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Review

Recent Advancements in the Atopic Dermatitis Mechanism

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Abstract

Atopic dermatitis (AD) is a recurrent, chronic, inflammatory, itchy skin disorder that affects up to 20% of the pediatric population and 10% of the adult population worldwide. Onset typically occurs early in life, and although cardinal disease features are similar across all ages, different age groups and ethnicities present distinct clinical characteristics. The disease imposes a significant burden in all health-related quality of life domains, both in children and adults, and a substantial economic cost both at individual and national levels. The pathophysiology of AD includes a complex and multifaceted interplay between the impaired dysfunctional epidermal barrier, genetic predisposition, and environmental contributors, such as chemical and/or biological pollutants and allergens, in the context of dysregulated T_H2 and T_H17 skewed immune response. Regarding the genetic component, the loss of function mutations encoding structural proteins such as filaggrin, a fundamental epidermal protein, and the more recently identified variations in the epidermal differentiation complex are well-established determinants resulting in an impaired skin barrier in AD. More recently, epigenetic factors have facilitated AD development, including the dysbiotic skin microbiome and the effect of the external exposome, combined with dietary disorders. Notably, the interleukin (IL)-31 network, comprising several cell types, including macrophages, basophils, and the generated cytokines involved in the pathogenesis of itch in AD, has recently been explored. Unraveling the specific AD endotypes, highlighting the implicated molecular pathogenetic mechanisms of clinically relevant AD phenotypes, has emerged as a crucial step toward targeted therapies for personalized treatment in AD patients. This review aims to present state-of-the-art knowledge regarding the multifactorial and interactive pathophysiological mechanisms in AD.

Keywords: atopic dermatitis; atopic eczema; pathophysiology; skin barrier disruption; immunopathogenesis; skin microbiome; exposome; endotypes

1. Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disorder, affecting up to 25% of children and 10% of adults, depending on the geographical area [1]. Although almost 85% of AD cases appear before the age of 5 years, the onset of the disease in adults is not uncommon, with almost 25% of the patients reporting symptoms only after adulthood. The characteristic clinical features of the highly pruritic eczematous lesions, consisting of papules and patches and the subsequent exudation and excoriation in the acute phase as well as the chronic lichenified, hyperpigmented lesions are similar across all ages, although distinct clinical characteristics present across different age groups and ethnicities [2]. Even though AD is not associated with mortality and is therefore underreported compared to other fatal diseases, it imposes a significant morbidity burden due to the humanistic and psychosocial effects, both for patients and their families [3].

The two previously main pathogenetic hypotheses, the 'outside–in' and the contrasting 'inside–out', which prioritize either the epidermal barrier dysfunction or the dysregulated immune activation as the primary trigger in the pathophysiology of AD, are now integrated into a complex and multifaceted model, including the genetic component and, the effect of environmental pollutants, in the context of a dysregulated T_H2 and T_H17 skewed immune response [4]. Concerning the genetic component, the lower expression of terminal differentiation markers, such as filaggrin (FLG) and loricrin (LOR), and the respective barrier permeability defect associated with the epithelial lipid film impairment and increased transepidermal water loss (TEWL) are well-established determinants [5]. Thus, the skin in AD is prone to the penetration of exogenous agents, potentially facilitating a dysbiotic microbiome [6] and further contributing to keratinocyte damage and sustained skin inflammation [7]. Notably, the interleukin (IL)-31 network, comprising several cell types, such as macrophages, basophils, and the

generated cytokines, is also involved in the pathogenesis of the itchiness in AD [8].

The evolution of endotypes in AD and the ongoing research on the determination of non-invasive biomarkers have emerged as an important step toward targeted therapies for personalized treatment in AD patients [9]. This review aims to present state-of-the-art knowledge on the complex, multifactorial, and interactive mechanisms that contribute to the vicious cycle of the pathophysiology of AD and present up-to-date therapeutic interventions.

2. Advances in Immunopathogenesis

The dysregulated T cell-mediated immune response, including different patterns of cytokine release, has a strong and robust role in the pathogenesis of AD. The disrupted skin barrier enhances exposure to environmental allergens, which can either activate skin antigen-presenting cells, such as the inflammatory dendritic epidermal cells (IDECs), resulting in the subsequent "allergic response", or induce the chemokine milieu from keratinocytes, such as the thymic stromal lymphopoietin (TSLP), and interleukins (IL)-23, IL-25, and IL-33, reinforcing the T2 response and the induction of IL-4 and IL-13, IL-31 cytokines though type 2 human innate lymphoid cells [10]. This, in turn, promotes the class switch of B cells to plasmacytes toward specific IgE induction. Nevertheless, in chronic AD cases, a T_H1 and T_H17 dominance is noted, mediated by interferon-gamma (IFN-γ)/tumor necrosis factor-alpha (TNF-α) and IL-17, respectively, while T_H22 responses driven by IL-22, are also present [11].

IL-4 and IL-13 represent the two main T2-cytokines associated with AD pathogenesis. In addition to promoting T2 responses and recruiting eosinophils, they damage the skin barrier by downregulating the expression of structural proteins such as filaggrin, loricrin, and lipids, while they concomitantly increase collagen disposition, resulting in skin remodeling and lichenification. Moreover, they contribute to the neurogenic itch by directly stimulating pruritogenic sensory neurons, as will be further discussed later [12]. IL-4 and IL-13 also stimulate the expression of 3β-hydroxysteroid dehydrogenase-1 and androgens, resulting in decreased levels of triglyceride concentration in sebocytes and keratinocytes within the epidermis, further damaging the atopic skin; thus, inhibition of 3β-hydroxysteroid dehydrogenase-1 could serve as a potential therapeutic target, by restoring triglyceride content in the human skin [13]. Induction of IL-13 by cutaneous mast cells in response to the damaged skin directly inhibits the T_H1-associated interleukin IL-12 and the subsequent IFN-γ release from CD4+ T cells, suppressing T_H1-mediated immune response to cutaneous encountered antigens in AD [14]. In this context, dupilumab, an IL-4 receptor alpha antagonist (IL-4Rα) that blocks the IL-4/IL-13 signaling pathway, has been granted approval as an add-on treatment for patients with uncontrolled moderate to severe AD from the age of 6 months. Phase 3 clinical trials have demonstrated dupilumab's safety, tolerability, and efficacy in all age groups, while pediatric studies have also shown significant improvements in validated scores, assessing symptoms and signs in AD patients, and, interestingly, decreasing the likelihood of skin infections in preschool-aged children [15–17]. The selective IL-13 blockade with tralokinumab, a human immunoglobulin IG4 monoclonal antibody that neutralizes cytokine IL-13 and interrupts the activation of IL-13Rα1 and, to a lesser extent, IL-13Rα2 receptor subunits, or lebrikizumab, are currently approved for the treatment of AD in adolescents and adults, after showing substantial improvement in the morbidity of AD, as assessed by the Investigator's Global Assessment scale (IGA) and Eczema Area and Severity Index (EASI-75) scores and the intensity of itching and sleep loss [14,18,19].

