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Role Of Gut Microbiome In Pathogenesis And Management Of Atopic Dermatitis

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Abstract

Background:

Atopic dermatitis (AD) is a chronic inflammatory disease with increasing global prevalence and substantial socioeconomic burden. Traditionally explained by epidermal barrier defects and immune dysregulation, AD is now recognized as a systemic disorder influenced by the **gut–skin axis**, where alterations in the gut microbiome contribute to disease initiation and progression.

Aim:

This review synthesizes current evidence on the role of the gut microbiome in the **pathogenesis** of AD and evaluates microbiome-targeted **management strategies** including probiotics, prebiotics, synbiotics, dietary interventions, and fecal microbiota transplantation (FMT).

Findings:

Patients with AD exhibit gut dysbiosis characterized by reduced microbial diversity, depletion of short-chain fatty acid (SCFA)–producing taxa, and impaired tryptophan and bile acid metabolism. These microbial changes promote Th2/Th17-skewed immune responses, barrier dysfunction, and systemic inflammation. Preventive probiotic supplementation during pregnancy and infancy reduces AD risk by approximately 20%, particularly with *Lactobacillus rhamnosus GG* and *Bifidobacterium breve*. Treatment trials demonstrate modest, strain-specific improvements in clinical scores (SCORAD/EASI), though results remain inconsistent. Prebiotics and synbiotics show emerging potential, while postbiotic strategies remain experimental. Dietary interventions, especially Mediterranean-style diets and fermented foods, enhance

microbial diversity and exert anti-inflammatory effects, whereas restrictive elimination diets without confirmed food allergies are discouraged. Early RCTs of capsule-based FMT in moderate-to-severe AD demonstrate clinically meaningful reductions in disease severity with good short-term safety.

Conclusion:

The gut microbiome plays a pivotal role in AD pathogenesis and represents a promising therapeutic target. While probiotics and dietary modulation offer safe, accessible adjuncts, FMT and postbiotics require further validation. Future research should focus on **strain-specific interventions, standardized biomarkers, long-term safety, and personalized microbiome profiling** to enable precision medicine in AD management.

Keywords: Atopic dermatitis; gut microbiome; probiotics; synbiotics; fecal microbiota transplantation; gut–skin axis; precision dermatology.

1. Introduction

1.1 Burden of Atopic Dermatitis Globally

Atopic dermatitis (AD), also known as eczema, is one of the most prevalent chronic inflammatory skin diseases worldwide, affecting approximately 15–20% of children and 2–10% of adults, with higher prevalence in developed countries [1,2]. The disease imposes a significant socioeconomic burden, including healthcare costs, reduced productivity, and impaired quality of life due to persistent itching, sleep disturbances, and psychosocial stress [3]. The global prevalence of AD has shown a rising trend over the last three decades, particularly in urbanized regions, highlighting the impact of environmental and lifestyle factors [4]. Severe and persistent cases often require systemic immunomodulators, which further increase economic costs for both patients and healthcare systems [5].

1.2 Conventional Understanding of AD Pathogenesis

The pathogenesis of AD has traditionally been explained by a complex interplay between genetic, immunological, and environmental factors. One of the key contributors is **epidermal barrier dysfunction**, primarily associated with mutations in the *filaggrin* gene (FLG), leading to reduced structural proteins and ceramide imbalance in the stratum corneum [6]. This compromised barrier facilitates transepidermal water loss (TEWL) and allows allergens, microbes, and irritants to penetrate the skin more easily, triggering inflammation [7].

Another crucial factor is **immune dysregulation**, particularly the overactivation of type-2 helper T cells (Th2). Cytokines such as IL-4, IL-5, IL-13, and IL-31 dominate the acute phase of AD, resulting in chronic pruritus and inflammation [8,9]. Chronic phases often involve additional immune pathways, including Th22 and Th17, further contributing to disease heterogeneity [10]. This evolving understanding has led to targeted biologic therapies such as dupilumab and tralokinumab, which specifically inhibit type-2 cytokines [11].

1.3 Why the Gut Microbiome Matters: The Gut–Skin Axis

Although skin barrier defects and immune dysregulation remain central to AD pathogenesis, recent evidence suggests that the **gut microbiome** plays a pivotal role in disease onset and progression [12]. The gut harbors trillions of microorganisms whose metabolic activity influences systemic immunity through microbial metabolites such as **short-chain fatty acids (SCFAs), bile acids, and tryptophan derivatives** [13,14]. These metabolites regulate T regulatory (Treg) cell differentiation, suppress pro-inflammatory Th2 responses, and help maintain epithelial barrier integrity [15].

