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Overcoming drug delivery barriers and challenges in topical therapy of atopic dermatitis: A nanotechnological perspective

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ABSTRACT

Atopic dermatitis (AD) is an inflammatory disorder centered around loss of epidermal barrier function, and T helper 2 (Th2) immune responses. The current understanding of disease heterogeneity and complexity, limits the rational use of existing topical, systemic therapeutic agents, but paves way for development of advanced therapeutic agents. Additionally, advanced nanocarriers that deliver therapeutics to target cells, seem to offer a promising strategy, to overcome intrinsic limitations and challenges of conventional, and traditional drug delivery systems. Ever-evolving understanding of molecular target sites and complex pathophysiology, adverse effects of current therapeutic options, inefficient disease recapitulation by existing animal models are some of the challenges that we face. Also, despite limited success in market translatibility, nanocarriers have demonstrated excellent preclinical results and have been extensively studied for AD. Detailed research on behavior of nanocarriers in different patients and tailored therapy to account for phenotypic variability of the disease are the new research avenues that we look forward to.

1. Introduction

Atopic dermatitis (AD) is an autoimmune cutaneous malady characterized by recurrent bouts of eczematous lesions, transepidermal water loss, and emotional distress. It imposes a significant psychosocial burden on patients as a result of its unsightly appearance and functional restrictions that it imposes during its existence. It also escalates the likelihood of developing ailments, viz. asthma, arthritis, allergic rhinitis, food allergy and other immune-mediated inflammatory ailments besides mental derangement. It is at present understood as a life-lasting disposition with variable clinical expressions and manifestations, with epidermal barrier defect acting as the central driving force for its descent. It has a complicated etiology in which genetic and immune mechanisms collude with environmental factors to influence disease manifestations.

Anti-inflammatory drugs like topical corticosteroids, PDE-4 inhibitors, topical calcineurin inhibitors, biologics, JAK-STAT inhibitors, and anti-histamines are the mainstay of AD treatment, which preserve the skin barrier function. Topicals may be used as an interim treatment step before beginning systemic therapy in patients with joint involvement, evidence of topical treatment failure, or in case adverse psychological bearings are observed in them. Topical therapy can be used in conjunction with systemic therapy or phototherapy in chronic conditions. New treatment options must be developed because of the high incidence of AD and apprehensions vis-à-vis the side-effects of long term corticosteroids such as fragile skin, striae, telangiectasies, delayed

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wound healing and increased vulnerability or worsening of infections (e.g. candidiasis). Engineered nanomaterials and nanocarriers have spawned new possibilities and potential challenges significantly different from natural materials and particles. Nanocarriers are nano range (10–1000 nm) particles loaded with active ingredient prepared from biocompatible materials that allow for effective delivery, improved stability, excellent entrapment, and enhanced drug molecule penetration. Nanoemulsions, nanoparticles (lipidic and polymeric), and vesicular carriers (liposome, ethosome, transferosome) are few of the nanocarriers which have been designed to effectively treat AD.

Also relevant murine and non-murine animal models for AD have been reported, that advance the discovery and evaluation of novel treatments. Generally, these animal models propose to mimic various aspects of human AD pathophysiology. However the disease's diversity and failure of existing models to emulate disease complexity wholly make the translatability difficult. This review looks at the various challenges of AD treatment, as well as contemporary research in the realm of new drug delivery systems vis-à-vis AD and also the future promises in the therapy.

2. Treatment challenges for AD

Complex pathogenesis, dearth of an appropriate animal model that would completely mimic AD expression in humans, and the risks associated with current treatment options all pose challenges to AD therapy.

2.1. Pathogenesis

The precise mechanism underlying the inception of AD is still unknown. The progression of AD, distinct from normal skin, depends pathologically on a range of coordinated events, including the stimulation of circulating immune cells, the secretion of signaling molecules and growth factors. Each of these occurrences contribute to the formation of scaly skin, lichenification, and spongiosis. Because of the heterogeneity that AD manifests with different age groups, ethnicity, demographics, clinical presentations, presence or lack of fillagrin mutation, IgE (Immunoglobulin) status, and presence of distinct cytokine axes, a new nomenclature called 'AD spectrum disorder' is being proposed. Patients with concomitant allergy diseases may also exhibit a unique endotype in AD patients. Additionally, AD manifests more in younger children, and the incidence of the disease decreases with age, with the elderly displaying more prominent Th1/Th17 axes. Patients with S. aureus infection also displays unique endotype with greator IgE levels [1]. Similarly extrinsic AD is associated with sensitization to environmental allergens, increase serum IgE levels, elevated eosinophillic recruitment, Th2 cytokines (IL-4,IL-5,IL-13), whereas intrinsic AD is associated with late onset, mild severity, predominance in female patients, increased metal allergy, presence of cytokines IL (Interleukin)− 17, IL-22, unperturbed skin barrier dysfunction, raised IL-9, IL-20, IL-24, SNP (single nucleotide polymorphism) in IL-31 gene [2]. Intrinsic AD has significantly excess Th22, IL-23/Th17 and Th1 activities in comparison with extrinsic lesional skin. Study of AD progression in human body can be simplified into following sections.

2.1.1. Immune tolerance, barrier dysfunction and proinflammatory cytokines

The disturbance in the equilibrium of self antigen discrimination versus non self antigen recognition leads to AD like hypersensitivity disorders. Association studies have recognized 34 genomic regions which are likely to posses one or more AD susceptibility-associated genetic variant [3].

Disruption of the skin barrier is a well-known etiological factor in the pathogenesis of AD. Skin barriers proteins such as filaggrin, hornerin, loricrine, involucrine dysfunction or tight junction proteins dysfunction (claudins), decreased lipids (long chain fatty acids, ceramide), decreased serine proteases (SPINK 5-serine protease inhibitor kazal type 5), dwindled antimicrobial peptides expression (β-defensin, cathelicidin, calprotectin) leads to decreased skin hydration, increased skin pH, increased penetration of allergens, microbes, decreased bacterial diversity (more of staphylococcus, corynebacterium and less of streptococcus, propionibacterium), increased transepidermal water loss (TEWL) and increased activation of pattern recognition molecules such as TLR (Toll like receptor), NOD (Nucleotide binding oligomerisation) like receptor, C-type lectin receptor (CLR) [4]. CLR transduce via MyD88 (Myeloid differentiation primary response 88), activation protein AP1, NFκB and cause increased release of proinflammatory cytokines (TSLP-Thymic stromal lymphopoetin, IL-1β, IL-33, IL-25), chemokines (TARC-Thymus and activation regulated chemokine, MDC-Macrophage derived chemokine). In AD, two distinct phases are identified: initial Th2 response and subsequent class switching to Th1 response via IL-12, IL-18 [5,6].

2.1.2. Recruitment of diverse immune machinery to orchestrate different immune response

Immune response begins when antigen presentation cells langerhan cells, dDC (dermal dendritic cells), IDEC (inflammatory dendritic epidermal cells) armed with FCϵRI, OX40, process the antigen, carry it to the lymph node where antigen is presented via MHC class II to stimulate the Th2 cell responses [7]. ILC-2 (innate lymphoidal cells) cells then cause the release of IL-5, IL-13 and finally activate plasma cells for IgE production. Further, it is observed that phosphodiesterase activity increases particularly in monocytes. Additionally, proinflammatory prostaglandin E2 increases, which inhibits the Th1 response and increase IL-4 production of Th2 cells. The apoptosis of eosinophils is also seen. As far as pruritis is concerned, histamine dependent and independent mechanisms are involved. Both H1 and H4 receptors are engaged. Furthermore, TSLP provokes stimulation of sensory neurons of skin by activation of TRPA1 (Transient receptor potential). Likewise, IL-31 is expressed on keratinocyte and neuron fibers to mediate pruritis. In AD, Basophils too drift to the inflammation site and secrete an array of mediators such as cytokines, chemokines, and proteases which act on macrophages, innate lymphoid cells, fibroblasts, and endothelial cells [8]. In addition AD patients' skin has activated autoreactive T cells that demonstrate release of IFN-γ, IL-17, IL-2, TGF-β, GM-CSF, andplay significant role in progression of chronic AD.