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is significant in the pathogenesis of AD and inflammation. The JAK family consists of four intracellular kinases, JAK1, JAK2, JAK3, and TYK2, which are activated in pairs when cytokines bind to their respective receptors [20]. Specifically, JAK1 mediates the IL-4, IL-5, IL-13, IL-22, TSLP, and IFN-γ signaling pathway, while JAK2, JAK3, and TYK2 are partially involved by interacting with JAK1 [20]. Activation of these individual JAK kinases leads to phosphorylation of the STAT proteins, which dimerize and translocate to the cell nucleus to induce gene transcription after binding to specific DNA sequences. The IL-4/IL-13-dependent JAK/STAT pathway involves the STAT6 and STAT3 proteins. Various STAT6 polymorphisms have been associated with elevated IgE levels and increased susceptibility to AD. STAT6 upregulates the expression of the T2-specific transcription factor GATA3 and promotes a class switch to IgE in B cells, hence, regulating T cell proliferation and T2 differentiation [21]. Considering this, the JAK/STAT pathway has been acknowledged as a novel therapeutic target for patients with moderate to severe AD. Inhibition of the JAK/STAT pathway by either abrocitinib (JAK1), baricitinib (JAK1/2), upadacitinib (JAK1), and the topical ruxolitinib (JAK1/2) downregulates the aforementioned inflammatory pathway in AD (Fig. 1). Abrocitinib is a safe and effective therapeutic agent, currently approved for adults and adolescents in the USA and UK with moderate to severe AD, while approval for 12 to 18-year-old AD patients is currently awaited in Europe [22–24]. Upadacitinib and baricitinib have been licensed for adolescents/adults and children from the age of 2 years with moderate to severe AD, respectively [25,26]. In addition, ruxolitinib, a JAK1/2 inhibitor, is the only drug in this class currently approved for topical use [27]. Delgocitinib, a pan-Janus kinase inhibitor in an ointment form, has been approved for moderate to severe adult chronic hand eczema and is still under trial for atopic dermatitis in the pediatric population [28]. All JAK inhibitors have shown significant improvements

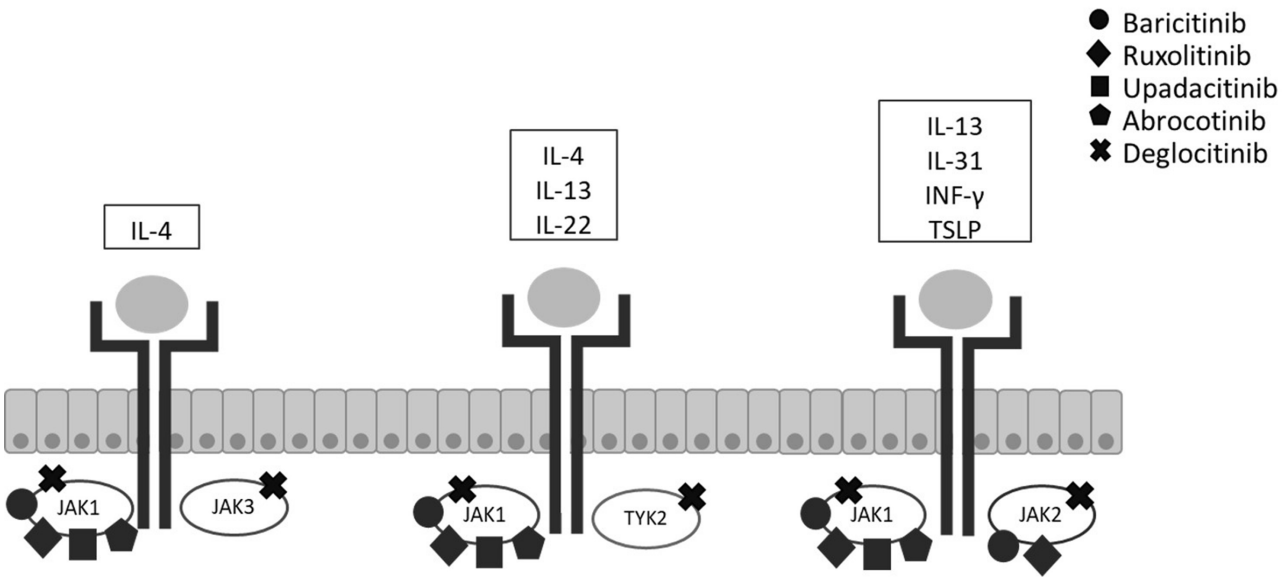

Fig. 1. Janus kinase/signal transducer and activator of transcription (JAK/STAT) inhibitors in atopic dermatitis (AD) inflammatory pathway. IL, interleukin; IFN-γ, interferon-γ; TSLP, thymic stromal lymphopoietin.

in AD severity markers, such as the EASI and IGA scores, while a profound beneficial effect on itching is apparent from the first week of treatment. Of note, laboratory tests are required before and during the treatment, while certain limitations in their use hold for patients at risk of thromboembolic incidences and those older than 65 years.

In addition to epithelial damage and allergen exposure activating the T_H2-mediated immune response, T regulatory cell (Tregs) dysregulation promotes T2 dominance in AD. Tregs usually suppress T2 expression; however, under presentation, the potential favoring of the T2-mediated immune response has been observed in AD patients compared to healthy controls [29,30]. Such reduction and compromised functionality of Tregs might also be attributed to exposure to tobacco smoke during pregnancy and microbiome dysbiosis [31,32]. Notably, immunomodulatory strategies toward the activation of Tregs have been proposed, aiming at long-term remission of AD [30].