The concept of the **gut–skin axis** proposes that intestinal dysbiosis—characterized by reduced microbial diversity and depletion of SCFA-producing taxa—can lead to systemic low-grade inflammation and increased susceptibility to allergic skin diseases such as AD [16]. Early-life factors, including mode of delivery, breastfeeding, antibiotic exposure, and diet, strongly influence gut microbial composition and have been correlated with AD risk in children [17,18]. This suggests that interventions targeting the gut microbiome may represent a promising adjunct to conventional AD therapies.

1.4 Purpose and Scope of This Review

Given the growing recognition of the gut microbiome's role in AD, this review aims to provide a comprehensive synthesis of current knowledge regarding its involvement in both **pathogenesis** and **management**. We will first examine how gut microbial dysbiosis contributes to AD development through immune, metabolic, and barrier-related pathways. Next, we will analyze evidence from clinical studies investigating microbiome-targeted interventions, including **probiotics, prebiotics, synbiotics, dietary strategies, and fecal microbiota transplantation (FMT)**. Finally, we highlight ongoing challenges, research gaps, and future directions to guide precision microbiome-based strategies in AD management.

By integrating mechanistic insights with clinical evidence, this review seeks to clarify whether the modulation of the gut microbiome can offer safe, effective, and durable adjunctive therapies in the context of current AD treatment paradigms.

2. Pathogenesis of Atopic Dermatitis and the Gut Microbiome

2.1 Core Pathophysiology of AD

2.1.1 Epidermal Barrier Defects

One of the central pillars in the pathogenesis of atopic dermatitis (AD) is **epidermal barrier dysfunction**. Genetic studies have shown that mutations in the *filaggrin* gene (FLG) are strongly associated with AD, especially in patients with early-onset and persistent disease [1]. Filaggrin is critical for maintaining the structural integrity of the stratum corneum, and its deficiency results in impaired keratin aggregation, reduced natural moisturizing factors, and increased transepidermal water loss (TEWL). This compromised barrier

facilitates the entry of allergens, irritants, and microbes, perpetuating cutaneous inflammation [2]. Additionally, lipid abnormalities, particularly ceramide imbalance, further weaken the skin barrier, creating an environment conducive to chronic inflammation and microbial colonization [3].

2.1.2 Immune Dysregulation

Beyond barrier abnormalities, **immune dysregulation** is another hallmark of AD. The disease is predominantly mediated by type-2 helper T cells (Th2), which secrete cytokines such as **IL-4, IL-5, IL-13, and IL-31**, contributing to pruritus, eosinophilia, and chronic inflammation [4]. IL-31 is directly linked to itch severity and neuronal sensitization [5]. In acute AD lesions, Th2 dominance is evident, whereas chronic lesions often show additional involvement of **Th17 and Th22 pathways**, which contribute to keratinocyte hyperplasia and barrier dysfunction [6]. The identification of these immune circuits has driven therapeutic advances, particularly monoclonal antibodies (dupilumab, tralokinumab) and Janus kinase (JAK) inhibitors, which specifically target type-2 signaling [7].

2.2 Gut Microbiome Composition in Health vs. AD

2.2.1 Diversity and Stability of Healthy Gut Flora

The **human gut microbiome** is a dynamic ecosystem composed of bacteria, archaea, fungi, and viruses, playing a pivotal role in digestion, immune development, and host homeostasis. In healthy individuals, microbial communities are characterized by high diversity and stability, with dominant phyla including **Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria** [8]. A balanced microbiota supports immune tolerance by stimulating regulatory T cells (Tregs) and producing metabolites such as short-chain fatty acids (SCFAs) that suppress inflammation [9].

2.2.2 Dysbiosis in Infants and Adults with AD

In AD, **gut microbial dysbiosis** is consistently reported across age groups. Infant studies demonstrate reduced microbial diversity and depletion of beneficial taxa such as *Bifidobacterium* and *Faecalibacterium prausnitzii* in those who later develop AD [10]. Similarly, adults with AD exhibit increased abundance of pro-inflammatory microbes (e.g., *Escherichia coli*) and decreased SCFA-producing species, correlating with disease severity [11]. These alterations weaken immunological tolerance and promote systemic low-grade inflammation. Importantly, longitudinal cohort studies suggest that early life dysbiosis may precede AD onset, indicating a potential causal relationship [12].

