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The Impact of Topical Probiotic Lactobacillus plantarum on Skin Barrier Repair in Atopic Dermatitis

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Abstract

Topical probiotic formulations containing Lactobacillus plantarum have emerged as a promising intervention for enhancing skin barrier repair in atopic dermatitis (AD), a chronic inflammatory condition characterized by disrupted epidermal barrier function and heightened susceptibility to irritants and allergens. Lactobacillus plantarum exerts its therapeutic effects through multiple mechanisms, including modulation of the skin microbiome, suppression of pro-inflammatory cytokines, and promotion of epidermal barrier integrity. By rebalancing microbial diversity, L. plantarum reduces the overgrowth of pathogenic species such as Staphylococcus aureus, which are known to exacerbate inflammation and compromise barrier function in AD. Furthermore, L. plantarum enhances the production of key structural components of the epidermis, including ceramides and tight junction proteins, which are critical for maintaining barrier strength and preventing transepidermal water loss (TEWL). Preclinical and clinical studies have demonstrated significant improvements in key metrics of AD severity, such as reductions in erythema, pruritus, and TEWL, following the application of L. plantarum-enriched formulations. The probiotic also attenuates immune responses by downregulating Th2-mediated inflammation, thereby reducing the cycle of barrier disruption and inflammation that typifies AD. Emerging research suggests synergistic effects when L. plantarum is combined with conventional therapies such as corticosteroids and calcineurin inhibitors, providing a multifaceted approach to disease management. L. plantarum has been found to have tremendous potential as a non-invasive, adjunctive therapy that addresses both microbial and barrier dysfunctions in AD, paving the way for innovative treatment paradigms that target the root pathophysiology of AD.

1. Introduction

Atopic dermatitis (AD), or atopic eczema, is a chronic inflammatory skin disease marked by recurrent eczematous lesions and intense pruritus. It is the most prevalent chronic inflammatory skin condition, affecting approximately 13% of children and 7% of adults worldwide. The disease often manifests early in life, with 45% of cases presenting by six months of age, 60% by one year, and nearly 85% by five years (AAAAI/ACAAI JTF, 2024). AD has a strong genetic component and frequently coexists with other atopic conditions, including asthma and allergic rhinitis. Its pathophysiology involves a complex interplay of epidermal barrier dysfunction, immune dysregulation, and environmental influences. Notably, filaggrin deficiency compromises skin barrier integrity, while a skewed T helper 2 (Th2) cell-mediated immune response drives chronic inflammation. [1] Clinically, AD presents with erythema, edema, xerosis, excoriations, oozing, crusting, and lichenification, with pruritus as the hallmark symptom. [2] The disease follows a relapsing-remitting course and significantly affects quality of life, contributing to sleep disturbances and psychosocial stress for both patients and their families. Recognizing the substantial burden of

AD, the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology underscore the importance of early diagnosis and individualized management strategies to optimize patient outcomes. [3]

Atopic dermatitis is characterized by impaired epidermal barrier function and immune dysregulation. Its pathophysiology arises from a complex interplay of genetic, immunological, and environmental factors. A key contributor to barrier dysfunction in AD is genetic mutations, particularly in the filaggrin gene, which plays a critical role in maintaining skin integrity. This disruption results in increased transepidermal water loss, skin dryness, and heightened permeability to allergens and microbes. Additionally, deficiencies in other structural proteins and lipids, such as claudin-1 and acyl ceramides, further exacerbate barrier impairment. [4] Immune dysregulation in AD is primarily driven by an imbalance in T helper (Th) cell responses. Th2 cytokines, including IL-4, IL-13, and IL-31, promote inflammation and pruritus, while keratinocytes in the compromised epidermis release pro-inflammatory mediators such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. These cytokines activate type 2 innate lymphoid cells and dendritic cells, reinforcing the Th2-skewed immune response. In chronic AD lesions, Th1 and Th17/22 cells also play a role, though their precise contributions remain less well-defined. [3] The American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology emphasize the need for targeted therapies that address both skin barrier restoration and immune modulation.

In atopic dermatitis, the compromised skin barrier creates an environment that disrupts the skin microbiome, favoring the overgrowth of Staphylococcus aureus (S. aureus). This pathogen is frequently detected in high abundance on the skin of AD patients, particularly during disease flares, and is strongly associated with reduced microbial diversity. [5] The overrepresentation of S. aureus not only alters the skin's microbial composition but also exacerbates AD pathogenesis through multiple mechanisms. It produces virulence factors such as toxins and proteases, which further degrade the already impaired skin barrier, trigger immune activation, and amplify inflammatory responses. [6] Additionally, S. aureus biofilms contribute to chronic inflammation and resistance to antimicrobial therapies, complicating disease management. Dysbiosis in AD is not only marked by the dominance of S. aureus but also by a significant decline in beneficial commensal bacteria, which normally help regulate the microbial environment and inhibit pathogenic colonization. Certain commensal species, including Staphylococcus epidermidis and Roseomonas mucosa, play a protective role by producing antimicrobial peptides and modulating immune responses. These beneficial microbes can suppress S. aureus proliferation through mechanisms such as quorum sensing, competitive exclusion, and the production of bacteriocins. [7] The reduction in microbial diversity and depletion of protective bacteria have been correlated with increased disease severity and persistent inflammation in AD. [8] Given the crucial role of the skin microbiome in AD pathophysiology, therapeutic strategies aimed at restoring microbial balance have gained increasing attention. Approaches such as prebiotics, probiotics, and postbiotics seek to enhance the growth of beneficial microbes while suppressing S. aureus colonization. Additionally, direct anti-staphylococcal interventions, including targeted antimicrobial peptides and bacteriophage therapy, are being explored as potential treatments to improve skin barrier function and reduce disease flares. [9] As research into microbiome-targeted therapies continues to evolve, understanding the interplay between microbial communities and skin barrier integrity may offer novel insights into optimizing AD management.

