

The gut-skin axis: Emerging insights in understanding and treating skin diseases through gut microbiome modulation (Review)

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Abstract. Emerging evidence indicates a significant association between the composition and functionality of the gut microbiome and various skin disorders, including psoriasis, atopic dermatitis, acne and several dermatological conditions. The gut-skin axis theory describes a complex bidirectional communication network between the gut and the skin, providing mechanistic insights into the pathogenesis of certain cutaneous diseases. Specifically, the gut microbiome influences skin health through the regulation of systemic immunity, inflammatory responses and metabolic pathways. Advances in high-throughput sequencing and bioinformatics technologies have substantially enhanced the understanding of the role of the gut microbiome in skin pathology. Clinical and preclinical studies have demonstrated that restoring gut microbial homeostasis via interventions such as faecal microbiota transplantation, probiotics and prebiotics can ameliorate symptoms of skin diseases. Furthermore, personalized microbiome-based therapies, next-generation probiotics and dietary modifications hold promise for refining gut-skin interactions and advancing precision medicine in dermatology.

Therapeutic strategies targeting the gut-skin axis offer novel avenues for innovative dermatological treatments, with future breakthroughs potentially involving microbial community engineering, postbiotics and artificial intelligence in microbiome-related diagnostics. This narrative review summarizes recent advances in gut-skin axis research, explores its potential in the prevention and management of selected dermatoses and discusses future trends and scientific developments in the field.

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1. Introduction

The skin, as the largest organ of the human body, provides a protective barrier against mechanical, microbial, chemical and allergenic insults (1). The gastrointestinal tract, a crucial mucosal immune organ, maintains immune homeostasis through dynamic interactions between the microbiome and the intestinal immune system (2). The intestinal mucosal immune function is mediated by the mucus layer, epithelial barrier and resident immune cells, all of which engage with the gut microbiota (3). The collective genome of gut microbes is termed the 'gut microbiome,' which is intimately linked to long-term health (4). As interfaces with the external environment, both the gut and skin host diverse microbial communities and are richly innervated and vascularized. As early as 1930, John H. Stokes and Donald M. Pillsbury proposed an intrinsic relationship

between gut microbiota and skin inflammation, conceptualizing the ‘gut-skin axis’ (5). Recent advances in microbiology and immunology have begun to clarify the mechanisms through which gut microbiota influences skin health. Lee and Sung (6) identified immune pathways by which alterations in gut and skin microbiota contribute to dermatopathology, while Szanto *et al* (7) suggested that gut microbiota modulation may hold therapeutic potential for specific skin disorders. These findings not only validate the gut-skin axis theory but also open new avenues for clinical dermatology. In the context of increasing antibiotic resistance, therapeutic strategies are shifting toward alternatives such as probiotics, prebiotics and dietary interventions, which can restore microbial balance and modulate immune responses to improve skin health (8,9). This review examines novel strategies for treating skin diseases from the perspective of the gut-skin axis and explores future translational research directions.

2. Gut microbiome and skin health

Basic concepts and functions of the gut microbiota. The gut microbiota comprises diverse and dynamic microbial communities residing in the human gastrointestinal tract (10) (Fig. 1A). Anatomically and functionally, the gut is divided into the small and large intestines, each with distinct physiological conditions and microbial populations (11). Numerous factors influence the gut microbiota (Fig. 1B), with diet being a primary determinant of its structure and function (12). The gut microbiota evolves from infancy and changes in composition and diversity over time within an individual (13). There is considerable interindividual variation in gut microbial composition. Through host-microbe coevolution, the gut microbiome plays a critical role in regulating host physiology, including metabolism, immune development and behavioral responses (14,15).

Skin microbial composition and its function. As the body's outermost barrier, the skin is continuously exposed to environmental factors and serves as the first line of immune defense (16). The skin microbiota consists of microbial communities adapted to the cutaneous environment through long-term colonization, persisting in the chemical milieu of the stratum corneum, sweat and sebaceous secretions (17). Environmental factors such as ultraviolet radiation, temperature, humidity, sebum levels, oxygen availability and pH create distinct ecological niches across skin regions, leading to spatial variation in microbial composition (18). Based on physiological characteristics, Mahmud *et al* (19) classified skin into sebaceous (e.g., between eyebrows), moist (e.g., forearm flexure) and dry (e.g., palmar forearm) types. Lipophilic bacteria dominate sebum-rich areas, whereas dry regions may support a more diverse microbiota (Fig. 1C).

