICAL-DERMAL/INTRADERMAL MANIFESTATIONS: -

In 45% of cases, AD starts in the first six months, and in 70% of cases, it lasts through childhood and up to the age fiveyears [34].Atopic dermatitis is classified as an adult disease when specific symptoms remain till maturity and when an outbreak alternating with intervals of greater or lesser remission.Atopic dermatitis affects 10% of adults and 20% of children worldwide at the moment, and cases are rising in developed nations as we speak [35,36]. The detrimental emotional and monetary effects are on par with those brought on by epilepsy or diabetes. In addition to the disease's specific symptoms, pruritus-induced sleeplessness and a decline in focus and attention also increases absenteeism from work, which results in financial loss [37,38].

Atopic dermatitis manifests as imperfectly delineated erythema and pruritus on the skin, and vesicles change from acute stage to chronic condition, including liquefaction.

Xerotic skin that appears to be common and frequently covers large areas [Figure: 1 (a)][39–41].Post-scratch abrasions arise as a result of the connection between xerosis and pruritus, increasing infection risk.Any area of the skin can be affected by atopic dermatitis, with lesions spread according to symmetry, especially in movable areas. The age of onset greatly impacts the location and morphology, for instance: For infants, this mostly affects their faces, their neck, the scalps, elbows as well as the knees[Figure: 1 (b)] [39–41].

(a) (b)

Figure 1: - (a) Lesions presentas erythematous plaques with well-defined borders.It is covered with fine scales and xerotic and itchy areas, whichheavily involves the trunk and abdomen per se. **(b)** Symmetrical erythematous plaques abetted by xerosis, pruritus, with fine non-adherent scales that involves the facie of the baby (mostly cheekbones, chin& forehead).

9. EXTRA-DERMAL/INTRADERMAL MANIFESTATIONS: -

9.1 Allergic Rhinitis: -The "atopic march," which is a progression of multiple allergy illnesses over time, is the clearest direct proof indicating atopic dermatitis is a systemic medical condition[42,43].The earliest signs of atopy commonly present in children as AD and food allergies. According to an increasing number of studies, these kids develop a combination of allergic rhinitis as well as allergic asthma, thus dermatitis comes before hypersensitivity towards aeroallergens in these kids[44]. Although the potential danger is likely exaggerated due to numerous studies have comprised of participants having serious cases of atopy as the majority of those requires hospitalisation, up to 50% of individuals with AD can develop asthma, that will ultimately be linked to Allergic Rhinitis[45].

Immune hypersensitivity brought on by an increase in Immunoglobulin-E blood levels, that encourages and facilitates food options, cutaneous, including respiratory allergic reactions, constitutes the primary pathogenic mechanism of atopy [46].

The classic trio of Allergic Rhinitis and Bronchial Asthma, as well as Atopic Dermatitis share many pathophysiological characteristics, such as altered immune cells, aberrant cyclic nucleotide adjustments, and the mediators of inflammation with related allergens. However, more recent study has shown that the type 2 AD is somewhat more distinct from an atopy and related immunological disorders.

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Type-2 immune system reactions are distinguished by the elevated serum levels of mast cells, basophils, as well as T-helper cells (Th2) as well as high amounts of synthesised Interleukins such as IL-4, IL-5, IL-9, IL-13, and IL-31. Identification of type-2 inflammation is crucial for individuals with coexisting respiratory illnesses when deciding on a target therapy [47,48].

The medical condition known as allergic rhinitis is brought on by a complicated interplay between genetic and environmental variables. It appears to be characterised by a significant immunological response from aeroallergens, wherein particular IgE-type antibodies that take part, leads to either acute or long-term nasal mucosal irritation. The histamine as well as cysteine leukotrienes are two of the most widely recognised chemical mediators that regulate the inflammatory response. In accordance to the meta-analysis, rhinitis occurs in 40.5% of people that are suffering from AD [49,50]. Additionally, those suffering from early-onset atopic dermatitis (more than two years), as opposed to those who developed it in adolescence or adult life, exhibited a higher prevalence rate of the rhinitis. Recent research revealed that due of decreased IgE levels, individuals who acquire it later in their childhood experience less severe atopic manifestations.

