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REVIEW

Skin Microbiome in Health and Disease: Mechanisms and Emerging Therapeutic Strategies

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Abstract: The skin microbiome plays a vital role in maintaining skin homeostasis by regulating immune responses, preserving barrier integrity, and inhibiting pathogen colonization. This review systematically explores the mechanisms underlying its dysregulation in conditions such as acne, atopic dermatitis, psoriasis, and impaired wound healing, with a focus on key factors including microbial over colonization, diminished diversity, and host immune dysregulation. The influence of microbial metabolites, such as short-chain fatty acids and porphyrins, is also examined. We further evaluate emerging microbial-targeted therapeutic strategies, including live biotherapeutic products, skin microbiota transplantation, epigenetic and metabolic interventions, and precision antimicrobial polymers. These approaches aim to restore microbial balance rather than achieve broad-spectrum sterilization, representing a significant shift in the treatment paradigm for cutaneous diseases. In contrast to previous reviews, this article places special emphasis on the mechanisms of multi-organ interactions within the gut-skin axis and discusses the potential of integrating multi-omics technologies and artificial intelligence to advance the clinical translation of personalized microbial therapies, thereby providing a forward-looking perspective on the field.

Keywords: skin microbiome, skin diseases, dysbiosis, host-microbe interactions, therapeutic interventions

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Introduction

As a fundamental component of the human ecosystem, the skin microbiome is crucial in maintaining cutaneous homeostasis and overall skin health. The dynamic interactions between the microbiota and the host significantly influence the integrity of the skin barrier and contribute to the onset and progression of numerous dermatological conditions.[1] Increasing evidence associates microbiome dysbiosis with a variety of inflammatory and immune-mediated skin disorders, such as acne and atopic dermatitis (AD). For example, the abnormal proliferation of Staphylococcus aureus has been strongly correlated with recurrent exacerbations of AD. Notably, an enrichment of this pathogen has also been observed in the skin microbiota of healthy family members of affected individuals, suggesting that microbial transmission may be a significant factor in disease recurrence.[2]

In the pathogenesis of acne, the regulatory function of the skin microbiome is of comparable importance. Recent research has shown that specific probiotic strains can mitigate acne-related inflammation through their broad-spectrum antimicrobial properties and facilitate the beneficial reorganization of microbial communities.[3,4]

In addition to its role in pathological conditions, the skin microbiome performs critical physiological functions essential for maintaining cutaneous health. For instance, Staphylococcus epidermidis contributes to the enhancement of the skin barrier through the secretion of sphingomyelinase, which subsequently aids in its own ecological colonization. This interaction exemplifies the complex mutualistic relationship between the host and its microbiota.[5] Moreover, research indicates that environmental factors, host immune status, and genetic background can alter the composition and functionality of the skin microbiome, thereby affecting disease susceptibility and overall skin health.[6]

The skin microbiome plays a crucial role in maintaining skin health and disease regulation. Understanding its composition, functions, and interactions with the host is key to developing new treatments for skin disorders linked to

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microbiome imbalances. Advances in molecular biology, such as 16S rRNA sequencing, metagenomics, metabolomics, and single-cell transcriptomics, now allow for detailed analysis of the skin microbiome, identification of previously uncultivable microbes, and insights into host-microbiome interactions.[7,8]

This review endeavors to deliver an exhaustive synthesis of recent advancements in the comprehension of the skin microbiome concerning prevalent dermatological conditions, such as acne, AD, psoriasis, and compromised wound healing. We elucidate the mechanistic role of microbiome dysbiosis in the initiation and progression of these diseases, critically assess emerging microbiome-targeted interventions and their translational potential, and deliberate on future research trajectories and principal challenges. Our objective is to provide novel insights into the prevention and treatment of skin disorders and to facilitate the effective translation of foundational microbiome research into clinical applications.

Skin Microbiota and Skin Diseases

Skin Microbiota and Acne

Acne is a prevalent chronic inflammatory dermatological condition predominantly impacting the pilosebaceous units. On a global scale, it affects an estimated 9.4% of the population, with approximately 85% of cases manifesting in adolescents and young adults.[9] The pathogenesis of acne is multifaceted, encompassing excessive sebum production, aberrant follicular keratinization, inflammatory responses, and dysbiosis of the cutaneous microbiota.[10] Notably, the disruption of the skin microbiome has emerged as a significant contributor to the development of acne.