Concept of intestinal microecological dysbiosis and its association with skin diseases. According to Petersen and Round (20), dysbiosis refers to alterations in complex biological communities. In the context of the gut microbiome, dysbiosis manifests in three primary forms: Loss of beneficial microbes, overgrowth of pathogenic microorganisms and reduced overall microbial diversity. These forms may occur

independently or concurrently (20). In microbiome research, α -diversity measures species richness within a sample, while β -diversity assesses structural differences between samples, revealing characteristic dysbiosis patterns in skin diseases (21). Key factors contributing to gut microbiota imbalance include perinatal factors (e.g., mode of delivery), lifestyle (diet, stress, smoking) and medical interventions (e.g., antibiotics, chemotherapy) (Fig. 1B). Gut dysbiosis has been implicated in numerous diseases, including common skin disorders such as atopic dermatitis (AD), psoriasis, acne and alopecia areata (21). Research on rare skin diseases like lichen planus (LP) and autoimmune bullous dermatoses (AIBD) may also find breakthroughs through the gut microbiome (22).

3. The ‘gut-skin axis’ theory

Theoretical basis and background. The ‘gut-skin axis’ theory is part of the broader ‘gut-organ axis’ framework, emphasizing bidirectional communication between the gut and other organs via neurological, endocrine and immune pathways (23). This theory integrates multiple organs, the gut and the immune system with the gut microbiota (24). The gut and skin share structural and functional similarities, including embryonic origin, symbiotic microbial communities, innervation patterns and immune functions (19). As internal and external surfaces in contact with the environment, they utilize similar signaling and innervation pathways. T-cell-mediated immune responses often manifest in both intestinal and cutaneous tissues (25).