According to a German study, genetic variables may be a contributing factor to the link connecting allergic rhinitis and atopic dermatitis. Irrespective of the degree or age of onset at which their dermatitis first appeared, both patients possessed a mutation that affected the gene called Fillagrin gene, and this suggested to slightly enhance their probability for developing Rhinitis. [51,52].

9.2 Allergic Bronchial Asthma: -The phrase "sole disease of the airways" captures the connection in between asthma and allergic rhinitis or any other inflammation related respiratory disorders. According to statistics, 29–35% of kids with AD get allergic asthma (bronchial asthma), while kids with AD that get rhinitis are at a far higher risk of getting it (99.3%). Bronchial hyper-reactivity, which is prevalent in AD patients as well but not required by the diagnostic criteria for an asthma, is a significant factor in the pathogenesis of Asthma [53,54].

These research' findings point to a striking connection between the pathophysiology of atopic dermatitis and allergic bronchial asthma. Aero-allergens are the primary cause of origin for both, although AD lesions are often made more severe either by being exposed or by direct contact. Elevated serum level of antigen-specific Immunoglobulin-E that binds to the allergen-specific T-cells of the skin that is injured, serve as immunologic proof for the detrimental effects of exposure to respiratory allergens. The pathogenesis of AD and asthma, the loss of epithelial integrity thus becomes a key factor [55,56].

9.3 Food Allergies: -Regarding the pathogenic factors, diagnostic standards, and treatment regimen forpatients suffering from AD, typically 20–40% have been food allergies—impressive progress has been accomplished over the past few decades[57]. Based on one's age, the degree of severity of the accompanying Atopic disorders its associated comorbidities, and their reactions towards the therapy, these clinical manifestations might take many different forms. A number of pathogenic processes underlie the connection between AD and food allergies, majority of which are type-2 inflammatory immunologic disorders or IgE-mediated pathways.

There are actually two ideas that explain the connection in the scientific literature: -

a) The first suggests that AD may be brought on by a food allergy or made worse by it;

b) The second suggests that AD causes the food allergy.

Most studies demonstrate that dietary allergens either contribute to the onset of AD or exacerbate current symptoms, giving the disease the impression of being more severe [58-60].

The **Provocation test** is the **Gold standard** for determining the presence of a food allergy, regardless of its cause. On the other hand, a new-born with severe AD may acquire several food sensitivities that can be highlighted by high serum concentrations of a particular IgE titer or by the presence of a positive skin scratch test. Eggs, dairy, and nuts are the main food allergens linked to AD in infants. Eggs and, to a lesser extent, dairy products are to be blamed for the worsening of eczemas; nuts, on the other hand, are particularly responsible for acute and even anaphylactic allergic reactions [61].

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9.4 Ophthalmic Pathology:-While keeping in mind that research initiatives examining the connection between AD and Ophthalmic illnesses are rather uncommon, certain scientific findings point to alterations in the ocular surface in patients with AD.The most prevalent of them are detached Retinas, Blepharitis, Conjunctivitis, Uveitis, as well as Keratoconus. Over time, ocular problems affect 25–50% of those with atopic dermatitis. [62].

9.5 Digestive Disorders: -One of the pathologic extra-cutaneous symptoms of AD is Gastroenterological Dysfunction. It is particularly prevalent in children and is typically accompanied by high blood IgE levels. Additionally, it was shown that atopy patients' duodenal juice samples had higher levels of reactive immunoglobulins. The enhanced transport of antigens to the intestinal mucosa's functionally inadequate surface encouraged specific IgE activation. This mechanism showed that there may be a correlation between atopy and digestive problems as well as the potential role of anomalies in gastrointestinal tract in the development and cause of AD. In children with Atopic Eczema, clinical skin signs frequently come before gastrointestinal problems in current practise.