2.1.3. Mutation of T regulatory cell and dysregulation of inflammation by it

At the advent of fiery immune responses, the 'regulatory arm' serves to limit collateral damage [9]. There is poorly regulated control of inflammation via natural Treg cells in AD. Specific mutation in the transcription factor specific to CD4+ CD25+ T-reg causes frenzied Th2 responses. Antigen-specific activation of T cells can be suppressed by T cells of either Tr1 (and their cytokines IL-10 and TGF-β) or CD4+ CD25+ T-reg phenotype however they cannot avert keratinocyte apoptosis induced by activated effector T-cell [10]. Table 1 enumerates all of the cytokines that may play a significant role in AD.

2.2. Absence of suitable animal models

There is a need of an ideal animal model that would wholly emulate the histological and immunophenotypic attributes of AD as can be seen in humans. While many immunological and genetic animal models have been devised already, neither model shows all associated limitations of the disease characteristics. Also because of the disease heterogenicity and present models mimicking 'allergic dermatitis' more closely rather than AD, **Gilhar et al., 2021** suggests the establishment of minimum criteria for mouse models to be representative of human AD and examines how each of the existing models fits certain criteria but not others. Three well studied murine models are known namely, spontaneous mutation, epicutaneous sensitization and transgenic mice. In the following section, we will look at some animal models and their shortcomings:

Table 1
Cytokines that contribute in AD.

S.No	Cytokine name	Role in AD	Reference
1	IL-4	Th2 cell differentiation is induced, as is B cell IgE isotype class switching.	[11]
2	IL-5	Th2 cells produce a significant amount of this maturation and differentiation cytokine. ILC-2, as well as eosinophils also produce this cytokine. It has a chemotactic effect on eosinophils.	[12]
3	IL-10	Suppresses the allergen specific Th1, Th2 cells and allergen specific IgE	[13]
4	IL-13	Produced by Th2 cell, it is the key stimulator for inflammation and participate in several stage of the maturation and differentiation of B-cells.	[14]
5	IL-16	Predominant in acute lesions, it has chemotactic responses to T cells, monocytes and eosinophils in AD	[15]
6	IL-17	Higher in intrinsic AD, reduces expression of fillagrin and involucrin	[16]
7	IL-23	Dendritic cells and macrophages activation release the cytokine. CD8+ T cells are multiplied and IL-17 produced under its influence.	[17]
8	IL-22	Downregulates profillagrin, enhances AMP production together with IL-17. This cytokine induces epidermal proliferation	[18]
9	IL-25	Produced from injured epithelial cells, it activates ILC-2, capable of amplifying Th2 response	[17]
10	IL-31	Induces sensory nerve elongation branching and thus involved in the pathomechanism of pruritus	[19]
11	IL-33	It activates ILC-2, functions through the ST2 (suppression of tumorigenicity) receptor, and inhibits the keratinocytes' expression of β-defensin 2. ILC-2 express IL-5 and IL-13 under influence of this cytokine.	[20]
12	IL-1β	Encourages Th17 development. After activation, its release from the epidermis is a primary event which supports inflammatory conditions through the induction of different cytokines, proinflammatory mediators and adhesion molecules.	[21]
13	IL-9	Acts via the JAK-STAT pathway. It helps in inflammation regulation, helps to kindle mast cell proteases, inflammatory cytokines and chemokines production, thereby causing mast-cells mediated allergic responses.Synergism with IL-4 improves IgE production besides memory B cell differentiation.	[22]
14	IL-24	In intrinsic AD, this cytokine is associated with increased epidermal hyperplasia.	[23]
15	IFN-γ	The coupled IL-12 and IL-18 expression in the chronic phase of AD results in its production. It is a strong stimulant of fibrosis.	[24]
16.	TSLP	Dendritic cells are activated, thereby stimulating generation of Thymus and activation regulated chemokine (TARC) as well as Macrophage derived chemokine (MDC)	[25]

2.2.1. Spontaneous mutation model or inbred model

A multitude of factors, like errors in DNA replication, spontaneous injuries and transposable genetic elements, can be used to trigger spontaneous mutations. Under pathogen-free conditions, these mice develop spontaneous eczematous dermatitis with augmented immune responses to percutaneous antigens. These include flaky skin mice (ma/ma, Flgft/ft) and NC/Nga mice with barrier defects and immune-related gene defects respectively. However, these may be valuable for studying only one specific overactive pathway involved in AD.

2.2.2. Induced by epicutenous application with sensitizers

AD may be brought about by hapten (e.g. oxazolone, trichloronitrobenzene), allergen (e.g., ovalbumine, house dust mite), or MC-903 (calcipotriol-induced). This model generates time-modulated induction that is relevant to different mouse strains, but it is labor-intensive and requires a variable protocol in terms of doses and duration. In addition, in contrast to the Th2 response seen in AD, the response produced in this model is initially Th1 dominant, which may eventually shift to Th2 response following repeated sensitization. Also, varied sensitization may occur while using the same dose of hapten.

2.2.3. Transgenic models

These have a single gene ablation or overexpression, as opposed to AD, which is a polygenic ailment. This model does not posses multiple factors associated with AD. For example, transgenic or knockout mice that overexpress IL-4 or IL-13 [26,27]. Further, this model lacks complexity, and the substance used for inducing this model could have a harmful effect or it may affect disease phenotype. Additionally it is a time-consuming model.

Aside from these models, the humanized mouse model proposed in recent years, although promising in many ways, only investigates a single pathway and is expensive [28]. As a result, an ideal animal model must be created that shares with humans, numerous genetic, histology and morphology parallels and likewise responds to treatment. In addition, the models should be replicated easily, affordably, and ethically.

2.3. Existing treatment approaches

AD treatment options generally include 3 major modes: topical therapy, phototherapy, and systemic therapy. Topical therapy is preferred for AD treatment. In the event that topical therapy is ineffective or the condition is persistent, phototherapy and systemic medications are recommended. A detailed list of available drugs, their mechanisms for action, pharmacokinetics, adverse effects is given in Table 2, while Fig. 1 pictorially presents the treatment options available for AD along with molecular targets. Phototherapy and systemic agents have a variety of side effects, such as hepatotoxicity, adrenal suppression, renal toxicity, hyperlipidemia, cutaneous malignancies. Furthermore, traditionally formulated AD therapeutic agents have issues such as lower safety profile for long-term use, increased dosing frequency and other side effects.

The formulation development research is aimed at addressing the weaknesses of traditional dosage forms by developing drug delivery systems which provide reduced dosing frequency, ease of administration, sustained release to enable enhanced therapeutic benefit to patients. Advance drug delivery strategies use novel carriers like liposome, nanoparticles, SLN, NLC, microsphere, nanosphere, nanocapsule, dendrimer, as well as micelle for inviolable and efficient performance.

3. Novel AD colloidal drug carriers

Novel systems for the delivery of drugs are designed to improve the therapeutic benefits of existing drugs, to secure and effectively deliver medicines and to provide for the space and time-related demands of the body. These systems for drug delivery use a particulate or vesicular systems between 10 nm and 0.4 μm in size. Colloidal drug carrier is a one-of-a-kind entity that is essential for the safe transport of loaded drugs and their delivery to the desired site of action. Targeted medicines enable access to the best quantity of medications while reducing noxious effects and improve the therapeutic index. Using this targeted approach systemic after-effects are reduced significantly. The ideal colloidal carrier must survive anatomical barriers, be selectively recognized by target cells via the surface ligand, be biodegradable and non-toxic, and be able to stabilize drug:ligand complexes in biological environments.

These new colloidal systems have a wide range of advantages over traditional systems, including reduction in degradation and loss of medicines, increased bio-availability, increased drug accumulation at the target site, preventing deleterious effects, flexibility in handling medicines and improved patient compliance. Aside from the benefits outlined thus far, the associated high production cost, stability, and

Table 2
Current disease management strategies for AD.