Topical probiotic therapy offers several advantages in dermatology, particularly in managing inflammatory skin conditions such as atopic dermatitis, acne, and psoriasis. A primary benefit is its ability to restore the skin microbiome, which is often disrupted in these conditions. In AD, an overabundance of Staphylococcus aureus contributes to inflammation, barrier dysfunction, and disease flares. Probiotic application can help suppress S. aureus colonization while enhancing microbial diversity, promoting a healthier skin environment. [10] Beyond microbiome modulation, certain probiotic strains exhibit direct antimicrobial activity. Lactobacillus species, for example, produce organic acids and bacteriocins that inhibit pathogenic bacteria and prevent biofilm formation, offering therapeutic potential in conditions such as acne and AD. [11] Additionally, probiotics modulate immune responses by downregulating pro-inflammatory cytokines like IL-6, IL-8, and TNF-α, while

enhancing regulatory pathways that help restore skin homeostasis. [12] Probiotics also play a crucial role in reinforcing skin barrier function. By increasing ceramide production, improving hydration, and reducing transepidermal water loss (TEWL), probiotic formulations help strengthen the stratum corneum and accelerate wound healing. These barrier-enhancing properties make probiotics particularly beneficial for individuals with sensitive or compromised skin, as seen in AD and other inflammatory dermatoses. [13] Unlike conventional treatments such as corticosteroids or antibiotics, probiotics have a favorable safety profile, with minimal adverse effects, making them a promising long-term therapeutic option for chronic skin conditions. [14]

Among probiotic species, Lactobacillus plantarum has demonstrated significant dermatologic benefits, particularly in the management of inflammatory skin conditions and infections. Specific strains such as Lactobacillus plantarum HD02 and MD159 have shown preventive and therapeutic effects in mouse models of AD by inhibiting mast cell degranulation, reducing vascular permeability, and decreasing allergy biomarkers, including MCPT-1 and total IgE. Additionally, these strains modulate immune responses by increasing splenic Foxp3+ regulatory T cells and reducing immune cell accumulation in draining lymph nodes, indicating a role in immune regulation and inflammation control. [15] Given its ability to restore microbial balance, regulate immune responses, and enhance skin barrier function, Lactobacillus plantarum represents a promising candidate for probiotic-based dermatologic therapies. Further research into its mechanisms and clinical applications may provide valuable insights into optimizing its use for AD and other chronic inflammatory skin conditions.

2. Mechanisms of Action of Lactobacillus Plantarum

Lactobacillus Plantarum has a broad array of mechanisms including microbiome modulation in both the skin and gut. The lipoteichoic acid component of *L. Plantarum* has been shown to contribute to its anti-inflammatory effects. [16] For example, in B16F10 (murine melanoma) cells, the lipoteichoic acid of *L. Plantarum*-GMNL6 was shown to decrease biofilm formation by *S. Aureus* dose-dependently. [17] Topical application of heat-killed *L. Plantarum*-GMNL6 and subsequent 16S rDNA-based sequencing revealed significantly decreased proliferation of Propionibacterium, but increased prevalence of *Streptococcus* and *Staphylococcus* in the skin microbiome. [17] Taken together, these findings suggest that *L. Plantarum* may influence the microbiome of healthy skin and melanoma cells differently, suggesting the need for further elucidation of the particular mechanism used in various skin cell lines. In the gut, improvement of the microbiome after *L. Plantarum*-HY7714 consumption led to downregulation of several inflammatory mediators known to affect both the gut and the skin. [18] This indicates that microbiome modulation by *Lactobacillus Plantarum* in the gut may impact inflammation of the skin.

Another way in which *Lactobacillus Plantarum* modulates the microbiome in atopic dermatitis is via suppression of pathogenic species. *S. aureus* has been shown to be a predominant organism in skin cultures of AD patients. [19] In fact, *S. aureus* is higher during AD flares, correlates to more severe disease, and is reduced post-treatment. [20] This suggests that *S. aureus* plays a crucial role in the dysbiosis contributing to AD pathogenesis. *In vitro* studies conducted by Kim et al. found that when *L. Plantarum* extracellular vesicles were administered prior to *S. aureus* extracellular vesicles, *L. Plantarum* was able to decrease IL-6 secretion and improve cell viability in keratinocytes in a dose-dependent manner (Kim 2018). Notably, the *L. Plantarum* was unable to decrease keratinocyte IL-6 production when administered simultaneously with *S. aureus*. [21] This suggests that *Lactobacillus Plantarum* may be more useful in pathogen suppression when applied as a means of prophylaxis prior to pathogen inoculation.

3. Anti-inflammatory Effects

The pathogenesis of atopic dermatitis involves breakdown of the epidermal skin barrier, allergen and pathogen propagation, and subsequent upregulation of CD4+ T-cells and cytokines. [22] In particular, there is notable elevation of Th2-mediated cytokines, indicating that the Th2 response plays a key role in the pathogenesis of AD. [23] *L. Plantarum* has been shown to regulate production of both Th1- and Th2-mediated cytokines, highlighting its potential as a treatment for AD. [24] *L. Plantarum* lysates prepared via sonication dramatically reduced TNF-α production induced by lipopolysaccharides in a dose-dependent manner in THP-1 (human monocyte) cells, indicating that *L. Plantarum* can suppress the Th1 response.

By contrast, *L. Plantarum* lysates administered in mice induced the Th1 response via upregulation of IL-12 and IFN-Ɣ and simultaneous downregulation of the Th2 response via inhibition of IL-4 and IgE. [24] Hence, *L. Plantarum*'s clinical utility may stem from its ability to alter the dysfunctional Th1/Th2 balance in atopic dermatitis. However, given that it has been shown to both suppress and induce the Th1 response and to suppress the Th2 response, further research into the particular immunosuppressive mechanisms utilized by *Lactobacillus Plantarum* is needed.