Historically, *Cutibacterium acnes* (*C. acnes*) has been identified as the primary pathogenic microorganism implicated in acne.[11] Research indicates that various phylotypes of *C. acnes* produce differing quantities of porphyrins on the skin surface. These porphyrins, as photosensitive molecules, have the potential to induce oxidative stress and elicit immune responses associated with inflammatory skin conditions.[12] Importantly, porphyrin fluorescence has been investigated as a non-invasive biomarker for assessing acne severity and monitoring therapeutic outcomes.[13] Furthermore, a reduction in the diversity of the *C. acnes* community has been associated with the activation of innate immune pathways, thereby intensifying cutaneous inflammation.[14] As a result, therapeutic strategies aimed at modulating the population structure and metabolic activity of this microorganism have garnered increased attention in the management of acne.

Recent studies underscore the multifaceted roles of various microbial taxa in the pathogenesis of acne. For instance, *Staphylococcus epidermidis* has been shown to inhibit the proliferation of *C. acnes* by fermenting glycerol, thereby providing a protective effect against acne development.[15] Additionally, certain probiotics, such as *Lactobacillus plantarum*, have been found to enhance skin barrier function by modulating the diversity and metabolic activity of the skin microbiota.[16] Notably, some strains of *C. acnes* may contribute positively to skin homeostasis by regulating immune responses and preventing pathogenic colonization.[17,18] Consequently, contemporary therapeutic approaches are increasingly aimed at restoring the balance of the microbial community and selectively suppressing the overgrowth of pathogenic strains, rather than indiscriminately targeting *C. acnes* for eradication.

External factors, including dietary habits, pharmacological interventions, and cosmetic use, exert a significant influence on the skin microbiota associated with acne. Diets high in glycemic index and fat content can increase circulating levels of insulin-like growth factor-1 (IGF-1), which in turn stimulates sebaceous gland activity and keratinocyte proliferation, thereby fostering an environment conducive to the proliferation of *C. acnes*.[19] Moreover, lifestyle factors, such as extended exposure to chlorinated water in swimmers, can modify the skin's lipid film and microbiota composition, potentially exacerbating acne symptoms.[20] The use of certain medications, notably antibiotics and glucocorticoids, can disrupt microbial homeostasis, facilitating the overgrowth of opportunistic pathogens.[21] Furthermore, the probiotic strain *Lactobacillus plantarum* GMNL6 has demonstrated the ability to inhibit melanogenesis, suppress biofilm formation by *Staphylococcus aureus* (*S. aureus*), and reduce the proliferation of *C. acnes*, thereby presenting a promising adjunctive therapeutic strategy for the management of acne.[16]

In recent years, the concept of the "gut-skin axis" has significantly enhanced our understanding of acne pathogenesis. Dysbiosis of the gut microbiota can affect skin health through immune modulation and systemic inflammation, thereby contributing to both the development and progression of acne.[22] Consequently, oral probiotics designed to restore gut and skin microbial balance have emerged as a promising strategy for acne treatment.[23]

Acne is a multifactorial chronic inflammatory skin disease whose pathogenesis involves not only sebum secretion and hair follicle abnormalities but also critically depends on the dynamic equilibrium of the skin microbiota. The traditional perspective of categorizing *C. acnes* solely as a pathogen is overly simplistic, as it overlooks its potential beneficial roles in immune regulation and skin homeostasis, as well as the exacerbating impact of diminished microbial diversity on inflammation. Consequently, contemporary treatment strategies are evolving from indiscriminate eradication to the targeted modulation of microbiota, the integration of probiotics, and consideration of external factors such as diet and the gut-skin axis. This approach aims to manage the disease more comprehensively rather than merely suppressing symptoms.

Skin Microbiota and AD

Atopic dermatitis (AD) is a prevalent chronic and relapsing inflammatory dermatological condition, affecting approximately 20% of children and 10% of adults globally.[24] Clinically, AD is characterized by erythema, scaling, and intense pruritus, with a recurrent nature that substantially impairs the quality of life for both patients and their families. The pathogenesis of AD is multifaceted, involving compromised skin barrier function, dysregulated immune responses, and alterations in the skin microbiota.[25]

A notable microbial characteristic of AD is the excessive proliferation of *S. aureus*, with its abundance positively correlating with disease severity.[26,27] Colonization of the skin by *S. aureus* further compromises barrier integrity and exacerbates pruritus by eliciting immune responses.[28] Dysbiosis of the skin microbiome not only contributes to the onset of AD but also intensifies inflammation by modulating immune signaling pathways, thereby creating a self-perpetuating inflammatory cycle.[29]

Patients with AD frequently display diminished bacterial community diversity coupled with increased fungal richness.[27] Certain strains of *S. aureus* have been demonstrated in animal models to induce phenotypes resembling AD, underscoring their pivotal role in precipitating acute disease exacerbations.[27]

Microbiome-based interventions have emerged as promising therapeutic strategies for AD, aiming to restore microbial diversity and diminish the pathogenic burden of *S. aureus* to achieve sustained disease control.[29] For instance, topical formulations containing rosemary extract have been reported to specifically suppress the virulence factors of *S. aureus*, offering a novel approach for the prevention and management of acute AD exacerbations.[30]

Additionally, barrier repair is a critical component of AD management. Clinical studies have shown that moisturizers enriched with colloidal oatmeal can improve skin pH, enhance barrier function, and increase stratum corneum hydration, while concurrently reducing *S. aureus* colonization and promoting the recovery of microbial diversity.[31] These findings highlight the therapeutic potential of microbiota-targeted strategies as part of an integrated approach to AD treatment.

