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BARRIER REPAIR NANO FORMULATIONS AND PHOTOTHERAPY FOR ATOPIC DERMATITIS (AD)

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ABSTRACT A common inflammatory skin condition that can affect both adults and children is atopic dermatitis (AD). It is the most prevalent inflammatory skin condition and is brought on by a variety of inherited and environmental causes. Strong type 2 immune responses and anomalies in terminal keratinocyte for Atopic dermatitis (AD) is a common inflamed skin condition that can affect both adults and children. The emergence of numerous novel topical and systemic medications through clinical trials, which may hold significant promise for the treatment of AD, marks the beginning of a new era. Phototherapy is also used as second line treatment for AD, which includes six principles.

KEYWORDS : Atopic dermatitis (AD), skin, pathophysiology, nano formulation, polymeric nanoparticles, SLN, phototherapy.

Introduction-

Atopic dermatitis (AD) is a common inflamed skin condition that can affect both adults and children. It is the most prevalent inflammatory skin condition brought on by hereditary and environmental interactions. Atopic dermatitis is characterized by skin barrier dysfunction, skin inflammation and itchy skin. A vulnerability to cutaneous infections, particularly those caused by certain viruses like herpes simplex and bacteria like Staphylococcus aureus (S. aureus), is also linked to AD. It causes skin rashes which can be itchy and dry (1) .

The onset, progression, and chronicity of AD are all influenced by the intricate interactions between skin barrier failure, skin inflammation, and itch. Skin barrier dysfunction causes epicutaneous sensitization and increased sensitivity to external stimuli in the skin (2).

Topical moisturizers, topical corticosteroids, topical calcineurin inhibitors, phototherapy, and systemic immunotherapies are currently the predominant treatments. For moderate-to-severe AD topical corticosteroids are first-line treatment, immunosuppressants are also used, but they have significant side effects. Genetic and environmental factors also contribute to AD (3).

STRUCTURE OF HUMAN SKIN

Skin, the outermost organ in the body, covers the whole outside. Its three component layers are the epidermis, dermis, and hypodermis, and each has a unique architecture and function. As the body's first line of defence against viruses, UV rays, toxins, and mechanical injury, the complex network that makes up the skin's structure protects the body from these threats. Skin also regulates temperature and the amount of water released into the environment (4).

Layers of skin:

- Epidermis
- Dermis
- Hypodermis

Epidermis is the first layer of human skin which is further categorised into stratum basale (the deepest portion of the epidermis), stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (the most superficial portion of the epidermis). Epidermis layer of skin also consists of cells like Keratinocytes, Melanocytes, Langerhan's, and Merkel's cells (5).

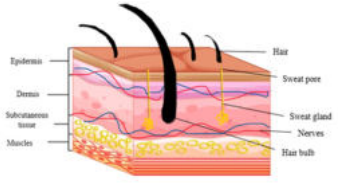

Figure 1: Structure of Skin

The dermis is home to the sweat glands, hair, hair follicles, muscles, sensory neurons, and blood vessels. The dermis is situated near to the hypodermis, also referred to as the subcutaneous fascia. Structure of human skin is depicted in figure 1.

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

Pathophysiology of atopic dermatitis is initiated by barrier dysfunction, skin inflammation, and itch as shown in figure 2. Another reason of developing atopic dermatitis is genetic factor, due to mutations and impaired expression of filaggrin (FLG) gene. Filaggrin is the gene that encodes structural protein essential for skin barrier formation (6).

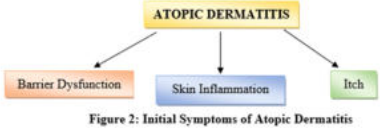

Figure 2: Initial Symptoms of Atopic Dermatitis

Dysregulation of skin barrier impair lipid metabolism with reduction of ceramides. Ceramides are fats and lipids that are naturally produced in skin to provide moisture and acts as a barrier and prevents entry of allergens from external environment. Reduction in level of ceramides leads to transdermal water loss, due to which penetration of allergens, irritants, and microbes is increased. Disruption of the barrier results in epidermal hyperplasia, persistent inflammation, and cellular infiltrates of dendritic cells, eosinophils, and T lymphocytes (6).

When microbes enter, innate immune system acts as first line defence system against microbial pathogens. This led to severe eczema or itchy skin (7). Pathophysiology is shown in figure 3.

