The Role of Gut Microbiota in the Pathogenesis and Management of Atopic Dermatitis: A Review of Current Evidence

Authors:

1. Wiktoria Jedlikowska

Heliodor Swiecicki Clinical Hospital, Poznań, Poland

https://orcid.org/0009-0002-7874-9911

2. Natalia Sidz

University Clinical Center in Gdansk, Poland

80-952 Gdansk, Debinki 7

https://orcid.org/0009-0005-0685-4175

3. Monika Brzozowska

Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Jagiellońska 13/15, 85-067 Bydgoszcz

https://orcid.org/0009-0006-5574-0059

4. Natalia Wieczorek-Durdzińska

Regional Blood Donation and Transfusion Center in Racibórz, Henryka Sienkiewicza 3A,47-400 Racibórz

https://orcid.org/0009-0005-6115-1640

5. Natalia Furlepa

Samodzielny Publiczny Zakład Opieki Zdrowotnej w Łukowie: Łuków, Poland, PL

21-400 Łuków, ul. Doktora Andrzeja Rogalińskiego 3

https://orcid.org/0009-0002-8163-2087

6. Robert Rzenno

Samodzielny Publiczny Zakład Opieki Zdrowotnej w Myślenicach

ul. Szpitalna 2, 32-400 Myślenice, Polska

https://orcid.org/0009-0003-3838-3262

7. Karolina Wojciechowska

Regionalny Szpital Specjalistyczny im. dr. Władysława Biegańskiego w Grudziądzu

Doktora Ludwika Rydygiera 15/17, 86-300 Grudziądz

https://orcid.org/0009-0004-4535-0327

8. Marcelina Matuszewska

Samodzielny Publiczny Szpital Kliniczny im.prof. W. Orłowskiego CMKP

ul. Czerniakowska 231, 00-416 Warszawa

https://orcid.org/0009-0002-2301-669X

9. Katarzyna Wicha

1st Military Clinical Hospital with Polyclinic of Independent Public Health Care Unit in Lublin

Aleje Racławickie 23, 20-049 Lublin, Poland

https://orcid.org/0000-0001-8822-2182

10. Magdalena Tomaszewska

Uniwersytecki Szpital Kliniczny nr. 1 im Norberta Barlickiego w Łodzi

ul. Stefana Kopcińskiego 22, 90-153 Łódź

https://orcid.org/0009-0009-4567-394X

Abstract

Introduction and purpose

Atopic dermatitis (AD) is a chronic inflammatory skin disease caused by genetic, immunological, environmental, and microbial factors. Recent studies highlight the gut microbiota's role in AD pathogenesis, particularly through the gut–skin axis and immune modulation. This review summarizes current knowledge on the involvement of gut microbiota in AD and explores microbiota-targeted therapies.

Materials and methods

A literature review was conducted using PubMed, Google Scholar, and sources by recognized researchers from Poland and abroad. Search terms included: "atopic dermatitis," "gut microbiota," "dysbiosis," "short-chain fatty acids," and "gut-skin axis." Both experimental and clinical studies were analyzed.

Description of the state of knowledge

The gut microbiota plays a crucial role in immune regulation and maintaining epithelial barriers. Dysbiosis, characterized by reduced microbial diversity and lower levels of SCFA-producing bacteria, leads to increased intestinal permeability, Th2-biased responses, and inflammation—factors linked to AD severity. Butyrate, a key microbial metabolite, improves skin barrier function and modulates inflammation. Therapies such as probiotics, prebiotics, fiber, and fecal microbiota transplantation (FMT) may help restore gut balance and alleviate symptoms.

Conclusion

Gut microbiota is a key factor in AD development and management. Adjusting microbial composition

through diet, supplements, and microbiota-based interventions offers promising adjunctive treatment strategies. More clinical trials are needed to standardize protocols and confirm long-term effectiveness and safety.

Keywords

Gut microbiota; Atopic Dermatitis; Dysbiosis; Short-chain fatty acids; Gut–skin axis.