The emergence and persistence of localised inflammation underlies a disturbance of the intestinal membrane's proper functioning in the context of immunological hypersensitivity. The degree of severity of skin lesions present inAD has been shown to improve with treatments that attempt to reduce membrane permeability. These findings support the link between atopy and gut morpho-functional problems[63].

9.6 Autoimmune Diseases: -It is generally recognised that people with atopy have an increased chance of developing autoimmune disorders, and new research has identified AD as a notable risk factor for the onset of autoimmune diseases.Children suffering from AD, especially those having lactose intolerance, are more likely to have immunological diseases, particularly thyroid disorders.Epidemiological evidence on Multiple Sclerosis, Rheumatoid Arthritis as well as Type-I Diabetes Mellitus indicates that the Th1-mediated inflammatory responses provide defence against atopy, and atopy may lessen the degree of severity but not always the onset of autoimmune diseases [64].

More so than a generalised inflammatory response, the link between auto-immunity &atopy is typically predicated on the exacerbated reaction in individuals with higher levels of Ig-E . In serum samples of patient' with AD or as a result of a favourable in vitro reaction to autoantigens, the initial finding of Immunoglobulin-E auto-antibodies targeted against human protein molecules was originally reported around 25 years back. However, as dermatitis is largely an atopic condition, the term "auto-immunity" has never been claimed. The term "auto-allergy" has been used to describe this IgE-mediated self-activity, and there is still substantial study being done on how it affects and how severe the disease is [65].Accurate diagnosis and individualised treatment of AD and potential auto-immune comorbidities will result from knowledge of the role of IgE auto-antibodies in the pathophysiology of AD, targeting of the antibodies, and research into the relationship between auto-IgE and the disease severity [66,67].

9.7 Psychological Comorbidities: -Children and adults who are diagnosed with atopic dermatitis experience unfavourable psychological effects from the disease. Atopic dermatitis is considered to be a long-term pathology with varying outbreaks with remissions. 90% of the time, it starts before the age of five and affects 1 in 5 kids. Along with physical pain, they have psychological changes like fluctuating emotions, sleep and behavioural issues, attention-deficient disorder, depressive disorders, anxiety, and social withdrawal, particularly throughout puberty. Additionally, their family members must deal with the expenses as part of medical care, the challenges concerning with the effects of lack of sleep, and the disease's detrimental aesthetic effects on society [44].

Both in adults and children, psychological elements are seen as provoking, and their management is a part of the overall management of the illness. Numerous research conducted in the last few decades have revealed that people with AD often have inferior quality of life, rage issues, hostility, and unhappy marriages.Stress is an important factor contributing for starting as well as keeping the outbreaks of AD, which is thought to be a psychosomatic illness.

Stress causes the epidermal barrier to become more permeable and can trigger a systemic inflammation through the generation of pro-inflammatory neuropeptides. On the contrary, the

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neuropeptides secreted within the skin of people with AD affect the central nervous system, impairing behaviour as well as abilities related to recognition and perception. The disease's unfavourable visual effects are themselves a stressor with a high psychosocial unfavourable impact. According to research, the immune system, together with the central and peripheral nerve systems, have a significant impact on how different dermatological illnesses manifest. A novel conceptual framework for the "**Neuro-Immuno-Cutaneous System"**was therefore provided [68,69].