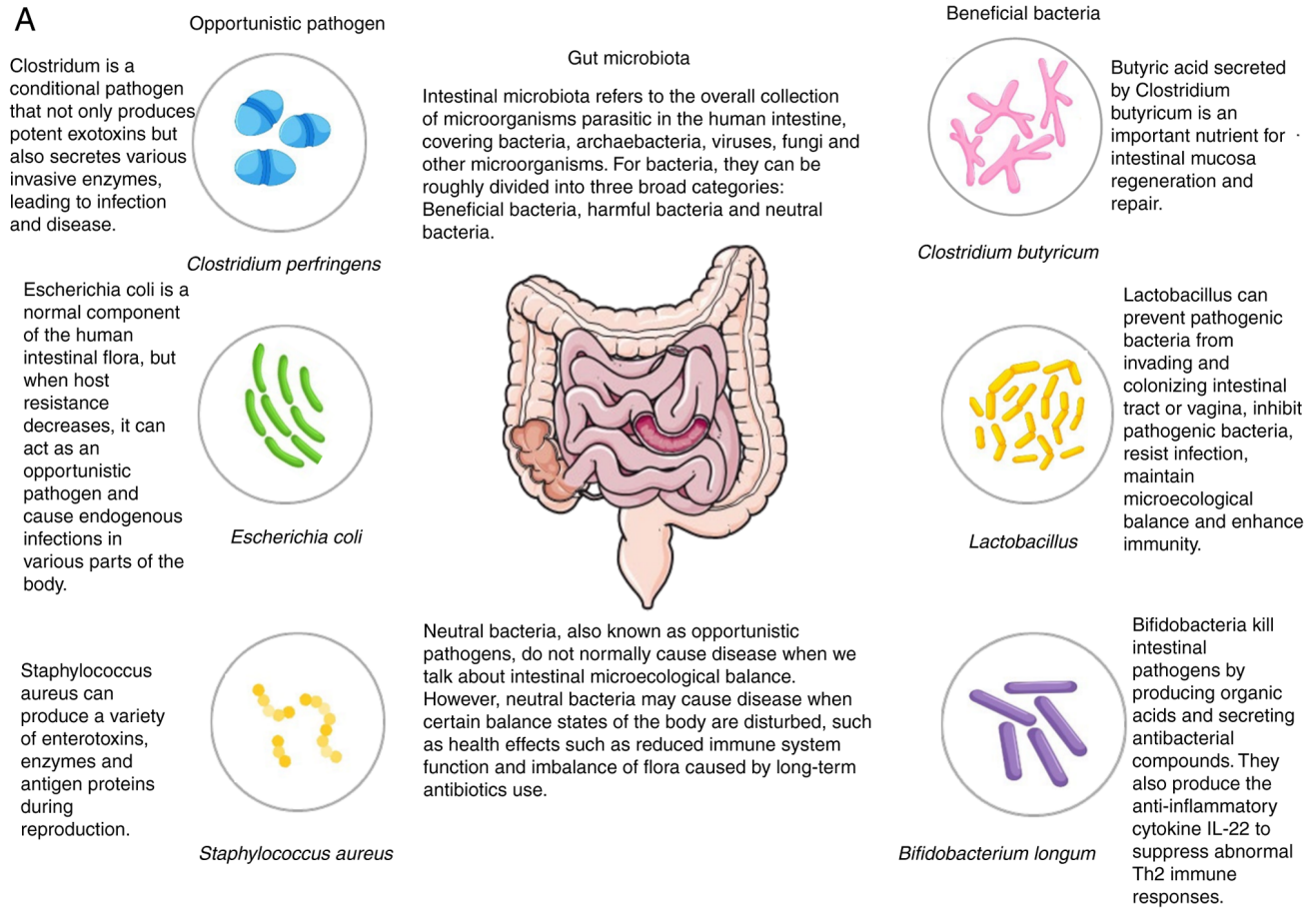
The gut microbial community is central to maintaining gut-skin homeostasis and underpins the gut-skin axis theory (26). The gut microbiota includes bacteria, fungi, parasites, protozoa and viruses, with bacteria predominating (27). Over 90% of gut bacteria belong to the Bacteroidetes and Firmicutes phyla (28). The Bacteroidota-to-Firmicutes ratio is commonly used to assess gut microbiota characteristics and diversity (29). Gut bacteria can be categorized as beneficial (e.g., Bifidobacteria, Lactobacillus) or opportunistic pathogens (e.g., Staphylococci, Clostridia), which may cause infection under certain conditions (30).

Ways in which gut microbes affect skin health. Alterations in gut microbiome composition, metabolism and immunity can impact skin health. Manos (31) identified interspecies communication within microbial communities as a key factor in maintaining cutaneous homeostasis and responding to environmental stressors, with dysregulation contributing to skin disease. External factors such as genetics, diet, antimicrobials, and lifestyle influence microbial diversity (32) (Fig. 2A).