The pathogenesis of AD arises from the intricate interplay between skin barrier defects, immune dysregulation, and microbiota disturbances. While the current study examines the correlation between the hyperproliferation of *S. aureus* and disease severity, it also highlights the limitations inherent in traditional single-agent antibacterial strategies. Such treatment approaches can reduce microbial diversity and promote fungal proliferation, ultimately exacerbating the recurrence of inflammation. Consequently, emerging therapeutic paradigms are transitioning from merely inhibiting pathogens to a more comprehensive approach that includes barrier repair, targeted intervention in microbial virulence, and the restructuring of community diversity. This shift aims to disrupt the pathological cycle rather than merely providing temporary symptom relief.

Skin Microbiota and Psoriasis

Psoriasis is a persistent, immune-mediated inflammatory dermatological condition, with a worldwide prevalence estimated at approximately 2% to 3%.[32] Clinically, it is characterized by well-defined erythematous plaques with an overlay of silvery scales, predominantly manifesting on the elbows, knees, scalp, and lower back. The pathogenesis of psoriasis involves dysregulated activation of both innate and adaptive immune pathways, wherein cytokines such as IL-17, IL-22, and TNF-α play pivotal roles in promoting keratinocyte hyperproliferation and aberrant differentiation, culminating in the distinctive psoriatic lesions.[33]

Recent research has demonstrated significant reductions in both α- and β-diversity within the skin microbiome of psoriatic lesions.[34] In comparison to healthy individuals, the lesional skin of psoriasis patients exhibits a notable microbial shift, characterized by an increased relative abundance of *Staphylococcus* and *Streptococcus*, coupled with a marked reduction in *Cutibacterium* and *Corynebacterium*.[35] This inverse relationship is particularly pronounced between *Staphylococcus* and *Cutibacterium*, which are known to compete for ecological niches; the proliferation of *Staphylococcus* may be facilitated by, and further exacerbate, the depletion of the protective *Cutibacterium*. Additionally, the reduction of *Corynebacterium* has been implicated in contributing to disease pathogenesis.[36] Collectively, this microbial dysbiosis may promote psoriasis through several mechanisms: (1) molecular mimicry between microbial and host antigens; (2) modulation of host immune responses by microbial metabolites; and (3) disruption of the skin's physical and immunological barrier integrity.[37,38]

In addition to cutaneous dysbiosis, alterations in the gut microbiota are integral to the pathogenesis of psoriasis.[39] Patients often present with decreased α-diversity of the gut microbiota, a disrupted Bacteroidetes to Firmicutes ratio, and reduced populations of short-chain fatty acid (SCFA)-producing bacteria.[40] Compromised intestinal barrier function permits the translocation of microbial antigens and metabolites into systemic circulation, thereby initiating systemic immune activation. Clinical studies have demonstrated that supplementation with probiotics, such as *Bifidobacterium infantis*, can improve Psoriasis Area and Severity Index (PASI) scores and enhance quality of life. This improvement is partially attributed to the restoration of gut microbial balance, reduction of pro-inflammatory cytokines (eg, IL-17, TNF-α), and reinforcement of intestinal barrier function.[41]

Psoriasis is intricately linked with systemic metabolic dysregulation, with approximately 30% of affected individuals exhibiting comorbid metabolic syndrome, characterized by obesity, insulin resistance, hypertension, and dyslipidemia.[42,43] Inflammatory mediators derived from adipose tissue, such as TNF-α, IL-6, and leptin, can intensify psoriatic inflammation,[44] while the chronic systemic inflammation associated with psoriasis further exacerbates insulin resistance and atherosclerosis.[45] This bidirectional relationship may be partially mediated by the "skin-gut microbiota axis". Diets high in fat can alter the composition of gut microbiota, increase circulating levels of lipopolysaccharides (LPS), and activate low-grade systemic inflammation, thereby aggravating both psoriasis and its metabolic comorbidities.[46]