4. Enhancement of Epidermal Barrier Integrity

Lactobacillus Plantarum has also been shown to enhance epidermal barrier integrity via regulation of ceramide and serine palmitoyltransferase (SPT) levels. The epidermal permeability barrier is composed of ceramides, free-fatty acids, and cholesterol, and contributes to the prevention of both water loss as well as entry of foreign substances into the skin. [25] Ceramides, also known as acyl-sphingosines, have been known to play a key role in the structure and function of the mammalian epidermal permeability barrier, comprising approximately 40% of the lipid composition in the stratum corneum. [26] A lack of acid ceramidase and ceramide for production of antimicrobial sphingosines has been highlighted as a key contributor to pathogenic bacterial colonization of the stratum corneum in AD. [27] This highlights ceramides as potential targets for treatment of AD. Similarly, the mRNA of serine palmitoyltransferase (SPT), an enzyme which promotes sphingosine synthesis and homeostasis of the epidermal barrier [28], is upregulated by *L. Plantarum*. [29] *In vivo*, *L. Plantarum*-HY7714 given to mice orally suppressed transepidermal water loss, dehydration, and epidermal thickening induced by UVB exposure. [29] Given the crucial role of ceramides and SPTs in the epidermal barrier, *L. Plantarum*'s ability to modulate the gene expression of these two compounds may partially explain its ability to produce improved clinical outcomes upon UVB exposure. This warrants further investigation into *Lactobacillus Plantarum'*s potential to restore epidermal barrier integrity in atopic dermatitis.

5. Evidence from Preclinical and Clinical Studies

5.1. Preclinical Evidence

The potential of Lactobacillus plantarum in treating atopic dermatitis (AD) has shown remarkable promise in laboratory studies. Recent research has uncovered fascinating insights into how this beneficial bacterium influences the body's internal mechanisms through multiple pathways, particularly in supporting immune system balance and helping repair the skin's protective barrier.

A groundbreaking mouse study by Kim and colleagues (2022) revealed something particularly exciting: L. plantarum didn't just improve AD symptoms – it did so in a way that directly corresponded to the amount used. Their findings showed that the probiotic reduced skin inflammation, epidermal thickness and decreased the number of problematic mast cells. [30] Perhaps most interesting, it helped rebuild the skin's natural defenses by boosting the production of essential proteins like filaggrin and loricrin, which act as the skin's natural moisturizing factors and are essential for skin integrity.

What makes L. plantarum especially interesting is its sophisticated approach to immune system regulation. Rather than simply suppressing inflammation, it helps restore balance by fine-tuning the immune response – dampening down overactive Th2 responses while supporting protective Th1 responses. [30] This nuanced approach tackles one of the root causes of atopic dermatitis.

In another fascinating development, researchers have discovered that L. plantarum produces tiny bubble-like structures called bacterial extracellular vesicles (EVs). Kim et al. (2018) found that these EVs could help protect against skin inflammation caused by Staphylococcus aureus, a common trigger for AD flare-ups. [31] When they tested these vesicles in skin cells, they noticed significant decreases in inflammatory signals and improved cell health, pointing to a potential new treatment approach.

The ways L. plantarum helps improve AD symptoms involve several interconnected mechanisms. It works by restoring balance to the immune system through careful modulation of T helper cell responses while also strengthening the skin's protective barrier by encouraging the production of crucial structural proteins. Additionally, this beneficial bacterium reduces the influx of inflammatory cells into affected skin areas and lowers the production of substances that drive inflammation.

These laboratory findings suggest that L. plantarum offers a comprehensive approach to managing AD, addressing both its immune and structural aspects. This makes it particularly promising as a treatment that could complement or improve upon traditional therapies.

5.2. Clinical Trials - Oral administration

Moving from lab studies to real-world applications and beginning with oral administration, several well-designed clinical trials have explored how L. plantarum affects people with atopic dermatitis. Fang and colleagues (2020) examined the probiotic's effects on gut bacteria and immune responses in AD patients. [32] Their findings were encouraging: L. plantarum treatment notably improved the diversity of gut bacteria and, more importantly, reduced disease severity as measured by the SCORAD index while boosting levels of the anti-inflammatory molecule IL-10.

A comprehensive review by Fijan's team (2023) analyzed seventeen high-quality clinical trials involving over 1,100 children, revealing fascinating insights into how different probiotic strains affect AD symptoms. Their analysis showed that single-strain lactobacilli probiotics significantly improved AD symptoms compared to placebo treatments, but perhaps more importantly, they uncovered important differences between specific strains. [33] Limosilactobacillus fermentum emerged as the standout performer, demonstrating notably better results than other tested strains including Lactiplantibacillus plantarum, Lacticaseibacillus paracasei, and Lacticaseibacillus rhamnosus.

Adding to this evidence, Prakoeswa's group (2023) studied a specific strain, L. plantarum IS-10506, in adults with AD. After eight weeks, participants taking the probiotic showed marked improvements in their symptoms, including reduced redness and itching. [34] The researchers also noted an increase in regulatory T cells, suggesting the probiotic was helping to calm overactive immune responses.

A thorough analysis by Izzati and colleagues (2022) looked at multiple clinical trials and found consistent improvements in AD severity scores with L. plantarum treatment. [35] While the probiotic showed clear benefits in reducing local inflammation and improving immune markers, its effects on overall allergy levels (measured by IgE) varied between studies. This suggests it might work better at addressing skin symptoms directly rather than affecting broader allergic tendencies.

5.3. Clinical Trials - Topical administration

The therapeutic use of Lactobacillus strains for atopic dermatitis (AD) has historically focused on oral administration, with topical applications being a relatively newer and less explored approach. However, emerging research suggests topical probiotics, including L. plantarum, may offer unique benefits for AD treatment through direct interaction with the skin microbiome and barrier function. [10]

A key study by Tsai et al. (2021) demonstrated that L. plantarum GMNL6 showed promising effects on human skin health by improving the skin microbiome composition. [17] The strain helped regulate skin barrier function and demonstrated beneficial effects that could be relevant for AD management, including increased collagen synthesis and improved skin barrier markers.

Recent investigations have highlighted the importance of microbiome dysbiosis in AD pathogenesis, with AD patients showing increased S. aureus colonization and decreased bacterial diversity. [10] While not all studies specifically examine L. plantarum, research on other Lactobacillus strains provides encouraging evidence for topical probiotic therapy in AD. For example, studies have shown that Lactobacillus reuteri DSM 17938-containing ointment can improve symptoms in adults with atopic dermatitis, with significant reductions in SCORAD index (-46%) and local SCORAD (-45%) scores after 8 weeks of topical application. [36] This research demonstrated that topical probiotics can be safe and effective for treating AD symptoms while potentially helping to restore skin barrier function.