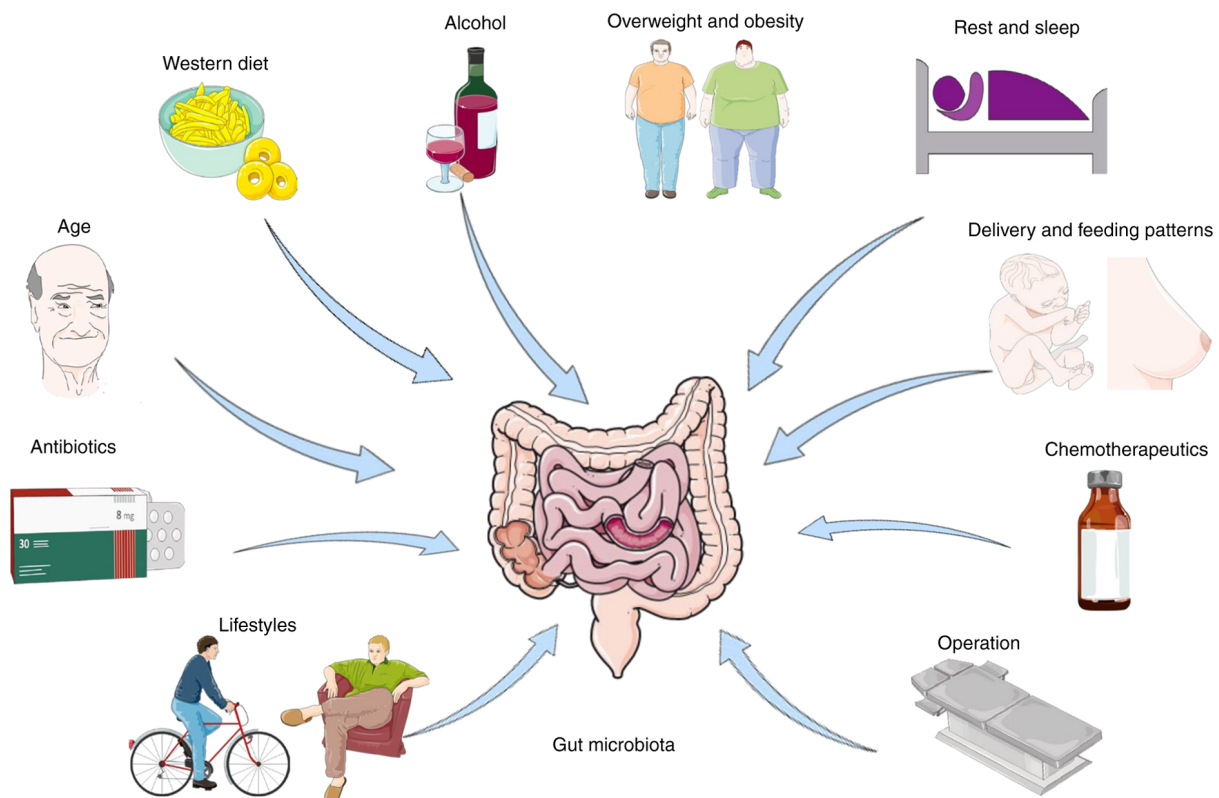
Gut dysbiosis is associated with multiple disease states (33) (Fig. 1D). Olejniczak-Staruch *et al* (34) reported significant gut dysbiosis in patients with psoriasis, characterized by increased abundance of *Campylobacter*, *Helicobacter*, *Escherichia coli*, *Alcaligenes* and *Salmonella*. Similarly, infants with AD show reduced Bifidobacteria and increased *Clostridium difficile* and *E. coli* (35).

Gut microbiota-derived metabolites mediate skin interactions through short-chain fatty acids (SCFAs), tryptophan metabolites and amine derivatives (e.g., trimethylamine N-oxide), which exert systemic effects via specific receptors (36). SCFAs play important roles in immune regulation;

A



B

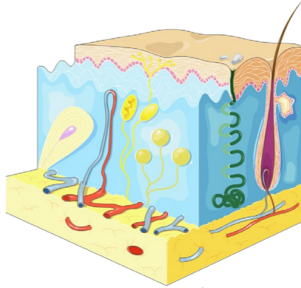


The gut microbiota has a strong association with factors including genetics, age and sex, which can provide a reference for individualized accurate diagnosis and treatment. Gut microecosystems not only evolve with host age, but also have a large plasticity, and their composition changes with factors such as the host's diet, lifestyle, antibiotic use and other factors. Antibiotics use is one of the most direct causes of flora imbalance. Antibiotics not only kill pathogens, but also reduce the diversity, abundance and uniformity of host protoflora.

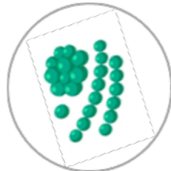
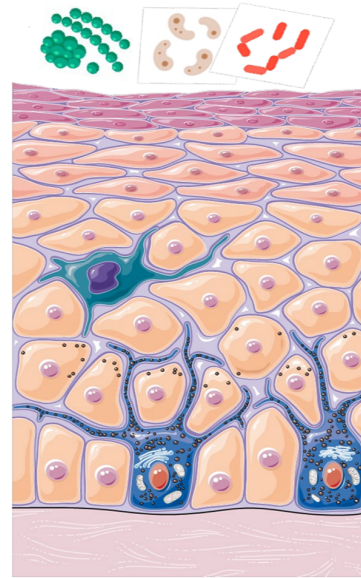
Figure 1. Continued.