Regarding other mediators involved in the pathogenesis of AD, IL-18, a proinflammatory cytokine stimulated by epithelial damage and staphylococcal colonization, promotes T2-mediated inflammation by activating basophils and mast cells. Elevated IL-18 levels have been associated with increased AD morbidity, while IL-18 deficiency in murine models ameliorated AD skin lesions by decreasing IL-4 levels and mast cell infiltration [33,34]. Nevertheless, its pleiotropic function in AD has not been fully elucidated. Moreover, high serum IL-21 levels in AD patients, primarily produced by T_H17 cells, are associated with increased disease severity compared to healthy controls [35]. IL-21 has also been implicated in the pathogenesis of AD either by directly promoting the T2 pathway or suppressing the T_H1 immune response through INF-γ downregulation [36]. In this respect, the beneficial effects of upadacitinib might also be attributed to the downregulation of IL-21 [25,37]. IL-22, a T_H22 mediator upregulated in acute and chronic AD, impairs the skin barrier by suppressing proteins critical for epidermal differentiation, enhances antigen sensitization, and promotes a biased T2 immune response, while it contributes to the pathogenesis of chronic itching in AD by promoting the expression of itch-inducing cytokines [38]. Blockade of IL-22 using the monoclonal antibody Fezakinumab downregulates multiple immune pathways associated with AD, such as T_H1, T_H2, T_H17, and T_H22, in patients with high serum IL-22 levels and has been proven safe and efficient in individuals with severe AD [39].

The increased phosphodiesterase 4 (PDE4) activity observed in AD results in the reduction of intracellular cyclic adenosine monophosphate (cAMP), a negative regulator of cytokine production, leading to the augmented production of proinflammatory mediators and cytokines transcription involved in acute and chronic inflammation. Preventing cAMP breakdown by inhibiting PDE4 suppresses proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-12, and IL-23. The PDE4 inhibitor, Crisaborole is approved for topical treatment in patients older than two years old with mild to moderate diseases [40], while another promising selective PDE4 inhibitor, Difamilast (also OPA-15406 or MM36), has undergone phase II trials in pediatric and adult patients with mild-to-moderate AD, with positive results [41].

Innate and adaptive immune cells, such as basophils, eosinophils, and macrophages, contribute highly to AD pathogenesis. Basophils participate in the initiation of AD through increased expression of IL-4 and interactions with keratinocytes and dermal macrophages, resulting in epider-

mal hyperplasia and skin barrier dysfunction [42]. Circulated eosinophils in patients with AD express increased and upregulated histamine receptor 4 (H_4R), mediated by IL-4 and IL-13 through the JAK/STAT pathway, leading to increased production of IL-31 [43]. It has been shown that the IL-18 receptor (IL-18Rα) is also upregulated in the eosinophils of AD patients and that histamine enhances IL-18 expression in eosinophils through H_2R and H_4R, suggesting a key role for IL-18 and histamine in eosinophil-mediated inflammation in AD [44]. Ruxolitinib significantly abolishes H_4R expression in eosinophils, indicating a novel potential for AD treatment [43], while direct H_4R antagonist also improves disease severity, mainly by targeting pruritus [45]. M2 macrophages are a major cellular source of IL-31 in AD, and their interaction with TSLP, periostin, and basophils contributes to AD pathogenesis and the itch–scratch cycle. Immunohistochemical analysis of skin biopsy samples from patients with AD reveals significant infiltration of IL-31-expressing M2 macrophages, CD68+ macrophages, and basophils in AD skin lesions [8]. The number of IL-31-expressing M2 macrophages positively correlates with the increased expression of TSLP and periostin in the epidermis of AD lesions and the severity of the disease. In a murine model of AD, the depletion of basophils resulted in reduced IL-31 expression by M2 macrophages [8]. Furthermore, M2 macrophages produce the C–C motif chemokine ligand 18 (CCL18), a chemokine strongly associated with increased morbidity in AD patients [46]. CCL18 is upregulated in AD skin through tissue-resident antigen-presenting cells in response to environmental factors [47]. More profoundly, IL-4 and IL-13, and to a lesser extent IL-10, upregulate CCL18 expression, while such an increase further stimulates H2R on IL-4 and IL-10-activated macrophages [47]. Targeting IL-4/IL-13 pathways or employing histamine receptor antagonists therapeutically could regulate CCL18 expression and lead to a shift from an inflammatory state to a more balanced, homeostatic condition. The role of IL-31 in AD pathogenesis and pruritus, and as a novel therapeutic option, will be thoroughly discussed in the "itch" paragraph below.

The dysregulated immune response in AD is intricate and multidimensional, affecting the antigenic response, the induction of inflammation, the disruption of the cutaneous architectural integrity, and pruritus. Rectifying the imbalanced immune response holds potential advantages in the pathophysiological facet of AD and potentially the progression of an atopic march.

3. Advances in Understanding and Restoring Epidermal Barrier Dysfunction

The cardinal role of epidermal barrier dysfunction in the induction and perpetuation of AD is well established. The "leaking epithelial barrier" results in chronic peri-epithelial inflammation in the epithelium-lined human organs, including the skin, the gastrointestinal and respiratory systems, and, consequently, in certain autoimmune, metabolic, and neuropsychiatric diseases [48]. Primarily, the skin acts as a barrier for physical, chemical, and microbial agents; thus, for impairment, a dysbiotic microbiota, impaired remodeling, local immune responses, and increased TEWL facilitate the penetration of allergens and translocation of microbiota to the subepithelial areas, subsequently activating systemic immune responses and prolonging chronic epithelial damage.

The epithelial barrier consists of four cell layers: The stratum basal, the stratum spinosum, the stratum granulosum (SG), and the stratum corneum (SC) within the epidermis. The SC is a semipermeable barrier in the outer part, consisting of corneocytes embedded in a protein-loricrin (LOR) and involucrin- shell, called an envelope, and surrounded by lipids, such as free fatty acids, ceramides, and cholesterol [49]. During the differentiation of keratinocytes, the released keratin (KRT)-1 and KRT-10 in the spinum and the granular layer of the epidermis contribute to the consistency of keratinocytes. In the context of T2 dominance in AD patients, decreased levels of KRTs, desmoglein (DSG)-1 and desmocolline (DSC)-1, and epidermal differentiation-related molecules have been observed [45].

