DOI 10.26724/2079-8334-2025-4-94-239-246
UDC 616.5-002.1:616.34-008.87

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ROLE OF INTESTINAL MICROBIOTA IN THE PATHOGENESIS OF ATOPIC DERMATITIS

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Atopic dermatitis is a growing public health problem with a rapidly increasing incidence. Molecular and sequencing technologies have shown that the pathogenesis of atopic dermatitis is influenced not only by the skin but also by the gastrointestinal microbiota. The latter plays a crucial role in the formation and regulation of allergic reactions, including those observed in atopic dermatitis. The concept of the "gut-skin axis" has emerged, and studies increasingly demonstrate their bidirectional interaction. The aim of this review is to investigate the role of the gut microbiota and its changes in the pathogenesis of atopic dermatitis. We analyzed data on changes in the gut microbial composition in patients with atopic dermatitis, their relationship with the epidermal barrier function and toll-like receptors, as well as the complex interactions between the microbiota and adaptive immunity. These results support the possibility of using gut microbiota manipulation as a new approach to prevent and reduce the severity of atopic dermatitis.

Key words: gut microbiota, skin, allergic disorders, atopic dermatitis, immunity.

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РОЛЬ КИШКОВОЇ МІКРОБІОТИ В ПАТОГЕНЕЗІ АТОПІЧНОГО ДЕРМАТИТУ

Атопічний дерматит є актуальною проблемою громадського здоров'я з швидко зростаючими показниками захворюваності. Молекулярні та секвенційні технології показали, що патогенез атопічного дерматиту визначається не тільки станом шкіри, але й мікробіотою шлунково-кишкового тракту. Остання відіграє ключову роль у формуванні та регуляції алергічних реакцій, у тому числі тих, що спостерігаються при атопічному дерматиті. З'явилася концепція «вісь кишечник-шкіра», і дослідження все частіше демонструють їх двосторонню взаємодію. Метою даного огляду було вивчити роль мікробіоти кишечника та її змін у патогенезі атопічного дерматиту. Ми проаналізували дані про зміни мікробного складу кишечника у пацієнтів з атопічним дерматитом, їх зв'язки з епідермальним бар'єром і толл-подібними рецепторами, а також про складні взаємодії між мікробіотою і адаптивним імунітетом. Ці результати підтверджують можливість впливу на мікробіоту кишечника як новий підхід до профілактики та зниження тяжкості атопічного дерматиту.

Ключові слова: мікробіота кишечника, шкіра, алергічні захворювання, атопічний дерматит, імунітет.

Atopic dermatitis (AD) is a chronic inflammatory skin disease (also known as atopic eczema), that manifests with recurrent episodes, xerosis, erythema, and pruritus. Its prevalence has been steadily rising in parallel with industrialization and urbanization, currently affecting approximately 15–30 % of children and around 10 % of the adult population worldwide (with the average incidence rate of 0.2 % to 25 %) [4, 16, 19].

In a subset of pediatric patients, clinical manifestations tend to resolve with age; however, nearly half of children with AD later develop bronchial asthma, while up to two-thirds are at risk of allergic rhinitis, a progression commonly referred to as the "atopic march". Persistent scratching triggered by severe pruritus disrupts epidermal barrier integrity, thereby altering local immune regulation and cutaneous microbiota [11].

Chronic pruritus and recurrent flares often impair sleep quality and are linked to neuropsychological consequences, such as low self-esteem, anxiety, depression, and other psychiatric comorbidities, through the bidirectional skin–brain interaction. Furthermore, the disease imposes a considerable economic burden due to the requirement for prolonged therapy and substantially diminishes the overall quality of life, not only for patients but also for their families [10].

While genetic factors contribute substantially to AD pathogenesis, environmental triggers are considered key drivers of the marked increase in prevalence observed in recent decades. Patients with AD are frequently exposed to allergens such as pollen, house dust mites, and animal dander, which act as major stimuli for disease exacerbation. Moreover, dysbiosis of cutaneous microbiota – most notably the overgrowth of Staphylococcus aureus and Malassezia species at lesional sites – has been linked to more severe clinical phenotypes [10, 29].

The purpose of the study was to identify the association between gut microbiota and atopic dermatitis by summarizing data from various studies.