2.3 Mechanistic Pathways Linking Gut to Skin

2.3.1 Microbial Metabolites

The gut microbiota exerts systemic effects through its **metabolic byproducts**. Among these, SCFAs such as acetate, propionate, and butyrate are crucial in maintaining epithelial integrity and modulating immune responses. SCFAs act by promoting Treg differentiation and suppressing pro-inflammatory Th2 responses, thus preventing allergic inflammation [13]. In addition, **tryptophan metabolites**, particularly indole derivatives, activate the **aryl hydrocarbon receptor (AHR)**, enhancing barrier function and antimicrobial peptide expression in keratinocytes [14]. Bile acids, further modified by gut microbes, influence innate immune pathways and shape systemic inflammatory responses [15]. Together, these metabolites form essential links in the **gut–skin axis**.

2.3.2 Intestinal Permeability and Systemic Inflammation

The concept of **"leaky gut"** has gained attention in AD research. Increased intestinal permeability, indicated by elevated serum zonulin and fecal calprotectin, has been observed in subsets of AD patients [16]. This impaired gut barrier allows translocation of microbial components such as lipopolysaccharides (LPS), which stimulate systemic inflammation and exacerbate cutaneous immune activation [17]. While causality remains debated, animal models and preliminary human studies support the notion that restoring gut barrier integrity may ameliorate AD symptoms [18].

2.3.3 Interaction with Cutaneous Immune Responses

Gut dysbiosis indirectly influences the **cutaneous immune microenvironment**. Dysregulated gut microbiota skews systemic cytokine profiles, favoring Th2/Th17 responses that exacerbate skin inflammation [19]. Moreover, microbial metabolites regulate keratinocyte differentiation and antimicrobial peptide production, directly influencing skin barrier stability [20]. This bidirectional communication between the gut and skin underscores the systemic nature of AD pathogenesis.

2.4 Modifying Factors in Early Life

2.4.1 Mode of Delivery

Early microbial colonization is significantly influenced by **birth mode**. Vaginal delivery exposes infants to maternal vaginal and gut microbiota, enriching colonization with *Lactobacillus* and *Bifidobacterium* species. In contrast, Cesarean section delivery results in reduced microbial diversity and delayed colonization, predisposing infants to atopic disorders including AD [21]. Meta-analyses confirm a modest but consistent increase in AD risk among Cesarean-born infants [22].

2.4.2 Breastfeeding vs. Formula Feeding

Breastfeeding shapes the infant microbiome through human milk oligosaccharides (HMOs), which selectively promote the growth of *Bifidobacterium* species and enhance immune tolerance [23]. Breastfed

infants demonstrate lower incidence of AD compared with formula-fed counterparts, although results vary by population and study design [24]. Formula feeding, particularly when supplemented with probiotics or prebiotics, may partially mitigate this risk but lacks the full protective spectrum of breast milk [25].

2.4.3 Antibiotics and Diet

Early-life **antibiotic exposure** is one of the strongest disruptors of gut microbiota, leading to reduced diversity and enrichment of opportunistic pathogens [26]. Multiple studies link infant antibiotic use with higher AD risk, supporting the hypothesis that dysbiosis precedes disease onset [27]. Diet is another critical modulator: low-fiber, high-fat Western diets are associated with diminished SCFA production, while fiber-rich or Mediterranean-style diets promote microbial diversity and anti-inflammatory metabolites [28]. These findings highlight the importance of early-life exposures in shaping microbiota trajectories and influencing AD risk.

3. Microbiome-Targeted Management Strategies

3.1 Probiotics

3.1.1 Evidence in Prevention

The use of **probiotics in the prevention of atopic dermatitis (AD)** has been extensively studied, particularly in maternal and infant supplementation trials. Several meta-analyses suggest that probiotic administration during pregnancy and early infancy modestly reduces the risk of AD development in high-risk infants [1]. The most consistent benefit is observed when supplementation spans both prenatal and postnatal periods, particularly with *Lactobacillus rhamnosus GG* (LGG) and multi-strain formulations [2]. The World Allergy Organization (WAO) guidelines conditionally recommend probiotics for pregnant and breastfeeding women, as well as infants at high risk of allergic disease, although the certainty of evidence is rated as low [3]. Importantly, protective effects appear to be **strain-specific** and may not extend to all populations, underscoring the importance of targeted selection.

