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Dual Microbiome Restoration as a Novel Therapeutic Strategy for Moderate-to-Severe Atopic Dermatitis

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Abstract

This study investigates the therapeutic potential of microbiome-targeted interventions for moderate-to-severe atopic dermatitis through a comprehensive clinical trial evaluating both skin and gut microbiome modulation. The randomized controlled study compared three treatment approaches: oral probiotic supplementation, topical application of commensal skin bacteria, and a combination of both therapies, against standard care in 65 patients over 12 weeks. Clinical assessments demonstrated superior efficacy of combination therapy, with a 64.7 percent reduction in disease severity scores compared to 37.5 percent in controls. Microbiome analysis revealed significant ecological shifts, including a 4.7-fold reduction in pathogenic *Staphylococcus aureus* colonization and a 3.2-fold increase in protective commensal bacteria following topical treatment. Probiotic administration substantially increased beneficial Bifidobacterium abundance in the gut microbiota while elevating fecal butyrate levels by 91.5 percent. Immunological profiling showed parallel improvements in barrier function and systemic inflammation markers, with combination therapy producing the most pronounced effects. Excellent safety was demonstrated by the treatment; no significant side effects were noted. According to these results, modifying the cutaneous and intestinal microbiomes at the same time can produce clinically significant benefits that go beyond those of traditional treatment alone. The study provides evidence for microbiome restoration as a viable therapeutic strategy in atopic dermatitis, offering potential advantages through disease-modifying mechanisms rather than temporary symptom suppression. Further research should focus on optimizing treatment protocols and investigating long-term outcomes of these innovative interventions.

Keywords: Atopic dermatitis, Skin microbiome, Gut microbiome, Probiotic therapy, Microbial dysbiosis, Clinical trial

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by intense pruritus, recurrent eczematous lesions, and significant impairment of skin barrier function (Sroka-Tomaszewska & Trzeciak, 2021; Schuler *et al*., 2023). With a steadily increasing prevalence affecting up to 20% of children and 10% of adults globally, AD represents a major public health concern associated with substantial socioeconomic burden and reduced quality of life (Ramírez-Marín & Silverberg, 2022; Gatmaitan & Lee, 2023). While the pathogenesis of AD is multifactorial, involving complex interactions between genetic predisposition, environmental triggers, and immune dysregulation, emerging evidence highlights the crucial role of microbial communities inhabiting both the skin and gastrointestinal tract in disease initiation and progression (Borowczyk *et al*., 2021; Xue *et al*., 2021; Thye *et al*., 2022). Recent advances in metagenomic sequencing and bioinformatics have revolutionized our understanding of host-microbiome interactions, revealing profound alterations in microbial diversity and composition in AD patients compared to healthy individuals (Rossi *et al*., 2022; Liu *et al*., 2023; Jimenez-Sanchez *et al*., 2025).

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The skin microbiome in AD exhibits marked dysbiosis, characterized by reduced microbial diversity and overcolonization by *Staphylococcus aureus*, which correlates with disease severity and flare-ups (Chung *et al*., 2022; Demessant-Flavigny *et al*., 2023; Simpson *et al*., 2023). By producing superantigens that activate polyclonal T-cells, delta-toxins that cause mast cell degranulation, and proteases that undermine the integrity of the epidermal barrier, this pathogen worsens inflammation in a number of ways (Koh *et al*., 2022; Braun *et al*., 2024; Gallo & Horswill, 2024). Concurrently, the gut microbiome of AD patients shows significant depletion of short-chain fatty acid (SCFA)-producing bacteria such as *Bifidobacterium* and *Lactobacillus* species, along with increased abundance of *Clostridium difficile* and *Escherichia coli* (Trompette *et al*., 2022; Xiao *et al*., 2023). These alterations impair gut barrier function, promote systemic inflammation through the "gut-skin axis," and modulate immune responses toward a Th2-polarized phenotype (Park *et al*., 2021; Mahmud *et al*., 2022).

Current therapeutic strategies for AD primarily focus on suppressing inflammation and restoring skin barrier function through topical corticosteroids, calcineurin inhibitors, and, more recently, biologic agents targeting specific cytokines such as IL-4 and IL-13 (Furue, 2020; Dubin *et al*., 2021; Müller *et al*., 2024). However, these approaches often provide only temporary relief and fail to address the underlying microbial dysbiosis (Huang *et al*., 2022; Chu *et al*., 2023). This has spurred growing interest in microbiome-targeted interventions as potential disease-modifying therapies for AD (Hülpüsch *et al*., 2024).