1. Introduction

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin disorder characterized by pruritus, erythema, and xerosis. It predominantly affects children, with global prevalence rates ranging from 15% to 30%, and persists into adulthood in approximately 10% of cases [1]. The disease significantly impacts patients' quality of life, leading to sleep disturbances, social isolation, and psychological distress [2].

The pathogenesis of AD is multifactorial, involving genetic predisposition, environmental factors, immune dysregulation, and microbial influences [3]. Genetic studies have identified mutations in the filaggrin gene, which encodes a protein essential for skin barrier integrity, as a significant AD risk factor [4]. Environmental exposures, such as allergens, pollutants, and microbial agents, can trigger or exacerbate disease flares. Immunologically, AD is characterized by a skewed Th2-dominant immune response, leading to elevated levels of interleukins IL-4, IL-5, and IL-13, which promote inflammation and IgE production [5].

In recent years, the role of the microbiome, particularly the gut microbiota, has garnered attention in understanding the pathogenesis of AD. The gut microbiota comprises a diverse community of microorganisms that play a crucial role in immune system development and function. Dysbiosis, or an imbalance in the gut microbial community, has been implicated in various inflammatory and autoimmune diseases, including AD [2].

The concept of the gut-skin axis proposes a bidirectional communication pathway between the gut and the skin, mediated through immune, metabolic, and neuroendocrine signaling. Metabolites produced by gut microbiota, such as short-chain fatty acids (SCFA) and tryptophan derivatives, can influence systemic inflammation and immune responses, potentially affecting skin health [6].

This review aims to synthesize current evidence on the role of gut microbiota in the pathogenesis and management of AD. By examining recent studies and clinical trials, we seek to elucidate the mechanisms underlying the gut-skin axis and explore potential therapeutic strategies targeting the gut microbiome to ameliorate AD symptoms [6].

2. Gut Microbiota: Overview and Immunological Functions

The gut microbiota comprises a complex community of microorganisms residing in the gastrointestinal tract, playing a pivotal role in maintaining host health. This microbial ecosystem is integral to various physiological processes, including digestion, metabolism, and immune system development. A balanced gut microbiota is essential for the proper function of the immune system, influencing both innate and adaptive immune responses [7].

The gut microbiota of healthy adults is primarily composed of bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Notably, Firmicutes and Bacteroidetes alone account for approximately 90% of the total microbial population [8]. Despite this general pattern, the composition and relative abundance of specific bacterial taxa can vary significantly between individuals [9]. It is also important to highlight that each person develops a unique gut microbiota profile, influenced by genetics, early-life exposures, and environmental factors [9]. Once established, the composition of the gut microbiome tends to remain relatively stable throughout an individual's life [10].

The gut microbiota plays a critical role in the development and regulation of the immune system. It interacts with intestinal epithelial cells, macrophages, dendritic cells, neutrophils, and innate lymphoid cells to shape innate immunity [11]. In adaptive immunity, it influences the differentiation and function of T and B lymphocytes. These interactions are essential for maintaining immune homeostasis and tolerance to commensal microorganisms and dietary antigens [11].

Dysbiosis refers to an imbalance in the microbial community characterized by a reduction in beneficial commensals, an overgrowth of potentially pathogenic species, or a decrease in overall microbial diversity [12]. Dysbiosis in the gut microbial community, can lead to impaired immune responses and is associated with various inflammatory and autoimmune diseases [11].

The composition and stability of the gut microbiota are modulated by multiple influences: host genetic makeup, dietary patterns, antibiotic exposure, body mass index, and lifestyle-related factors such as physical activity, smoking, sleep quality, and psychological stress [8].

This dysbiosis can lead to impaired immune tolerance and enhanced Th2-mediated inflammation, characteristic of AD [6].

Certain gut microbiota species possess enzymes that enable the fermentation of carbohydrates, leading to the production of gases, alcohols, organic acids, and SCFAs, such as primarily butyrate, propionate, and acetate [13].