S. No	Drug name	Mode of action	Side effects	Pharmacokinetics	Reference
I	Topical				
I	Calcineurin Inhibitors				
a)	Tacrolimus	Inhibits calcineurin phosphatase and hence naïve T cell activation. Lowers antigen-presenting cells-dendritic and langerhans cell numbers in skin	Pruritus, burning, skin infections, erythema, flu-like symptoms, folliculitis, herpes simplex infections.	Low Bioavailability, 75–99% Protein Binding, Liver Metabolism by cytochrome P450 system, t1/2 : 11.3 h, Bile Excretion, Dosing : 0.03–0.1%	[29]
b)	Pimecrolimus	Acts akin to tacrolimus, but has no influence on langerhans cells, has inferior cutaneous permeation.	Burning, stinging, itching, pain, soreness, greater incidence of viral infection.	Low Bioavailability, 99.5% Protein Binding, Hepatic Metabolism, Fecal Excretion, Dosing : 1%	[30]
ii	Tars	Antibacterial, antipruritic, anti-inflammatory effects. Activates Nrf2 (nuclear factor-erythroid 2-related factor. Acts on aryl hydrocarbon receptor and strengthens skin barrier functions, increases filaggrin expression.	Burning, stinging, acne eruptions, tar folliculitis,dermatitis, atrophy, telangiectases, pigmentation, tarry black urine, nausea, vomiting, phototoxicity and carcinogenic	Dosing : 0.5–5%	[31]
iii	PDE4 inhibitors				
a)	Crisaborole	Escalates intracellular cAMP levels that suppresses proinflammatory cytokines- IL-2, IL-4, IL-5, IL-10, IL-13, IL-17, IL-23, IFN-γ and TNF-α,	Burning and stinging at site of application, nausea, emesis, and diarrhea	Low Bioavailability, t1/2 : 7.17 h Dosing: 2%	[32]
iv	Corticosteroids				
	Clobetasol Propionate, Halobetasol propionate, Betamethasone dipropionate, Mometasone Furoate, Hydrocortisone valerate, Triamcinolone acetonide	Allay inflammatory mediators and cytokines reduce *S. aureus* populace	Atrophy of skin, bruising, telangiectasies, striae, depigmentation, acne, impetigo, hypertrichosis, secondary infections	Liver Metabolism, Kidneys Excretion	[33,34]
V	Antihistamine				
a)	Doxepin	Non sedative, H1/ H2, muscarinic receptors antagonist. Inhibits itch-inducing effects of substance P at skin receptors.	Drowsiness, localized stinging, and burning, dry mouth, pruritus, eczema, CNS excitation and hypertension.	Metabolism : hepatic, Dosing : 5%	[35]
vi	Miscellaneous agents				
a)	Naltrexone	Opioid antagonist that relieves pruritus	Sleep disturbance	Dosing : 1%	[36,37]
b)	Delgocitinib	Janus kinase inhibitor that are vital for signaling commenced by diverse cytokines like IL-4, IL-12, IL-23, TSLP, and IFN. Represses skin inflammation, enhance skin barrier function, and mitigate pruritus.	Allergic conjunctivitis, dental caries, acne, allergy, nasopharyngitis, folliculitis, influenza	Dosing : 0.5% b.i.d	[38]
c)	Ruxolitinib	JAK 1/2 inhibitor	Nasopharyngitis, diarrhea, bronchitis, ear infection, raised eosinophil count, urticaria, folliculitis, tonsillitis, rhinorrhea.	Dosing : 0.15–1.5% q.d Bioavailability: 5.68%	[39]
II	Systemic therapy				
i	Biologics				
a)	Dupilumab	It inhibits IL-4R, a common part of IL-4 and IL-13 receptor. Also pro-inflammatory cytokines release, chemokines release, IgE. Causes upregulation of epidermal barrier proteins	Conjunctivitis, oral herpes, cold sores on the mouth/lips	Bioavailability: 60% Dosing : 600 mg initial dose followed by 300 mg weekly	[40]
ii	Immunosuppressants				
a)	Cyclosporin	Inhibits calcineurin (CaN) and thereby IL-2 and hence reduced activation and maturation of many cell types engaged in cell-mediated immunity.	Arterial hypertension, nephrotoxicity, hypertrichosis, neurological, gingival hyperplasia, gastrointestinal effects, hypomagnesaemia, hyperkalaemia, tremor, myalgia, headache, fatigue	Bioavailability : 30%, Excretion : Bile, Dose : 3–5 mg/kg/day	[41]
b)	Azathioprine	Inhibition of purine synthesis, resulting in a halt in DNA, RNA, and protein synthesis; Meddles cell metabolism and impede mitosis, particularly in leukocytes.	Bone marrow suppression, cancer, GI symptoms. Leukopenia, fever, chills, cough, hoarseness, myalgia, problematic urination, fever, rigors, arthralgia, occasionally pancreatitis and hepatotoxicity.	Bioavailability : 47% Dose : 0.75 ± 3.2 mg/kg/day	[42]
c)	Mycophenolate mofetil	Immunosuppressant that represses De novo synthesis of guanosine nucleotides for T and B lymphocyte proliferation by inosine monophosphate dehydrogenase (IMPDH) reversible inhibition.	GI effects, hepatotoxicity, nephrotoxicity, peripheral edema, arthralgia, bone marrow suppression, arrhythmia, and mild reversible cytopenia.	Dose: 2 g	[43]

(*continued on next page*)

Table 2 (*continued*)

S. No	Drug name	Mode of action	Side effects	Pharmacokinetics	Reference
d)	Methotrexate (MTX)	Cellular proliferation of lymphocytes require purines and pyrimidines, their synthesis is blocked by MTX due to inhibition of dihydrofolate reductase.	Bone marrow suppression, anemia, thrombocytopenia, gastrointestinal effects, pneumonitis and hepatotoxicity	Dosing: 2.5 mg/day for 4 days in a week	[44]
iii	Leukotriene inhibitors				
a)	Monteleukast	It is a leukotriene inhibitor. Eosinophils, mast cells, and macrophages release inflammatory mediators LTC4, LTD4 (leukotriens) that results in cytokine production, and Th2 profile.	Headache and abdominal pain.	Dosing : 5 mg daily for 24 weeks	[45]
III	Phototherapy				
I	Ultraviolet B therapy	Decrease IL-5, IL-13, IL-31 levels, induces T-cell apoptosis, reduces dendritic cells, t hickens the stratum corneum and improves the epidermal barrier, thereby reducing allergen, irritant entry, as well as limiting eczema. Inhibit superantigen production, influences antimicrobial peptide and messenger ribonucleic acid (mRNA) levels, giving it an antibacterial effect.	Photoaging, cutaneous cancer	Dosing : 130–400 mJ/cm^2	[46]
ii	Ultraviolet A therapy	Collagen synthesis is increased while calcineurin is inhibited and TNF-α, IL-12, IFN-γ are suppressed. Causes T-cell and mast cell apoptosis. Exerts its effect by generating reactive oxygen species (ROS)	Burning, stinging, pruritus, skin erythema and tenderness, claustrophobia, lupus flare, folic acid depletion, photooncolysis, hepatotoxicity	Dosing : 40–130 J/cm^2	[47]
iii	Ultraviolet A and 8-methoxypsoralens (PUVA)	8-methoxypsoralen (8-MOP) is an effective photosensitizing agent. Lowers epidermal hyperinnervation and modifies lymphocyte activity.	Continuous therapy causes untimely ageing, melanoma, squamous cell carcinoma, basal cell carcinoma	Dosing : 8-MOP (0,0006%) 30–60 min before irradiation, UV-A exposure after 20–30 min	[46]
iv	Full spectrum light (FSL)	Decreases cytokines, reduction in adhesion molecule expression, inhibition of scratching behavior	Erythema, dryness pruritus, and burning sensation	Dosing : 130 J/cm^2, 3 time in a week	[47]

characterization concerns continue to be significant limitations. As shown in Fig. 2 novel colloidal drug carriers can be divided into two categories, according to their constituents: those made from lipids and those made from polymers. Table 3 Summarizes formulations explored for atopic disease, the preparation techniques used, and main outcomes attained, aiming at AD treatment.