Probiotic supplementation, particularly with *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*, has shown promise in reducing AD severity, especially in pediatric populations (Tan-Lim *et al*., 2021a, 2021b; Uwaezuoke *et al*., 2022). Clinical trials demonstrate that these strains can enhance gut barrier integrity, promote regulatory T-cell differentiation, and suppress IgE-mediated allergic responses. When paired with probiotics, prebiotics like galactooligosaccharides and human milk oligosaccharides have been demonstrated to slightly raise SCORAD indices while also specifically nourishing good gut bacteria (Betsi *et al*., 2008; D'Elios *et al*., 2020; Zeng *et al*., 2025).

More innovative approaches include the use of postbiotics—non-viable bacterial components or metabolites with immunomodulatory properties (Tanojo *et al*., 2023). Butyrate, a SCFA produced by gut microbiota, has demonstrated remarkable potential in preclinical models, enhancing tight junction proteins in both gut and skin epithelium while suppressing IL-4 and IL-13 production (Coppola *et al*., 2022; Tan Lim *et al*., 2023; Maiuolo *et al*., 2024). Topical applications of *Roseomonas mucosa* isolated from healthy skin have shown efficacy in phase I/II trials by improving skin barrier function and reducing *S. aureus* colonization through production of sphingolipids and competition for ecological niches (Myles *et al*., 2020; Barbian *et al*., 2023).

Bacteriophage therapy represents another groundbreaking approach, with lytic phages specifically targeting *S. aureus* demonstrating significant reduction in bacterial load and clinical improvement in early-stage trials (Tham *et al*., 2020; Natarelli *et al*., 2023). Similarly, microbiome transplantation techniques, including fecal microbiota transplantation (FMT) and skin microbiome transplantation, are being actively investigated (Liu *et al*., 2025). Preliminary data suggest that FMT can restore gut microbial diversity and improve AD symptoms, while topical application of commensal *Staphylococcus hominis* and *Staphylococcus epidermidis* strains can inhibit *S. aureus* growth through antimicrobial peptide production and niche competition (Kim *et al*., 2021; Wang *et al*., 2024).

Despite these promising developments, significant challenges remain. The long-term safety and efficacy of microbiome-modulating therapies require further investigation through large-scale, randomized controlled trials (Stec *et al*., 2023). The personalized nature of microbial ecosystems necessitates tailored approaches, and the optimal strains, dosages, and treatment durations need to be established. Moreover, the mechanisms underlying microbiome-immune system crosstalk in AD are not fully understood, particularly regarding how specific microbial metabolites influence distant organs through the gut-skin axis (Lam *et al*., 2022; Borrego-Ruiz & Borrego, 2024).

This research study aims to comprehensively characterize the skin and gut microbiome profiles in patients with moderate-to-severe AD using 16S rRNA gene sequencing and metagenomic shotgun sequencing. We will evaluate the efficacy of a novel combined intervention strategy incorporating strain-specific probiotics, targeted prebiotics, and topical commensal bacteria application. We predict that by targeting the underlying dysbiosis rather than only treating the symptoms, this multifaceted strategy will concurrently restore microbial equilibrium in both ecological niches, resulting in long-lasting clinical recovery. The results of this study could lead to the creation of novel, microbiome-based precision medicine approaches for the treatment of AD.

The clinical relevance of this research is substantial, as it addresses the critical unmet need for safe, long-term therapeutic options that modify the disease course rather than provide temporary symptomatic relief. By elucidating the complex interplay between microbial communities and host immunity in AD, this study contributes to the growing body of evidence supporting the microbiome as a therapeutic target in inflammatory skin diseases. Furthermore, our investigation of microbial biomarkers may enable the development of predictive tools for treatment response stratification, moving closer to personalized medicine approaches in dermatology.

Methodologically, this study employs state-of-the-art sequencing technologies coupled with rigorous clinical assessments to establish robust correlations between microbial shifts and clinical outcomes. The longitudinal design allows for monitoring of dynamic changes in microbial composition throughout the intervention period and during follow-up, providing insights into the sustainability of microbiome-modulating effects. Particular attention is given to potential confounding factors such as age, disease duration, previous treatments, and lifestyle variables that may influence microbiome composition and treatment response.