Moreover, alterations in lipid synthesis, lipid content, and structure reduction in AD patients further compromise skin integrity [50]. The lipid chain length of ceramides and free fatty acids and the levels of elongases 3 and 6 (ELOVL3, ELOVL6), which play a significant role in lipid chain elongation, is decreased in both the lesional and non-lesional AD skin [51,52]. Expression of the elongases is also downregulated by IL-4 and IL-13 under the control of STAT6, suggesting a crosstalk between the inflammatory and the barrier components in AD [51]. Alterations in enzymic expression in AD have also been reported for stearoyl Coa desaturase, SCD, ELOVL1, aSmase, GBA, and CerS3, further enhancing lipid abnormalities [52].

Filaggrin (FLG) is an important structural protein responsible for the keratinocyte shaping and positioning of the cytoskeletal components. During FLG degradation, the newly formed urocanic acid and pyrrolidine carboxylic acid contribute to SC hydration, thus, preserving skin integrity [53]. Loss-of-function *FLG* gene mutations are the most important genetic risk factors for AD due to alterations in lipid delivery, the decrease in FLG monomers, and natural moisturizing factors produced by FLG metabolites [54,55], while the resulting altered skin pH leads to impaired lipid construction and cell apoptosis [56]. Furthermore, FLG and LOR, involucrin, and keratins 1,10 are downregulated in the presence of T2 inflammation cytokines, such as IL-4, IL-13, IL-22, and IL-31, in a process mediated by OVO-like 1 (OVOL1), an upstream transcription factor for these proteins [49,57]. The T2 cytokines and IL-25 downregulate the expression of corneodesmosin, potentially contributing to increased viral penetration [58].

Specifically, OVOL1 activation induces translocation from the cytoplasm to the nucleus and upregulates FLG, while interference by the inflammatory cytokines on OVOL1 decreases FLG expression [59]. IL-13 also inhibits involucrin in an OVOL1-independent way, promoting barrier dysfunction [60], while it reduces the expression of skin barrier proteins and lipids by acting on keratinocytes, regulating the expression of metalloproteinase (MMP)-9 [61]. The IL-4/IL-13 inflammatory pathway blockade with dupilumab has been shown to restore epidermal barrier properties and improve skin hydration [62]. Importantly, the data indicate a restorative effect of dupilumab in AD by progressively ameliorating systemic and cutaneous abnormalities [63].

Granzyme B, an apoptotic protease, also increases skin-barrier permeability through the fracturing of FLG and E-cadherin [64], while upregulated enolase-1 (ENO-1) leads to tight junction defects due to abnormal keratinization [65].

Tight junctions (TJs) form a complex intracellular barrier in the SG, while claudin is the major adhesion structural protein in TJs. Downregulation of claudins and the presence of single nucleotide polymorphisms in the *CLDN1* gene lead to TJ defects and increased TEWL in patients with AD [66].

Emerging therapeutic modalities aiming at epidermal barrier functionality restoration by decreasing epidermal hyperplasia, cytokine infiltration, and increasing skin-barrier protein production, such as spirodelapolyrhiza (SPE) and Olea europaea leaf extract (OLE), have been proposed [67]. Glucoseskin application in high concentrations can increase claudin-1 and FLG production [68], while Cimifugin, a bioactive Chinese herb, and the orally administrated PAG (DL-propargylglycine) improve TJs function by suppressing allergic inflammation [69,70]. In an *ex vivo* model, the microorganism component Aquaphilus dolomiae induced immunomodulatory and antimicrobial peptides, thus, indirectly restoring skin barrier integrity when applied in cell cultures obtained from patients with AD [71]. Delgocitinib, a JAK kinase inhibitor, in an ointment formulation, ameliorates TJ function without eliminating claudin expression [72], and bortezomib, a proteasome inhibitor, upregulates claudin-1 expression [73].

Aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor that controls skin barrier protein activation by regulating the epidermal differentiation complex (EDC) [74]. Several plant-based extracts have shown beneficial effects through binding to AHR and upregulating the expression of barrier protein genes and skin integrity, such as tapinarof, a small molecule produced by bacteria, diosmin, a natural agonist derived from the Rutacae family, and other medical remedies, such as Rhodiola crenulate and Artemisia princeps [60,75–77]. It has been postulated that AHR antagonists increase the production of FLG, involucrin, and LOR via the OVOL-1 transcription factor pathway [60].

The epidermal barrier plays a pivotal role in AD by serving as the primary defense mechanism against external irritants and allergens. Thus, agents that restore and maintain an intact barrier are important.

4. Advances in Skin Microbiome Dysbiosis

Skin is inhabited by a complex community of bacteria, fungi, and viruses, which constitute the skin microbiota and impose immunomodulatory and protective effects against pathogenetic microbes [78]. The skin microbiome in AD patients is dysbiotic, defined by imbalanced bacterial composition and diversity [57,79], with reduced commensals, while the increased number of skin pathogens has been positively associated with AD severity [80]. *Staphylococcus* (*S*). *epidermidis* represents the most abundant species in human skin, facilitating the defense against other pathogens and contributing to skin epithelialization, while such responses are also induced by Corynebacterium, Propionibacterium, and Streptococcus sp. [81]. Microbiome dysbiosis in AD impairs immune responses and, in response to the exposome effects, contributes to the “leaking epithelium”, the subepithelial translocation of dysbiotic microbiota and opportunistic pathogens [82]. However, whether skin leakage precedes microbial dysbiosis or vice versa remains controversial.

In infancy, skin colonization with commensal *S. epidermidis* promotes tolerance mechanisms via the induction of regulatory T cells. On the contrary, in the predominance of *S. aureus*, which can penetrate via the epidermis more so through a disrupted epithelial barrier, via its superantigen components, a promoted B cell differentiation and induction of T2 cytokines, such as IL-4, IL-13, IL-22, and TSLP, is noted [83]. Furthermore, excessive colonization of *S. aureus* on the skin leads to biofilm formation and secretion of virulence factors, which further stimulate keratinocytes and Langerhans cells to release T2 inflammatory responses [84,85]. Biofilm propensity by *S. aureus* and *S. epidermidis* has been positively associated with AD severity and epidermal dysfunction [86].