C

A variety of bacteria, fungi, viruses, mites and other small arthropods form the skin microbiome or skin flora. The skin microbiome, cells on the skin surface, sweat, sebum and other substances, as well as the external environment together constitute an ecosystem, which plays an important role in maintaining the health of host skin.



According to the water and oil characteristics of different skin parts, the skin is mainly divided into oily, wet and dry parts. *Propionibacterium* and *Malassezia* are mainly enriched in oily parts, and *Propionibacterium* and *Staphylococcus* are mainly enriched in wet parts. The microbial composition of oily parts is stable, while that of dry parts changes significantly with time.



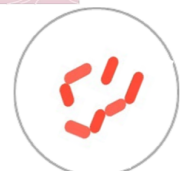
Staphylococcus epidermidis

Staphylococcus epidermidis is a conditional pathogen. Although it generally does not produce exotoxin and coagulase, it can sometimes cause purulent infection.



Malassezia

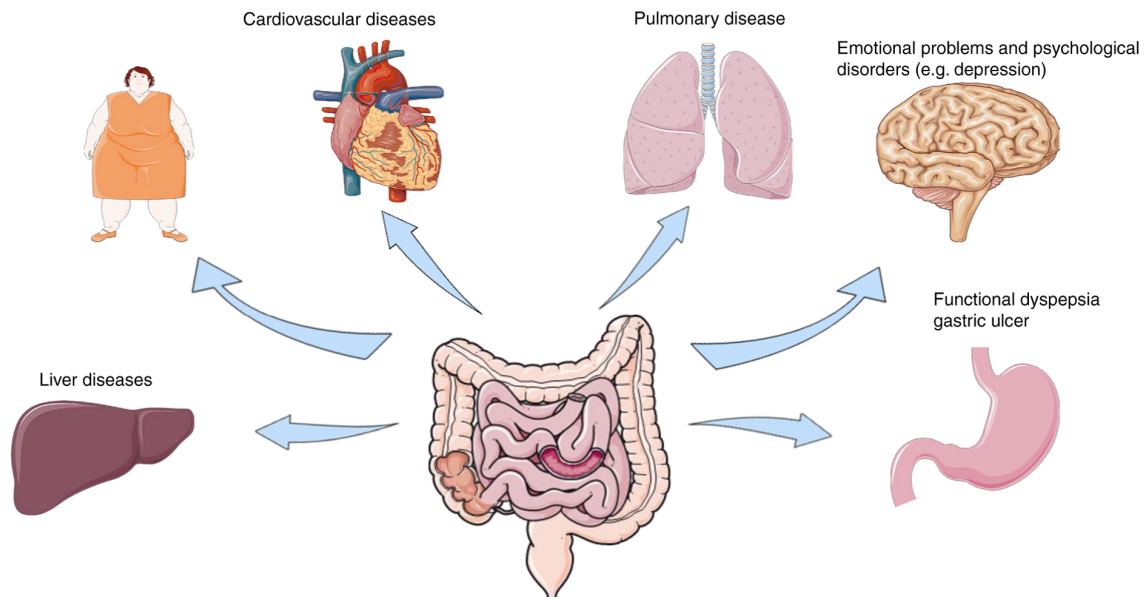
Malassezia is a fungus that can cause superficial cuticle and hair follicle infections. It is mainly distributed in sebum rich areas such as the scalp and face.