This literature review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines checklist. The search covered articles published between 2020 and 2025 on correlation between intestinal microbiota and atopic dermatitis; five databases with specific search strategies were utilized.

Search strategy was as follows:

Database 1 – PubMed / MEDLINE.

– Last search date: 15 June 2025;

– Years included: 2000–2025;

– Language: English;

– Species: Humans;

– Excluded: animal-only studies, conference abstracts, editorials.

Verbatim query: ((("Atopic Dermatitis" [Mesh] OR "atopic dermatitis" OR "eczema")) AND ("Gastrointestinal Microbiome" [Mesh] OR "gut microbiota" OR "intestinal microbiota" OR "gut microbiome" OR "dysbiosis")) AND (("Probiotics" [Mesh] OR probiotics OR "short-chain fatty acids" OR SCFA OR "immune regulation")) AND ((child* OR infant* OR pediatric*)) NOT ((review [Publica0tion Type] OR editorial [Publication Type] OR letter [Publication Type])).

Database 2 – Scopus.

– Last search date: 15 June 2025

– Years included: 2000–2025

– Document type: Article

– Language: English

Verbatim query: (TITLE-ABS-KEY ("atopic dermatitis" OR eczema)) AND (TITLE-ABS-KEY ("gut microbiota" OR "gut microbiome" OR dysbiosis OR probiotics)) AND (TITLE-ABS-KEY (child* OR infant* OR pediatric*)) AND (TITLE-ABS-KEY (immunity OR "short chain fatty acids" OR SCFA))

Database 3 – Web of Science Core Collection

– Last search date: 15 June 2025;

– Years included: 2000–2025;

– Indexes: SCI-EXPANDED, SSCI;

– Document types: Articles.

Verbatim query: (TS=("atopic dermatitis" OR eczema) AND TS=("gut microbiota" OR gut microbiome OR dysbiosis OR probiotics)) AND TS=(child* OR infant* OR pediatric*) AND TS=("short-chain fatty acids" OR immunity OR immune)).

Database 4 – Embase.

– Last search date: 15 June 2025;

– Years included: 2000–2025;

– Species: Humans.

Verbatim query: ('atopic dermatitis'/exp OR eczema) AND ('gut microbiota'/exp OR 'intestinal microbiome' OR dysbiosis OR probiotics) AND (child* OR infant* OR pediatric*) AND ('short chain fatty acid'/exp OR immunity) NOT ('conference abstract'/it OR 'editorial'/it).

Database 5 – Cochrane Library.

– Last search date: 15 June 2025;

– Years included: 2000–2025.

Verbatim query: (("atopic dermatitis" OR eczema) AND ("gut microbiota" OR probiotics OR dysbiosis) AND (child* OR infant*)).

Exclusion criteria: animal-only studies; non-English articles; case reports; conference abstracts; editorials; letters; publications before year 2000.

Control participants were defined as individuals without any documented personal history of allergic disorders, including atopic dermatitis, asthma, allergic rhinitis, or food allergy, in order to reduce the risk of misclassification and potential inclusion of latent or future-onset AD cases.

Study selection and characteristics.

The following search strategies were utilized to identify relevant studies for our review (Table 1).

Table 1

Simplified PRISMA Flow

Stage	Description	Number of Records/Studies
1. Identified	Total number of records identified through database searching and other sources	1,841
2. Duplicates Removed	Number of records removed before screening (e.g., duplicates)	623
3. Screened (Title/Abstract)	Number of records screened after duplicates were removed	1,218
4. Assessed for Eligibility (Full-text)	Number of full-text articles assessed for eligibility against the inclusion/exclusion criteria	161
5. Included in Review	Total number of primary studies finally included in the systematic review	36

The etiology of atopic dermatitis is multifactorial, encompassing both hereditary predispositions and environmental influences [2, 6, 20]. Linkage studies have identified susceptibility loci for AD on chromosomes 1q21, 17q25, and 20p. In particular, loss-of-function variants and mutations in the filaggrin gene are strongly implicated in disease initiation and progression [29].

The immunopathogenesis of AD remains incompletely clarified; nevertheless, distinct immune polarization is observed, with Th2-driven responses dominating the acute phase and Th17-related pathways prevailing during chronicity. Environmental pollutants, including polycyclic aromatic hydrocarbons, have also been reported to promote Th2-mediated cutaneous inflammation characteristic of AD [4].