3.1. Lipid based colloid carriers

These are made of physiological lipids, lipid-based colloidal carriers and therefore have the distinct advantage of being well tolerated and nontoxic. These systems can interact with lipids of the stratum corneum, allowing for greater penetration, deposition of active ingredients in deeper skin layers, where the immune cells recide. Lipidic vesicles that are highly flexible and deformable such as transferosome, ethosome may have greator penetration. Furthermore phospholipids, which are important component of the majority of these systems functions as promoter of skin passage. Active compounds may also be adsorbed on the epidermal layer if vesicles fuse with SC and help in mitigating skin inflammation. In addition, the aqueous component present in these systems may cause an increase in SC hydration, reduction in TEWL and prove to be beneficial in AD. Also, these systems may interact with skin and generate a hydrophobic layer on the surface, causing an occlusive effect that may be advantageous [81]. A detailed discussion is provided below, of several kinds of lipid-derived colloidal carriers that have served as suitable vehicles for drug administration to AD patients.

3.1.1. Liposomes

These are made to look like biological membranes and are composed of naturally derived phospholipids with varied lipid chains (e.g., egg Phosphatidylethanolamine) or other surfactants. They enclose themselves to form lipid bilayers with an aqueous core. Because of their capability to incorporate both hydrophobic and lyophobic molecules, enhanced solubility of the incorporated drug, compatibility, and biodegradability, these are being used to deliver drugs to the desired site. Several studies have demonstrated their ability to improve permeation flux and penetration across the stratum corneum (SC), resulting in greater efficacy and therapeutic outcomes [82]. **Verma et al., 2003** attempted to explain the kinetics of liposome penetration using confocal laser scanning microscopy with entrapped and unentrapped carboxyfluorescein, and found that there was enhanced penetration into the SC and perhaps deeper skin layers. Entrapped drug in liposomes becomes bioavailable when it is optimally released at a sufficient rate and for adequate period of time to exert the desired therapeutic effect [83]. **Jung et al., 2011** created liposomes for topical delivery of adenosylcobalamin (AdCbl), which demonstrated a 17-fold increase in permeation when compared to plain AdCbl gel [54]. **Jahn et al., 2014** made proliposomes (which are free-flowing powders that spontaneously form liposomes upon dissolution) in order to deliver adipose stem cell derived protein extract (AAPE) for AD. They caused a noteworthy decline in IgE levels in atopic mice [57]. Betamethasone valerate (BMV) laden liposomes were developed by **Eroglu et al. in 2014.** Human fibroblast cells were used to test the toxicity. Skin irritation was reduced, paw edoema inhibition was increased, mast cell suppression and improvement in TEWL was observed [84].

Transferosomes are modified liposomes that are made up of phospholipid and a single chain surfactant or edge activator that gives them vesicle fluidity. Because of their ability to squeeze along stratum corneum's sealing lipid matrix, they have high skin penetration. They accommodate a broad array of solubility profiles, are effective carriers for drugs with low and high molecular weight, preserve the encapsulated drug from metabolic degradation, have high entrapment efficiency, biocompatibility, biodegradability, and can carry a large amount of drug [85]. **Goindi et al., 2013** generated an optimized formulation of cetirizine dihydrochloride based on the phospholipid/drug/charge inducer ratio and edge activator concentration. The mean cumulative

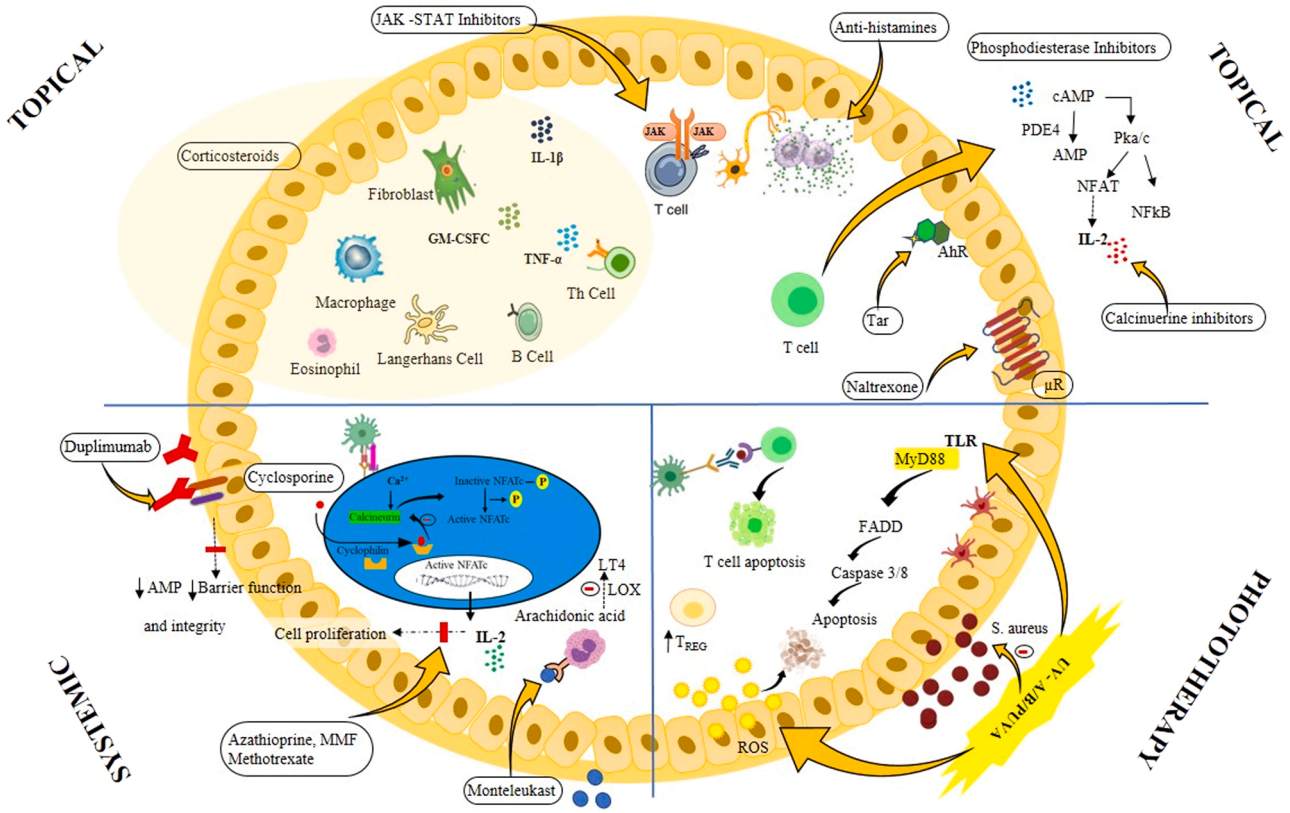

Fig. 1. Therapeutic strategies in the management of AD: Topical therapy comprises corticosteroids that lessen the number, effects of numerous inflammatory cell types, cytokines like interleukins, tumor necrosis factor (TNF), granulocyte-monocyte colony stimulating factor (GM-CSF) and has immunosuppressive effects; Calcineurin inhibitors which inhibits calcineurin phosphatase and hence calcium dependent IL-2 gene transcription (via NFAT i.e. nuclear factor of activated T cells) which is responsible for naïve T cell activation and lowers antigen-presenting cells; Phosphodiesterase inhibitors that lowers cAMP levels; Janus kinase inhibitors and Tar (working on AhR: Aryl hydrocarbon receptor) which are anti-inflammatory agents; Naltrexone an opioid receptor antagonist; and H1/H4 receptor blockers that are anti-pruritic agents.
In AD, systemic therapy is non-specific and includes Azathioprine a purine antagonist; Cyclosporin an IL−2 inhibitor; Mycophenolate mofetill (MMF) an inhibitor of inosine dehydrogenase monophosphate; Methotrexate a dihydrofolate reductase inhibitor; Monteleukast that inhibits leukotrienes synthesis via inhibition of lipoxygenase (LOX); and duplimumab a humanized monoclonal antibody whose inhibition improves skin barrier and anti-microbial peptides (AMP) level.
UV based phototherapy works by suppressing inflammation and inducing apoptosis in pathogenic cells. Phototherapy comprises UVB that lessens *Staphylococcus aureus* levels, causes considerable reduction in the number of langerhan cells, as well as an increase in T regulatory cells; UV-A that causes indirect DNA damage by reactive oxygen species, increases TLR activation that raises myeloid differentiation primary response 88 (MyD88), and initiates keratinocyte apoptosis via FAS-associated death domain protein (FADD), caspase 3 activation; Psoralens that covalently binds to the DNA, inhibiting cell proliferation and altering gene expression profiles.