The epidermal fungi, although not considered direct pathogenetic agents, contribute to AD initiation and exacerbation. Specifically, in *Candida sp.*, *C. albicans*, and *C. parapsilosis*, colonization is increased in AD patients compared to healthy adults, while *Malassezia* species, especially *M. restricta*, *M. globose*, *M. furfur*, and *M. sympodialis*, are frequently detected in AD lesions during disease flares [87]. Ruxolitinib has been shown to reduce *Malassezia* in an *in vitro* skin model; however, data on the effect of JAK inhibitors in the microbiome of AD patients is limited [88]. Patients with increased AD morbidity are significantly more often colonized with non-*Malassezia*

species and with an increased diversity of fungi species, including *Alternaria*, *Aureobasidium*, *Aspergillus*, and *Cladosporium sp*. [89,90]. Finally, Ascomycota AD skin colonization is related to higher IgE titers and aggravation of AD severity [91]. Of note, colonization with fungi is site-dependent, i.e., Malassezia sp. being more abundant in the scapula; this phenomenon is potentially associated with variations in TEWL [92].

Treatment options might influence both dysbiosis and dysbiosis-associated inflammation. Bleach baths with sodium hypochlorite in bathing water containing oil are still recommended as a treatment option in the most recent European Academy of Dermatology and Venerology (EADV) guidelines [93], although a recent meta-analysis concluded that their beneficial effect through a decrease in S. aureus colonization, per se, is not adequately documented. Thus, they should be used cautiously since adverse effects might be noted [94].

The emollient application can ameliorate AD symptoms by decreasing *S. aureus* colonization and increasing microbial variety in the skin [95]. In most AD cases, emollient "plus" products combine vehicles and active components using substantial efficacy data. Emollient formulas of 1% colloidal oat or 5% Vitreoscilla filiformis lysate cream decrease the *S. aureus* population and increase skin microbial richness [96,97]. However, the long-term effect of emollients on the microbiome and skin pH is still debated [98,99].

Autologous microbiotherapy is an evolving treatment option with satisfactory results and only minor adverse effects [100]. *S. aureus* can be decreased by other coagulase-negative *Staphylococcus sp*. (*S. epidermidis*, *S. hominis*, *S. warneri*, *S. capitis*) that can grow on the healthy skin of AD patients [101]. *Roseomonas mucosa*, a Gram-negative skin commensal, contributes to tissue repair through sphingolipid production and stimulating cholinergic signaling and to flagellin expression through the TNF-mediated signaling pathway, thereby ameliorating AD symptoms [102,103]. *Nitrosomonas eutropha*, an ammonia-oxidizing bacteria, suppresses the T_H2-mediated response through the upregulation of IL-10 and reduction of *S. aureus* colonization [104]; the topical treatment is currently undergoing clinical trials for individuals with mild to moderate AD [104,105]. Current prebiotic, probiotic, and postbiotic formulations have limited evidence regarding the guidelines to allow a recommendation for their use as therapeutic agents in AD [93].

IL-13 decreases antimicrobial peptides and promotes epidermal dysbiosis [106]. In this respect, the anti-IL4/IL-13 monoclonal antibody, Dupilumab, improves skin dysbiosis by inhibiting *S. aureus* growth and restoring microbial skin dysbiosis; meanwhile, it also increases *S. epidermidis* and *S. hominis* [62,107].

The key role of skin microbiome dysbiosis in the integrity of the skin barrier and the interplay between microbiome, exposome, skin-barrier leakage, and host immune response highlights the necessity for targeted interventions aiming at rebalancing the skin microbiome.

5. Advances in Understanding the Role of the Exposome

The role of the exposome in the multidimensional model of AD pathogenesis has recently been explored. The concept of the exposome was introduced in 2005 by Wild *et al*. [108], highlighting the bidirectional interaction of the external environment and human health and disease, complementing the gene—environmental associations in the pathogenesis of allergic diseases. Exposome refers to the total of the environmental exposures that an individual experiences throughout a lifetime and their effect on their health outcomes (Fig. 2). The recently introduced "meta-exposme" includes the complete set of environmental factors that impact halobionts, encompassing a holistic perspective of the policies and practices that shape the environment [109]. Within this concept, distinct exposures include allergens, pollutants, irritants, lifestyle choices, diet, stress, socioeconomic parameters, climate change, microbial agents, etc. [110]. The exposome is further classified, with a high degree of overlap, as the general external: Climate, biodiversity, urbanization, and socioeconomic contexts; the specific external: allergens, pollutants, tobacco smoke, diet, lifestyle factors, and microbes; the internal: Inflammation, metabolism, and oxidative stress exposome [111]. The exposome is the "master regulator" in the interplay between a disrupted and "leaky" epithelium barrier, microbiome, genome, and immune dysregulation in AD [112]. In a simplified model, the exposome contributes to AD pathogenesis by disrupting the epithelium barrier, contributing to the crosstalk with the disturbed skin microbiome, and through epigenetic regulation of the genome of predisposed individuals. The leaky epithelium initiates a vicious cycle of chronic inflammation in AD, which is further supported by microbiome translocation and imbalance under the concept of epithelium barrier hypothesis, as previously described [48].

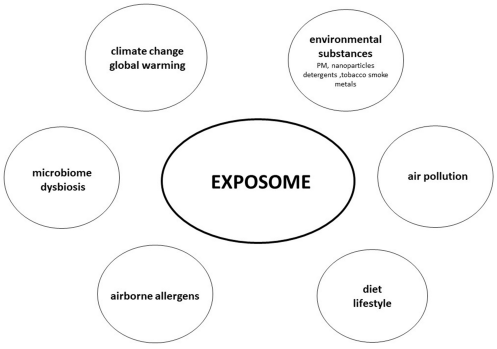

Fig. 2. Factors that modulate the exosome and participate in the pathophysiology of AD.