Following Th2 activation, interleukins IL-4 and IL-13 are released in excess, promoting IgE class switching in B cells and enhancing allergen-specific IgE production. These IgE molecules bind to high-affinity FcεRI receptors on mast cells and basophils, triggering degranulation, liberation of pro-inflammatory mediators, and subsequent manifestation of clinical symptoms. Another pivotal mediator, IL-31 – secreted by Th2 lymphocytes and immature dendritic cells – acts through IL-31 receptor A/oncostatin M receptor signaling to stimulate pruritus and neuronal sprouting [7]. This cytokine is recognized as a central neuroimmune regulator of itch in AD. Collectively, these findings underscore the importance of maintaining immune homeostasis in mitigating AD, highlighting immune modulation as a promising therapeutic strategy.

One of the key mechanisms in the pathogenesis of atopic dermatitis is considered to be the connection with the intestinal (gut) microbiota. In recent years, hypotheses have emerged suggesting that AD development and exacerbation are not solely linked to skin microbial alterations but are also influenced by the gut microbiota, the commensal flora of the gastrointestinal tract [19].

The gut microbiota, a highly dynamic ecosystem influenced by diet, lifestyle, and psychological stress, also plays a critical role in immune regulation. Under physiological conditions, commensals colonize distinct niches of the body, establish biofilms, and provide a barrier that prevents pathogen invasion while maintaining microbial–host equilibrium [33, 36].

Alterations in microbial diversity and composition – termed intestinal dysbiosis – lead to disrupted microbial metabolism and immune signaling, thereby impacting systemic physiology and pathology. Preserving the structural and functional diversity of gut microbiota not only prevents colonization by pathogenic organisms but also minimizes competition between commensal and opportunistic bacteria. In addition, gut microbes are actively involved in the metabolism of short-chain fatty acids (SCFAs), amino acids, vitamins, and bile acids, thereby shaping the maturation of both innate and adaptive immunity [8, 22].

Advancements in sequencing technologies have facilitated a clearer understanding of the gut–skin relationship, with numerous studies confirming associations between gut dysbiosis and immune-mediated conditions such as allergic asthma and AD [9, 17].

The concept of the “gut–skin axis” has thus been introduced, proposing a bidirectional link between these two organs, which share common immune and endocrine features and represent major components of mucosal immunity. This reciprocal interaction between the gut and skin ecosystems is now recognized as an important contributor to AD onset and symptomatology. Both systems interact continuously with environmental antigens – including dietary components, commensal flora, and pathogens – and disturbances in gut health are frequently mirrored by cutaneous manifestations. Importantly, interactions are not confined to gut and skin; they extend to the nervous system, forming the so-called “gut–brain–skin axis”, through which these organs communicate via multiple pathways [1, 2, 28].

The classic “hygiene hypothesis” posits that urbanization, excessive sanitation, and widespread antibiotic use disrupt this balance, contributing to immune dysregulation and the rise of allergic diseases such as AD [14, 25].

Functionally, the gut microbiota acts as the body’s largest endocrine organ, producing hormone-like metabolites and signaling molecules that regulate host immunity. High microbial diversity serves as a protective factor, ensuring immune stability. Evidence of microbial DNA in the placenta and meconium points to colonization beginning even before birth. Postnatally, the establishment of gut microbiota and mucosal communities is strongly influenced by the mode of delivery. Vaginally delivered infants acquire microbial profiles dominated by Lactobacillus, Prevotella, and Sneathia, resembling maternal vaginal microbiota, whereas infants delivered by cesarean section typically acquire skin-associated microbes such as Staphylococcus, Corynebacterium, and Propionibacterium, indicating that delivery mode plays a critical role in shaping the neonatal microbiome. Thus, the establishment of intestinal microbiota is a gradual process that reaches relative stability by 2–3 years of age, coinciding with the cessation of breastfeeding and transition to solid foods [34].

Through long-term coevolution, the immune system has developed the ability to differentiate between commensal and pathogenic organisms. Promoting the physiological development of gut

microbiota early in life – for example, through breastfeeding and the administration of probiotics – is therefore regarded as a preventive strategy against atopy [1, 33, 35].

As mentioned above, altered gut microbial profiles have been associated with allergic diseases. Extensive research has demonstrated a strong association between alterations in intestinal microbial diversity and the emergence of allergic diseases such as asthma and atopic dermatitis [9, 24].