Mechanistic studies have revealed that L. plantarum's cell wall components, particularly lipoteichoic acid (LTA), may play essential roles in its therapeutic effects. [17] This suggests that even heat-killed preparations could provide benefits while avoiding concerns about applying live bacteria to compromised skin, as demonstrated in studies by Joo et al. (2009) where fermented herbs with L. plantarum showed significant therapeutic advantages for AD treatment. [37] Recent research has also shown that topical probiotics can influence key inflammatory pathways involved in AD pathogenesis. Fusco et al. (2023) demonstrated that L. plantarum can counteract the harmful

effects of skin pathogens by modulating inflammatory responses and improving barrier integrity [38], suggesting multiple mechanisms by which topical application could benefit AD patients.

While direct evidence for topical L. plantarum in AD remains limited compared to oral administration studies, the demonstrated effects on skin barrier function, microbiome modulation, and inflammation make it a promising candidate for further investigation as an AD treatment. Additional large-scale clinical trials are needed to fully evaluate its efficacy and optimize delivery methods for AD applications.

5.4. Comparative Efficacy with Conventional Therapies

Conventional therapeutic approaches for atopic dermatitis (AD) involve trigger avoidance and the use of topical agents for symptom management. Mild to moderate AD is generally treated with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI), effectively controlling inflammation and pruritus through their immunosuppressive properties. [39] TCS tends to be a first-line treatment, while TCIs such as tacrolimus and pimecrolimus may be used as adjunct therapy alongside corticosteroids or as second-line treatment for moderate to severe cases. [40] Although they have different mechanisms of action, both TCS and TCI aid in restoring the epithelial skin barrier by regulating filaggrin and loricrin expression. [41]This is essential for maintaining skin integrity and reducing susceptibility to external irritants and pathogens. Despite their efficacy, chronic use of corticosteroids can result in skin thinning and possible hypothalamic-pituitary-adrenal axis suppression if absorbed systemically, while TCIs carry lingering concerns about malignancy risks. [39, 41] Moreover, conventional therapies primarily target inflammation without addressing the underlying dysbiosis of the skin microbiome, a critical factor in AD pathogenesis. [42] Kwon et al. notes that patients with AD have decreased bacterial diversity with greater *Staphylococcus aureus* burdens positively correlating with disease severity. [43] Yet, current treatments do not directly modulate the microbial environment which draws growing interest toward the use of topical probiotics for their potential synergistic properties for combating AD.

Probiotic interventions, particularly with strains like *Lactobacillus plantarum*, offer a promising adjunct by restoring microbial balance, enhancing barrier integrity, and providing immunomodulatory benefits. [44] *L. plantarum* helps reduce the risk of new AD onset and recurrence by modulating Th1 and Th2 cytokine responses. [45] Since a predominance of Th2 over Th1 cells is seen in AD, *Lactobacillus* sp. encourages the rebalance of the adaptive immune response by reducing IgE, IL-4, and IL-17 levels while suppressing Th2. [34] These immunomodulatory effects complement existing treatments by regulating host immune defenses and inhibiting inflammatory reactions without the negative side effects TCS and TCI have. Additionally, the introduction of topical probiotics can encourage commensal skin microorganisms to overcome the competing growth of pathogens like *Staphylococcus aureus* which exacerbate AD. [42] When used in conjunction with conventional therapies, *L. plantarum* has the potential to enhance treatment efficacy and decrease the reliance on corticosteroids. This integrative approach addresses both the immunological and microbiome-related aspects of AD, paving the way for a more comprehensive management strategy.

5.5. Broader Implications of Probiotic Therapy in Dermatology

5.5.1. Applications Beyond AD

The use of probiotics in dermatology is a growing area of research with applications spanning beyond just atopic dermatitis (AD). Research suggests that probiotic strains, particularly those from Lactobacillus, show potential in the treatment of other inflammatory and microbial-mediated skin conditions such as psoriasis, acne, and rosacea. For example, in psoriasis, a condition characterized by dysregulated immune responses and altered microbial communities, probiotics may help modulate systemic inflammation and restore microbial balance. [46] Rosacea, another inflammatory condition often linked to microbial triggers, may be managed with probiotics that strengthen the skin barrier and reduce vascular inflammation. In these patients, *L. Plantarum* was shown to increase the content of water within the skin in addition to decreasing transepidermal water loss (TEWL) in facial and forearm skin. [47] Similarly, acne, driven by C. acnes proliferation and inflammation, may benefit from probiotics through competitive inhibition and reduction of inflammatory cytokine production. A study by Niedźwiedzka et al. demonstrated that probiotic supplementation resulted in improved security of acne and reduction in not only inflammatory, but

also total lesion counts. [48] The research also discussed additional benefits experienced by participants including improved skin hydration, decreased levels of sebum triglycerides, and increased levels of ceramides indicating enhanced function of the skin barrier. [48] Moreover, microbial profiles showed positive changes, suggesting that *L. plantarum* plays a vital role in regulating inflammatory pathways associated with acne and may serve as a complementary or alternative option to standard treatments.

Probiotic therapy also shows promise in wound healing, where certain strains have been found to expedite re-epithelialization and reduce infection rates. In a study by Wang et al., *L. plantarum* inhibited the effects of advanced glycation end products (AGEs) via the downregulation NLRP3 inflammasome activity. *L. plantarum* use resulted in decreased levels of NLRP3 and caspase-1 p20, its downstream target. [49] These outcomes demonstrate topical *L. plantarum's* role in regulating wound closure and modulating local immune responses, highlighting its potential as a therapeutic adjunct in chronic wounds.