10. ORAL PRESENTATIONS LINKED WITH ATOPIC DERMATITIS: -

Although the relationship connecting oral lesions and atopy is not entirely unfamiliar, the pathological processes behind such a connection are still poorly understood, and there are only few investigations on the subject. Patients suffering from ADcould develop alterations in the oral mucosa in addition to impairment of the skin, respiratory system, or even digestive system. Investigations have shown that people who have a personal or familial history of atopy are more susceptible to allergies, can have higher IgE serum levels, and are more likely to develop **Benign Migratory Glossitis** (geographical tongue).The shared mechanism behind this connection appears to be chronic inflammation. A recurring condition known as benign migratory glossitis has been characterised by modifying the phases of aggravation and the remission. Clinically, this is distinguished by a linear hyperkeratosis enclosing an erythematous area with the **hypotrophic filiform papillae**, usually present on the tongue's margins as well as on the dorsal face. Although it is mostly asymptomatic, certain individuals do experience pain or burning sensations, especially when eating something spicy or acidic[70].

Although Marks et al. described the elevated prevalence of atopy (Dermatitis, Rhinitis and Asthma) in patients with geographical tongue, Benign Migratory Glossitis is therefore not a particular indicator of the atopy and can occur in other different medical conditions such as Psoriasis, Liver disease, and deficiency of vitamins [71].

A minor diagnostic need for atopy is **Atopic Cheilitis** (lip inflammation). The clinical symptoms of angular cheilitis include erythema (reddening of the lips), with scales, pronounced radial folds,& irritative commissural lesions (Angular Cheilitis). The majority of the cases of Atopic (allergic) Cheilitis were brought on by contact-related sensitivity that is typically brought on by cosmetics like lip balms or lipsticks[72]. But it is also important to consider the probability of **"Sicca" Cheilitis** in relation with AD.

Fordyce Granules, that are typically found on the labial and jugal mucosa in people in good health, are absent from the mouth or are present in low numbers, as well as other oral symptoms of atopy. RecurringAphthous Stomatitis, Fungiform PapillaryHypertrophy, Oral Candidiasis, and Irritative Stomatitis are some of the oral conditions[73]. Despite the fact that none of these pathological disorders are specifically related to atopy, decades of research have demonstrated their link with atopy.

11. DISEASE COMPLICATIONS: -

Superinfections brought on by a variety of pathogens, including bacteria, viruses, and fungus, can exacerbate eczema. Staphylococcus aureus frequently colonises the skin of an AD patient, especially if the eczema is not adequately treated. Such bacteria do not even need to be present for antibiotic treatment to be effective. However, impetigo, which causes weeping crusted sores, can occur if staphylococci become invasive, indicating the need for topical or, preferable, oral medicines. [74].

Some people recommend bathing the skin with antiseptic products like Chlorhexidine to reduce the number of microorganisms there. However, Chlorhexidine might cause secondary sensitization. A number of viral illnesses, such as **Molluscum Contagiosum**, which is caused by the pox virus and manifests as tiny, umbilicated papules that are dome-shaped and pearly in colour, are more common in AD patients.Herpes virus is another common skin superinfection in people AD. This type of herpes infection has the potential to spread and result in **Eczema Herpeticum**, a broad vesicular eruption that usually affects the scalp, face, and the upper chest. For Eczema Herpeticum, systemic antiviral therapy is necessary.

12. NON-PHARMACOLOGICAL, PHARMACOLOGICAL TREATMENT: -

Improvement of patients' quality of life, pathology severity reduction, infection prevention, and long-term disease management are the four main goals of AD therapy. [75,76].Current

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therapeutic approaches advise applying emollients to the skin to hydrate it, reduce skin inflammation, and regenerate the skin's structure [77,78,79]. One of the main therapy modalities is the application of moisturisers to soften the skin affected by AD illness. Pharmaceutical strategies include the usage of topically applied corticosteroids that minimises the inflammation, antibiotics (specifically anti-microbials) to eliminate infections brought on by the pathogenic bacteria or parasites as well, antihistaminic to lessen pruritic manifestations, and calcineurin inhibitors for the purpose of preventing the spread of eczema and additionally minimise inflammation.

Additionally potential treatments include phototherapy and immunomodulation through systemic immunosuppressant medication delivery [80,81].