These metabolites exert their effects through various mechanisms, including the inhibition of histone deacetylases (HDACs) and activation of G-protein-coupled receptors (GPCRs) such as GPR41, GPR43, and GPR109A [14]. By modulating gene expression and immune cell activity,

SCFAs contribute to the maintenance of intestinal barrier integrity, regulation of inflammatory responses, and overall immune system homeostasis. The production and effects of SCFAs are influenced by dietary factors, highlighting the potential for dietary interventions to modulate gut microbiota composition and function for health benefits [15].

SCFAs produced by the gut microbiota significantly impact the differentiation and function of T helper (Th) cells and regulatory T cells (Tregs) [16]. SCFAs also support intestinal barrier integrity by stimulating mucin production [17]. SCFAs can enhance the generation of Tregs, which play a crucial role in maintaining immune tolerance and preventing excessive inflammatory responses. This modulation of T cell subsets by SCFAs underscores the gut microbiota's influence on immune system balance and function [14].

Moreover SCFAs lower the intestinal pH, creating an antimicrobial environment that inhibits pathogen growth. In conditions of increased intestinal permeability, microbial metabolites may enter the bloodstream, triggering systemic inflammation and affecting skin homeostasis [8]. Butyrate, for instance, has been shown to promote the differentiation of Th1 and Th17 cells, which are involved in the defense against pathogens and the pathogenesis of autoimmune diseases. Further butyrate suppresses IL-12 and promotes IL-10 production in monocytes [18]. Overall, gut microbiota and its metabolites play a crucial role in shaping both innate and adaptive immunity [19].

3. Gut Microbiota and the Pathogenesis of Atopic Dermatitis

Gut dysbiosis refers to an imbalance in the intestinal microbiota, characterized by a reduction in beneficial microorganisms and an overgrowth of potentially harmful ones. This microbial imbalance can lead to impaired immune tolerance and enhanced Th2-mediated inflammation, which are characteristic of AD [2].

Studies have identified characteristic alterations in the composition of the gut microbiota in patients with AD. In children with AD, there is an increased abundance of proteolytic bacteria such as Enterobacter, Klebsiella, and Escherichia coli, along with a reduced presence of lactic acid-producing bacteria, including Lactobacillus and Bifidobacterium. In adult patients with AD, higher levels of Bacteroides, Enterobacteriaceae, and Clostridium perfringens have been observed, whereas healthy adults show greater abundance of SCFA - producing bacteria such as Lactobacillus, Bifidobacterium, Faecalibacterium prausnitzii, and Clostridium [6].

A key mechanism linking gut dysbiosis to AD is the disruption of the intestinal epithelial barrier, commonly referred to as "leaky gut." In a healthy gut, tight junctions between epithelial cells prevent the passage of harmful substances into the bloodstream. However, in the context of dysbiosis, these tight junctions can become compromised, allowing bacteria, endotoxins, and other antigens to translocate across the intestinal barrier [22]

This increased intestinal permeability facilitates the entry of microbial products into systemic circulation, triggering systemic inflammation and immune responses that can affect distant organs, including the skin. In AD, this process contributes to the activation of Th2 cells and the production of pro-inflammatory cytokines, exacerbating skin inflammation and skin barrier dysfunction [23].

SCFAs, play a crucial role in maintaining intestinal barrier integrity and modulating immune responses [17]. In AD patients, dysbiosis is often associated with reduced SCFA production, leading to weakened gut barrier function and increased susceptibility to inflammation [24].

SCFAs with other microbial metabolites—such as amino acid derivatives, oligosaccharides, and glycolipids contribute to the formation of the gut's mucous layer [25]. Butyrate, in particular, strengthens tight junctions between intestinal epithelial cells by inducing IL-10 receptors and regulating proteins such as occludin, zonulin, and claudins [26]. It also modulates oxygen consumption in epithelial cells, promoting stabilization of hypoxia-inducible factor (HIF), which supports barrier function and creates an environment favorable for commensal bacteria [22]. Additionally, butyrate activates AMP-activated protein kinase, further enhancing tight junction integrity [27]. Improved epithelial barrier function limits microbial translocation and systemic inflammation, ultimately reducing the risk of skin barrier disruption and inflammatory responses in conditions such as AD [22].