3.1.2 Evidence in Treatment

For individuals with established AD, probiotics have shown **mixed results**. Randomized controlled trials (RCTs) report modest improvements in clinical severity scores such as SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index) in children and adults [4,5]. Benefits are particularly associated with single-strain *Lactobacillus* or *Bifidobacterium* formulations, though outcomes are not universally reproducible [6]. For example, some RCTs demonstrated reductions in SCORAD by 20–30% after 8–12 weeks of probiotic use, while others reported no significant effect [7]. Variability in baseline severity, probiotic strains, dosing, and trial design likely accounts for these discrepancies. Current dermatology guidelines therefore do not endorse probiotics as standard therapy but acknowledge their potential as adjunctive interventions in selected patients [8].

3.1.3 Safety Considerations

Probiotics are generally well tolerated in healthy and immunocompetent individuals, with gastrointestinal side effects being the most common adverse events [9]. However, rare cases of bacteremia and fungemia have been reported in immunocompromised patients or those with indwelling medical devices [10]. Product quality and strain viability remain significant concerns, as commercial probiotic formulations often lack consistency in strain identity and dose. Regulatory oversight is essential to ensure safety and efficacy, especially in vulnerable populations [11].

3.2 Prebiotics, Synbiotics, and Postbiotics

3.2.1 Mechanistic Rationale

Prebiotics are non-digestible substrates, such as galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS), that selectively stimulate the growth of beneficial gut microbes, particularly *Bifidobacterium* spp. and SCFA-producing taxa [12]. **Synbiotics**, a combination of probiotics and prebiotics, are designed to enhance colonization and functional activity of administered strains. **Postbiotics**, defined as bioactive microbial metabolites such as SCFAs, peptides, or cell-wall components, act directly on host pathways, bypassing the need for live organisms [13]. These strategies collectively aim to restore immune tolerance and enhance epithelial barrier function.

3.2.2 Current Evidence and Limitations

Clinical studies on prebiotics and synbiotics for AD prevention and treatment remain limited. Some infant trials report reduced eczema incidence with supplementation of GOS/FOS blends, though effects are modest and population dependent [14]. Synbiotics have shown promise in small RCTs, with improvements in SCORAD scores and increased abundance of *Lactobacillus* spp. in the gut [15]. However, inconsistencies in formulations and lack of long-term follow-up limit generalizability. Postbiotic therapies are still in preclinical or early clinical stages, but butyrate supplementation and AHR ligand analogues have shown immunomodulatory benefits in animal models [16]. Larger, standardized trials are needed before these strategies can be integrated into routine AD management.

3.3 Diet and Lifestyle

3.3.1 High-Fiber and Mediterranean Diet Effects

Dietary interventions represent a low-cost and widely accessible means of microbiome modulation. **High-fiber diets**, particularly those rich in plant-based foods, enhance SCFA production and microbial diversity, thereby dampening systemic inflammation [17]. Epidemiological studies suggest that adherence to a **Mediterranean-style diet**, characterized by high intake of fruits, vegetables, legumes, olive oil, and fish, is associated with lower risk of AD in children and improved symptom control in adults [18]. The anti-

inflammatory and antioxidant properties of such diets may synergize with microbiome effects to confer protection.

3.3.2 Role of Fermented Foods

Fermented foods (e.g. yogurt, kefir, kimchi) are natural sources of live microbes and metabolites that can positively influence gut ecology. A randomized controlled feeding study demonstrated that regular consumption of fermented foods increases microbial diversity and reduces markers of systemic inflammation [19]. While specific data on AD remains limited, incorporating fermented foods is considered a safe adjunctive strategy with potential microbiome-mediated benefits.

3.3.3 Risks of Restrictive Elimination Diets

Elimination diets are often attempted by patients with AD under the assumption of food-related triggers. However, unless guided by clear evidence of **IgE-mediated food allergy**, restrictive diets carry risks of nutritional deficiencies, impaired growth in children, and worsened quality of life [20]. Current guidelines recommend against elimination diets as a standard approach for AD management, emphasizing instead balanced diets that promote microbiome stability [11].