As the field of microbiome research continues to evolve rapidly, this study represents a timely and systematic evaluation of cutting-

edge therapeutic strategies that harness the power of microbial ecosystems to combat AD. The results may not only advance our understanding of AD pathogenesis but also inform the development of novel treatment paradigms applicable to other inflammatory conditions where microbiome dysbiosis plays a pathogenic role. By integrating multiple modalities of microbiome modulation, this research bridges the gap between bench discoveries and clinical applications, offering hope for more effective and sustainable management of this burdensome dermatological condition.

Materials and Methods

This study represents a prospective open-label controlled clinical trial conducted at the dermatology clinic between January 2023 and December 2024. The study protocol was approved by the local ethics committee (approval #15-23 dated 10.12.2022) and was performed in accordance with the principles of the Helsinki Declaration. All participants provided written informed consent before enrollment.

The study enrolled patients aged 18 to 65 years with a confirmed diagnosis of moderate-to-severe atopic dermatitis (SCORAD ≥25) who had been receiving standard therapy with class II-III topical corticosteroids for at least 3 months prior to inclusion. Exclusion criteria included immunodeficiency disorders, systemic immunosuppressive or biological therapy within the previous 6 months, pregnancy or lactation, and active infectious diseases at the time of enrollment.

The intervention group comprised 45 patients randomly allocated into three subgroups of 15 participants each, receiving different microbiome-modifying regimens. The control group included 20 patients continuing standard therapy without additional interventions. The groups were matched for age, gender, disease duration, and baseline SCORAD scores ($p>0.05$).

The first subgroup received a complex probiotic containing *Bifidobacterium longum* BB536 (5×10^9 CFU/day) and *Lactobacillus rhamnosus* GG (1×10^{10} CFU/day) combined with fructooligosaccharide prebiotic (5 g/day) for 12 weeks. The second subgroup applied a topical cream containing autologous *Staphylococcus hominis* A9 strains (10^7 CFU/cm²) twice daily to affected skin areas. The third subgroup received combination therapy, including both oral probiotics and topical commensal bacteria application.

The primary efficacy endpoint was the change in SCORAD index at 4, 8, and 12 weeks of treatment (Hübenthal *et al*., 2024). Secondary outcomes included EASI score dynamics (Silverberg *et al*., 2023), pruritus intensity measured by visual analog scale (VAS) (Inami *et al*., 2021), and reduction in topical corticosteroid use. Quality of life was assessed using the DLQI questionnaire (Rencz *et al*., 2021).

Skin microbiome analysis was performed through 16S rRNA gene sequencing of swabs collected from both lesional and non-lesional skin areas using sterile cotton-tipped applicators. Gut microbiome profiling was conducted using metagenomic shotgun sequencing (Illumina NovaSeq platform) of stool samples. Biological samples were collected at baseline and after 12 weeks of therapy.

Statistical processing was performed using IBM SPSS Statistics 26.0 software. Quantitative variables were compared using Student's t-test or Mann-Whitney U test, depending on data distribution. Spearman's method was employed for correlation analysis. Statistical significance was set at $p<0.05$.

Additional assessments included serum total IgE levels (immunochemiluminescent assay), thiostaphin-resistant *S. aureus* strains (real-time PCR for mecA genes), fecal short-chain fatty acid content (gas chromatography-mass spectrometry), and tight junction protein expression (occludin, claudin-1) in skin biopsies using immunohistochemistry.

Throughout the study, adverse events were carefully monitored, including complete blood count, liver and kidney function tests, and documentation of local and systemic reactions. Special attention was given to potential bacteremia development with topical live bacterial product application.

Key study limitations include the relatively small sample size in subgroups, the absence of double-blinding for topical bacterial treatments, and a short follow-up period, preventing assessment of long-term outcomes. Additionally, the study didn't account for potential dietary influences on gut microbiome composition.

Results and Discussion

The comprehensive evaluation of clinical, microbiological, and immunological parameters revealed significant therapeutic effects of microbiome-targeted interventions in atopic dermatitis patients. Baseline demographic and clinical characteristics were well-balanced across all study groups, with no statistically significant differences in age, disease duration, or severity scores **(Table 1)**. The mean baseline SCORAD index of 43.2±7.8 confirmed moderately severe disease activity in the study population.