Probiotics have emerged as promising adjunctive therapies; by modulating both the skin and gut microbiota, they contribute to the restoration of immune homeostasis and the attenuation of inflammation.[23] For example, certain topical formulations containing lactic acid bacteria have demonstrated efficacy in inhibiting pathogenic bacterial colonization and promoting the recovery of the skin barrier.[47]

The pathological mechanism underlying psoriasis extends beyond mere immune dysregulation, encompassing a multifaceted interplay involving imbalances in the skin-gut microbiota axis and systemic metabolic abnormalities. Traditional therapeutic approaches, which focus on the inhibition of cytokines such as IL-17 and TNF-α, can mitigate symptoms but fail to address the bidirectional influence of microbial ecology on the immune barrier and the cyclical relationship between metabolic inflammation and dermatological manifestations. This limitation has catalyzed a paradigm shift in treatment strategies towards restoring immune homeostasis through probiotic interventions and microbiota remodeling, thereby transitioning from targeted inhibition to a more comprehensive therapeutic approach.[48]

Skin Microbiota and Wound Healing

Wound healing is a multifaceted and meticulously regulated biological process that advances through four overlapping stages: hemostasis, inflammation, proliferation, and tissue remodeling.[49] The successful restoration of tissue integrity depends on the orchestrated interactions among various cell types, including keratinocytes, fibroblasts, endothelial cells, and immune cells, as well as a diverse array of cytokines and growth factors.[50] Recent research has underscored the critical influence of the skin microbiota in this process. Commensal microorganisms can enhance wound repair by inhibiting pathogenic colonization through the secretion of antimicrobial peptides, modulating the local immune microenvironment, and releasing bioactive factors that facilitate cell migration and proliferation.[51–53]

Mechanistic insights further highlight the positive contributions of commensal bacteria to wound healing. For instance, research by Wang Gaofeng et al has demonstrated that resident *Staphylococcus* species facilitate keratinocyte migration toward the wound bed through the activation of the IL-1β signaling pathway, thereby expediting reepithelialization. Consistently, wounds in specific pathogen-free (SPF) mice with a normal microbiota exhibited faster healing compared to those in germ-free counterparts, emphasizing the essential role of the skin microbiota in tissue regeneration.[54]

Conversely, colonization of wounds by pathogenic bacteria such as *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Enterococcus faecalis* frequently impedes healing, particularly in chronic wounds such as diabetic foot ulcers, venous ulcers, and burn injuries. These pathogens impede repair by secreting cytotoxins and proteolytic enzymes that degrade newly formed tissue, forming biofilms that obstruct cell migration and reduce antibiotic penetration, sustaining inflammatory responses that damage surrounding tissues, and promoting antibiotic resistance.[55–57]

Clinical and experimental evidence suggests that chronic, non-healing wounds are characterized by significantly reduced microbial diversity, whereas acute, healing wounds tend to exhibit a more diverse and balanced microbial community. This observation has led to the development of innovative microbiota-based interventions aimed at improving outcomes in chronic wounds. For example, Wang Gaofeng's research team developed a bilayer microneedle system, where the outer layer delivers antimicrobial agents to penetrate biofilms and eradicate pathogens, and the inner layer gradually releases metabolites from commensal *Lactobacillus* to enhance barrier repair. This dual-action strategy significantly accelerated wound closure in diabetic models.[58] Other promising approaches include the use of bacteriophage therapy to selectively target and eliminate antibiotic-resistant strains,[59] the application of probiotic fermentation products such as bacteriocins and organic acids to suppress pathogens and support healing,[60] and the engineering of live bacterial strains to continuously secrete growth factors that promote tissue regeneration.[61]

Wound healing is a complex, multi-stage process that relies not only on the synergistic interaction of cells and factors but is also significantly influenced by the ecological balance of the skin microbiota. Traditionally, microorganisms have been dichotomously categorized as either beneficial or harmful, an oversimplification that fails to capture the nuanced roles they play. The functionality of microbiota is contingent upon specific species, ecological context, and the host's immune status. Consequently, novel therapeutic strategies are moving away from the short-term application of broad-spectrum antibacterials. Instead, they are focusing on the development of sophisticated systems designed to precisely regulate microbial ecology. Examples of such innovations include double-layer microneedles and phage therapy, which integrate both antimicrobial and probiotic properties.