As part of the external exposome, global warming and climate change impact the development and exacerbation of AD. Floods caused by global warming and polar ice melting are associated with an increased risk of emergency visits due to increased morbidity and severity of AD in children. It is plausible that floods increase humidity, environmental dampness, allergen levels in the environment, indoor molds, and contaminated water, thereby contributing to AD exacerbation in sensitized children [113]. Exposure to increased levels of relative humidity means daily temperatures, precipitation, nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM10), and pollen counts are also positively associated with AD severity and exacerbation rates [114]. In accordance, a follow-up birth cohort study (T-CHEQ) showed that early exposure to NO_2 and O_3 was associated with an increased risk of AD occurrence in children (hazard ratio 1.07, 95% CI 0.99–1.15) [115,116]. Nevertheless, the currently recommended limits for the concentrations and exposures of environmental irritants are arbitrary, with significant variations between different centers. Despite UV light being a therapeutic intervention in AD patients, harmful UV-B light reaching the Earth's surface along with climate change, industrialization, and increased smoke, clouds, and particulate matter levels may hamper the positive effect on AD [117]. Exposure to high concentrations of PM 2.5 (meaning $<$2.5 µm in diameter) emitted during wildfires disrupts skin epithelium barriers by damaging the structural proteins (FLG, E-cadherin), and lipids in the epidermis [118,119]. Titanium dioxide (TiO_2) nanoparticles are a prominent nanomaterial extensively employed in various everyday products, such as sunscreens. While no conclusive proof of substantial penetrations of nano-sized TiO_2 particles beyond the stratum corneum is reported, suggesting the safety of fine TiO_2 particles for the skin, multiple research studies indicate that they induce adverse effects on mammalian cells and skin inflammation. Such an effect depends on their size and shape, with acicular nanoparticles disrupting the epithelium skin barriers by altering cell junctions and the induction of inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, and TNFa) [120].

It is well established that exposure to synthetic detergents is associated with an increased risk of work-related eczema, e.g., in professional cleaners, potentially through increased TEWL [121]. Noteworthy, during the COVID-19 pandemic, the augmented use of disinfectants resulted in an increased number of AD cases and exacerbations [122].

Tobacco smoke, one of the most toxic substances in the environment, affects not only the epithelium in the airway but also the integrity of the skin barrier. Active or passive exposure to tobacco smoke is associated with an increased prevalence of AD in childhood by directly inhibiting Tregs function and impairing their ability to secrete the anti-inflammatory cytokine IL-10 following exposure to benzene [123].

Most importantly, climate change has altered and prolonged pollen season, whereas air pollution determinants, such as NO_2, act as an adjuvant to the airborne allergens, thereby increasing their allergenicity and contributing to exacerbation in AD [124]. Moreover, allergens with proteolytic activity, such as certain pollens and group 1 house dust mites, disrupt barriers and contribute to the vicious cycle of inflammation, microbiome dysbiosis, and epithelium leakage [125]. Recently, the role of airborne allergens in AD pathogenesis has been suggested by the beneficial effects of aeroallergen immunotherapy in patients with AD, which reduces severity and improves quality of life [126].

Westernization in dietary habits has been consistently associated with AD development and severity [127]. Increased consumption of processed foods is correlated with AD severity, while low vitamin C and E intakes are inversely associated with AD [128,129]. Meanwhile, the relationship between fatty acid intake and AD remains controversial [130,131].

In summary, the exposome, representing a lifetime of environmental exposures, is a key factor in the complex model of AD pathogenesis. As highlighted by the exposome, the bidirectional interaction between the external environment and human health disrupts epithelial barriers, chronic inflammation, and immune dysregulation in AD. Addressing these diverse exposome components is vital for developing comprehensive strategies to mitigate the risk and progression of atopic dermatitis.

6. Advances in Itch Pathogenesis

The pathogenetic mechanism in chronic itching, which is a hallmark and the most troublesome symptom in AD, is multifactorial and occasionally individualized [132]. It is well established that the itch in AD is mainly mediated via non-histaminergic pathways; thus, histamine and the respective bioactive amines contribute minimally to the itch pathogenesis, while type 2 cytokines (IL-4, IL-13, IL-31), epithelium alarmins (TSLP, IL-33, IL-25), neuropeptides, neurotrophins, the vicious "itch–scratch cycle", and microbiome dysbiosis with epithelium leakage, act synergistically in chronic pruritus [45,133].

6.1 Type 2 Cytokines and Alarmins

The discovery of the IL-4 receptor subunit a (IL-4Ra) on pruritus-sensing nerves has signaled a new era in the chronic itch pathogenesis by demonstrating that type 2 ILs can directly activate sensory nerves via the JAK1–2/STAT pathway [134]. Moreover, IL-4 and IL-13 induce kallikrein (KLK-7) in normal keratinocytes, which mediates the itch pathogenesis via skin–neural mechanisms [135]. IL-4 has an additional role in AD pruritus by enhancing neural responsiveness to pruritogens [134], which by definition include biogenic amines, proteases, and neuropeptides, which in turn activate afferent dorsal ganglion neurons and receptors such as TRPV1 and TRPA1 [136]. Subsequently,

new therapeutic targets aiming at inhibiting IL-4R using monoclonal antibodies and JAK inhibitors are developed [137,138], while the inhibition of IL-13 using monoclonal antibodies attenuates the itch in AD [18,19].

The T2 cytokines, IL-4, IL-13, and IL-31, act through the TRP channel ankyrin transmembrane protein 1 (TRPA1) and the transient receptor potential (TRP) channel vallinoid 1 (TRPV1) by activating the calcium influx in the sensory fibers [134], while TSLP acts directly on the sensory nerves by binding to its receptor. The release of TSLP by epidermal cells is upregulated by activated T cells and crosstalk with other immune cells [139]. TRP channels, responsive to both intracellular and extracellular signals, chemical compounds, mechanical stimuli, temperature fluctuations, and osmotic stress, contribute to sensory perception and play a role in AD. Furthermore, activation of the TRPV3 and T cells can further augment TSLP production and the itch sensation [140]. The anti-TSLP monoclonal antibody, tezepelumab demonstrated a substantial, yet not statistically significant, improvement in the pruritus rating scale (NRS), Investigator's Global Assessment (IGA), and also 50% and 75% reductions in the Eczema Area and Severity Index (EASI50 and EASI75, respectively), with 50% and 75% reductions in the SCORing AD index (SCORAD50 and SCORAD75, respectively) [141].