3.4 Fecal Microbiota Transplantation (FMT)

3.4.1 Pilot Studies in Moderate–Severe AD

FMT, involving the transfer of stool from healthy donors to restore recipient microbiota, has emerged as a powerful therapeutic tool in gut-related disorders. Early-phase studies in **moderate-to-severe AD** patients have shown promising results, with improvements in EASI scores and durable engraftment of donor microbiota [22]. A recent RCT using capsule-based FMT reported clinically meaningful reductions in AD severity compared with placebo, supporting further investigation [13].

3.4.2 Safety, Regulation, and Feasibility

Despite encouraging data, FMT carries safety and regulatory concerns. Potential transmission of multidrug-resistant organisms (MDROs) has been reported, highlighting the need for rigorous donor screening [14]. Long-term durability of benefit remains uncertain, and ethical questions persist regarding pediatric use. Currently, FMT remains experimental for AD and is restricted to clinical trials in specialized centers [25].

3.5 Integration with Standard of Care

3.5.1 Positioning alongside Biologics and JAK Inhibitors

Modern AD treatment guidelines prioritize topical corticosteroids, calcineurin inhibitors, phototherapy, biologics (dupilumab, tralokinumab), and JAK inhibitors for moderate-to-severe cases [20]. Microbiome-targeted therapies should be considered as **adjuncts** rather than replacements for these proven interventions.

For instance, probiotics or dietary optimization may reduce flare frequency or corticosteroid dependency but are unlikely to replace biologics in severe disease [20].

3.5.2 Practical Clinical Decision Flow

In practice, clinicians may adopt a **stepwise approach**:

1. Optimize skin care and anti-inflammatory therapy per guidelines.
2. Encourage dietary patterns supportive of microbial health (Mediterranean, fermented foods).
3. Consider probiotic or synbiotic supplementation in high-risk children or motivated adults, with clear expectations of modest benefit.
4. Explore investigational options such as FMT only within clinical trials.

This integrated model positions microbiome modulation as a complementary tool, aligned with precision dermatology principles [28].

4. Research Gaps and Future Directions

4.1 Strain-Specific vs. Generalized Probiotic Use

One of the most persistent challenges in translating microbiome science into clinical practice for atopic dermatitis (AD) is the **heterogeneity of probiotic interventions**. Current meta-analyses often pool studies using different strains, doses, and treatment windows, making it difficult to determine which specific probiotic formulations are effective [1,2]. Evidence suggests that strains such as *Lactobacillus rhamnosus GG* and *Bifidobacterium breve* may reduce AD incidence or severity, while others show little to no effect [3]. This inconsistency highlights the urgent need for **strain-specific trials** with well-defined dosing regimens and mechanistic endpoints. Without such clarity, clinical recommendations remain tentative, limiting integration into standard care [4].

4.2 Standardization of Outcome Measures

Another critical gap lies in the **lack of standardized outcome measures** across clinical trials. While validated clinical indices such as SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index) remain the gold standard for assessing disease severity, they are subjective and influenced by inter-observer variability [5]. Few studies incorporate **mechanistic biomarkers** such as serum cytokines, SCFA levels, intestinal permeability markers (zonulin, calprotectin), or microbial diversity indices [6,7]. Future trials should combine **clinical severity scales with molecular and immunological readouts**, enabling researchers to link microbiome modulation to biological pathways. Such integration will also clarify whether observed clinical benefits are mediated by microbiome-driven immune reprogramming or other indirect mechanisms.

4.3 Long-Term Safety and Durability of Interventions

Most existing studies on probiotics, synbiotics, and fecal microbiota transplantation (FMT) in AD are limited to **short durations (8–16 weeks)** [8]. As a result, the **long-term safety, efficacy, and durability** of microbiome-targeted therapies remain unclear. For example, while probiotics are generally well tolerated, rare cases of bacteremia in immunocompromised patients raise safety concerns [9]. Similarly, FMT carries risks of transmitting multidrug-resistant organisms (MDROs) despite stringent donor screening [10]. Moreover, the persistence of therapeutic benefit following cessation of probiotics or FMT has not been consistently evaluated. Longitudinal cohort studies and extension trials are necessary to determine whether microbiome modulation offers **sustained remission** or merely transient symptom relief.

4.4 Role of Personalized Microbiome Profiling in Precision Dermatology

Emerging evidence underscores the variability in **host–microbiome interactions** across individuals, driven by genetics, diet, environment, and early-life exposures [11]. This variability suggests that "one-size-fits-all" interventions may be suboptimal. Advances in **metagenomics, metabolomics, and machine learning** now allow detailed characterization of individual microbiomes and prediction of therapeutic responses [12]. Personalized microbiome profiling could enable clinicians to tailor interventions—such as selecting specific probiotic strains, dietary modifications, or postbiotic supplements—to the unique microbial and immunological landscape of each patient [13]. Such approaches align with the broader movement toward **precision dermatology**, but they require robust data integration pipelines, cost-effectiveness analyses, and clinical validation.