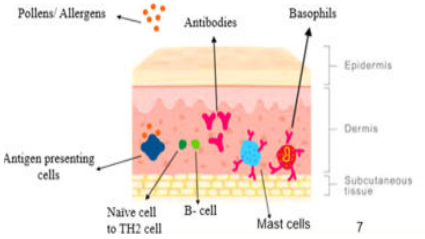

Figure 3: Illustration of Barrier Dysfunction Due to Entry of Allergens

NOVEL THERAPIES FOR ATOPIC DERMATITIS

T helper (Th) 2 responses, such as IL-4, IL-5, IL-13, IL-31, and CCL18, and Th22 responses, such as IL22 and S100A proteins, are indicative of AD start in acute lesions. IL-4 and IL-13, two Th2 cytokines, have been shown to be crucial in the pathophysiology of AD (8).

Topical and systemic therapies are widely used as depicted in table 1 and 2:

Table 1: Topical Agents for Atopic Dermatitis

AGENT	TARGET	DRUG	PHASE
OPA15406	PDE4	Topical PDE4 inhibitor	Phase II published
Crisaborole	PDE4	Topical PDE4 inhibitor	Phase III published
JTE-052	JAK	Topical JAK inhibitor	Phase II published
Tofacitinib	JAK1/3	Topical JAK1/3 inhibitor	Phase II published
PAC-14028	TRPV1	Topical TRPV1 antagonist	Phase II published
Tapinarof	AhR	AhR modulating agent	Phase II published

Table 2: Systemic Agents for Atopic Dermatitis

AGENT	TARGET	DRUG	PHASE
Dupilumab	IL-4Ra	Anti-IL-4Rα mAb	Phase II published
Tralokinumab	IL-13	Anti-IL-13 mAb	Phase II published
Lebrikizumab	IL-13	Anti-IL-13 mAb	Phase II published
Apremilast	PDE4	PDE4 inhibitor: oral small molecule	Phase II published
Ustekinumab	IL-12/23p40	Anti-p40 mAb	Phase II published

The most popular excipients for non-pharmacological treatment of a variety of inflammatory skin conditions by reducing their acute symptoms are moisturizers (9) The benefits of moisturizer formulations are linked to their composition, which includes a variety of substances serving several purposes:

I) Occlusive substances that form a hydrophobic layer on the skin surface and reduce trans epidermal water loss (TEWL)
ii) Humectants that prevent drying; and/or
iii) Vegetable oils containing essential free fatty acids (such as those found in sunflower, safflower, corn, and others) and/or skin-lipids (such as ceramides and their derivatives) for re-establishing the skin barrier
iv) Botanical ingredients with anti-inflammatory molecules (e.g., apigenin)

Due to lack of target specific- drug delivery via conventional methods, several nanomedicines with innovative technologies have been developed from past few years, which is providing nano-based formulation with increased efficacy and reduced side effects. (10)
This approach promotes target- specific drug delivery, increase residence time, increases bioavailability, and decreases systemic toxicity (11)

Nano Formulation Based Drug Delivery for Atopic Dermatitis-
In terms of improving the treatment of skin disorders, a great deal of research has been done on nano-based formulations for the topical delivery of various medications over the past ten years. Due to site-specific distribution, the nanoencapsulation lowers the doses necessary for biological activity and thereby lowers adverse effects (12).

Improved carriers with adjustable physicochemical properties and better permeation, retention, and diffusion can protect unstable compounds against degradation and denaturation, leading to-

i) Enhanced effectiveness (targeted delivery to the inflammation site increases the drug bioavailability and avoids hepatic metabolism)
ii) Increased hydrophilic and hydrophobic compound solubility
iii) Improved safety profile (allows for low medication dosage, reducing side effects such itchiness and allergy brought on by traditional topical drug forms).
iv) Higher patient compliance as a result of improved symptoms, fewer side effects, and lower costs.
v) Enhanced carriers with adjustable physicochemical properties and increased permeability, retention, and diffusion to preserve unstable chemicals against degradation and denaturation (13)

Polymeric Nanoparticles-
For topical drug delivery, polymeric nanoparticles are biocompatible and biodegradable. For bioadhesive effects, they offer excellent entrapment effectiveness and sufficient surface charge. In comparison to conventional formulations, the nanoencapsulation offers additional benefits such regulated drug distribution, a decrease in systemic absorption, and decreased toxicity (14).