12.1 Non-Pharmacological Approaches: -

12.1.1 Moisturizers: -Emollients, humectants, and occlusive agents are all used in the complex composition of skin moisturisers. The most frequently used humectants are glycerol, lactic acid, or urea; some of the most widely used emollients are glyceryl and glycol stearate as well as soy-derived sterols; and generally used occlusive agents are dimethicone, petrolatum, mineral oils[82], and nanoparticles [83]. Every single patient's unique skin features determine which emollient should be used.Emollients used topically should provide extensive skin lubrication and are frequently used on dried and lichenified skin[76].

Occlusive agents are employed to stop skin water loss because of their capacity to produce an occlusive film.Humectants help SC hydration while additionally enhancing skin hydration, contrasting to occlusive agents, which do not penetrate into the skin. However, during skin penetration, they hold onto the water molecules rather than forming an occlusive barrier[84]. Scents as well as perfumes should not be included in daily moisturisers because they may trigger allergies and make already ill skin even more dysfunctional.Emollients that include ceramides and fatty acids could potentially be superior compared to conventional emollients, though it has not yet been scientifically confirmed, despite the wide range of data from the literature that is presently accessible [80,76].Consequently, emollients should to be considered as the first-line of treatment for AD [85].

12.1.2 Bathe&Wet Wraps: -An AD patient must take a bath every day as a requirement of life. Its goal is to eliminate irritants, skin scales, and allergies that have built up on the skin's surface over time [86]. The application of wat wraps prevents dry skin, additional cutaneous rash, and itching by reducing skin water loss. The following process should be followed:

a) Before anything else, the patient needs tobathe.

b) Next, simply massage the emollients or corticosteroids directly onto their skin.

After applying wet bandages to the treated skin areas, the usual dry attire is put on last. Due to improved drug absorption, topical corticosteroidadministration offers greater benefits when combined with wet wraps [75,86].

12.2 Pharmacological Approaches: -

12.2.1 Topical Corticosteroids: -Topical corticosteroids are one of the main treatments for AD. Only low-potency corticosteroids should be used when treating youngsters with this class of compounds. Only when low-potency corticosteroids are ineffective is there an exception to this rule. Therefore, high-potency corticosteroids are used to prevent dire situations[76]. Users and carers of this class of medications must be aware of how to control them in order to reduce side effects (such as skin stretch marks or skin shrinking), which could lead to low patient compliance because to corticosteroid phobia[80,87].To increase the effectiveness of cortico-therapy, the doctor's advice and dose adjustments are essential [75].

12.2.2 Antibiotic Treatments: -Patients with S. aureus infections are advised to take antibiotics in order to stop the spread of the bacteria that would otherwise infect other patients. Oral or intravenous administration are also options. In severe cases of AD, patients having S. aureus infections may be treated with antibiotics, which helps to clear bacterial clusters and improves the patients' clinical condition. Despite this, it has not yet been demonstrated that topical antibiotic use is beneficial for treating concurrent S. aureus infection in AD patients[86,76]. However, the selection of the antimicrobial medication is crucial for avoiding the impacts of the microorganisms' resistance [75].

12.2.3 Antihistamines: -The most significant illness symptom influencing these individuals' quality of life is Pruritus[75]. Antihistamines are

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frequently employed to lessen generalised itching. But rather than effectively treating eczema, these medications are utilised to reduce its symptoms[80].Scientific studies are somewhat inconclusive; for example, some claim that antihistamines are not superior to placebo. Others, however, display an antipruritic result [88,89].

One negative effect of the1st generation antihistaminicare related to the sedative properties they possess, that can be employed to good effect in AD patients who experience frequent sleep disturbances [88,89].