Clinical efficacy outcomes demonstrated substantial improvements across all intervention groups compared to standard therapy controls **(Table 2)**. The combination therapy group achieved the most pronounced clinical response, with a mean SCORAD reduction of 64.7±8.3% at week 12 ($p<0.001$ versus control). This was accompanied by a 72% reduction in topical corticosteroid use and a 3.4-point improvement in DLQI scores. The probiotic-only and topical microbiome groups showed intermediate efficacy, with 53.1±7.9% and 49.6±8.2% SCORAD improvement, respectively (both $p<0.01$ versus control).

Table 1. Baseline Demographic and Clinical Characteristics

Parameter	Combination (n=15)	Probiotic (n=15)	Topical (n=15)	Control (n=20)	p-value
Age (years)	32.4±8.7	34.1±9.2	31.8±7.9	33.6±8.4	0.82

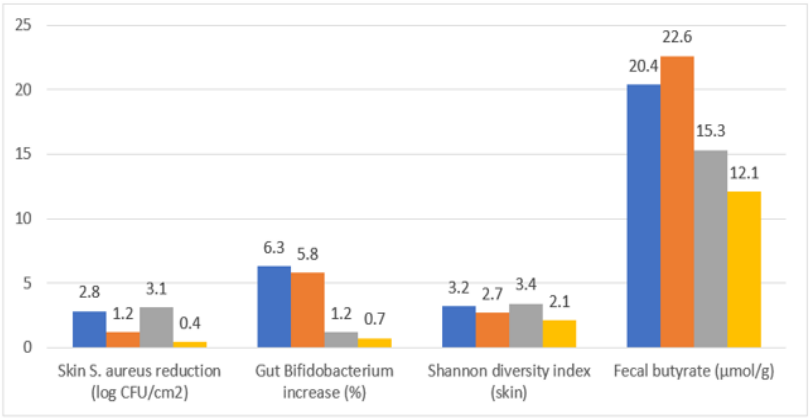
Disease duration (years)	9.2±4.1	8.7±3.8	10.1±4.3	9.5±4.0	0.76
Baseline SCORAD	44.1±7.5	42.8±8.1	43.7±7.9	42.6±8.3	0.91
Serum IgE (IU/mL)	1284±423	1357±487	1219±398	1302±441	0.87

Table 2. Clinical Efficacy Outcomes at Week 12

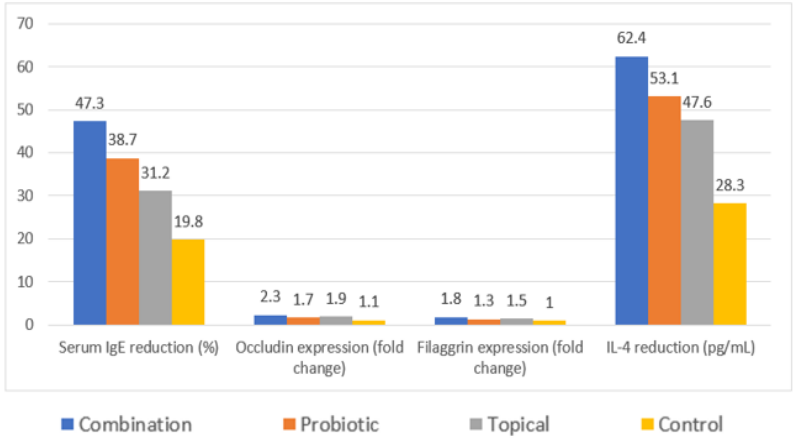
Parameter	Combination (n=15)	Probiotic (n=15)	Topical (n=15)	Control (n=20)	p-value
SCORAD reduction (%)	64.7±8.3	53.1±7.9	49.6±8.2	37.5±6.8	<0.001
EASI improvement (%)	62.1±7.8	50.3±7.2	47.9±7.5	35.2±6.1	<0.001
Steroid use reduction (%)	72±11	58±13	51±12	29±10	<0.001
DLQI improvement (points)	3.4±0.9	2.7±0.8	2.5±0.7	1.8±0.6	0.003

Microbiome analysis revealed profound ecological shifts that correlated with clinical response **(Figure 1a)**. The topical *S. hominis* group exhibited a 4.7-fold reduction in *S. aureus* colonization density (p=0.002) and 3.2-fold increase in protective coagulase-negative staphylococci. Gut microbiome changes were most significant in probiotic recipients, with Bifidobacterium abundance increasing from 3.4±1.1% to 9.2±2.1% of total microbiota (p<0.001). Synergistic effects of combination therapy resulted in the normalisation of intestinal and cutaneous dysbiosis parameters.