6.2 The "Itch Cytokine" IL 31

The so-called "itch cytokine" IL-31 is a major pruritogenic component in AD, which binds to its receptor in the peripheral sensory nerve fibers in the epidermis and dermis and enhances the secretion of other pruritogens [142]. Moreover, IL-31 activates STAT3 in astrocytes via lipocalin-2 production, enhancing additional itch signals in the spinal cord [143]. The newly described IL-31 network compromises alternatively activated anti-inflammatory macrophages (M2), TSLP, periostin, and basophils. Specifically, M2 is one of the main sources of IL-31 in human AD skin lesions, while expression of TSLP and periostin promote IL-31 production by macrophages, as was shown in murine models. Direct depletion of macrophages reduces the itch, while the combined blockage of basophils, TSLP, and periostin only attenuates the itch by reducing IL-31-producing macrophages [8]. Furthermore, IL-31 promotes the release of brain-derived natriuretic peptide (BNP) from the dorsal root ganglionic neurons and skin cells, contributing to the itchy sensation [144]. The central role of IL-31 in AD pathogenesis and itch, per se, is supported by phase 3 clinical studies of Nemolizumab, a humanized monoclonal antibody against IL-31 receptor, showing that subcutaneous administration of Nemolizumab in addition to topical agents, effectively improves pruritus compared to the placebo in individuals with AD; thus, it has been granted approval in adults and adolescents for the treatment of itching associated with AD [145,146].

6.3 Neurotransmitters and Neurotrophins

The cutaneous neurosensory system occupies a central position in pruritus pathogenesis, dispersing throughout skin layers and interacting with multiple mediators and receptors. An increased density of sensory neurons is noted in the skin of AD patients, resulting in exacerbated responses to a variety of pruritogens, such as neurotrophins (nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)) [147]. NGF levels are strongly associated with itch severity and AD eruptions [148]. Moreover, neurotransmitters released from nerve fibers can modulate the immune system in the skin and vice versa [149,150].

More recently, the Mas-related G-protein-coupled receptor X2 (MRGPRX2) on the surface of mast cells, basophils, and eosinophils has been implicated in the itch pathogenesis as an itch receptor [151]. Activation of the receptor via neuropeptides, such as substance P, degranulates mast cells, while their mediators induce an itch by binding to the protease-activating receptor 2 (PAR2) [149]. MRGPRX2 blockade with selective inhibitors holds promise as a potential target in allergic diseases, including AD [152].

Chronic pruritus poses a formidable challenge in clinical practice due to the interplay with skin disruption and inflammation, creating a vicious cycle that complicates AD management while also posing a significant burden on the quality of life of patients. Further knowledge of the underlying mechanisms of a chronic itch in AD is crucial for developing targeted therapies aimed at alleviating the itch and managing AD effectively.

The intricate and multifactorial interplay of well-established and novel pathogenetic mechanisms associated with AD, including dysregulated immune responses, disruption of the epithelial barrier, pruritus, microbiome dysbiosis, and the influence of the exposome is illustrated in Fig. 3. This complexity contributes to the wide range of clinical variations seen in individuals with AD. Comprehending these different pathogenetic elements is crucial to defining effective treatment strategies, as the heterogeneous nature of AD requires an individualized approach to optimize therapeutic outcomes. The novel therapeutic options in association with their corresponding targeted pathogenic mechanisms are presented in Table 1.

7. Endotypes

AD is remarkably heterogeneous; thus, determining the different endotypes might offer a comprehensive understanding of the disease's underlying pathophysiology and reveal potential treatment targets. Various subtypes of potential AD biomarkers have been identified and categorized based on their suggested use. For diagnostic purposes, nitric oxide synthase 2 (NOS2) and cutaneous T cell-attracting chemokine (CTACK)/CCL27 can differentiate AD from psoriasis in cases of psoriasiform dermatitis, while T_H2 and T_H22-related cytokines and chemokines have been suggested for monitoring disease severity and ac-

Table 1. Novel mechanisms implicated in the pathogenesis of AD and the corresponding therapeutic targets.

Pathogenetic mechanism and therapeutic targets	Corresponding treatments
Dysregulated T cell-mediated immune response	
JAK/STAT signaling pathway	- Abrocitinib (JAK1 inhibitor), Baricitinib (JAK1/2 inhibitor) - Upadacitinib (JAK1 inhibitor) - Ruxolitinib (JAK1/2 inhibitor) *topical treatment* - Delgocitinib (JAK1/2/3, TYK2 inhibitor) *topical treatment*
IL-4/IL-13	- Dupilumab (IL-4Rα, IL-13Rα1 inhibitor) - Tralokinumab (IL-13 inhibitor) - Lebrikizumab (IL-13 inhibitor)
IL-31	- Nemolizumab (IL-31R inhibitor)
IL-21	- Upadacitinib
IL-22	- Fezakinumab
PDE4 activity	- Crisaborole (PDE4 inhibitor) *topical treatment* - Difamilast (PDE4 inhibitor) *(undergoing trials)*
Basophils and eosinophils	- Ruxolitinib (¯H4R expression on eosinophils) - H4R antagonists
Epidermal Barrier Dysfunction	
Tight junctions (TJs)	- Spirodelapolyrhiza extract - Olea europaea leaf extract - Glucoseskin application - Cimifugin - DL-Propargylglycine
Aryl hydrocarbon receptor (AHR)	- Tapinarof (AHR agonist) - Rhodiola crenulate (AHR agonist) - Artemisia princeps (AHR agonist) - Diosmin (AHR agonist)
Skin barrier proteins and lipids	- Crisaborole (PDE4 inhibitor) - Difamilast (PDE4 inhibitor) - Topical formulations with glucoseskin, spirodelapolyrhiza, Olea europaea - AHR agonists
Chronic Itch	
IL-4, IL-13	- Dupilumab (IL-4Rα and IL-13R inhibitor) - Janus Kinase inhibitors - Tralokinumab, Lebrikizumab (IL-13 inhibitors) - TRP channel modulators (TRPA1, TRPV1)
IL-31	- Nemolizumab (IL-31R inhibitor)
Epithelium alarmins (TSLP, IL-33, IL-25)	- Tezepelumab (anti-TSLP)
Neurotransmitters	- NGF and BDNF inhibitors - MRGPRX2 inhibitor
Microbiome Dysbiosis	
S. aureus colonization	- Bleach baths
Fungal dysbiosis	- Autologous microbiotherapy - Emollients enriched with microbiome supportive components
Exposome	
Environmental allergens and irritants	- Targeted immunotherapy
Air pollution	- Protection from environmental exposure to PM 2.5 - Avoidance of synthetic detergents
Climate change and UV-B light	- Monitoring and management of AD during prolonged pollen season
Dietary factors	- Reducing processed food consumption - Adequate intake of vitamins C and E