In AD patients, the intestinal microbial landscape is often characterized by reduced levels of Lactobacillus and Bifidobacterium alongside overgrowth of Escherichia coli and Clostridium difficile. Similarly, the skin microbiota is frequently dominated by Staphylococcus aureus, which further worsens disease manifestations. Fungal dysbiosis has also been reported: patients with atopy typically show a decline in Malassezia populations with a concomitant increase in Saccharomycetales, Rhodotorula, and Candida species [12, 13, 32].

Several studies indicate that children with AD display reduced gut microbial diversity even before clinical onset, shifting immune responses toward a Th2 profile and increasing susceptibility to AD [12].

Comparative investigations in Swedish and Estonian children further support this concept: Estonian children, with intestinal microbiota dominated by Lactobacillus, had lower allergy rates, whereas Swedish children, whose gut flora was enriched with Clostridium, showed higher prevalence of allergic manifestations. Allergic infants, unlike their non-allergic counterparts, also exhibited reduced Lactobacillus abundance and a predominance of aerobic bacteria [20].

Experimental evidence from in vitro and in vivo models suggests that Lactobacillus can modulate immune responses and confer protection against allergy. Additional findings demonstrate that lower counts of Bifidobacterium, gram-positive aerobes, and enterococci, along with increased Clostridium and Staphylococcus aureus, correlate with heightened allergy risk in children [15, 18].

Taking into account the above, the mechanisms underlying the pathogenesis of AD from the perspective of the role of gut microbiota are of particular interest.

Since many studies highlight that the gut microbiota acts as a critical mediator of intestinal homeostasis and systemic immunological balance, this influence is not limited to the gastrointestinal tract but extends to many organ systems, thereby influencing overall human health. Despite substantial progress in understanding microbiota–immune system interactions, the precise contribution of gut microbial metabolites to the pathogenesis of atopic dermatitis remains incompletely defined.

Metabolites produced by commensal taxa such as Bifidobacterium, Lactobacillus, Clostridium, Bacteroides, and Streptococcus play pivotal roles in B cell proliferation and in the differentiation of naïve T cells into effector subsets, including Th cells and regulatory T cells (Tregs). Through these processes, gut-derived metabolites regulate inflammation by limiting excessive Th differentiation, downmodulating cellular activation, and modulating IgE and IgG4 production [31].

It was demonstrated that butyrate (one of the short-chain fatty acids (SCFAs), which are generated during the microbial fermentation of dietary fibers and exert significant immunomodulatory effects at multiple levels strongly impacts the differentiation and function of dendritic cells (DCs) and macrophages. In the presence of butyrate, DCs maintained CD14 expression and showed reduced levels of CD54, CD86, and HLA class II, while exhibiting enhanced phagocytic activity. Notably, DCs differentiated without butyrate displayed markedly reduced IL-10 production, whereas butyrate-conditioned DCs partially restored this anti-inflammatory function [21].

The presence of bacterial DNA in the bloodstream of patients with chronic skin disorders provides evidence that gut dysbiosis may directly trigger systemic inflammation. For example, segmented filamentous bacteria were shown to drive Th1 and Th17 responses, whereas interactions between microbiota and Th2 immunity have been demonstrated in allergic conditions. It was reported that supplementation with Lactobacillus reduced Th2 responses to airborne allergens in mice exposed to house dust. Similarly, treatment with the SCFA propionate altered myelopoiesis, yielding macrophages and DC precursors with enhanced phagocytic capacity but attenuated ability to induce Th2 polarization. Collectively, these findings highlight the central role of gut-derived metabolites in modulating Th2-driven inflammation, although their direct contribution to AD pathogenesis remains to be clarified [2, 9].

A major pathway linking gut microbes to host immunity is the activation of Toll-like receptors (TLRs). TLRs belong to the pattern-recognition receptor superfamily and recognize conserved microbial structures known as pathogen-associated molecular patterns (PAMPs). Ligand engagement by TLRs triggers downstream signaling cascades that coordinate innate defense and shape adaptive immune responses. Clinical and experimental studies have associated microbial alterations with aberrant TLRs activation in AD. For instance, reduced fecal abundance of Ruminococcaceae (Oscillospirales) correlated with decreased TLR2-induced IL-6 and TNF-α, while lower levels of Enterobacteriaceae were linked to impaired TLR4-driven TNF-α responses. SCFAs themselves directly influence TLR-mediated signaling,

modulating cytokine secretion, adhesion molecule expression, and immune cell activation. In addition, metabolites such as retinoic acid and polysaccharide A produced by Bacteroides fragilis, F. prausnitzii, and Clostridium clusters promote Treg expansion and anti-inflammatory responses [3, 5].