4. The Gut-Skin Axis

The gut and skin are connected through the gut-skin axis, a bidirectional communication pathway involving immune, metabolic, and neural signals [28]. Key mediators involved in this axis include norepinephrine, serotonin, acetylcholine, and tryptophan [29].

Compounds derived from the gut microbiota, such as tryptophan and γ-aminobutyric acid (GABA), participate in direct signaling pathways and exert opposite effects. In individuals with AD, tryptophan has been associated with an intensification of itching, while GABA appears to alleviate it [30,31].

Gut bacteria metabolize tryptophan into various bioactive compounds, including indole derivatives, which can activate the aryl hydrocarbon receptor (AhR) in immune and epithelial cells. AhR activation modulates skin homeostasis, promotes barrier function, and regulates immune responses. In AD, dysregulation of tryptophan metabolism may result in reduced AhR ligands, contributing to chronic inflammation and impaired skin repair [32].

Additionally, elevated levels of serotonin may contribute to pruritus as part of the inflammatory response. In contrast, reduced concentrations of acetylcholine observed in AD skin lesions may indicate a potential anti-inflammatory function [30,31].

Dysbiosis is a key initiating factor in disrupting gut–skin communication. This microbial imbalance results in increased intestinal permeability, which facilitates the translocation of bacterial antigens and endotoxins (e.g., lipopolysaccharides, LPS) into the bloodstream [33].

These microbial products interact with pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) on immune cells, triggering innate immune activation. The downstream effects include the secretion of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) and chemokines, which can circulate systemically and reach the skin, promoting cutaneous inflammation and Th2-type immune polarization, characteristic of AD [23].

The hypothalamic–pituitary–adrenal (HPA) axis is a central component of the body's stress response system. Chronic psychological or physiological stress can alter the gut microbiota composition, suppress SCFA production, and increase intestinal permeability [34]. In turn, microbial metabolites can influence the HPA axis by altering the levels of cortisol and other neuroactive substances, which feed back into the gut and skin [35].

An increase in cortisol levels can enhance both intestinal and skin barrier integrity by modulating the concentration of circulating neuroendocrine molecules, including tryptamine, trimethylamine, and serotonin. This modulation may alter intestinal permeability by activating cortisol receptors expressed on epithelial, immune, and endocrine cells, eliciting localized responses [35]. Moreover, cortisol-related changes in gut motility may also impact the composition of the gut microbiota [22].

5. Dysbiosis and Atopic Dermatitis: Evidence from Human and Animal Studies

A cross-sectional study by the team of Li Yu et al. examined differences in gut microbiota composition between infants with AD and healthy controls. Fecal samples from 20 infants diagnosed with AD and 25 healthy infants aged 1 to 6 months were analyzed using full-length 16S rRNA gene sequencing. Although overall microbial richness and diversity did not differ significantly between the groups, taxonomic analysis showed a predominance of Firmicutes, Proteobacteria and Bacteroidetes in both cohorts. In particular, a statistically significant reduction in the relative abundance of the genus Streptococcus was observed in the AD group compared to the control group. These findings suggest a potential link between reduced Streptococcus abundance and the occurrence of AD in

early infancy, although further large-scale studies are warranted to clarify the role of this genus in the pathogenesis of AD [34].

A large prospective cohort study investigated the impact of early-life gut microbiota composition on the development of atopic diseases, focusing on the role of specific bacteria in the onset of these conditions. Scientists examined the gut microbiota of 957 infants at 1 month of age, participants in the KOALA Birth Cohort Study, using quantitative real-time PCR. Information on atopic symptoms, such as eczema and wheezing, was collected via repeated questionnaires. In addition, total and specific IgE levels were measured in venous blood samples obtained during home visits when the infants were 2 years old. A clinical diagnosis of AD was made during these visits according to UK Working Party criteria [35].