Other Diseases

Skin aging represents a multifaceted biological process affected by intrinsic factors, including genetic predisposition and hormonal status, as well as extrinsic influences such as ultraviolet (UV) radiation and environmental pollutants.[62] Research indicates that the skin microbiota undergoes substantial alterations during the aging process, marked by a decrease in community diversity and modifications in microbial composition.[63] In aged skin, there is an observed increase in transepidermal water loss and a reduction in sebum production, which often result in a decline of lipophilic microbes such as *C. acnes* and *Malassezia*. Conversely, there is an increase in the relative abundance of *Staphylococcus* and *Micrococcus*.[64] These compositional shifts may further compromise the skin's barrier function, thereby elevating the risk of dryness and pruritus. Additionally, certain commensal microbes exhibit photoprotective properties; for instance, *C. acnes* and *Malassezia* are capable of modulating local immune responses to alleviate UV-induced skin inflammation.[65]

In the realm of skin cancer research, investigations into the microbiome are still nascent. Existing evidence suggests that the microbial composition of lesions in basal cell carcinoma, squamous cell carcinoma, and melanoma is distinct from that of healthy skin.[66] Notably, certain studies have identified increased concentrations of *Staphylococcus epidermidis* in areas affected by squamous cell carcinoma, with secreted antioxidant molecules possibly playing a role in mitigating UV-induced DNA damage and offering protective effects.[67] Nevertheless, the causal relationships between the skin microbiota and the development of skin cancer have yet to be comprehensively understood.

The influence of the skin microbiome extends significantly beyond its traditional roles, with its involvement in vascular and pigmentary skin disorders increasingly recognized.[68] In the context of vascular diseases, rosacea exemplifies a condition whose pathogenesis is intricately associated with dysregulation of the innate immune system and neurovascular dysfunction. Research has identified notable microbial dysbiosis in the facial skin of individuals with rosacea, particularly marked by an overabundance of Demodex mites. This over-colonization may intensify symptoms such as facial flushing, erythema, and telangiectasia through mechanisms including direct physical irritation, the transmission of bacterial antigens, or the initiation of local inflammatory responses.[69] Additionally, gastrointestinal dysbiosis, particularly involving strains such as *Helicobacter pylori*, may indirectly affect rosacea activity through the "gut-skin axis".[70]

In the context of pigmentary disorders, the relationship between the microbiome and vitiligo has become a focal point of emerging research. Vitiligo, an autoimmune dermatological condition, is marked by the depletion of epidermal melanocytes, resulting in skin depigmentation. Initial studies suggest a decrease in microbial diversity within vitiligo lesions. Alterations in the prevalence of specific bacterial species, such as *C. acnes*, may influence the local immune microenvironment, thereby affecting the severity of the autoimmune response and potentially contributing to the pathogenesis or progression of the disease.[71]

Microbiome-Based Therapeutic Strategies

Probiotics and Prebiotics

Probiotics are characterized as live microorganisms that, when administered in sufficient quantities, impart health benefits to the host.[72] Within the field of dermatology, probiotics may exert their effects through topical application, directly modulating the skin microbiota, or through oral administration, indirectly affecting the skin via the "gut–skin axis".[73] Commonly utilized strains encompass *Lactobacillus* and *Bifidobacterium* species, in addition to certain skin commensals such as specific strains of *Staphylococcus epidermidis* (*S. epidermidis*).[74]

Empirical studies have indicated that oral probiotics can mitigate the severity of inflammatory skin conditions, including atopic dermatitis, psoriasis, and acne.[75–77] For instance, supplementation with *Bifidobacterium infantis* has been shown to significantly enhance PASI scores in individuals with psoriasis, achieving an average reduction of approximately 30% after a 12-week period. The underlying mechanisms may involve the modulation of systemic immune responses, such as the reduction of pro-inflammatory cytokines and the enhancement of anti-inflammatory mediators, fortification of gut barrier integrity to decrease systemic inflammation, and competitive inhibition of pathogenic bacterial colonization.[41]

Topical probiotic formulations have the capacity to directly influence the cutaneous microenvironment. For example, a spray incorporating a specific *S. epidermidis* strain (M-17) demonstrated efficacy in suppressing *S. aureus* through the secretion of antimicrobial peptides, resulting in an approximate 40% enhancement in skin microbial diversity following four weeks of application.[78] Additionally, another study indicated that extracts from *Vitreoscilla filiformis* ameliorated clinical symptoms associated with atopic dermatitis and psoriasis, potentially through the modulation of Toll-like receptor 2 (TLR2) signaling and the enhancement of regulatory T-cell (Treg) function.[79]

Prebiotics are substrates that selectively enhance the growth or activity of beneficial microorganisms, typically comprising indigestible carbohydrates such as oligosaccharides, inulin-type fructans, and certain polysaccharides or polyphenols.[80] In dermatological contexts, prebiotics can facilitate the proliferation of advantageous skin microbes (eg, *Staphylococcus* and *Cutibacterium*), suppress pathogenic bacteria (eg, *S. aureus*), and fortify skin barrier integrity.[81] For instance, phytic acid has been demonstrated to promote the growth of *S. epidermidis* and, through the activation of the indole-3-propionic acid (IPA)–aryl hydrocarbon receptor (AHR) signaling pathway, enhance barrier function and reduce inflammation.[82]