percentage amount permeated was twice in comparison to conventional cream, and it was far more effective in reducing itching than the conventional cream, with significant reductions in dermal eosinophil count and erythema score [55]. **Kang et al., 2010** created oregonin transferosomes and discovered a fourfold increase in deformability index when compared to conventional liposomes. The treatment was found to be effective in normalization and mitigation of immune-related responses in AD. Skin or blood levels of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-4, IgE as well as eosinophills were examined and considerable reduction in their levels was observed [52]. **Kang et al., 2010** discovered that peptide-conjugated elastic liposomes (Pep1-EL) of taxifolin glycoside (TXG) significantly accelerated skin barrier function recovery in comparison with controls and also regulated AD-associated immune responses such as serum IL-4, IgE, and INF-γ [51] **Kang et al., 2011** utilized Tat peptide-admixed transferosomes to encapsulate hirsutenone (HST), a naturally occurring immunomodulator. The skin severity score and immune-related responses such as nitric oxide synthase, cyclooxygenase-2, IL-4, IL-13, IgE, and eosinophil levels were significantly improved in diphenylcyclopropenone AD-induced NC/Nga mice [53]. **Kim et al., 2009** devised a cationic transferosome of IL-13 antisense oligonucleotide (ASO) and tested its cytotoxicity using the XTT assay. *In vitro*, the IL-13 ASO/cEL complex inhibited IL-13 secretion in Th2 cells in a dose- and ratio-dependent manner. Furthermore, IL-4 and IL-5 levels were considerably lessened. Besides, IL-13 ASO/cEL-treated AD mice demonstrated decreased invasion of inflammatory cells in the epidermal and dermal layers, as well as loss in skin thickness [56].

3.1.2. *Ethosomes*

Ethosomes are ethanol modified liposomes that act as a reservoir system containing phospholipids, ethanol (<40%), glycerol, as well as water. They are malleable, elastic vesicles which showenhanced penetration and drug release to the various layers of skin. These vesicles are soft, flexible. Besides ethanol in its composition provides sustained drug delivery by imparting a negative charge to the vesicles and can act as a carrier for both hydrophilic and hydrophobic drugs [86]. **Li et al., 2012** created tacrolimus ethosomes that outperformed traditional liposomes in terms of encapsulation efficiency and exhibited greater penetration than commercial ointment. Further mast cell accumulation was reduced, and allergic reactions were effectively suppressed [58]. **Goindi et al., 2014** created and tested a cetirizine dihydrochloride ethosome having improved rheological and spreadability properties. In comparison to

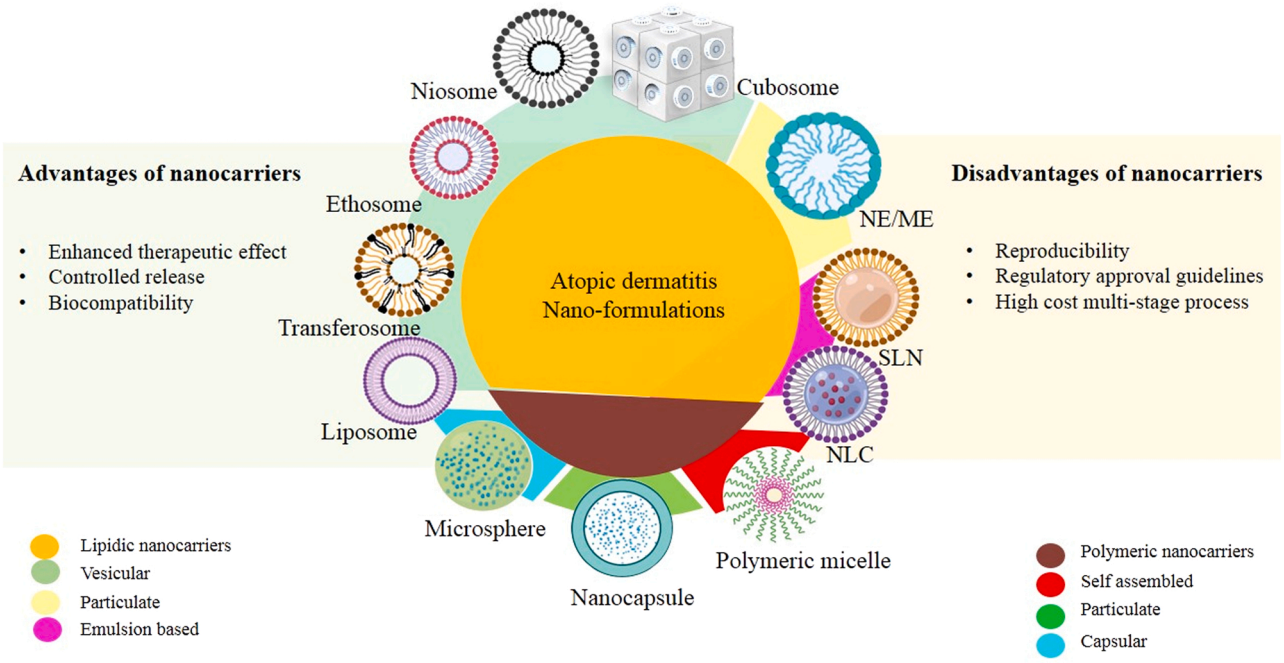

Fig. 2. Lipidic and polymeric nanoparticles for drug delivery in AD.
Lipidic carrier comprises vesicular systems with phospholilipid bilayer shells encasing solvent core stabilized by cholesterol and surfactants; particulate carriers that are lipid matrices with dispersed or dissolved drug; and emulsion systems with two immiscible liquids dispersed with aid of surfactant. Among polymer carriers are self assembled carriers which are intricate hierarchical structures with randomly arranged units; particulate systems with drug dissolved or dispersed in polymeric matrix; and capsular systems having drug reservoir enclosed in polymeric membrane.

traditional formulations, *ex vivo* permeation studies on mouse skin revealed that cetirizine-loaded ethosomal vesicles had the highest permeation flux and retention in skin. Oxazolone sensitized atopic AD mice were treated with an optimized formulation and better scratching score, erythema score, reduced hyperplasia of skin as well as reduced eosinophil count of dermis was observed [87].

3.1.3. Niosomes

Niosomes are vesicles composed of single-chain non-ionic surfactant molecules often combined with cholesterol. The advantage of niosomes is their advanced chemical stability and cost effectiveness. These can entrap a wide array of compounds (lipophobic, lipophilic, and amorphous drugs) and impart controlled and sustained drug release [88]. **Pal et al., 2020** optimized levocitirizine niosomes using the box-behnken design. When compared to optimized chitosan nanoparticle gel, higher retension and permeation were observed. Additionally *in vivo* studies revealed reduction in erythema and scratching frequency [89].

3.1.4. Phytosomes

These are prepared by adding stochiometeric amount of phospholipid and standardized herbal extract in aprotic solvent like dioxane and acetone, which are then precipitated by non solvent such as aliphatic hydrocarbon. They have active ingredient as an integral part of the vesicle membrane. The formulation's distinct advantages include better absorption, enhanced bioavailability, skin permeation [90]. Hyperkeratosis, proinflammatory cytokine IL-1β, IgE proliferation, and mast cell infiltration were all decreased by topical *Centella asiatica* phytosomes, according to **Ho et al. 2018** [91]. **Togni et al., 2019** studied the effects of curcumin phytosomes and discovered that clinical manifestations such as itch, eczema, dryness, loss of sensitivity, and edoema were all reduced. Additionally oxidative stress was reduced, skin oxygenation, blood flow improved, and skin characteristics like oil, water content, hydration, and elasticity also showed improvement [92].