The results showed that the presence of Escherichia coli at 1 month of age was significantly associated with an increased risk of developing eczema at 2 years of age, with a higher risk observed as the number of E. coli colonizing the infants increased. In contrast, Clostridium difficile colonization was associated with an increased risk of developing eczema, recurrent wheezing and allergic sensitization. Additionally, the presence of *Clostridium difficile* was associated with a higher likelihood of receiving a clinical diagnosis of AD during the home visit [35].

In conclusion, this study provides evidence that differences in gut microbiota composition in early infancy precede the development of atopic manifestations. While *E. coli* was associated specifically with eczema, *C. difficile* was linked to all atopic outcomes, suggesting that the mechanisms underlying these associations may differ. Further research is needed to explore these mechanisms and the potential role of gut microbiota in the prevention and treatment of atopic diseases [35].

Liu et al. investigated the association between gut microbiota composition and the severity of AD in early infancy. Sixty-two infants (mean age 4.7 ± 1.9 months) diagnosed with varying degrees of AD were stratified into mild, moderate, and severe groups based on the SCORAD (Scoring Atopic Dermatitis) index. Gut microbial composition and functional profiles were analyzed using 16S rRNA gene sequencing, and the impact of AD on quality of life was assessed via validated questionnaires. The results revealed a significant reduction in the abundance of *Clostridium sensu stricto* and *Collinsella*, along with an increase in *Parabacteroides* in the severe AD group compared to the mild group. Furthermore, a positive correlation was observed between SCORAD scores and the relative abundance of *Bacteroides* and metabolic pathways involved in sphingolipid and glycosphingolipid metabolism, while *Clostridium sensu stricto* was negatively correlated with disease severity. These findings suggest that alterations in butyrate-producing (such as Clostridium sensu stricto) and

sphingolipid-producing bacteria (Parabacteroides, Bacteroides), along with their associated functional pathways, are linked to AD severity in infancy, highlighting the potential role of the gut microbiome in disease progression and therapeutic targeting [36].

Le Duc's team conducted interesting studies to assess and compare fecal SCFA profiles in infants with AD and healthy controls within the GUSTO birth cohort. A total of 64 infants were categorized into three groups: non-allergen sensitized AD, allergen sensitized AD, and healthy controls. Across 164 stool samples collected at 3 weeks, and at 3, 6, and 12 months of age, concentrations of nine SCFAs were quantified using liquid chromatography tandem mass spectrometry. Longitudinal multivariate analysis, adjusted for potential confounders, revealed that levels of most SCFAs increased with age. Notably, significantly lower levels of acetic, propionic, and butyric acids were observed in infants with allergen-sensitized AD compared to healthy controls, while no such differences were observed in the non-sensitized AD group. SCFA levels were also influenced by factors such as presence of siblings, prenatal antibiotic exposure, and family history of atopy. These findings suggest a potential role of SCFAs, particularly in allergen-sensitized AD, in the early immunological development of atopic disease [37].

Ha-Jung Kim et al. onducted a study using a mouse model with antibiotic-induced gut microbiota dysbiosis in the context of AD, demonstrating that gut microbiota homeostasis may play a key role in the prevention of this disease [38].

The results revealed that mice treated with antibiotics exhibited significantly aggravated AD phenotypes, including elevated clinical scores, increased transepidermal water loss, and more severe histopathological changes compared to those treated with healthy feces or probiotics. Antibiotic-treated mice also demonstrated a significant increase in systemic immunoglobulin E production and skin IL 4 levels. Additionally, antibiotic treatment resulted in higher levels of IL17 and group 3 innate lymphoid cells (ILC3) in the gut, while suppressing the production of SCFAs and reducing the number of $FOXP3^+$ cells. These findings suggest that early-life gut microbiota alterations in mice play a critical role in AD development, potentially through SCFA production, which regulates the balance of $CD4^+IL17^+/CD4^+FOXP3^+$ regulatory T cells and ILC3s [38].