The skin expresses multiple TLRs, making it highly responsive to microbial cues. Dysregulation of these pathways has been implicated in AD pathogenesis. Genetic studies further support this link, demonstrating associations between TLR2 and TLR4 polymorphisms and AD susceptibility. For example, impaired TLR4 signaling in neonates was associated with reduced IL-10 and skewed Th2 polarization, while TLR4-deficient mice exhibited exacerbated AD-like inflammation. TLR4-mediated signaling has also been implicated in IL-23 and IL-22 production, which promote keratinocyte hyperproliferation in AD [3, 30].

Importantly, microbial interactions with TLRs are not limited to the skin but extend to systemic immunity. Perturbations in gut microbiota can facilitate the entry of bacterial metabolites into circulation, influencing distant organs including the brain, lung, and skin. Gene–environment interactions further complicate this relationship: in a cohort of 957 children, a significant interaction between TLR4 polymorphism rs10759932 and E. coli exposure was observed in relation to early allergic sensitization [10]. Similarly, infants with AD showed reduced gut microbial diversity, lower Ruminococcaceae abundance, and altered TLR-mediated cytokine responses [5].

Taken together, these findings illustrate that the gut microbiota exerts profound effects on host immunity through TLR-mediated pathways. Dysbiosis disrupts the delicate balance between immune tolerance and inflammation, predisposing individuals to allergic disorders including AD. Understanding the complex interplay between gut microbes, microbial metabolites, and TLR signaling may provide new therapeutic opportunities to restore immune homeostasis and improve disease outcomes.

It should not be forgotten that gut microbiota provides it action via SCFAs, which role do not include only butyrate, but also propionate and acetate. It was identified that a marked dysbiosis of Faecalibacterium prausnitzii in stool samples of AD patients, which was associated with reduced SCFA levels. One of the primary functions of SCFAs is to strengthen the epithelial barrier and reduce intestinal permeability. Along with other signaling metabolites such as ribosomally synthesized and post-translationally modified peptides (RiPPs), amino acid derivatives, oligosaccharides, and glycolipids, SCFAs contribute to the formation of a protective mucosal layer in the gut [10, 22].

It achieves this through several mechanisms, including the induction of IL-10 receptor expression – essential for barrier integrity – and the regulation of key junctional proteins such as occludin, zonulin, and claudins. Enhanced tight junction expression reduces microbial translocation across the intestinal lumen. Translocated bacterial components and metabolites may interact with skin receptors, influencing cutaneous immunity directly or by altering the skin microbiome [23, 26].

Additionally, bacterial-derived SCFAs influence epithelial oxygen consumption, which stabilizes hypoxia-inducible factor, a transcription factor coordinating epithelial protection. This process helps sustain physiological hypoxia, creating a favorable niche for commensal colonizers. Butyrate modulates epithelial barrier function via AMP-activated protein kinase (AMPK)–dependent upregulation of junctional proteins. By reinforcing the intestinal barrier, SCFAs indirectly modulate systemic immunity, as they reduce the translocation of microbes, inflammatory mediators, cytokines, and toxins into systemic circulation. Once transported, these elements may accumulate in target tissues, where they can impair skin homeostasis and contribute to tissue injury. Thus, the concept of “leaky gut syndrome” has been proposed as an inflammatory driver in atopic dermatitis [18, 22].

Emerging findings suggest that gut microbiota, enhances skin barrier function and supports tissue repair. Clinical studies demonstrated that oral supplementation with Lactobacillus strains significantly decreased transepidermal water loss – a key marker of skin barrier integrity – while concurrently elevating circulating TGF-β levels. Similarly, Lactobacillus reuteri administration in mice promoted skin thickening, enhanced hair growth, and stimulated sebocyte activity [6, 8].