3.1.5. Solid lipid nanoparticles

These are nano-sized colloidal carriers containing appropriate ratios of lipids, surfactants, and drugs. They are made up of solid lipids. Compound stabilization, controlled release, targeted drug delivery, and high stability are distinct advantages offered by this system. In addition, lipophilic and hydrophilic drugs can be encapsulated in SLNs. They can be produced without the use of an organic solvent [93]. **Pople et al., 2010** prepared lipid nanoparticles with tacrolimus that were optimized (T-LN). Drug-excipient incompatibility and drug encapsulation in lipid were investigated using DSC and FT-IR, with 1 H NMR confirmation. When compared to the Protopic® reference, *in vitro* studies showed significantly increased drug release, cutaneous penetration, as well accumulation. T-LN and reference product showed similar occlusiveness with *in vitro* and *in vivo* occlusion studies. However, T-LN penetrated to deeper skin layers, which are home to the dendritic cells responsible for AD immunopathogenesis with higher drug levels. When compared to the reference, *in-vivo* skin retention revealed higher SC, epidermal, and dermal levels. Additionally draize test showed no signs of skin irritation [72]. **Kang et al., 2019** created thermosensitive solid lipid nanoparticles with a greator loading efficiency. *Ex vivo* skin penetration test using cut out rat dorsal skin indicated that topical product penetrates deeper into the skin in comparison to reference product (0.1% Protopic®). Additionally, TCR-SLNs provided deeper penetration of drugs than marketing product in an *in vivo* penetration test. Furthermore FT-IR images confirmed that TCR-SLN drug distribution reached deeper layers of the skin [70].

3.1.6. Nanostructured lipid carriers

NLC are an upgrade of solid lipid nanoparticles that are made up of a blend of lipids (solid as well as liquid) leading to partially crystallized lipid system. The system provides benefits such as improved drug bioavailability, modulated molecule release, improved skin penetration and retention. Furthermore, their small size lead to high adhesiveness and surface contact area, which promotes drug influx through the skin. Other characteristics of NLC include increased drug loading capacity,

Table 3
A brief synopsis of formulations, preparation methods, and experimental findings for the treatment of AD.

Formulation	Drug	Method of Preparation	Zeta potential/ size/PDI	*In vitro* evaluation/ *Ex vivo* permeation	*In vivo* evaluation	Reference
Liposome	Cyclosporin A	Lipid film hydration method	56.6-100.6 nm/ /-23.9 mV/0.107-0.367	10% ethanol incorporation enhanced penetration.	-	[48]
Liposome	Betamethasone valerate	Thin film hydration method	223nm/-27.4 mV/0.485	No permeation after 6h, 2.68 fold higher retention when compared commercial cream	Enhanced anti-inflammatory effect.	[49]
Liposome	Anti RelA SiRNA	Small uni-lamellar vesicle fusion method	69.5 nm/-25.3mV	Deep dermal penetration observed	Suppression of ear hyperplasia, level of TNF-α, IL-6 decreased	[50]
Peptide conjugated elastic liposome	Taxifolin Glycoside	Reverse phase evaporation method	130 nm/+ 25 mV	Superior absorption, transepidermal water loss and skin surface hydration recovery was fast	Serum IL-4, IgE, and INF-γ (Interferon gamma) were regulated	[51]
Elastic liposome	Oregonin	Reverse phase evaporation method	130 nm/-9.3mV/<0.3	Greater permeation	Improved skin severity scores, decreased levels of iNOS, COX-2, IL-4, IgE, and eosinophils in either skin or blood.	[52]
Tat peptide admixed elastic liposome	Hirsutenone	Thin film hydration method	130 nm/-30 mV	Greater permeation	Decreased levels of iNOS, COX-2, IL-13, IL-4, IgE, and eosinophils in skin or blood.	[53]
Liposome	Adenosyl cobolamine	Thin film hydration method	106 nm/0.3 mV	Enhanced permeability, improved skin retention	Decreased score of lesion intensity, dorsal skin thickness, and total serum IgE	[54]
Elastic liposome	Cetirizine dihydrochloride	Thin film hydration method	139nm/ /+ 12.37 mV/ 0.247	Better penetration and permeation	Reduction in scratching score, IL-4, INF-γ erythema, dermal eosinophil count	[55]
Cationic elastic liposome	IL-13 antisense oligonucleotides	Sonication method	> 200 nm/ +30 mV	Improved uptake in human carcinoma cell and mouse embryonic fibroblast cells, no cytotoxicity	Dermal skin permeation, skin thickness decreased, IL-4, IL-5, IgE secretion decreased	[56]
Proliposome	Advanced adipose stem cell derived protein extract	Evaporation on matrix method	589 nm/-51mV	-	IgE levels decreased, skin thickening decreased, IL-5 levels decreased	[57]
Ethosome	Tacrolimus	Injection method	85 nm/+4.5/ 0.298	Greater penetration, ability to reach deeper epidermis	-	[58]
Nanocomposite β-Cycloethosomes	Fluocinolone acetonide (FA)	Injection Method	185 nm/-62 mV/0.213	Biphasic release, zero order release kinetics, greater penetration till stratum basale layer	-	[59]
Nanoemulsion Positive O/W	Ceramide-3, cholesterol, and palmitic acid SC lipids	High pressure homogenization	200nm/ +35 mV	-	Greater skin elasticity, humidity and spreadability	[60]
Nanoemulsion	Rice bran oil	Emulsion Phase inversion	69 nm	Low irritation potential	Improved skin moisture and pH values	[61]
Positive nanoemulsion	Prednicarbate	High pressure homogenization	120-240 nm/ +41-+60 mV/ 0.06-0.16	Release dependent on co-surfactant used or particle size and penetration was more for positively charged NE	-	[62]
Nanoemulsion	Pioglitazone	Water titration method	182 nm/ 12.37mV/ 0.352	73.6% of drug released from NE after 34 h of assay 25% permeated after 12.5 h of assay	Decreased pro-inflammatory cytokines, lower dermal thickness, Reduced erythema and inflammation	[63]
Nanoemulsion	Clobetasol propionate	Aqueous phase titration method	-	-	Higher level of anti-inflammatory activity was observed, but no skin irritation was observed.	[64]
Ag-NLC	-	High pressure hot homogenization	−50 mV	Bacterial killing time shortened	Skin erythema and inflammation reduced	[65]
Chitosan nanoparticles	Hyaluronic acid modified Betamethasome valerate	High Pressure Homogenisation-evaporation	223 nm, /+ 49 mV/ 0.344	Exhibited sustained and controlled delivery of active in acidic mileu Improved permeation, high drug deposition in epidermis and dermis	Reduced TEWL, erythema and dermatitis index	[66]
Poly caprolactone NPs	Hydrocortisone	Modified Solvent Displacement Method	200nm/~ −5 mV/0.030	Prolonged drug release	-	[67]
Eudragit NPs	Spin labelled dexamethasone	Nanoprecipitation technique	303nm/0.074	Release was pH dependent Higher penetration and retention	-	[68]
SLN	Cyclosporin A		73nm/-16mV	Skin permeation increased		[69]

(*continued on next page*)

Table 3 (*continued*)