Propionibacterium acnes

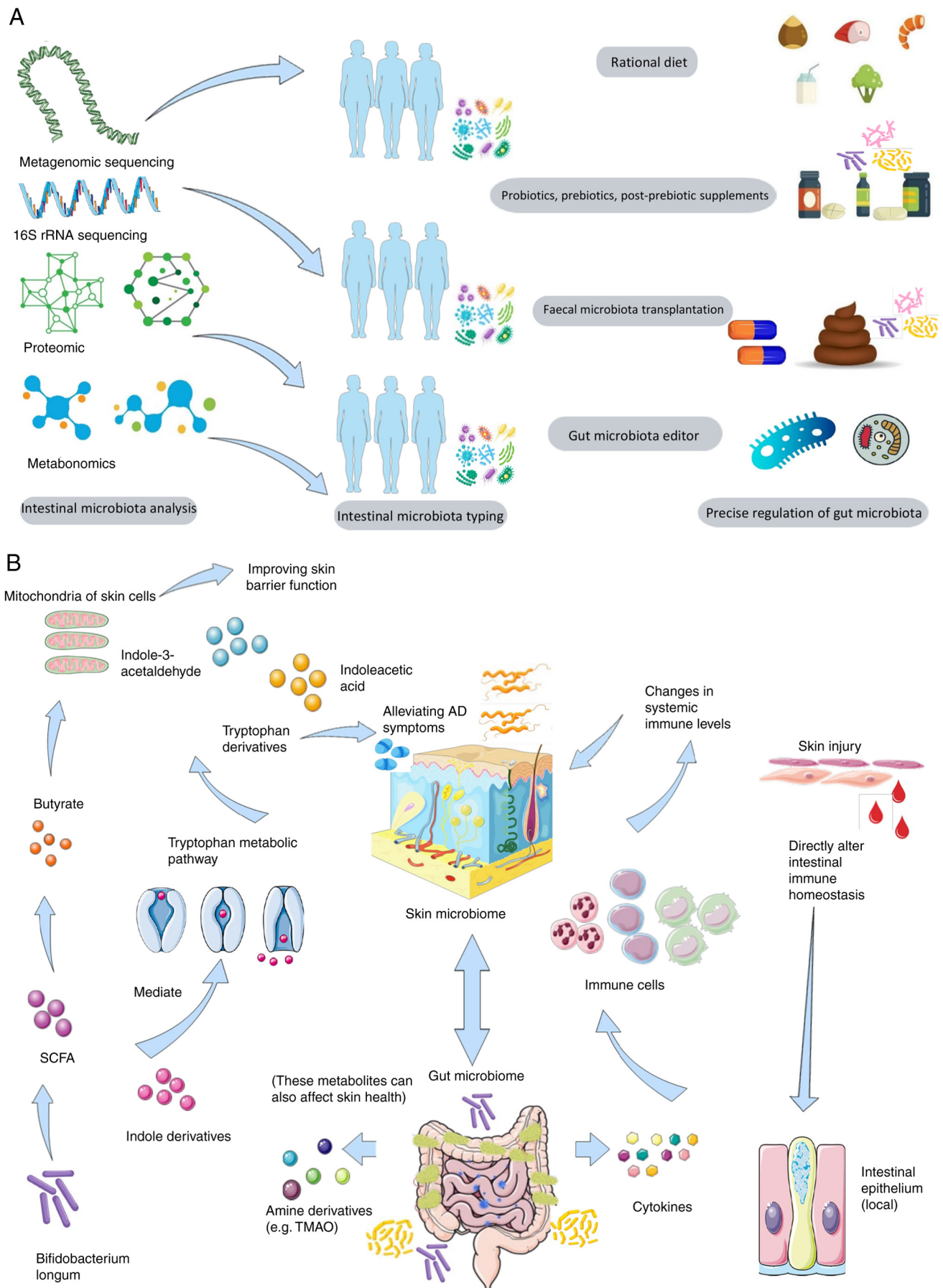
Propionibacterium acnes is the most important pathogen of acne. It is a lipophilic gram-positive anaerobe and the most abundant microorganism in the human hair follicle sebaceous gland.

D Obesity and metabolic diseases



Intestinal microecological imbalance is mainly caused by changes in the composition of intestinal flora, changes in bacterial activity or changes in bacterial distribution. According to the characteristics of the disease, it can be divided into three types: Proportion imbalance, location transfer and self-infection. Microbiome dysregulation impairs our ability to protect ourselves from pathogenic microbes. Pathogens that colonize the gut do not cause immediate toxic reactions or infections. They are latent and usually do not cause harm, but dysregulation of the flora causes them to overgrow uncontrollably, which is difficult to detect in the early stages and may eventually lead to many chronic health problems. For the digestive tract itself, dysregulation of the gut microbiota may lead to functional dyspepsia and irritable bowel syndrome, while at the level of other organs and systems, depression, liver disease, cardiovascular disease, lung disease and metabolic problems such as obesity have also been closely linked to dysregulation of the gut microbiota.