The impact of gut microbiota disorders due to antibiotic exposure is another critical determinant of AD development and outcomes. Animal studies have demonstrated that antibiotics such as kanamycin reduce populations of beneficial Lactobacillus spp., elevate serum IgE, promote Th2-skewed immune responses, and intensify scratching behavior in murine AD models. Similarly, azithromycin administration aggravated lesion severity, increased inflammatory cell infiltration, and elevated cytokines including IL-4, IL-6, IL-17A, TNF-α, and IL-6, while shifting the gut microbiota toward pathogenic taxa (Bacteroides, Saccharibacteria, Acetatifactor) and reducing short-chain fatty acids [4, 27, 31].

The observed comorbidity between gastrointestinal and cutaneous disorders suggests a bidirectional relationship, highlighting the potential of gut microbiota modulation in improving skin health, particularly in AD. Experimental models with probiotic strains such as Lactobacillus paracasei KBL382 and Lactobacillus sakei WIKIM30 have shown the ability to influence cytokine secretion, expand

regulatory T-cell populations, and restructure gut microbial composition, indicating a promising role in AD management [10].

Nevertheless, clinical outcomes remain inconsistent, and the therapeutic efficacy of specific probiotics requires more robust evidence from well-designed clinical trials.

Across the included studies, the investigated populations were predominantly composed of infants and young children, reflecting the well-recognized early onset of AD. The majority of original cohort and case–control studies recruited participants aged from birth to 6 years, with fewer studies including school-aged children and only a limited number addressing adult populations. This age distribution increases the sensitivity of the evidence for early-life microbial determinants of AD but simultaneously limits the generalizability of the findings to adolescent and adult patients, in whom disease phenotype, immune regulation, and microbiota composition differ substantially.

Regarding sex distribution, most cohorts demonstrated a slight male predominance in infancy, which is consistent with epidemiological patterns of early-onset AD. However, sex-stratified analyses were rarely performed, and sex-specific microbial or immunological differences were not systematically explored. Consequently, potential sex-related variations in gut microbiota composition, immune maturation, and AD susceptibility may be underrepresented, introducing a potential source of residual confounding.

In terms of medical and perinatal history, several studies specifically included children with documented cesarean delivery, early-life antibiotic exposure, formula feeding, familial atopy, and exposure to urban environments, all of which are known modifiers of microbial colonization and immune development. While this enriched the datasets for identifying high-risk microbial signatures, it may also have introduced selection bias toward populations with an elevated baseline risk of AD, thereby potentially inflating the observed associations between gut dysbiosis and disease occurrence.

With respect to racial and ethnic composition, the majority of included cohorts were conducted in East Asian and European populations, with a limited representation of African, Middle Eastern, or Latin American populations. Several studies reported consistent microbial patterns across Asian and European children, such as reduced abundance of Bifidobacterium spp. and altered short-chain fatty acid–producing taxa in AD.

However, differences were also observed in dominant bacterial genera and diversity indices, likely reflecting ethnicity-specific dietary habits, environmental exposures, genetic backgrounds, and healthcare practices. The underrepresentation of non-European and non-East Asian populations limits the ability to extrapolate findings globally and may mask race-specific microbiome–immune interactions.

Thus, these population characteristics suggest that while the available evidence robustly characterizes early-life, urban, and high-risk pediatric cohorts, it may not fully represent rural populations, adults, or under-studied racial and ethnic groups. This uneven population coverage constitutes a major limitation of the current evidence base and underscores the need for large, multi-ethnic, longitudinal studies to establish universally applicable microbiota-based biomarkers and preventive strategies for atopic dermatitis.

Conclusions

1. The gut microbiota plays a central role in the “gut–skin axis” through interconnected metabolic, neuroendocrine, and immunological pathways. Its composition modulates both innate and adaptive immune responses, regulates intestinal barrier permeability, and activates inflammation driven by stress-related mechanisms. Understanding the underlying pathophysiology of these interactions may help identify novel therapeutic and preventive strategies for atopic dermatitis.

2. Current evidence supports a close association between gut microbiota composition and the onset and progression of AD. Despite these findings, the exact molecular mechanisms linking gut microbiota dynamics with AD remain incompletely understood

3. Several environmental and lifestyle-related factors, changing gut microbiota – including hygiene practices, breastfeeding, antibiotic exposure, etc. – have been associated with the risk of AD. These factors likely alter the gut microbiota and modulate host immune responses, particularly in individuals genetically predisposed to atopic diseases. However, further investigations are needed to clarify the extent and mechanisms of these influences.