Formulation	Drug	Method of Preparation	Zeta potential/ size/PDI	*In vitro* evaluation/ *Ex vivo* permeation	*In vivo* evaluation	Reference
		Hot Homogenization method			IL-4 and IL-5 level significantly decreased	
SLN	Tacrolimus	Modified emulsification and low temperature solidification	152 nm/ 0.25mV	A total of 22.52% of TCR-SLN-1 and SLN-2 were released after 24 h 24 hours after the ex vivo skin deposition test, 21.82% of the substance had accumulated	Deeper penetration observed	[70]
SLN	Auraptene	Hot homogenization and ultrasound method	140nm/-21.1mV/0.21	Biphasic release, initial burst then sustained release, Drug accumulation in skin 133.77 μg cm^{-2} after 24 h,	Improved anti-inflammatory activity	[71]
Lipid Nanoparticles	Tacrolimus	Hot melt emulsification using high pressure homogenization technique	75.9 nm/ 0.141 mV	Improved penetration to epidermal and dermal layer	Optimal anti-inflammatory effect	[72]
Chitosan NPs	Hyaluronic acid & Tacrolimus	High pressure homogenization–evaporation method	223nm/+49 mV	Initial rapid release followed by sustained release	-	[73]
Chitosan NPs	Nicotinamide & Tacrolimus	Ionic gelation method	108 nm/ 20.3mV/0.20/	Improved skin retention, no significant improvement in permeation	Enhanced skin permeation and retention Reduced AD-like, epidermis thickness, inflammatory cell infiltration, serum IgE levels	[74]
Chitosan NPs	Hydrocortisone and hydroxytyrosol	Ionic gelation method	228.5 ± 7 nm and +39 mV	-	Higher drug concentration in the epidermal skin layer	[75]
Nanocapsules	Betamethasone valerate	High pressure homogenization- solvent evaporation method	<250 nm/+58 mV/0.180	Biphasic release pattern, fickian diffusion, higher permeation and retention	-	[76]
Nanocapsules	Meloxicam	Interfacial deposition of preformed polymer	247–212 nm/-36 mV/0.14	Sustained release	Reduced oedema, Myeloperoxidase activity, lipid peroxidation	[77]
Nanocapsules	Cyclosporin	Solvent displacement method	162 nm/-36mV/0.061	Enhanced penetration into skin layers	Reduced TEWL, ear swelling, skin inflammation and production of pro-inflammatory cytokines	[78]
Starch Nanocapsules	ER143 – Human neutrophil elastase inhibitor	Emulsion-solvent evaporation method	487 nm/31.3 mV	Slower sustained release initially and faster release afterwards, enhanced penetration and retention	Improved anti-inflammatory response, decreased erythema, edema and neutrophil infiltration.	[79]
Lipid cubosomes	Houttuynia cordata	Sonication method	231 nm	Enhanced permeation	Improved lesion skin appearance, decreased IgE,IL-4, INF-γ levels	[80]

flexibility, improved stability, ease of preparation, scale-up feasibility, biocompatibility, non-toxicity, and enhanced targeting efficiency [94]. **Keck et al., 2013** developed nanostructured lipid carriers (NLC) using cetyl palmitate and hempseed oil, which were then combined with microsilver in the cream base. The particles were analyzed using coupling of field flow fractionation (FFF) and multiple angle light scattering (MALS). Adsorption of silver ions was demonstrated due to larger particle size of silver NLC. In 2,4-dinitro-1-fluorobenzene (DNFB) induced murine AD model, there was a measurable drop in ear thickness seen, also reduced erythema score was noted. Further the killing of *staphylococcus* by the synergistic action of silver and NLC was observed to be concentration dependent [65]. **Dantas et al., 2017** formed a tacrolimus-containing NLC with stearic acid/beeswax as the solid lipid and oleic acid as the liquid lipid. They showed small particle size, PDI< 1, and high zeta potential [95]. **Kong et al., 2016** prepared a betamethasome dipropionate topical ointment. Utilizing *in vitro* percutaneous permeation experiments, effect of surfactant concentration, proportion of solid and liquid lipids on skin retention and penetration were examined. The skin retention of W/O ointment containing drug-NLC was high, but penetration was low. W/O ointment prepared using drug-NLC performed better in terms of skin retention and drug release. According to the tissue distribution test, drug distribution was in the order: skin > muscle > blood. In the experiment topical ointment usage showed no irritation in mice [96].

3.1.7. Microemulsion

Microemulsions are clear isotropous blend of oil, water, surfactant and co-surfactant and offer valuable, facile, low cost formulation, better bioavailability, augmented absorption, enhanced penetration through the skin, thermodynamic stability (extended longevity), effortless formation (essentially spontaneous formation), newtonian behavior with less viscosity, greator surface area, hence elevated solubilization capacity, miniscule droplet size, controlled release, protection against oxidation and enzymatic hydrolysis [97]. **Lalan et al., 2012** created a tacrolimus microemulsion cream and discovered that it released and retained the drug more efficiently than the commercially available ointment. In addition, *in vivo* testing with a fluorescent marker indicated that skin treated with cream had an increased and profound accumulation of marker. Additionally ear swelling was significantly reduced in *in vivo* mouse studies. A semi-quantitative reverse transcriptase polymerase chain reaction exhibited a significant reduction in inflammatory cytokine gene expression with cream. The cream was more effective as observed on histopathology and morphological evaluations executed at the application site [98]. **Wang et al., 2019** generated a tacrolimus microemulsion system using menthol/camphor eutectic oil. It had greater penetration, greator impact on clinical symptoms and IgE levels. Anti-pruritic and substance P downregulation were also observed [99]. **Neubert et al., 2016** created a dimeric ceramide microemulsion system and observed its penetration into various skin layers to be better [100].

3.1.8. Nanoemulsion

These are thermodynamically unstable and kinetically stable blends of two immiscible liquid phases, one of which is dispersed in another as small spherical droplets (r < 100 nm). Some of its potential benefits include enduring stability, elevated optical clarity, improved bioavailability, augmented drug loading, and upgraded preservation against chemical as well as enzymatic degradation [101]. **Yilmaz et al., 2006** developed oil/water nanoemulsions (PN) which were positively charged, enclosing ceramide 3B as well as SC lipids (PNSC) like ceramide 3, cholesterol, and palmitic acid. NE were then analyzed for efficacy in improving skin hydration, elasticity, and erythema. PNSC creams were evaluated against PN creams, NNSC creams (negatively charged o/w nanoemulsion as well as SC lipids), and Physiogel® cream, a commercially available SC lipid formulation. In terms of elevating skin hydration and elasticity, PNSC outperformed PN and NNSC [60]. **Baspinar et al., 2010** created a prednicarbate nanoemulsion using phytosphingosine (to restore skin's barrier). The formulation was optimized by investigating the effect of homogenizer type, its cycles, pressure, temperature, on particle size, emulsion physical stability and prednicarbate chemical stability. According to the study it was proposed that high temperature should be used for making nanoemulsions, along with low homogenization pressures and greator homogenization cycles [62].

3.2. Colloidal carriers based on polymer

Polymeric colloidal carriers make up a significant portion of cargoes that aid in the advancement of drug delivery technology by allowing for the controlled and customized release of therapeutic agents to achieve desired curative outcomes. These carriers are primarily made up of natural or synthetic polymers that encase the drug moiety within micro or nanosystems. As transcutaneous flux is directly proportional to drug concentration, polymeric nanocarriers with excellent drug loading capability may help obtain high transcutaneous flux. Furthermore skin inflammation is on the outermost layer in AD and these systems have a longer circulation time, show greator deposition on the skin surface, both of these factors may prove to be beneficial in AD. Additionally, high structural stability owing to their tough matrix and sustained release are other advantages of polymeric systems [102]. The following section goes over the different types of polymeric colloidal carriers that have been studied in AD treatment.

3.2.1. Polymeric micelles

Polymeric micelles are colloidal carriers with diameters ranging from 10 to 100 nm that are composed of block or graft copolymers and combine to form hydrophobic cores or hydrophilic shells. They have benefits such as improved tissue penetrability, reduced toxicity, controlled drug release, high stability, and biocompatibility [103]. **Assem et al., 2019** synthesized beclomethasone dipropionate micelle. The morphologically optimal formulation with the maximum skin deposition was used to prepare hydroxypropyl methylcellulose hydrogel. The viscosity of hydrogel, it's *ex vivo* deposition study, *in vivo* histopathological studies was assessed, and compared to the commercially available cream Beclozone®. Compared to Beclozone®. The prepared hydrogel was more effective at treating sub-chronic dermatitis and caused less irritation in the animal model [104]. **Napimoga et al., 2019** prepared and evaluated prostaglandins-poloxamer hydrogel formulation and assessed its activity in AD, induced by 2, 4–dinitrochlorobenzene (DNCB) in mice. Decreased infiltration of mast cell in AD, reduced serum IgE levels, reduced TNF-α were obsereved [105]. Hydrocortisone (HC)-loaded micelles were combined with a carbomer hydrogel to create a composite by **Yuan et al., 2020.** The skin permeation rate was found to be increased and the total HC transmission was increased. In addition, inflammatory symptoms, skin irritation as well as adverse systemic effects were reduced compared to HC cream [106].