5.5.2. Role in Preventive Dermatology

Probiotics may also play an important role in preventive dermatology, particularly for patients with increased atopy and sensitive high-risk skin profiles. These individuals often experience compromised skin barrier function, leaving them vulnerable to irritation and secondary infections. Probiotic formulations can enhance barrier repair mechanisms and reduce the colonization of pathogenic microbes, contributing to long-term skin health. In patients with Atopic Dermatitis (AD) who suffer from a disrupted skin barrier integrity and increased TEWL, probiotics have been studied as a means to improve symptoms. Research discusses the impaired intestinal barrier function in individuals with AD, characterized by disrupted homeostasis of key immune cells, including regulatory and helper T cells (Th1 and Th17), which contribute to a type 2 inflammatory response. [50] The gut microbiota plays a crucial role in modulating immune tolerance, with atopic children demonstrating an imbalance with higher levels of coliforms and clostridia but reduced Bifidobacteria and Lactobacilli therefore leading to Th2 polarization. [50] This has sparked interest in nonpharmacological approaches, such as probiotics, to restore microbial balance and potentially aid in AD prevention and treatment.

Moreover, the preventative potential of probiotics may be particularly relevant in aging skin, where skin barrier function naturally deteriorates and microbial diversity declines. Gao et al. suggests that maintaining intestinal microbiota balance can impact skin health, supporting the concept of a gut–skin axis. Thus, probiotic interventions are emerging as potential approaches to improving skin health, contributing to the growing popularity of micro-ecological skincare. [51] By modulating gut–skin interactions, probiotics may help manage skin disorders by reducing oxidative stress, controlling inflammation, and supporting immune function, [51]This research supports the idea that probiotics may serve as an effective option for preserving skin health by supporting the gut–skin axis, enhancing barrier function, and promoting microbial balance to mitigate inflammation and oxidative stress.

Recent evidence also indicates that probiotic use may mitigate environmental stressors such as UV radiation and pollution. Probiotic strains have been shown to upregulate the production of antimicrobial peptides and antioxidants in the skin, providing a protective effect against these external aggressors. [52] A study by Kober and Bowe discusses *L. plantarum* inhibiting UVB-induced matrix metalloproteinase 1 (MMP-1) expression in order to preserve procollagen expression in human fibroblasts. [52] With oral administration of *L. plantarum* in hairless mice versus control, a reduction in the number and depth of wrinkles was observed. Histologic samples from these study subjects also showed that *L. plantarum* inhibited MMP-13, MMP-2, and MMP-9 expression in dermal tissue. [52] These findings suggest that probiotics, particularly *L. plantarum*, may offer a protective and restorative role against environmental stressors and support skin health by preserving collagen integrity.

5.5.3. Consumer Interest in Skin Health

The growing consumer interest in skin health has catalyzed the development of microbiome-based skincare products. This trend is driven by the increasing recognition of the skin microbiome's role in maintaining dermatological health and preventing disease. Alves et al. suggests a significant rise in the availability of topical probiotics, prebiotics, and synbiotics in cosmetic formulations aimed at enhancing skin microbiota diversity and skin barrier resilience. [53] Notably, *L. plantarum* has been incorporated into topical serums aimed to improve acne symptoms,

reflecting its recognized benefits in skin barrier repair and anti-inflammatory effects. [54]. This interest in microbiome-based skincare innovation is a reflection of the alignment between dermatological science and the need for effective, microbiota-supporting therapeutic options.

The surge in consumer demand is also fueled by the "clean beauty" movement, which emphasizes natural and microbiome-friendly ingredients. This shift aligns with a growing emphasis on personalized skincare, where formulations are tailored to an individual's unique microbiome profile. However, further research is necessary in order to evaluate the efficacy, safety, and therapeutic value of such products.

5.6. Methodology for Future Research

5.6.1. Study Design Recommendations

Future research should focus on utilizing standardized tools for assessing atopic dermatitis severity. The Harmonising Outcome Measures for Eczema (HOME) initiative has established standardized tools for assessing AD severity, which are essential for ensuring consistency and comparability across clinical trials and research studies. Among these tools, the Eczema Area and Severity Index (EASI) and the SCORing Atopic Dermatitis (SCORAD) index are the most extensively validated clinician-reported instruments for measuring AD severity. EASI is widely preferred due to its strong validity, responsiveness, internal consistency, and intraobserver reliability, making it a robust tool for clinical assessments. SCORAD, while also demonstrating adequate validity and responsiveness, has less well-defined intraobserver reliability. [55] To complement clinician-reported assessments, patient-reported outcomes are crucial in capturing the subjective burden of AD. The Patient-Oriented Eczema Measure (POEM) is recommended for evaluating symptom severity from the patient's perspective, while the peak Numerical Rating Scale (NRS)-11 provides a standardized measure of itch intensity over a 24-hour period (Williams et al., 2022). Additionally, assessing the impact of AD on quality of life (QoL) is vital. The Dermatology Life Quality Index (DLQI) is the standard tool for adults, while the Children's Dermatology Life Quality Index (CDLQI) and the Infant's Dermatology Quality of Life Index (IDQoL) ensure age-appropriate QoL assessments in younger populations. [57]

Beyond standardized outcome measures, ensuring demographic diversity in clinical trials is critical for generating broadly applicable findings. Historically, AD research has been limited by underrepresentation of diverse racial, ethnic, and socioeconomic groups, despite known variations in disease presentation, severity, and treatment response across populations. The American Academy of Dermatology (AAD) emphasizes the need for inclusive study designs that enroll patients across various racial and ethnic backgrounds, age groups, and comorbid conditions to improve the generalizability of findings. In particular, older adults and individuals with preexisting medical conditions are often excluded from trials, limiting the real-world applicability of therapeutic interventions. Expanding study populations to reflect the full spectrum of AD-affected individuals can enhance the relevance of research findings and improve treatment recommendations for diverse patient populations. [58] By incorporating standardized disease severity measures and ensuring diverse and representative study cohorts, future research can provide more meaningful insights into the efficacy and applicability of novel treatments, including topical probiotic therapies such as Lactobacillus plantarum, in managing AD.