Recent experimental research conducted by Lv et al. investigated the role of gut-derived SCFAs in maintaining skin barrier function through their effects on keratinocyte metabolism and differentiation. Using mouse models and in vitro keratinocyte cultures, the study demonstrated that SCFAs—particularly butyrate and propionate—enhanced the expression of genes involved in epidermal differentiation and lipid metabolism, including *filaggrin*, *loricrin*, and *involucrin*. Topical or systemic administration of SCFAs improved transepidermal water loss (TEWL) and restored skin

barrier integrity in dermatitis models. Mechanistically, these effects were mediated through epigenetic modulation and activation of PPAR signaling pathways. Importantly, the authors highlighted that a diet rich in dietary fiber increases the production of SCFAs by the gut microbiota, suggesting that nutritional modulation may offer a protective effect on the skin barrier. These findings support the concept of the gut–skin axis and point to the potential of fiber-based dietary strategies in the management of AD [39].

6. Therapeutic Perspectives

6.1. Probiotics and Prebiotics: Potential in Modulating Gut Microbiota and Alleviating AD Symptoms

The modulation of gut microbiota through probiotics and prebiotics has emerged as a promising avenue in the management and prevention of AD [40]. Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host. A study by Banderowicz et al. found that probiotic supplementation—particularly with strains of *Lactobacillus*—was associated with reduced duration of AD therapy and improvement in allergic symptoms such as pruritus and erythema [41]. Several randomized controlled trials and meta-analyses have reported that probiotic supplementation, particularly with strains such as *Lactobacillus rhamnosus GG, Bifidobacterium breve*, and *Lactobacillus casei*, can reduce the incidence and severity of AD [6]. Mechanistically, probiotics may exert their effects by enhancing Treg populations, reducing Th2-driven inflammatory responses, decreasing serum IgE levels, and promoting the production of anti-inflammatory cytokines such as IL-10 [40].

Moreover, probiotics have been found to increase the production of SCFAs, such as butyrate and propionate, which play a critical role in maintaining epithelial integrity and regulating immune tolerance [42].

Prebiotics - non-digestible food components that selectively stimulate the growth and activity of beneficial gut bacteria, have also demonstrated therapeutic potential in AD. A recent meta-analysis of 38 studies involving over 127,000 participants showed that supplementation with prebiotics, probiotics, and synbiotics significantly reduced both the incidence and severity of AD, as measured by the SCORAD index. These effects were particularly notable in children with moderate to severe forms of the disease [43].

Synbiotics, a combination of probiotics and prebiotics, represent an even more promising therapeutic approach. Ibanez et al. demonstrated that synbiotic supplementation led to significant improvements in clinical scores and favorable shifts in gut microbiota composition and immune profiles in patients with AD [44].

Some studies suggest that combined administration of probiotics and prebiotics may have synergistic effects, further enhancing the immunomodulatory benefits and clinical outcomes in AD patients [40].

Although findings to date are promising, heterogeneity in study designs, probiotic strains used, treatment duration, and patient characteristics have led to variable outcomes across studies. Therefore, further large-scale, strain-specific, and mechanistically oriented clinical trials are necessary to establish standardized recommendations for probiotic and prebiotic use in the context of AD.