5. Results and Discussion

5.1 Results

5.1.1 Gut Microbiome Alterations in AD Patients

Across multiple cohort studies and systematic reviews, patients with atopic dermatitis (AD) consistently demonstrate **altered gut microbiota profiles** compared with healthy controls. Infants who later developed AD were found to have reduced abundance of *Bifidobacterium* and *Faecalibacterium prausnitzii* and increased colonization with *Escherichia coli* and *Clostridium difficile* [1]. In adults, cross-sectional studies using 16S rRNA sequencing confirm decreased microbial diversity, with depletion of short-chain fatty acid (SCFA) producers and enrichment of pro-inflammatory taxa [2]. A large Korean cohort study of 234 children showed that reduced microbial diversity at 6 months of age strongly predicted AD onset by 2 years [3].

5.1.2 Role of Microbial Metabolites

Microbial metabolites such as SCFAs, tryptophan derivatives, and bile acids play central roles in gut–skin communication. Butyrate-producing bacteria are significantly reduced in children with AD, correlating with

disease severity [4]. Metabolomic profiling of AD patients demonstrates lower levels of indole-3-lactic acid (a tryptophan derivative activating AHR pathways), which has known anti-inflammatory effects on keratinocytes [5]. These results highlight the functional consequences of dysbiosis, beyond compositional changes alone.

5.1.3 Probiotics in Prevention and Treatment

Evidence for probiotics in AD prevention is strongest in **maternal–infant supplementation trials**. A meta-analysis of 28 RCTs (over 6,500 participants) showed that perinatal probiotic use reduced the risk of AD in infants by ~20%, with greatest benefit seen when supplementation spanned both pregnancy and early infancy [6]. Specific strains such as *Lactobacillus rhamnosus GG* and *Bifidobacterium breve M-16V* were most effective.

In treatment trials, results are more heterogeneous. A 2023 meta-analysis including 27 RCTs found probiotics reduced SCORAD severity scores by an average of 7.2 points in children but showed no significant benefit in adults [7]. Strain-specificity emerged as crucial: single-strain *Lactobacillus* interventions appeared more effective than multi-strain combinations. Importantly, some RCTs reported no significant improvements, underscoring variability in outcomes [8].

5.1.4 Prebiotics, Synbiotics, and Postbiotics

Prebiotics (e.g., galacto-oligosaccharides) have demonstrated modest protective effects in infancy. A Dutch RCT of 259 high-risk infants found that supplementation with a prebiotic mixture reduced cumulative AD incidence at 6 months (9.8% vs. 23.1% in controls) [9]. Synbiotics have shown more consistent results: in a 2020 RCT, children with moderate AD receiving a synbiotic (LGG + fructo-oligosaccharides) had significant SCORAD improvement compared to placebo [10]. Postbiotic trials are still emerging; one pilot trial demonstrated that topical butyrate improved skin barrier recovery after damage, while oral postbiotics remain under evaluation [11].

5.1.5 Diet and Lifestyle Interventions

Dietary quality appears to influence AD risk and outcomes through microbiome modulation. Cross-sectional analyses of Mediterranean diet adherence show lower prevalence and severity of AD in children [12]. In contrast, Western-style diets high in fat and low in fiber correlate with increased AD risk [13]. A randomized controlled feeding study confirmed that fermented foods increase microbial diversity and decrease inflammatory cytokines [14], suggesting potential benefits for AD, although direct AD-specific trials are lacking.

5.1.6 Fecal Microbiota Transplantation (FMT)

FMT represents the most direct microbiome-targeting strategy. A 2025 randomized controlled trial (n=64 adults with moderate–severe AD) reported significant EASI improvement at 12 weeks in patients receiving

oral capsule FMT compared with placebo [15]. Engraftment analysis confirmed durable donor microbiota colonization. No serious adverse events occurred, though mild gastrointestinal symptoms were common. This represents the first high-quality evidence supporting FMT in AD, though replication is needed.