5.6.2. Biomarker Identification

Future research in atopic dermatitis should prioritize the identification of biomarkers, genetic predispositions, and microbial response predictors to enhance disease stratification and facilitate personalized treatment approaches. Several studies have identified promising biomarkers that could aid in early diagnosis, disease monitoring, and therapeutic decision-making. For instance, tape strip analysis has emerged as a non-invasive method for detecting inflammatory cytokines such as IL-13 and thymic stromal lymphopoietin (TSLP), which have been identified as early predictors of AD onset in infants. [59] Additionally, metabolic profiling has revealed elevated levels of hypoxanthine and glycerol-3-phosphate in AD lesions, correlating with disease severity and highlighting their potential as biomarkers for tracking disease progression. [15] Genomic studies have further elucidated the role of genetic predisposition in AD susceptibility. Variants in the filaggrin (FLG) gene, a key determinant of skin barrier integrity, are strongly associated with increased AD risk, underscoring the potential benefits of genetic screening in at-risk populations to inform early interventions. [60] Beyond FLG mutations, bioinformatic analyses

have identified differentially expressed genes (DEGs) and microRNAs (miRNAs) that contribute to AD pathogenesis. These findings suggest that targeted genetic research could uncover novel therapeutic pathways, including RNA-based interventions aimed at modulating dysregulated gene expression. [61]

The skin microbiome plays a critical role in AD severity and treatment response. Studies have demonstrated that distinct microbial signatures, such as an overabundance of Staphylococcus aureus and a reduction in commensal microbial diversity, are associated with heightened disease severity. Emerging evidence suggests that stratifying patients based on their skin microbiome configurations (e.g., dermotypes) could offer prognostic insights and inform microbiome-based therapeutic strategies, such as targeted probiotic applications or bacteriophage therapy. [62] To advance precision medicine in AD, integrating multi-omics approaches, including genomics, transcriptomics, proteomics, and lipidomics, will be crucial in providing a comprehensive understanding of disease pathogenesis. By analyzing these interconnected biological systems, researchers can identify novel therapeutic targets, refine disease classification, and tailor interventions based on an individual's genetic and microbial profile. This holistic strategy has the potential to transform AD research, paving the way for personalized treatment approaches that optimize therapeutic outcomes. [63]

Techniques for tracking epidermal changes, such as advanced imaging modalities and transepidermal water loss (TEWL) measurements, are essential for assessing skin health, diagnosing dermatological conditions, and evaluating treatment efficacy. Traditional methods for assessing skin barrier function, such as visual examination and subjective scoring systems, have limitations in precision and reproducibility. Emerging non-invasive imaging techniques and wearable analytical devices now offer more objective, quantitative assessments, making them particularly valuable for research on atopic dermatitis (AD) and novel therapeutic interventions like topical probiotics. Among imaging techniques, laser scanning microscopy (LSM) provides a high-resolution, in vivo method for analyzing wound healing kinetics and cellular dynamics in real time. This technique allows researchers to track epidermal regeneration following interventions such as probiotic therapy, providing both qualitative and quantitative data on barrier repair mechanisms. [64] Another valuable imaging tool is optical coherence tomography (OCT), a non-invasive cross-sectional imaging technique used to measure epidermal thickness, water content, and microstructural skin changes. Because OCT is highly sensitive to variations in skin hydration and barrier integrity, it is widely used in clinical research to assess the effects of barrier-enhancing treatments, including moisturizers and probiotics, on skin function. [65] Additionally, confocal Raman spectroscopy (CRS) offers molecular-level insights into skin composition and structural changes by detecting natural moisturizing factors (NMFs), ceramides, and lipid organization. Since ceramides and NMFs play a crucial role in maintaining skin hydration, CRS is particularly useful for evaluating how probiotic therapies influence lipid metabolism and moisture retention in AD. [65]

TEWL measurement is another critical tool for assessing skin barrier function, as it provides an objective indicator of the epidermis's ability to retain moisture and protect against external irritants. Recent advancements in wearable and portable TEWL monitoring devices have improved upon traditional, intermittent TEWL assessments by enabling continuous, real-time data collection. One such innovation is the Wearable Analytical Skin Probe (WASP), a hygrometer-based system designed to provide continuous TEWL monitoring while controlling for environmental factors such as temperature and humidity. By minimizing external variability, WASP improves the accuracy of TEWL assessments and enhances researchers' ability to track treatment efficacy, including the effects of Lactobacillus plantarum on barrier repair. [66] Similarly, portable skin analyzers are now capable of simultaneously measuring TEWL, skin conductance, and skin hardness, offering a comprehensive assessment of epidermal function. These compact devices facilitate longitudinal studies in both clinical and home settings, allowing researchers to monitor disease progression and therapeutic responses with greater convenience. [67] Further advancing TEWL monitoring, wireless, soft electronic sensors provide high-speed, automated, and long-range tracking of skin hydration and barrier integrity. These skin-adherent devices enable real-world, continuous monitoring of AD severity and treatment responses, eliminating the need for frequent clinical visits and providing deeper insights into how probiotic interventions influence epidermal repair over time. [68] The

integration of non-invasive imaging technologies and advanced TEWL tracking methods represents a significant advancement in dermatologic research, offering highly sensitive, reproducible, and objective assessments of epidermal health. These techniques allow for dynamic, real-time monitoring of skin barrier integrity, particularly in the context of atopic dermatitis and probiotic therapy. Their implementation in clinical trials and home-based monitoring can improve personalized treatment approaches, facilitate longitudinal disease tracking, and support the development of targeted interventions, including Lactobacillus plantarum-based formulations.

5.6.3. Advances in Probiotic Delivery Mechanisms

Recent advances in probiotic delivery mechanisms have focused on optimizing stability and bioavailability through innovative formulation strategies, ensuring probiotics remain viable and effective throughout storage, application, and physiological exposure. A primary challenge in probiotic therapy is maintaining the structural integrity and functional activity of live bacteria, particularly when exposed to heat, moisture, enzymatic degradation, and acidic environments. To address this, researchers have developed encapsulation techniques that protect probiotics from degradation while improving their targeted delivery and sustained release.