12.2.4 Calcineurin Inhibitors: -NSAIDs, or non-steroidal anti-inflammatory medications, include Calcineurin Inhibitors as well.They manifest their effects by preventing the transcription of the cytokine produced by activated T cells, which lowers the level of inflammation[90].These medications help the problem without causing skin shrivelling when applied to the affected parts of the skin[76].In short-term therapy, calcineurin inhibitors are a second-line option. Emollients and calcineurin inhibitors should both be used at the same time. To avoid a diluting effect, however, the formulations must be applied at specific times. Tacrolimus, a cream with moderate to strong corticosteroid qualities, and pimecrolimus, a cream with mild to moderate corticosteroid capabilities, are two more examples of topical immuno-modulators that have been successful in treating patients. It was demonstrated that both treatments reduced erythema, pruritus, and excoriations [91].

12.2.5 Phototherapy: -Frequent exposure to ultraviolet light, specifically Ultraviolet-A (UV-A) and Ultraviolet-B (UV-B), damages cells. Studiesusing UV-B showed that it can kill germs on the skin and prevent S. aureus from producing superantigens [92].Applying UV-A and UV-B rays along with topical corticosteroids may be a treatment strategy for eczema caused by AD.In spite of this, exposure to UV-A and UV-B radiation quickens skin ageing and escalates the likelihood of skin cancer [93,94].

12.2.6 Systemic Immunosuppressant Drugs: - The alternative treatment for life-threatening cases of AD are drugs like Methotrexate, Mycophenolate Mofetil, and Azathioprine substances, which are all part of the class of medications known as systemic immunosuppressant drugs when conventional ways such as the topicallyadministered corticosteroids & phototherapy are no more effective[76].Emollients must be administered concurrently to restore the skin's water-lipid film [75].

13. NANO-TECHNOLOGY FOR TOPICAL APPLICATIONS: -Materials smaller than **100 nm** are known as nanoparticles (NPs) [95,96], and are suggested for topical administration of medications intended for the treatment of skin disorders [86]. As NPs have an increased safety profile thus requires less medication due to site-specific administration, they could potentially reduce the negative side effects of conventional medications (such as topical corticosteroids).

In order to increase skin bioavailability, NPs have also been advocated as a favoured solution to insufficient skin permeability and low drug solubility [97,98].Numerous types of nanoparticles, including antibiotics and corticosteroids, are being suggested for the topical drug delivery for a variety of medications helpful in treating AD[99,100].

Table 3 illustrates many nanoparticle kinds employed in topical medication delivery. With the use of NPs, therapeutic objectives can be achieved by increasing drug retention time, boosting drug penetration through the SC, and creating superior drug release patterns.Therefore, NP-based drug formulations might be a better strategy than conventional drug formulations. The possibility of a decrease of significant negative effects that result in non-compliance by patients which leads to poor therapeutic outcomes constitutes one of the most significant upsides with NPs[101,102].

The lipid-based NPs, which are among the various NPs, have shown greater advantagessince they are compatible with the lipid skin-makeup[97,103-106].

Nanoparticles	Vesicular systems	Miscellaneous systems
Dendritic nanoparticles	Cubosomes	Nanoemulsions
Lipid nanoparticles	Ethosomes	
Polymeric nanoparticles	Liposomes	
	Proliposomes	
	Transfersomes	

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Table 3: - Different types of nanoparticles generally used for topical drug delivery.

14. NANO-PARTICLES FOR ATOPIC DERMATITIS: -

Hyaluronic acid was added to chitosan NPs that contained betamethasone valerate to enhance the medication's pharmacological effects and its ability to be delivered to specific areas [107]. In simulated skin, NPs showed a Fickian-diffusion release profile exhibiting improved permeability to the drug compared to the non-loaded drug. The dermal and epidermal medication retention was improved by encapsulating the particles with hyaluronic acid. Chitosan nanoparticles were combined with hydrocortisone and hydroxy-tyrosol, two molecules that are topical glucocorticoids and antioxidants, respectively, according to Siddique et al [108].The created cream was found to be safer and more tolerable, and the researchers noted no toxic or systemic side effects associated with the medications.Chitosan nanoparticles loaded with hydrocortisone demonstrated their ability to decrease trans-epidermal water loss, lessen the thickness of the affected skin patches, and lessen erythema [109]. The suggested NPs can effectively distribute medications that are related to glucocorticoids to treat AD patients' fibrosis and inflammation while also enhancing the suppleness of their connective tissues.