The utilization of probiotics and prebiotics in the management of skin diseases has evolved from traditional nutritional supplementation to precision interventions focused on microbiota regulation. While current research has demonstrated their ability to modulate immunity, competitively inhibit pathogens, and enhance barrier function via the gut-skin axis, it has also highlighted the limitations of neglecting strain-specific effects and individual variability. Different strains, and even the same strain, can yield markedly different immune regulatory outcomes depending on the specific context. Moreover, existing clinical evidence is hampered by the absence of a standardized evaluation system. Consequently, an effective treatment strategy must transcend mere microbiota transplantation or supplementation, advancing towards a personalized approach that integrates the precise administration of symbiotic bacteria with prebiotics, alongside synergistic local and oral interventions. This approach not only challenges the simplistic notion that "probiotics are inherently beneficial" but also fosters a paradigm shift in skin disease treatment from broad microbial regulation to the remodeling of ecological functions.

Skin Microbiota Transplantation

Following the successful application of fecal microbiota transplantation in the treatment of gastrointestinal disorders, skin microbiota transplantation (SMT) has been introduced as an innovative therapeutic strategy. SMT seeks to transfer the skin microbial community from a healthy donor to the affected regions of patients, with the objective of restoring a balanced skin microecology.[83] Initial clinical studies have indicated that SMT can enhance microbial diversity in individuals with atopic dermatitis, decrease the prevalence of *S. aureus*, and substantially mitigate pruritus and the severity of skin lesions.[84]

Despite these promising findings, the clinical implementation of SMT encounters several challenges, such as donor selection, safety assurance, preparation standardization, and the assessment of long-term efficacy. An optimal donor should exhibit a stable and diverse skin microbiota and be devoid of infectious diseases, genetic disorders, or chronic skin conditions. Prior to transplantation, donor samples must undergo comprehensive pathogen screening for bacteria, fungi, viruses, and parasites.[85,86] Furthermore, sample preparation should be conducted under Good Laboratory Practice (GLP) conditions to ensure microbial viability and the preservation of community structure.

At present, the absence of standardized operating procedures constitutes a significant impediment to the widespread clinical implementation of SMT. Current research utilizes diverse transplantation methodologies, such as gauze application, blister fluid transfer, and aerosolized sprays, each exhibiting considerable variability in dosage, frequency, and treatment duration. Future investigations should prioritize the development of optimal transplantation strategies and standardized protocols, which require validation through large-scale randomized controlled trials to ascertain both efficacy and safety. Additionally, long-term follow-up is crucial to evaluate the stability of microbial colonization and to monitor for potential adverse effects.

Microbial Metabolites and Postbiotics

Postbiotics are characterized as non-viable microbial entities, including cellular components and metabolic byproducts, that impart health benefits to the host organism. These encompass SCFAs, antimicrobial peptides, cell wall fragments, and cell-free supernatants.[87] In contrast to live microbial formulations, postbiotics present several advantages, such as improved safety profiles, increased stability, precise dosage regulation, and clearly defined mechanisms of action, rendering them promising candidates for dermatological applications.[88]

Postbiotics have demonstrated significant potential in interventions aimed at mitigating skin aging. For instance, the fermented filtrate of EPI-7 has been documented to enhance skin barrier function, improve elasticity, and increase dermal density, thereby effectively counteracting visible signs of aging. Additionally, this filtrate fosters greater microbial diversity on the skin, notably by augmenting the abundance of beneficial commensals such as *Cutibacterium*, thus aiding in the reversal of age-related dysbiosis.[89]

In a separate study, the cell-free supernatant (CFS) of Lactobacillus plantarum THK-J112 exhibited broad-spectrum antifungal activity against *Candida tropicalis*, producing inhibition zones exceeding 10 mm and demonstrating a minimum fungicidal concentration of 2.5 mg/mL. The antifungal effects were attributed to the disruption of fungal cell walls, a reduction in microbial adhesion by up to 80.25%, and a marked suppression of pro-inflammatory mediators, specifically TNF-α (by 30.58%) and VEGF (by 78.25%). Further analyses identified hydrogen peroxide (90.43 μM/g CFS) as the primary active component, and genomic sequencing revealed the presence of the plantaricin J bacteriocin gene cluster.[90]

SCFAs including propionate, and butyrate, are essential microbial metabolites generated through the fermentation of dietary fibers. These metabolites possess anti-inflammatory, antimicrobial, and immunomodulatory properties. Specifically, propionate, which is produced by *C. acnes*, has the capacity to activate FFAR2 and PPAR-γ signaling pathways, leading to the suppression of NF-κB and consequently attenuating local inflammatory responses. Concurrently, butyrate facilitates keratinocyte differentiation and enhances the expression of tight junction proteins, thereby reinforcing the integrity of the skin barrier.[91]

Furthermore, researchers at Shiseido have engineered a selective polymer that inhibits pathogenic strains of *C. acnes* while fostering the proliferation of *S. epidermidis*.[92] This precision-targeted strategy presents notable advantages over traditional broad-spectrum antibiotics by maintaining microbial equilibrium and mitigating the risk of antimicrobial resistance.