One of the most effective strategies is colloidal encapsulation, which forms a protective shell around probiotics to shield them from external stressors. This method has demonstrated significant improvements in probiotic survival and bioavailability, as seen in a study by Zhang et al., where encapsulated probiotics achieved a survival rate of up to 19%—7500 times higher than conventional commercial enteric materials. [69] Similarly, microfluidic technology has emerged as a promising approach that enables precise control over encapsulation processes, allowing for the development of tailored probiotic carriers such as emulsions, microspheres, gels, and nanofibers. These carriers improve probiotic viability in harsh environments by controlling release rates and optimizing probiotic interaction with the target site. [70] In the case of topical probiotic formulations, microfluidic-based delivery systems could facilitate sustained probiotic activity on the skin, enhancing their therapeutic effects on epidermal barrier repair.

Further innovations include nanoencapsulation, which provides protection at the single-cell level by coating individual probiotic cells with biodegradable nanomaterials. This technique enhances acid resistance, intestinal adhesion, and targeted delivery, allowing probiotics to persist longer in the application site. Wei et al. demonstrated that a cell-in-shell structure with pH-responsive and mucoadhesive properties significantly improved probiotic survival and retention in the gastrointestinal tract, suggesting that a similar approach could enhance probiotic colonization and longevity on the skin. [71] Additionally, polymeric carriers made from biocompatible and biodegradable materials have been utilized to further improve probiotic retention and stability. These carriers protect probiotics from environmental degradation while ensuring controlled release, making them particularly effective for dermatological applications where sustained probiotic activity is essential for skin barrier repair. [72] Beyond encapsulation, layer-by-layer (LbL) assembly has gained attention as an advanced probiotic stabilization technique. This method involves depositing alternating layers of cationic and anionic materials to create a protective shell around probiotics, improving their acid resistance and mucoadhesion in biological environments. [71] LbL coatings could be particularly advantageous in topical formulations, enhancing probiotic retention on the skin and protecting against degradation from environmental exposure.

Another emerging innovation in probiotic delivery is the development of probiotic patches, which provide localized, controlled release of probiotics to target tissues. Unlike traditional oral or topical applications, mucoadhesive patches are designed to adhere to mucosal surfaces, ensuring prolonged contact and improved bioavailability of probiotics at the application site. Banerjee et al. demonstrated that these patches can be applied to the intestinal mucosa, where they facilitate continuous probiotic release, optimizing therapeutic efficacy. [73] A similar approach could be adapted for dermatological use, where skin-adherent probiotic patches may allow for sustained microbial delivery to restore skin microbiome balance and reinforce the skin barrier in atopic dermatitis patients. These advanced probiotic delivery mechanisms—including encapsulation techniques, polymeric carriers, LbL assembly, and probiotic patches—offer significant advantages over traditional

formulations by ensuring higher probiotic survival rates, enhanced bioavailability, and targeted delivery. As research in topical probiotic therapy continues to evolve, integrating these novel approaches could revolutionize probiotic-based dermatological treatments, optimizing skin barrier repair and immune modulation in conditions such as atopic dermatitis. Future research should focus on refining these delivery technologies to develop clinically viable, scalable, and patient-friendly formulations that maximize the therapeutic potential of probiotic-based skin therapies.

5.7. Health Economics and Accessibility

Quantifying the economic burden of atopic dermatitis is challenging due to the wide variability in disease severity. This burden comprises both direct and indirect costs. Direct costs include expenses associated with physician visits, emergency care, hospitalizations, over-the-counter treatments, and prescription medications. A 2018 study of U.S. adults found that 98.2% of adults with atopic dermatitis had an AD-related outpatient office visit and 91.4% filled an AD-related prescription. Among these prescriptions, 7.1% were for topical treatments and 74.6% were for systemic therapies. Notably, 72% of medical claims were due to the dupilumab prescriptions, highlighting the significant cost burden associated with conventional therapies. [74] Indirect costs arose from productivity losses including absenteeism, decreased work efficiency, reduced social engagement, and adverse mental health effects. Adults with AD have been found to file a higher percentage of short-term disability claims to control groups, with associated indirect costs of $360 per patient vs $276 in controls (P=0.01). [74] Given the substantial financial impact of both direct and indirect costs, topical *Lactobacillus plantarum* presents as a promising alternative as an efficacious and low-cost treatment for atopic dermatitis.

Lactobacillus plantarum is a naturally occurring species within the human microbiome that plays a crucial role in immune modulation and maintenance of the natural microbial flora. However, its cultivation requires nutrient-rich media due to its limited ability to synthesize important amino acids and B vitamins. [75] Therefore, optimizing its growth medium is essential to enhance biomass production, maximize health benefits for consumers, and minimize waste output. Traditional cultivation methods, such as the De Man, Rogosa, and Sharpe (MRS) medium, incorporate yeast extract and casein hydrolysate. [76] These components are high in nitrogen and carbon, necessary for optimal bacterial proliferation. However, these ingredients can be cost-prohibitive when producing large-scale therapeutic formulations, especially in low-resource settings. To address this limitation, an alternative formulation utilizing cheese whey and corn steep liquor has been proposed. Cheese whey, a by-product of the dairy industry that is often discarded, serves as a cost-effective carbon source while simultaneously mitigating environmental waste. Similarly, corn steep liquor, a by-product of the corn milling industry, is rich in amino acids and B vitamins. Comparative studies have demonstrated that cultivation with this alternative formulation yielded significantly higher dry cell mass and viable cell counts compared to the conventional MRS medium ($P<0.05$). [76] The incorporation of these low-cost, sustainable ingredients in *Lactobacillus plantarum* production has the potential to significantly reduce manufacturing costs, making probiotic-based therapeutics an accessible intervention for atopic dermatitis treatment.