5.2 Discussion

5.2.1 Synthesis of Findings

The evidence indicates that gut microbiome dysbiosis contributes meaningfully to the pathogenesis of AD. Altered microbiota composition, reduced diversity, and functional deficits in SCFA and tryptophan metabolism are recurrent findings. These microbial imbalances correlate with disease severity and immune dysregulation, strengthening the gut–skin axis hypothesis. Clinical interventions targeting the microbiome—probiotics, prebiotics, synbiotics, diet, and FMT—demonstrate varying degrees of efficacy, with strongest evidence in **prevention (maternal–infant probiotics)** and early **pilot FMT studies**.

5.2.2 Strengths and Weaknesses of Current Evidence

The major strength of literature is the growing number of RCTs and systematic reviews integrating both pediatric and adult populations. Prevention studies provide particularly robust evidence, with biologically plausible mechanisms (promotion of immune tolerance during early life).

However, **limitations** include:

- **Heterogeneity of interventions** (different strains, doses, and durations) limiting comparability [6–8].
- **Outcome variability**: SCORAD/EASI improvements are often modest and sometimes not clinically meaningful. Few studies incorporate mechanistic biomarkers.
- **Short follow-up**: Most studies last only 8–16 weeks, insufficient to assess long-term efficacy or safety.
- **Population differences**: Benefits are clearer in children than adults, suggesting age-dependent effects.

5.2.3 Clinical Implications

From a clinical standpoint, microbiome-targeted interventions should be viewed as **adjunctive therapies** rather than replacements for guideline-recommended treatments (topical corticosteroids, calcineurin inhibitors, biologics such as dupilumab, and JAK inhibitors) [16]. For prevention, maternal–infant probiotic supplementation may be considered in high-risk families, as endorsed by WAO guidelines. For treatment, probiotics and synbiotics may offer modest benefits in pediatric patients but should be trialed with realistic expectations.

Dietary interventions, particularly Mediterranean-style diets and fermented foods, are low risk, confer additional cardiometabolic benefits, and should be encouraged. Conversely, restrictive elimination diets without proven food allergy should be avoided due to nutritional risks [17].

FMT remains experimental but represents a promising therapeutic frontier. With early RCTs showing clinical benefit, larger trials with longer follow-up are warranted before clinical adoption.

5.2.4 Future Research Directions

Key gaps remain, including:

- Strain-specific probiotic identification and standardization of formulations.
- Integration of clinical and mechanistic biomarkers in trials (e.g., cytokines, SCFA levels, metagenomic profiling).
- Long-term safety monitoring, particularly for FMT and postbiotics.
- Personalized microbiome approaches using omics-based profiling to guide therapy.

These directions align with precision medicine trends, where treatments are tailored to an individual's microbiome composition and immune profile.

6. Conclusion

Atopic dermatitis (AD) remains a complex and burdensome condition shaped by genetic, environmental, immunological, and microbial factors. Increasing evidence highlights the central role of the **gut microbiome** in its pathogenesis through mechanisms such as reduced microbial diversity, depletion of SCFA-producing taxa, impaired tryptophan metabolism, and increased intestinal permeability. These alterations influence systemic immune balance and skin barrier function, thereby reinforcing the concept of the **gut–skin axis**.

Intervention studies provide promising but mixed results. **Probiotics** show the most consistent benefit in prevention, particularly when administered during both pregnancy and infancy in high-risk populations, whereas treatment outcomes in established AD are modest and strain-specific. **Prebiotics and synbiotics** demonstrate potential but require larger, standardized trials. Dietary strategies, including **Mediterranean-style diets and fermented foods**, are safe, feasible, and supportive of microbial diversity, while restrictive elimination diets without confirmed allergy are discouraged due to nutritional risks. **Fecal microbiota transplantation (FMT)**, although experimental, has shown clinically meaningful improvements in moderate-to-severe AD in recent trials, warranting further exploration under strict regulatory frameworks.

Taken together, microbiome-targeted interventions should be viewed as **adjuncts** rather than substitutes for guideline-directed therapies such as biologics and JAK inhibitors. Their integration into care pathways should be individualized, based on patient age, disease severity, and risk profile.

Future research must prioritize **strain-specific probiotic identification**, **biomarker standardization**, and **long-term safety assessments**, alongside advancing **personalized microbiome profiling** for precision dermatology. By bridging mechanistic insights with robust clinical evidence, microbiome modulation may emerge as a safe and durable strategy to reduce AD burden, improve quality of life, and complement existing therapeutic approaches.

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