6.2. Dietary Interventions

Diet plays a crucial role in shaping the gut microbiome and may influence systemic inflammation and skin health in AD. Diets rich in fermentable fiber, polyphenols (e.g., from fruits, vegetables, green tea), and fermented products such as yogurt or kefir are associated with increased production of SCFAs, particularly butyrate[39]. SCFAs and dietary fiber play a crucial role in maintaining skin barrier integrity, thereby potentially preventing the development of AD and early allergic sensitization [2]. A fiber-rich diet favorably alters the composition of the gut microbiota by increasing the abundance of *Bacteroidetes* and *Bifidobacteriaceae*, while reducing the proportion of *Firmicutes*. These bacterial groups preferentially ferment dietary fibers, leading to enhanced SCFA production. Of particular interest is *Faecalibacterium prausnitzii*, one of the primary butyrate-producing bacteria, which synthesizes butyrate from acetate via the enzyme butyryl-CoA:acetyl-CoA transferase [2]. Recent evidence also suggests that minimizing processed foods, saturated fats, and excessive salt may further reduce AD severity [45].

6.3. Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) has emerged as an innovative therapeutic option aimed at restoring gut microbial balance, by transferring fecal microbiota from healthy donors to patients [46]. Preliminary data from animal models and human case series suggest that FMT can reduce AD severity by modulating gut microbiota composition and increasing SCFA-producing bacteria. In a recent study by Zhang et al., FMT in adults with moderate-to-severe AD led to improvements in Eczema Area and Severity Index (EASI) scores, decreased serum IgE levels, and notable shifts in gut microbial diversity [47]. Similar findings were observed in a murine model of AD by Jiang X et al., where FMT ameliorated skin inflammation and promoted colonization by beneficial microbes [48]. A randomized, double-blind, placebo-controlled trial by Liu et al. demonstrated that FMT significantly improved clinical outcomes in adults with moderate-to-severe AD. Patients receiving

FMT exhibited reductions in EASI scores, lower serum IgE levels, and notable shifts in gut microbiota composition, including increased abundance of beneficial microbes such as *Megamonas funiformis* [49]. Despite its potential, FMT requires further validation in large-scale randomized controlled trials to establish safety, optimal protocols, and long-term efficacy in AD treatment [48].

7. Conclusions

Current scientific evidence strongly supports the significant role of the gut microbiota in the pathogenesis and potential treatment of AD. The mechanisms linking gut dysbiosis to AD development include disruption of the intestinal epithelial barrier, reduced production of SCFAs, and activation of the gut–skin axis, which promotes systemic inflammatory responses. SCFAs—particularly butyrate and propionate—are of particular importance due to their role in modulating immune responses and maintaining skin homeostasis.

Supplementation with probiotics such as *Lactobacillus rhamnosus GG*, *Bifidobacterium breve* and prebiotics has shown therapeutic potential, as evidenced by selected clinical trials and meta-analyses. Synbiotics may further enhance clinical outcomes by synergistically influencing the composition of gut microbiota and modulating immune responses.

Despite promising findings, study results remain heterogeneous due to methodological differences, variability in bacterial strains used, duration of interventions, and diversity among study populations. There is a clear need for further large-scale, randomized, placebo-controlled clinical trials with standardized therapeutic protocols. Determining the long-term safety and efficacy of microbiota-targeted interventions in various age groups and clinical phenotypes of AD is essential.

Additionally, an interdisciplinary approach to AD management—including collaboration among dermatologists, gastroenterologists, immunologists, and dietitians—may improve therapeutic outcomes and deepen our understanding of disease mechanisms.

Author’s Contribution Statement:

Conceptualization, Wiktoria Jedlikowska and Natalia Furlepa; methodology, Monika Brzozowska and Robert Rzenno; software, Marcelina Matuszewska; check, Monika Brzozowska, Katarzyna Wicha and Natalia Sidz; formal analysis, Magdalena Tomaszewska; investigation, Natalia Wieczorek-Durdzińska and Robert Rzenno; resources, Marcelina Matuszewska and Natalia Sidz; data curation, Magdalena Tomaszewska and Natalia Furlepa; writing - rough preparation, Karolina

Wojciechowska and Katarzyna Wicha; writing - review and editing, Wiktoria Jedlikowska; visualization, Karolina Wojciechowska ; supervision, Wiktoria Jedlikowska; project administration, Monika Brzozowska

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