1) Atopic dermatitis (AD) is a continuously relapsing eczematous skin condition marked by recurrent outbreaks of itching, swelling, and rash. Tarakini A. P. Gunasegaran et *al*. tried to construct a moderate-potency TC, betamethasone valerate (BMV), in the form of chitosan nanoparticles (CS-NPs). In conclusion, we believe that HA-BMV-CS-NPs may be a potential nano delivery strategy for effective BMV dermal targeting and increased anti-AD efficacy (15)

2) Most new-born infants are affected by atopic dermatitis (AD), a chronic inflammatory skin condition. Catarina Rosado et *al.* used modified solvent displacement approach to fabricate poly (-caprolactone) (PCL) NPs, which were then characterized (16).

3) Mohammed A.S Abourehab et *al*. carried out preparation of tacrolimus (TCS) polymeric nanoparticles, for targeting deep layers with reduced side effects and improved therapeutic efficacy for the treatment of atopic dermatitis. In conclusion, we hypothesized that HA-based modification of TCS-CS-NPs could be an effective therapeutic strategy for the reasoned management of AD, particularly in children and adults who have steroid phobia (17)

4) Chitosan nanoparticles combined with fucoidan were developed by Barbosa et *al*. to deliver methotrexate to the irritated skin. The production of IL-1, IL-6, and TNF- may all be dramatically decreased by the nanoparticles (18).

Solid lipid nanoparticles-
Solid lipid nanocarriers (SLNC) have demonstrated excellent potential for use in drug delivery, particularly when it comes to regulating drug release and tissue targeting. With the right excipients and particle manufacturing techniques, solid lipid particles can transport both small molecule drug substances and biomacromolecules (19).

The strong biocompatibility of lipid excipients makes it possible to utilize SLNC in a variety of administration routes, including oral, parenteral, topical, ophthalmic, and pulmonary (20).

Mahmoud Reza Jaafari et *al.* prepared auraptene-loaded solid lipid nanoparticles (AUR-SLNs), to increase the anti-inflammatory properties of AUR. The response surface method was used to optimize the prepared formulations (21,22).

Nanoemulsions-
Nanoemulsions are aqueous, surfactant/co-surfactant (Smix), and oil phase systems that are homogenous, thermodynamically stable, and isotropic. According to reports, the o/w and w/o nanoemulsion droplet size ranges from 20 to 200 nm, depending on the system's makeup and the homogenization technique employed (23).

LSO-NE formulations were created in this work using the ultrasonic emulsification technique. They determined that LSO will be a suitable therapeutic candidate for AD therapy based on our molecular docking and ADMET calculations. (24)

Hydrogels-
Three-dimensional, hydrophilic polymeric matrices called hydrogels may absorb water and swell without disintegrating. Different formulations of hydrogels are shown in table 3. For example, conjugating a medicine to PEG can delay kidney filtration, which significantly lengthens the drug's plasma half-life (25).

Khushali Parekh et al. prepared tacrolimus-loaded mesoporous silica nanoparticles (TMSNs), to get around the problems with its solubility and efficient topical distribution. Observations as a whole indicate that MSNs included hydrogel as a promising novel formulation technique for topical administration of medicines with low solubility (26).

Vesicular Carriers-
For topical drug delivery, the vesicular technique is thought to be the best strategy. It is known that drugs transported by encapsulating in the vesicle created using phospholipids and non-ionic surfactants can enter and pass the skin. These vesicular transporters reduce the expense of treatment by increasing the drug's bioavailability particularly in regard to poorly soluble medications. (33)(34)

PHOTOTHERAPY

Phototherapy is considered as second line option for the treatment of atopic dermatitis. When chronic AD is resistant to first-line topical therapies, phototherapy may help elementary-aged children, adolescents, and adults.

The six methods for phototherapy in AD are the topic of this review: Broadband UVB is the first type, followed by the Goeckerman regimen (coal tar plus broadband UVB), narrowband UVB, excimer lasers for focused use, combination UVA/B, and UVA1. Inconveniences and side effects, such as limited availability to in-office treatment, difficulties complying to a three times weekly schedule, flare-ups from excessive heat, and an increased risk of skin cancer, limit the effectiveness of phototherapy in some patients (35). Principles of phototherapy are shown in figure 4.