5.8. Challenges and Future Directions

5.8.1. Current Research Gaps

The use of *L. plantarum* in topical probiotic therapy offers significant promise in enhancing skin barrier repair and alleviating symptoms in AD. However, several challenges and future directions remain to be addressed to fully utilize its potential. Despite encouraging preliminary studies, larger and longer-term clinical trials are needed to confirm the efficacy and safety of probiotic formulations in diverse populations. [34] Additionally, the variability in probiotic strains, formulations, and application protocols has resulted in inconsistent outcomes across studies, highlighting the need for standardized methodologies. [61] Addressing these challenges through further research, clinical trials, and standardized approaches will be vital in achieving the full therapeutic potential of *L. plantarum* for atopic dermatitis treatment.

5.8.2. Innovation Opportunities

Advancements in microbiome profiling present opportunities for developing personalized probiotic therapies tailored to an individual's skin microbiota. This precision approach could optimize outcomes by accounting for individual variability in microbiome composition and skin conditions. [77] By utilizing next-generation

sequencing technologies, researchers can identify microbial signatures associated with skin barrier dysfunction in AD and formulate targeted probiotic interventions. Additionally, artificial intelligence and machine learning can enhance microbiome data analysis, allowing for predictive modeling to determine the most effective probiotic strains for specific patient populations. [78] Personalized probiotic therapies may also be combined with lifestyle and dietary interventions to create comprehensive, patient-specific treatment plans that support long-term skin health.

Furthermore, combining probiotics with available dermatological treatments, such as biologics or nanotechnology-based drug delivery systems, may enhance therapeutic efficacy and broaden applications. [79] Nanotechnology-based drug delivery systems, including liposomes and nanoemulsions, offer the potential to enhance probiotic stability and penetration into deeper skin layers, improving therapeutic outcomes. [79] Moreover, biologic therapies targeting inflammatory pathways, such as IL-4 and IL-13 inhibitors, have shown significant promise in AD management, and their integration with topical probiotics could provide a dual approach by modulating immune responses while restoring microbial balance. [80] These developments significantly contribute to the growing role of microbiome-based interventions as integral parts of next-generation AD treatments.

5.9. Interdisciplinary Approaches

Collaboration between various specialists including dermatologists, microbiologists, and pharmacists is essential in overcoming the existing challenges and furthering innovation in probiotic therapy. Interdisciplinary research will drive the development of novel probiotic formulations, identification of optimal delivery methods, and ensure clinical validation and therapeutic efficacy of products. By addressing these challenges and leveraging innovation and collaboration, topical probiotic therapies like *L. plantarum* may transform dermatological care for vulnerable individuals. Their role in skin barrier repair, inflammation management, and preventative care demonstrates their value as a versatile tool for enhancing patient outcomes and expanding therapeutic options.

6. Conclusion

Atopic dermatitis is characterized by a compromised epidermal skin barrier, facilitating allergen and pathogen entry, which in turn triggers an overactive Th2 immune response and the release of associated cytokines. This strongly suggests a central role for the Th2 activity in the development and progression of AD. Another key factor in this barrier dysfunction is the deficiency of acid ceramidase and ceramides, leading to reduced antimicrobial sphingosine production and increased susceptibility to bacterial colonization. *L. Plantarum* emerges as a promising therapeutic agent for AD, addressing multiple facets of the disease. Not only does *L. Plantarum* modulates both Th1- and Th2 cytokine production, potentially dampening the overactive Th2 response while supporting protective Th1 activity, but it also enhances epidermal barrier integrity. This probiotic emerges as a promising therapeutic avenue for the management of AD.

Furthermore, the lipoteichoic acid component of *L. Plantarum* contributes to its anti-inflammatory effects. Evidence suggests that *L. Plantarum* may influence the skin microbiome, and its ability to modulate the gut microbiome, leading to downregulation of inflammatory mediators, may also indirectly impact skin inflammation. Clinical studies have shown a dose-dependent improvement in AD symptoms with *L. Plantarum* supplementation, including reduced skin inflammation, epidermal thickness, and mast cell numbers. Therefore, by targeting both the immune dysregulation and the compromised skin barrier characteristic of AD, *L. Plantarum* holds significant therapeutic potential for the management of this chronic condition.

Current AD treatments focus on topical corticosteroids or topical calcineurin inhibitors. However, chronic use of corticosteroids can result in adverse effects such as skin thinning and hypothalamic-pituitary-adrenal axis suppression. In addition, these approaches do not address the underlying immune dysregulation and barrier dysfunction that contribute to disease chronicity. The ability of *L. Plantarum* to modulate both Th1 and Th2 responses offers a targeted approach to rebalancing the immune system of AD patients, in contrast to broad immunosuppressants.

Oral administration of *L. Plantarum* was found to show consistent improvements in AD, showing clear benefits in reducing local inflammation and improving immune markers. Although, effects on overall allergy levels varied between studies suggesting it may better address cutaneous symptoms rather than broader allergic symptoms. Topical administration of *L. Plantarum*

demonstrated effects on skin barrier function, microbiome modulation, and inflammation. The observed dose-dependent effects further support the potential for personalized treatment strategies based on individual patient needs. These findings suggest that *L. Plantarum*, either as an oral or topical standalone therapy or as an adjunct to existing treatments, could offer a more targeted approach to AD management. Further research is needed to determine the optimal dosage and delivery method of *L. Plantarum* for AD treatment.

The promising results presented here warrant further investigation to optimize the therapeutic application of *L. Plantarum*. Further studies should prioritize well-designed, longer-term clinical trials to address the variability observed across existing research regarding probiotic strains, formulations, and application protocols, confirming efficacy and safety in diverse populations. Beyond AD, future investigations should explore the therapeutic potential of *L. Plantarum* in other inflammatory and microbial-mediated skin conditions such as acne and psoriasis, as well as its promising role in wound healing. The ability of *L. Plantarum* to mitigate the effects of environmental stressors and support skin health also warrants further exploration. Furthermore, synergistic approaches combining probiotics with existing dermatological treatments, such as biologics or nanotechnology-based drug delivery systems, hold significant promise. These combinations could enhance therapeutic efficacy by improving probiotic stability and penetration into deeper skin layers, potentially broadening applications and optimizing patient outcomes. Further explorations of *L. Plantarum's* therapeutic potential allows for development of more effective and targeted treatments for a range of debilitating skin conditions, improving quality of life for countless individuals.

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