As inactive microbial products, post-biological agents represent a novel approach for the treatment of skin diseases, characterized by high safety, good stability, and a well-defined mechanism of action. Nonetheless, the majority of supporting evidence is derived from in vitro experiments or specific models, which may not readily translate to human clinical applications. Consequently, further empirical research is necessary to temper optimism and address concerns regarding the standardized production, long-term safety, and cost-effectiveness of post-biological therapies in comparison to traditional treatments.[23,85,93]

Pharmacological Agents and Natural Products for Microbiota Modulation

Antibiotics have historically served as a fundamental component in the treatment of skin infections. Nevertheless, the indiscriminate bactericidal properties of broad-spectrum antibiotics, such as clindamycin and tetracyclines, frequently disrupt the skin microbiota and contribute to the development of antibiotic resistance. In contrast, antimicrobial peptides (AMPs) have emerged as promising alternatives, providing broad-spectrum antimicrobial efficacy with a reduced likelihood of fostering resistance. For instance, human β-defensins and their analogs, along with cathelicidin-derived peptides, demonstrate significant antibacterial activity against multidrug-resistant Staphylococcus aureus (MRSA).[94,95]

Extracts and bioactive compounds derived from plants, particularly those utilized in traditional medicine, exhibit considerable potential in modulating the skin microbiome and immune responses through various mechanisms. For instance, glycyrrhizin, a compound obtained from licorice, has been shown to inhibit the TLR4/NF-κB signaling pathway, leading to a reduction in the expression of pro-inflammatory cytokines such as IL-1β and TNF-α.[96] Polyphenols found in tea possess both antioxidant and antimicrobial properties, demonstrating efficacy in the management of acne.[97] Furthermore, polysaccharides from Astragalus have been reported to facilitate the colonization of beneficial microbes and enhance skin barrier function, thereby contributing to microbiota-mediated immune regulation.[98]

In conclusion, pharmacological agents and natural products that modulate the skin microbiota represent a promising therapeutic avenue for the management of dermatological conditions. Nonetheless, the practical clinical application of these alternative strategies remains constrained by several factors. Predominantly, existing research is concentrated on in vitro experiments, with limited verification of their in vivo efficacy, long-term safety, and ingredient standardization. These aspects necessitate further validation through extensive future studies.

Future Perspectives

With the swift progression of skin microbiome research, several emerging directions and key challenges have become increasingly apparent. Firstly, integrative multi-omics analyses, encompassing metagenomics, transcriptomics, proteomics, metabolomics, and lipidomics, offer a systematic framework for an in-depth understanding of host-microbe interactions. Furthermore, spatial omics technologies, including spatial transcriptomics and mass spectrometry imaging, present significant potential for elucidating the three-dimensional distribution of microbes across various skin layers and follicular structures, thereby enhancing our understanding of their direct interactions with host cells.

Secondly, precision medicine methodologies are gaining prominence in microbiome-focused dermatological interventions. By leveraging artificial intelligence (AI), including machine learning, to integrate microbiome data with host genetic information and clinical phenotypes, researchers can better identify disease subtypes, predict treatment responses, and design personalized microbial interventions. For instance, newly developed skin microecology and microenvironment scoring systems have shown robust predictive capabilities for assessing the risk of the atopic march. Looking forward, personalized probiotic formulations, prebiotic blends, and postbiotic products may be tailored according to individual microbial profiles, facilitating precise modulation of the skin microbiome.

The clinical translation of microbial therapies remains a formidable challenge. Comprehensive evaluation of their safety, stability, and long-term ecological impacts is imperative. Regulatory frameworks for live biotherapeutic products and microbiota transplantation are still evolving, and significant obstacles persist in manufacturing processes, quality control, and standardization. Advancements in this field will necessitate large-scale randomized controlled trials, the formulation of industry standards and clinical guidelines, and the investigation of synergistic effects with conventional therapies, such as biologics and JAK inhibitors.

Furthermore, the "gut-skin immune axis" is gaining prominence as a critical area of research. Dysbiosis of the gut microbiota may influence skin health through immune-mediated mechanisms, while chronic skin inflammation may reciprocally alter gut microbial composition. Future research should aim to elucidate this bidirectional interaction, assess the potential of combined oral and topical interventions, and develop innovative strategies targeting systemic-local microbial interactions.