Tacrolimus-loaded transfersomes, liposomes having the same medication, and the commercially available ointment (Protopic®), were all contrasted with one another.Tacrolimus was more well retained by transfersomes than by the other two[110].

The administration of nicotinamide& tacrolimus for treating AD has been suggested using chitosan nanoparticles[111],in comparison to a commercial ointment (Protopic®), and theirin-vitro and in-vivo permeability.According to the researchers, greater quantities of tacrolimus in the skin were caused by NPs' enhanced ability to permeate through and into the skin. Modest anti-AD results have been reported from this strategy when used as adjuvant therapy.

Topical administration of guar gum NPs was shown in a mouse in vivo investigation to diminish the infiltration of cells as well as the epidermal thickness in oxazolone-induced AD by decreasing both of these parameters[112]. The NPs utilised during this investigation were produced from Cyamopsis tetragonoloba, which contains galactomannan, which has been shown to encourage the cellular-absorption of macrophages through their overexpressed mannose receptors.

Tacrolimus-loaded chitosan nanoparticles were further coated in hyaluronic acid[113].Tacrolimus was maintained in both the epidermal and dermal layers of the skin, proving that the treatment was well targeted and reducing both trans-epidermal water loss and total erythema severity. Hyaluronic acid-coated particles also shown additional encouraging skin effects, such as anti-dermatitis, suggesting a potential effective strategy for identifying immunomodulatory medicines.

Tacrolimus-loaded lipid nanoparticles (NPs) enhanced skin penetration, reaching the deeper layers (with resident dendritic cells)[114]. Tacrolimus-loaded lipid NPs were found to have increased bioavailability as compared to the Protopic® ointment. A positive aspect is that there was no evidence of the drug's systemic distribution.

Levocetirizine-loaded flexible vesicles were tested for their capacity to pass through the skin safely and dermatologically.Results showed that this system had a better retention capacity than liposomes and met the criteria for skin safety. This was because of the flexible properties of the vesicles, which allowed the system to permeate through the skin and penetrate it[115].

A study that used the antihistamine levocetirizine also demonstrated that the membranes of these vesicles were more flexible when they were formed into elastic-vesicles and were applied topically. The ability of the vesicles to make their way via the pores in the body of an individual that are considerably smaller in size compared to their dimensions is dependent on how flexible they are. Along with lower erythema intensity and irritation, the drug's improved permeability was also seen[116]. Figure: 2depicts an illustration of potential AD treatment approaches employing nanoparticle