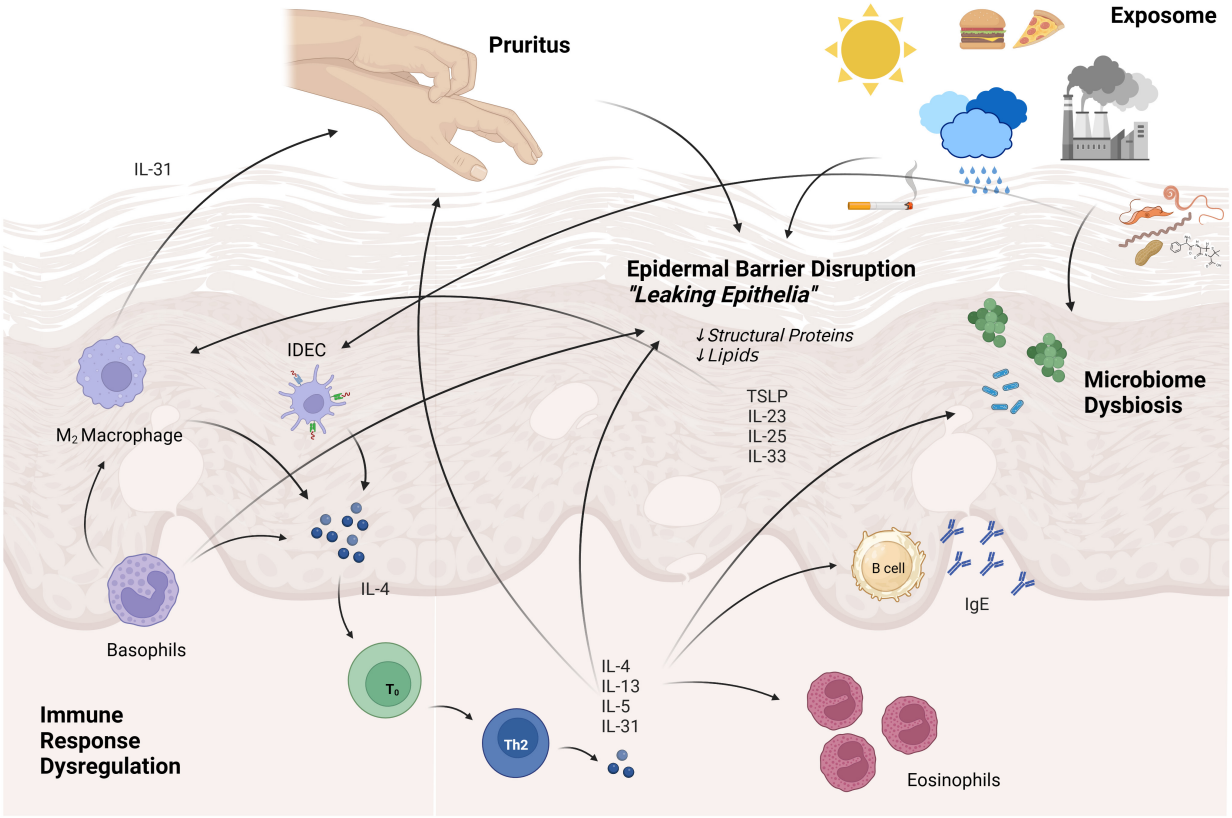

Fig. 3. The interplay among different pathogenic factors that contribute to the pathogenesis of atopic dermatitis. IL, interleukin; TSLP, thymic stromal lymphopoietin; IDEC, inflammatory dendritic epidermal cell.

tivity [153]. Moreover, markers for predicting treatment response to specific therapies, such as serum periostin and dipeptidyl peptidase-4 (DPP-4) levels, have also been used to respond to anti-IL-13 treatment [153].

Blood transcriptome analysis proposed two AD endotypes based on the eosinophil-related expression signature [154]. The eosinophil-high cluster exhibited a more pronounced overall dysregulation and a positive correlation between disease activity and signatures associated with IL-5 signaling, whereas the eosinophil-low endotype presented minimal dysregulation at the transcriptomic level and no association between disease activity and gene expression [154]. A recent study described four serum biomarker-based clusters: One with high levels of C–C chemokines and IL-1R1 dominance, the second based on the dominance of T_H1, T_H2, T_H17, and epithelial-related chemokines, the third T_H2, T_H22, and pulmonary and activation-regulated chemokine (PARC) dominated cluster, which was associated with significantly more severe disease, and the fourth, a T_H2 and eosinophil-inferior cluster, with the least inflammatory disease [155]. In adults with moderate to severe AD, two serum biomarkers-based clusters were identified: A low and a high inflammatory group, with the latter exhibiting a higher level of TNFβ, monocyte chemoattractant protein 3 (MCP-)3/CCL7, and IL-13 [156]. Differentiations in AD endotypes among ethnic groups have been the scope of recent studies and found that AD lesions on African Americans show enhanced infiltration of dendritic cells expressing the high-affinity IgE receptor (FcER1+), polarization towards T_H2/T_H22 immune responses and attenuation of the T_H1 and T_H17 axes compared to the respective European–American patients [157]. Moreover, AD in Asia is characterized by combined T_H2/T_H17 upregulation and features such as psoriasis [158] and less T_H1 expression compared to European Americans [159], indicating that racial differences need to be assessed when managing patients with more severe forms of AD.

8. Conclusions

AD is a complex and heterogeneous condition. Genetic predisposition, epidermal barrier disruption, dysregulated T cell-mediated immune response, skin microbiota dysbiosis, and the exposome effect form the critical components for the development of AD, while the itch is the major and most troublesome symptom that is mainly driven by IL-31 and complex neuro–immune crosstalk. The iden-

tification of distinct or even overlapping endotypes raises a translational evolution and leads to an impressive expansion of the therapeutic pipeline; thus, a more personalized treatment approach is now feasible and highly recommended in AD patients.

Abbreviations

AD, atopic dermatitis; TEWL, transepidermal water loss; IL, interleukin; JAK/STAT, Janus kinase/Signal transducer and activator of transcription; TJs, tight junctions; FLG, filaggrin; LOR, loricrin.

Author Contributions

PX, SG, MM, NGP designed the research study. MS, SK, NP, PX performed the research, interpreted data and wrote the manuscript. SG, MM, NGP, PX edited and reviewed the manuscript, PX supervised. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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