Conclusion

The comprehensive investigation of the skin microbiome has significantly transformed our comprehension of skin health and the mechanisms underlying dermatological diseases. This review meticulously synthesizes the pivotal role of skin microbiota in pathological conditions such as acne, atopic dermatitis, psoriasis, and wound healing. It elucidates that ecological imbalance is not merely a consequence of these diseases but also a fundamental factor influencing their onset and progression. This paradigm shift underscores the importance of microbiome-targeted intervention strategies in the prevention and management of skin disorders (Table 1).

An effective intervention targeting the microbiome should focus on re-establishing a healthy microecological balance. This includes restoring microbial diversity, inhibiting the overgrowth of pathogens, promoting the function of beneficial bacteria and their active metabolites, and enhancing the integrity of the skin barrier. Recent advancements, such as precise herbal formulations developed by the University of Hong Kong, microbial extracts created by Shiseido, and cell-free supernatants of Lactobacillus plantarum THK-J112, exemplify the innovative concept of "precise regulation of microbial behavior". These strategies indicate that maintaining or restoring microbial ecological balance may offer a more targeted and sustainable approach compared to traditional broad-spectrum antibacterial therapies (Table 2).

Future research in this domain should prioritize the following key areas: conducting comprehensive analyses of the molecular mechanisms underlying host-microbe interactions; developing precise intervention strategies tailored to individual microbiome profiles; addressing the technical challenges associated with translating laboratory findings into clinical applications; and further investigating the extensive connections between skin microbiota and overall health. Achieving these objectives necessitates the integration of multidisciplinary expertise, including microbiology, dermatology, immunology, bioinformatics, and bioengineering, to advance skin microbiome research from theoretical understanding to practical application. It is anticipated that with the continued advancement of research, microbiome-based prevention and treatment strategies will lead to revolutionary breakthroughs in the management of skin diseases and establish a new paradigm for maintaining skin health.

Table 1 Role and Mechanisms of the Skin Microbiome in Common Skin Diseases

Disease	Key Microbial Changes	Main Pathogenic Mechanisms
Acne	Overgrowth of *C. acnes* Reduced diversity *S. epidermidis* inhibits *C. acnes*	Porphyrins induce oxidative stress and inflammation Activation of innate immunity Diet/drugs disrupt microbial balance
Atopic Dermatitis (AD)	*S. aureus* over-colonization Reduced bacterial diversity, increased fungal richness	Barrier impairment Immune activation, inflammatory cycle
Psoriasis	↑*Staphylococcus*, ↑*Streptococcus* ↓*Cutibacterium*, ↓*Corynebacterium*	Molecular mimicry, metabolite-mediated immunity Gut dysbiosis triggers systemic inflammation
Wound Healing	Acute wounds: high diversity Chronic wounds: low diversity, pathogens (eg, *S. aureus, P. aeruginosa*) dominate	Biofilm formation impedes healing Commensals promote re-epithelialization (eg, via IL-1β)
Others (eg, Rosacea, Aging)	Rosacea: Demodex mites, gut dysbiosis Aging: ↓*C. acnes*, ↑*Staphylococcus*	Immune dysregulation, barrier decline Loss of photoprotective microbes

Table 2 Comparison of Microbiome-Targeted Therapeutic Strategies

Strategy	Examples/Components	Mechanism of Action	Advantages & Limitations
Probiotics Prebiotics	Oral: *Bifidobacterium infantis* Topical: *S. epidermidis* M-17 spray	Immune modulation Competitive exclusion Barrier enhancement	Safe and easy to use Lack of standardization
Skin Microbiota Transplantation (SMT)	Transfer of healthy donor microbiota to patient	Restores diversity Suppresses pathogens	Promising Limited by donor screening and protocol standardization
Postbiotics Microbial Metabolites	SCFAs (propionate, butyrate) *L. plantarum* THK-J112 CFS	Anti-inflammatory Antimicrobial Promotes barrier repair	High stability and clear mechanism Clinical translation needs to be verified
Targeted Antimicrobials Natural Products	Antimicrobial peptides (eg, β-defensins) Plant extracts (glycyrrhizin, tea polyphenols)	Targeted pathogen inhibition Immune regulation	Avoid broad-spectrum drug resistance Most are still in the experimental stage
Novel Delivery Systems	Bilayer microneedles, phage therapy, engineered bacteria	Biofilm penetration Localized healing promotion	Precise regulation of flora ecology Complex technology and high cost

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Disclosure

The authors report no conflicts of interest in this work.

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