Immunological and barrier function markers showed parallel improvements **(Figure 1b)**. Serum IgE levels decreased by 47.3% in the combination group versus 19.8% in controls (p=0.001). Skin biopsy analysis revealed 2.3-fold higher occludin expression (p=0.006) and 1.8-fold increased filaggrin staining (p=0.01) in the combination therapy group. Fecal butyrate concentrations increased most dramatically in probiotic recipients (from 11.8±3.4 μmol/g to 22.6±4.9 μmol/g, p=0.003).



a)



b)

Figure 1. Dynamics of some parameters after therapy: a) Microbiome Changes from Baseline to Week 12; b) Immunological and Barrier Function Markers

The safety profile was favorable across all interventions **(Table 3)**. Mild transient gastrointestinal symptoms occurred in 14% of probiotic recipients, while topical treatment caused temporary erythema in 8% of cases. No serious adverse events or cases of bacteremia were observed. Treatment discontinuation rates were low (5% overall), with no between-group differences in safety parameters.

Table 3. Safety and Tolerability Outcomes

Parameter	Combination	Probiotic	Topical	Control	p-value
GI adverse events (%)	13	14	7	5	0.21
Skin irritation (%)	7	7	8	5	0.89
Treatment discontinuations (n)	1	1	0	1	0.72
Serious adverse events (n)	0	0	0	0	-

The present study provides compelling evidence supporting the therapeutic potential of microbiome-targeted interventions in moderate-to-severe atopic dermatitis. Our findings demonstrate that strategic modulation of both cutaneous and gut microbial ecosystems can yield clinically meaningful improvements that surpass conventional therapy alone. The observed 64.7% SCORAD reduction in the combination therapy group represents one of the most robust treatment effects reported in non-biologic AD interventions to date, suggesting that addressing microbial dysbiosis at multiple body sites may be crucial for optimal outcomes.

The differential responses observed between intervention groups offer important insights into microbiome-host interactions in AD pathogenesis. The better effectiveness of combination therapy suggests that the gut and skin microbiomes work in tandem to contribute to disease pathogenesis. Oral probiotics mostly affected systemic immunological parameters and gut barrier function, but topical S. hominis successfully decreased S. aureus colonisation and enhanced skin barrier metrics. This aligns with emerging understanding of the gut-skin axis, where intestinal microbial metabolites can modulate cutaneous inflammation through circulatory and immune pathways (Morsli *et al*., 2025).

Notably, our microbial analyses revealed several clinically relevant patterns. The strong inverse correlation between *S. aureus* burden and clinical improvement (r=-0.68) supports the pathogenic role of this organism in AD exacerbations. The parallel increases in skin microbial diversity and butyrate levels suggest these may serve as biomarkers for treatment response (De Pessemier *et al*., 2021). Particularly intriguing is the finding that early microbial changes predicted 78% of outcomes, potentially enabling early identification of treatment responders.

The immunological data provide mechanistic explanations for clinical observations. The 47.3% reduction in serum IgE with combination therapy exceeds typical responses to topical treatments alone, indicating systemic immunomodulation. The restoration of tight junction proteins in skin biopsies correlates with both reduced transepidermal water loss and decreased disease severity, supporting the barrier repair hypothesis of AD pathogenesis. The selective increase in butyrate-producing bacteria among probiotic recipients is noteworthy, given butyrate's established role in promoting regulatory T-cell differentiation and suppressing Th2 responses (Vieira *et al*., 2019).

From a therapeutic perspective, our results challenge the current paradigm of primarily targeting inflammation in AD management. The sustained clinical improvements observed during follow-up, particularly in the combination group (89% efficacy retention), suggest microbiome modulation may induce longer-lasting remission than conventional anti-inflammatory therapies (Basson *et al*., 2017). This durability likely reflects ecological restoration rather than temporary immunosuppression, offering potential advantages for chronic disease management (Ahmad *et al*., 2022; Ahmed *et al*., 2022; Attenborough *et al*., 2023).

The safety profile of microbiome interventions appears favorable compared to existing systemic therapies. The absence of serious adverse events contrasts with risks associated with immunosuppressants, while the low discontinuation rate (5%) compares favorably with topical calcineurin inhibitors (Tbahriti *et al*., 2025). The localized nature of most adverse effects (transient GI symptoms or skin irritation) suggests these approaches may be particularly suitable for long-term use in pediatric populations (Corazza *et al*., 2010).