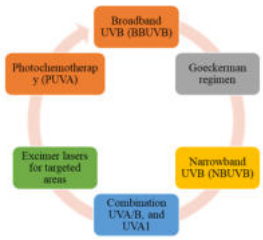

Figure 4: Six Paradigm of Phototherapy

1. Broadband UVB-
With the study of Nexman in 1948, which used irradiation from fluorescent and mercury arc lamps, particularly the Psorilux 9050, the use of BB-UVB (280-315 nm) therapy in AD. The latter enables better treatment control by allowing dosages of UV-A and UV-B to be adjusted separately (36)

2. Narrowband UVB
NB-UVB (311-313 nm), which does not emit shortwave UVB light, is significantly less erythemogenic than BB-UVB. The "Minimal Erythema Dose" (MED), which is the least amount of UV-B radiation that will cause erythema in a patient, is the most common approach for calculating UV-B dose delivery. Calculating UV-B based on a patient's skin phototype is another common method (37).

3. UVA and UVA1
UVA (315-400 nm) therapies have never been the primary choice for treating AD because they require lengthy exposure times to get effective levels. The advent of UVA1 (340–400 nm) lamps, which can completely eradicate UVA2 radiation (320–340 nm) and all of its negative effects, overcame this drawback. High doses can now be applied with UVA1 devices, which was not achievable with UVA devices (38,39).

4. Excimer Laser
A coherent light source with a single wavelength of 308 nm makes up this lamp. When compared to clobetasol propionate, excimer laser irradiation for 10 weeks has shown to produce positive results in the prurigo form of AD (40).

5. Photochemotherapy (PUVA, balneophototherapy)
The combination of UVA and psoralens, such as 8-methoxypsoralen and 8-MOP, is referred to as PUVA. PUVA therapy (topical or systemic) can help patients with mild or severe types of AD. Additionally, it is advised that PUVA therapy should only be used temporarily because it has been demonstrated to be mutagenic (41).

6. Goeckerman Regimen (coal tar + BBUVB)
The Goeckerman regimen is now frequently used in clinics alongside TCS, oral antihistamines, emollient baths, and/or systemic medications. This is mainly because of worries about tar's carcinogenic potential, rising inpatient healthcare costs for payers, and substitution with NBUVB and other more recent phototherapy techniques (42).

Formulations for Skin Barrier Repair-
The main concern lying with AD is impairment of skin barrier by reduction of skin natural lipids and fats such as ceramides and other fatty acids which leads to dry, flaky, red, and itchy skin. In an effort to replicate the combination of three physiologic lipids (ceramides, cholesterol, and free fatty acids) that are in charge of maintaining the function of the cutaneous permeability barrier, a subclass of barrier repair formulations has been created based on considerations of skin biology (43).

Hyaluronic acid (HA):
Hyaluronic acid (HA), a significant component of extracellular matrix has been widely employed in pharmaceutical and cosmetic sectors due to its purported pharmacological characteristics. According to studies, a number of HA-based transdermal delivery systems have been demonstrated to effectively localize the release of anti-psoriasis medications, exhibit high biocompatibility, and reduce skin inflammation caused by psoriasis (44).

Ceramides:
Numerous commercial lotions, creams, and moisturizers based on CERs 1 and 3 have been developed and put on the market, including Eucerin Smoothing Repair Dry Skin Lotion, Eucerin Eczema Relief Body Creme, CeraVe Moisturizing Lotion, and CeraVe Suncare Sunscreen Face SPF 30 (45).

Bioactive ingredients:
Bioactive ingredients decrease transepidermal water loss (TEWL), decreases neurosensory transmission of itch signal, inflammatory cells, and increases lipid synthesis (46). Various bioactive agents used are enlisted in table 4:

Table 4: Various Bioactive Ingredients Used for Repair of Skin Barrier

SNO.	BIOACTIVE INGREDIENTS	FUNCTIONS
1.	Petroleum	TEWL reduction and occlusion; lipid lattice reinforcement and AMP generation.
2.	Antioxidants	Lower ROS (reverse oxidative stress) to prevent oxidative damage.
3.	Niacinamide	By reducing TEWL, raising ceramides, and thickening the stratum corneum, epidermal barrier function can be improved, Anti-inflammatory.
4.	Cannabinoids	Reduce itching and inflammation by promoting lipid formation.
5.	Pre/Probiotics	TEWL should be reduced, and ceramide levels should be raised, to improve the skin barrier.

CONCLUSION-

Recent advances in our understanding of the genetic and immunologic pathways underlying cutaneous inflammation in atopic dermatitis have shed light on the disease's natural course and highlighted the vital functions of the immune system and the epidermal barrier. Both should be regarded as key targets for therapy since they both contribute to IgE-mediated sensitization. They comprise occlusive compounds to delay TEWL, humectants to draw moisture to the epidermis, and other mixtures of components to lessen swelling, lessen stinging, and supply substances to mimic the intercellular lipids.

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