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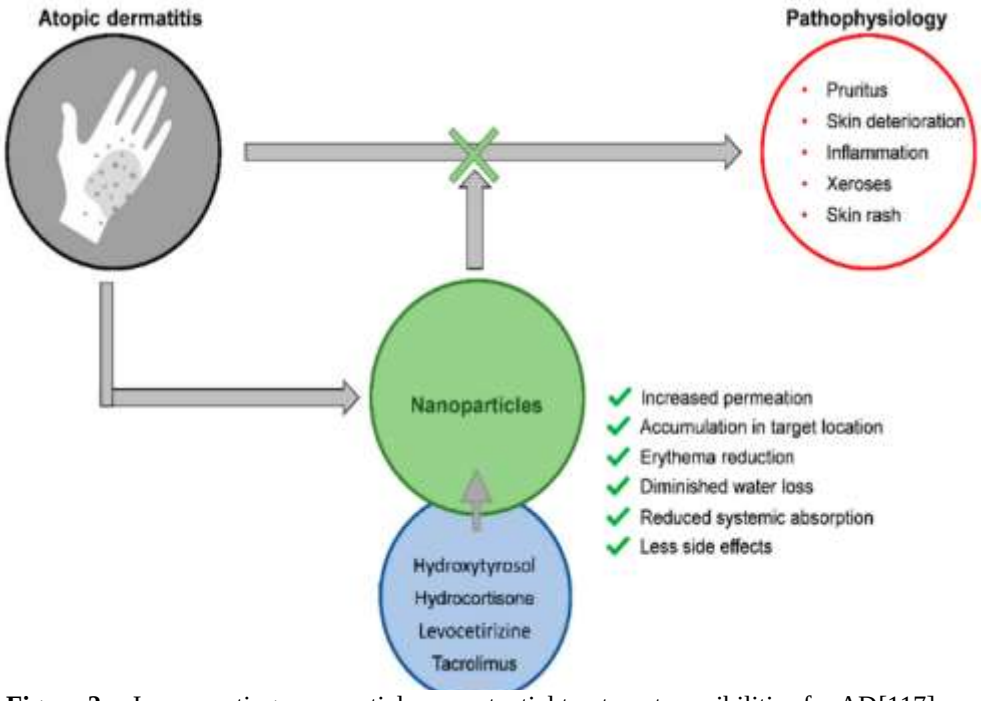

Figure 2: - Incorporating nanoparticles as potential treatment possibilities for AD[117].

15. PREVENTION: -

Three methods are thought of for preventing AD. They are: -

a) The first has to do with eliminating allergies generated from food.
b) The second entails with minimising interaction with antigen sources such as animal fur, pollen particles, dust mite, tobacco smoke, smog from traffic, and volatile organic contaminants (VOCs)[118-120].
c) The third combines the use regular skin emollients as well as lotions with the two aforementioned methods[47,86,120].

According to research so far, applying skin emollients on a daily basis can reduce a child's risk of AD by 30% to 50% [87,121].

II. CONCLUSION & DISCUSSION: -

The skin condition known as AD is complex, chronically inflammatory, and diverse due to interactions between immunological, genetic, and environmental variables. Although the incidence varies widely around the world, it is widespread in the majority of nations. According to recent data, AD affects both rich and emerging nations, and in poorer nations, it will compete for scarce resources. Due to its prevalence in most countries, prevalence that is rising, and mounting evidence that AD may advance to other allergy phenotypes, AD has emerged as an important public health issue.

The knowledge of how the skin barrier, genetic, and immunological variables interact has significantly improved during the past few years. For the disease to be prevented more effectively, it is crucial to have a better understanding of the major environmental risk factors that can be affected, altered, or adjusted. In general, AD is distinguished by its chronic pattern as well assignificant alterations in patients' as well as caretakers' quality of life.

The first-line therapies use medications such topical corticosteroids and/or topical calcineurin inhibitors to relieve pruritus, the accompanying inflammation, and to repair the integrity of the skin. Despite this, prolonged use of these drugs, particularly topical corticosteroids, causes skin to shrink because they stop the production of collagen. Due to their immature skin and potential systemic distribution of these medications in youngsters, there is a danger of serious unfavourable side effects.Due to the restricted ability of nanoparticles to penetrate the stratum corneum, topical therapies with them prevent the absorption of significant amounts of medication.

Since AD alters skin homeostasis, new therapies that concentrate on restoring normal skin function are urgently needed in order to control and

stop the ensuing inflammation. Due to large part to their exceptional qualities, NPs have seen a dramatic increase in daily usage in recent years. Patients are more likely to comply with therapy if the drug can target tissues or particular cells, the drug's release profile can be more effectively controlled, the skin can be penetrated or permeated, facilitating the NPs to interact with the skin's deepest layers, skin irritation is minimised, along with the drug's overall side effects are not as grave.

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