3.2.2. Microsphere

Microspheres are spherical, free-flowing polymer particles that are also known as microparticles. These are classified into two types: microcapsules and micromatrices.They provide benefits such as reduced dose, toxicity, reduced susceptibility to enzymatic drug degradation, targeted delivery, and enhanced bioavailability [107]. **Shi et al., 2017** developed Poly (d,l lactide-co-glycolide) microspheres that encapsulated tacrolimus. In the dermatitis affected BALB/c mice long-term reductions in ear swelling, dermatitis index, inflammatory cell accumulation, and serum IgE levels have been observed [108]. **Feng et al., 2014** created mizolastine-loaded microspheres and found that they significantly reduced ear thickness and dermatitis index in DNCB-induced BALB/c mice. Inflammatory cell infiltration into the ears was also reduced, as was the plasma level of IgE [109].

3.2.3. Nanocapsule

Nanocapsules are vesicular systems comprising of an inner liquid core surrounded by a polymeric membrane and have enormous potential as drug carriers due to numerous advantages, such as improving aqueous solubility, enhancing stability, facilitating tailored pharmacokinetic profile, permitting controlled release, and aiding oral drug delivery. In a starch-based nanoparticulate system (StNC) [110]. **Marto et al., 2018** encapsulated a human neutrophil elastase inhibitor (ER143). *In vitro* studies conducted on newborn pig skin revealed improvement informulation's release, permeation, and retention properties. Upon local application of croton oil to induce soreness in mice ear and consequently applying ER143, 98% reduction in erythema and edema was noted [79]. Meloxicam nanocapsules were formulated by **Weber et al., 2018** and improvement in edoema, reduction in myeloperoxidase activity, lesser thiobarbituric acid reactive species and non-protein thiol levels were observed in a DNCB-induced atopic model [77].

3.2.4. Dendrimers

These are versatile polymeric systems with a highly branched 3D architecture formed by adding monomers (one at a time) to formulate a non-covalently encapsulated drug, surface electrostatic interaction with the drug, or covalently cleavable linkages. These systems have several advantages, such as increased drug penetration, drug targeting, improved stability, solubility, and oral bioavailability [111]. **Radbruch et al., 2017** created a novel class of dendritic core-multishell nanocarriers (CMS). CMS exhibited greator built up in the stratum corneum but did not enter deeper viable epidermal layers in the wake of topical administration. The same results were obtained in AD mice, indicating that AD barrier changes had no effect on CMS penetration. CMS, which was injected subcutaneously, deposited in lymph nodes, liver, spleen, lung, and kidney. Moreover, morphometric assisted histopathological test, clinical data, did not indicate that CMS had toxicity or otherwise negative effects (local or systemic) and the severity or course of AD remained unaffected [112].

3.2.5. Nanofibrils

These are nanoscaled fibers with modifiable porosity, and a large surface area to volume ratio. Its well-documented features include modulable drug release, easy fabricability into various shapes, high drug loading capability, and localized delivery [113]. When **Izumi et al., 2016** analyzed chitin nanofibril, AD scores were found to be low, and hypertrophy and hyperkeratosis of the epidermis were reduced. The activation of nuclear factor-kappa B, cyclooxygenase-2, and inducible nitric oxide synthase was inhibited in both the epidermis and dermis. It had a suppressive effect on IgE levels and suppressive effect on AD that was comparable to corticosteroids [114]. **Shams et al., 2021** synthesized tacrolimus nanofibers with the necessary tensile strength and a sustained release profile. During study the cornified epidermis layers was found to be thinner [115].

4. Future perspective

AD is becoming more prevalent, particularly among those living in cities and in developing nations, and is the biggest non-fatal health burden associated with skin illnesses. Research is being extended to investigate the implications of factors such as dysregulated sleep, nutrition on the onset of AD. AD has intricate pathophysiology and there is currently no perfect therapy available. More targeted topical and systemic therapies are being researched as our understanding of the pathogenesis of AD is advancing, such as those inhibiting elevated Th2 cytokines or their receptors, like IL-4, IL-13 (e.g. Tralokinumab), IL-33 (e.g. Etokimab), TSLP, or Th22 (e.g. Fezakinumab) /Th17 cytokines (e.g. Secukinumab). Further, antipruritic medicines (e.g. Nemolizumab), phosphodiesterase inhibitors (e.g. Roflumilast), Janus kinase inhibitors (e.g. Ruxolitinib), anti-IgE antibody (e.g. Ligelizumab), histamine inhibitors (e.g. Adriforant) are also being investigated for AD [116]. Cost factor of these biologics however, might limit their use as a last resort as compared to low-cost, generic topical or oral systemic medicines. This may make it difficult to expand the market of biologics among patients with severe disease. Apart from the above mentioned therapeutic options anti-staphylococcal treatment and commensal strain transplantation are both promising therapies currently being examined for AD.

The phenotypic diversity in AD patients of various ethnic backgrounds along with better understanding of the molecular underpinnings of AD, urges for multimodality and personalized therapeutic development for AD patients in the future. There is also growing interest in identifying gene targets and individual or groups of biomarkers that characterize the disease's numerous clinical phenotypes. The emphasis is also increasingly turning towards preventive research. Probiotics, use of emollients from early years in high-risk newborns, omega-3 fatty acid supplementation, anti-histamine (cetirizine) for secondary prophylaxis, and topical fluticasone for reducing the development of future flares as tertiary preventive measure are some of the beneficial preventive therapies [117]. Targeted delivery of these agents, therapy adherence, is another challenge in AD treatment.

For effective delivery of bioactives in AD number of lipid nanocarriers explored outnumber polymeric nanocarriers. Both these systems have successfully contributed desirable attributes in drug delivery such as enhanced entrapment efficiency, skin penetration, retention, sustained release, reduced TEWL, reduced inflammation etc. Indepth study of nanocarriers', their impact *in vivo*, their ability to affect molecular targets, and toxicological profiling may aid their application.

5. Conclusion

Controlling AD necessitates fine-tuning the delicate four-way balance between Th1, Th2, Th17/22, and Treg cells. Topical, systemic, and phototherapy have been the traditional treatment strategies for AD management. Besides many successful and promising strategies discussed in this review, a number of therapeutic agents have failed the clinical trials for AD. FB-401 (used against inflammation and *Staphylococcus aureus* in AD), Lirentelimab (inhibits IgE, sIL-33, TSLP mediated mast cell activation), Tezepelumab (Anti-TSLP), Defelikefalin (κ-opioid receptor agonist), MOR-106 (Anti-IL-17 C), Apremilast (PDE4 inhibitor), Fevipiprant (Th2 suppression), Ustekinumab (for supression of Th1, Th17, Th22 axes) are few examples. This may be due to endotypic and phenotypic differences observed in AD patients, presence of distinct drivers of disease found in patients of different ethnicities and demographics. The failure highlights the need to thoroughly examine preclinical research methodologies, such as animal models used for determining the efficacy of treatments for AD. New biologics and small molecules being developed, pose other challenges in the AD drug delivery such as high cost, accessibility issues, risk of drug misuse due to poor information. When it comes to therapeutic drug delivery, the potential of nanocarriers to penetrate selectively into inflamed skin while having little side effects on healthy skin makes them a promising area of research for the disease. In addition, the physicochemical features of nanocarriers, such as size and surface charge, have influenced their deposition positively. However despite the positive potential, nanocarriers require more research as there is lack of in-depth *in vivo* investigation, their commercial viability and toxicity data are inadequate. Furthermore to accomplish successful customized therapy for AD, greater monitoring and access to high-end diagnostic equipments might be required. Looking ahead we can anticipate few promising directions: defining the disease and outcomes, finding common methodical patterns to the disease and conducting clinical trials for diverse populations and subtypes, or targeted treatment to a particular population group. Also, clinical translation and commercialization of nanocarriers would be aided by their thorough investigation at the molecular and cellular levels.

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Conflict of interest statement

None.

Data availability

No data was used for the research described in the article.

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