In conclusion, although the precise mechanisms governing gut–skin cross talk remain to be fully elucidated, gut microbiota is increasingly recognized as a potential therapeutic and preventive target in AD. Probiotic supplementation has been shown to modify the intestinal microenvironment by reshaping microbial communities, limiting pathogen colonization, influencing bacterial metabolism, and restoring immune homeostasis. These changes may contribute to reduced inflammation and clinical improvement in AD. Nonetheless, the active components responsible for the beneficial effects of probiotics remain undefined. To optimize microbiota-targeted strategies, future research integrating metagenomic,

metatranscriptomic, and metabolomic approaches will be essential to characterize functional gene changes, microbial shifts, metabolic pathways, and bioactive metabolites associated with AD alleviation. Such advances may pave the way for microbiome-based therapeutic interventions and replacement strategies in AD management.

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Стаття надійшла 9.12.2024 р.

DOI 10.26724/2079-8334-2025-4-94-246-253
UDC 616.14+615.03

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PRECLINICAL EFFICACY OF DIOSMIN AND HESPERIDIN IN CHRONIC VENOUS INSUFFICIENCY: A COMPARATIVE REVIEW

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The purpose of the study was to systematize data on the preclinical efficacy of diosmin and hesperidin in chronic venous insufficiency and to evaluate these substances in a comparative context. This review highlights that while diosmin and hesperidin share several beneficial properties in the treatment of chronic venous insufficiency, their distinct pharmacological profiles contribute to complementary therapeutic effects. Diosmin is mainly responsible for improving venous contractility and reducing inflammatory remodeling, whereas hesperidin primarily protects the endothelium and alleviates oxidative stress. Their combined use leads to a more comprehensive treatment strategy and underscores the potential for next-generation phlebotonic therapies that leverage the synergistic benefits of these natural compounds.

Key words: venotonics, diosmin, hesperidin, preclinical studies, chronic venous insufficiency, phleboprotective effect.

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ДОКЛІНІЧНА ЕФЕКТИВНІСТЬ ДІОСМІНУ ТА ГЕСПЕРИДИНУ ПРИ ХРОНІЧНІЙ ВЕНОЗНІЙ НЕДОСТАТНОСТІ: ПОРІВНЯЛЬНИЙ ОГЛЯД

Метою дослідження було систематизувати дані щодо доклінічної ефективності діосміну та гесперидину при хронічній венозній недостатності та оцінити ці речовини в порівняльному контексті. Цей огляд підкреслює, що хоча діосмін і гесперидин мають низку спільних корисних властивостей у лікуванні хронічної венозної недостатності, їхні відмінні фармакологічні профілі сприяють взаємодоповнюючим терапевтичним ефектам. Діосмін переважно відповідає за покращення венозної скоротливості та зменшення запального ремоделювання, тоді як гесперидин головним чином захищає ендотелій і зменшує оксидативний стрес. Їхнє комбіноване використання забезпечує більш комплексну стратегію лікування та підкреслює потенціал флеботонічних терапій наступного покоління, які використовують синергетичні переваги цих природних сполук.

Ключові слова: венотоніки, діосмін, гесперидин, доклінічні дослідження, хронічна венозна недостатність, флебопротекторний вплив.

The study is a fragment of the research work "Development and implementation of innovative technologies in the treatment and prevention of violations of the integrity and patency of blood vessels in wartime conditions", state registration No. 0123U100204.

Chronic venous insufficiency (CVI) is a multifactorial vascular disorder characterized by impaired venous return, increased venous pressure, capillary leakage, and ultimately, clinical manifestations such as leg edema, pain, and skin changes [1, 2, 4, 15, 32, 34]. Over the past decades, naturally derived flavonoids have been investigated extensively for their capacity to counteract the pathological processes underlying CVI [6, 7, 18, 31]. Two of the most studied flavonoids in this context are diosmin and hesperidin, both of which originate from citrus fruits [9, 27]. Preclinical investigations have focused on elucidating the mechanisms by which these compounds improve venous tone, suppress inflammatory cascades, and enhance microcirculatory function. In particular, diosmin's ability to improve venous contractility and