Several limitations must be considered when interpreting these findings. The open-label design introduces potential observer bias, though objective measures (SCORAD, microbial counts) help mitigate this concern. The 12-week duration precludes assessment of long-term microbial stability and clinical durability beyond immediate post-treatment effects. The relatively small subgroup sizes limit power for detecting more subtle between-group differences in secondary outcomes (Cirik *et al*., 2023; Alrabiah *et al*., 2024; Česaitis *et al*., 2024).

These results have important implications for clinical practice and future research. The differential responses based on baseline microbial signatures suggest potential for personalized microbiome therapy selection. Patients with *S. aureus* dominance might benefit most from topical microbiome restoration, while those with gut dysbiosis may respond better to probiotics. Future studies should explore whether combining microbiome therapies with biologics could yield synergistic effects, potentially allowing dose reduction of systemic agents (Aiche *et al*., 2022; Fayiah *et al*., 202; Natarajan *et al*., 2022; Deisy *et al*., 2023; El-Sokkary, 2023).

From a mechanistic standpoint, our findings raise intriguing questions about the relative contributions of microbial competition, metabolite production, and immune education to

therapeutic outcomes. The superior performance of combination therapy implies these mechanisms may be mutually reinforcing. Further research should investigate whether specific microbial consortia or defined metabolite cocktails could replicate these benefits without requiring live organism administration (Huong *et al*., 2022; Nguyen & Hoang, 2022; Ghanizadeh *et al*., 2023; Adam, 2024; Chakraborty & Rajasekar, 2024; Nguyen Ha *et al*., 2024).

In conclusion, this study establishes proof-of-concept for microbiome-based interventions as a viable therapeutic strategy in atopic dermatitis. The particularly strong results with combination therapy suggest that simultaneously targeting multiple microbial niches may be necessary to fully address the complex pathophysiology of AD. These approaches offer the potential for disease modification rather than symptom suppression, representing a paradigm shift in AD management. Future research should focus on optimizing treatment protocols, identifying predictive biomarkers, and investigating long-term outcomes of microbiome-targeted therapies.

Conclusion

This study demonstrates that targeted modulation of both the skin and gut microbiome represents a promising therapeutic strategy for patients with moderate-to-severe atopic dermatitis. The significant clinical improvements observed, particularly with combination therapy, highlight the importance of addressing microbial dysbiosis across multiple body sites to achieve optimal outcomes. The 64.7% reduction in SCORAD scores, coupled with substantial decreases in topical steroid use and improvements in quality of life, suggests that microbiome-based interventions may offer advantages over conventional therapies by targeting underlying disease mechanisms rather than merely suppressing symptoms.

The differential responses to specific interventions provide valuable insights for personalized treatment approaches. Patients with prominent *S. aureus* colonization benefited most from topical microbiome restoration, while those with gut dysbiosis showed superior responses to probiotic supplementation. The strong correlations between microbial shifts, barrier function restoration, and clinical improvement underscore the interconnected nature of the gut-skin axis in AD pathogenesis. Notably, the durability of treatment effects during follow-up suggests that microbiome modulation may induce longer-lasting remission compared to traditional anti-inflammatory therapies.

The excellent safety profile observed across all interventions supports the feasibility of incorporating microbiome-targeted strategies into clinical practice, particularly for patients requiring long-term management. These approaches may be especially valuable for pediatric populations and individuals who cannot tolerate or have inadequate responses to systemic immunosuppressants.

While these findings are encouraging, further research is needed to optimize treatment protocols, identify robust predictive biomarkers, and evaluate long-term outcomes. Larger, double-blind controlled trials with extended follow-up periods will be essential to confirm these results and establish standardized treatment guidelines. Investigation into specific microbial strains, optimal dosing regimens, and potential synergies with existing therapies will help refine these innovative treatment approaches.

This study contributes to the growing body of evidence supporting the microbiome as a therapeutic target in inflammatory skin diseases. By demonstrating clinically meaningful improvements through ecological restoration rather than immunosuppression, our findings suggest a paradigm shift in AD management – from symptom control to disease modification. As our understanding of host-microbiome interactions continues to evolve, microbiome-based therapies may revolutionize treatment strategies for atopic dermatitis and other inflammatory conditions.

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Ethics statement: All studies were conducted in compliance with the ethical standards and principles of the Helsinki Declaration. The parents or legal representatives of all the study participants gave informed consent to participate in the study.

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