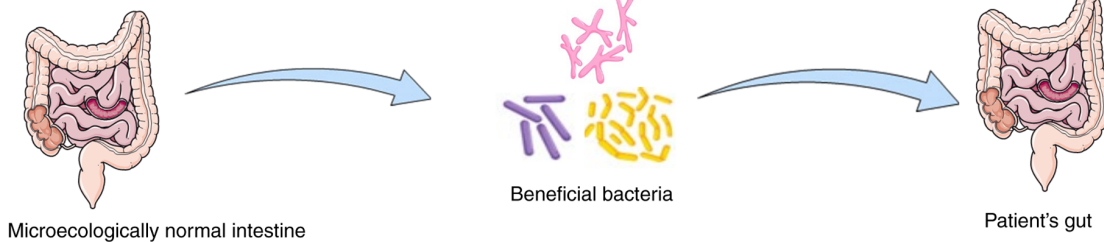
Figure 1. Basic components of the gut-skin axis (gut microbiota, skin microbiota) and the possible impact of gut microbiota on human health. (A) Members of the gut microbiota (mainly bacteria). Gut microbial communities maintain homeostasis through competitive exclusion, metabolic cross-feeding, and niche competition. (B) Factors that may affect gut microbiota composition, including diet, antibiotics, host genetics, age and environmental exposures. (C) Schematic representation of the skin microbiome. The skin surface exhibits an acidic pH, high salinity, low moisture and aerobic conditions, while the follicle-sebaceous unit is relatively anaerobic and lipid-rich. Commensal microbiota support skin barrier integrity through colonization resistance and immune modulation. (D) The gut-organ axis system, where the gut microbiota communicates bidirectionally with other organs (e.g., brain, kidney, liver, skin) via metabolites and microbial components through endocrine, neural and immune pathways.



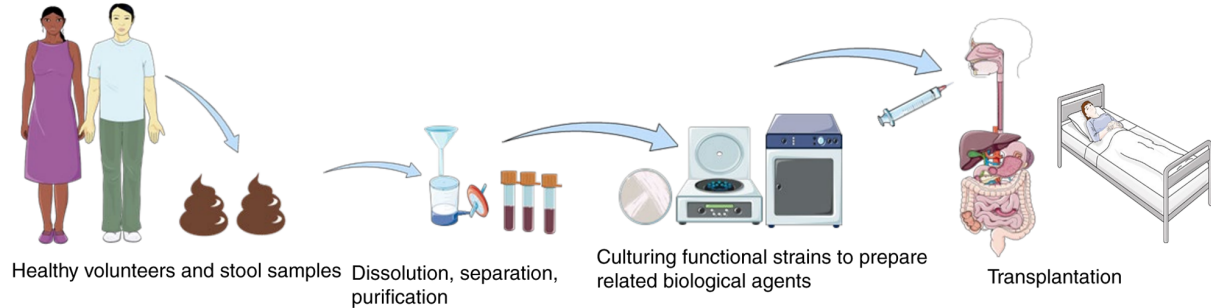
Intestinal microbiota can affect skin health in many ways, e.g. by producing chemicals such as short-chain fatty acids, affecting skin microbiota, regulating immune response, and affecting skin barrier function.

Figure 2. Continued.

C



Fecal microbiota transplantation (FMT) is the process of transplanting functional bacteria from healthy human feces into patients' digestive tracts in order to construct new intestinal microecology and thereby treat illness.



Therapeutic mechanism of fecal bacteria transplantation is mainly to regulate the composition of intestinal flora of patients. After fecal bacteria transplantation treatment, the microbial diversity in patients increased significantly, competing with harmful bacteria for growth, inhibiting their reproduction and preventing them from producing toxins.

D

Oral probiotics can increase the number and diversity of beneficial bacteria in the intestine, inhibit the growth of harmful bacteria, improve the barrier function of the intestine, reduce the inflammatory response and oxidative stress level of the skin.

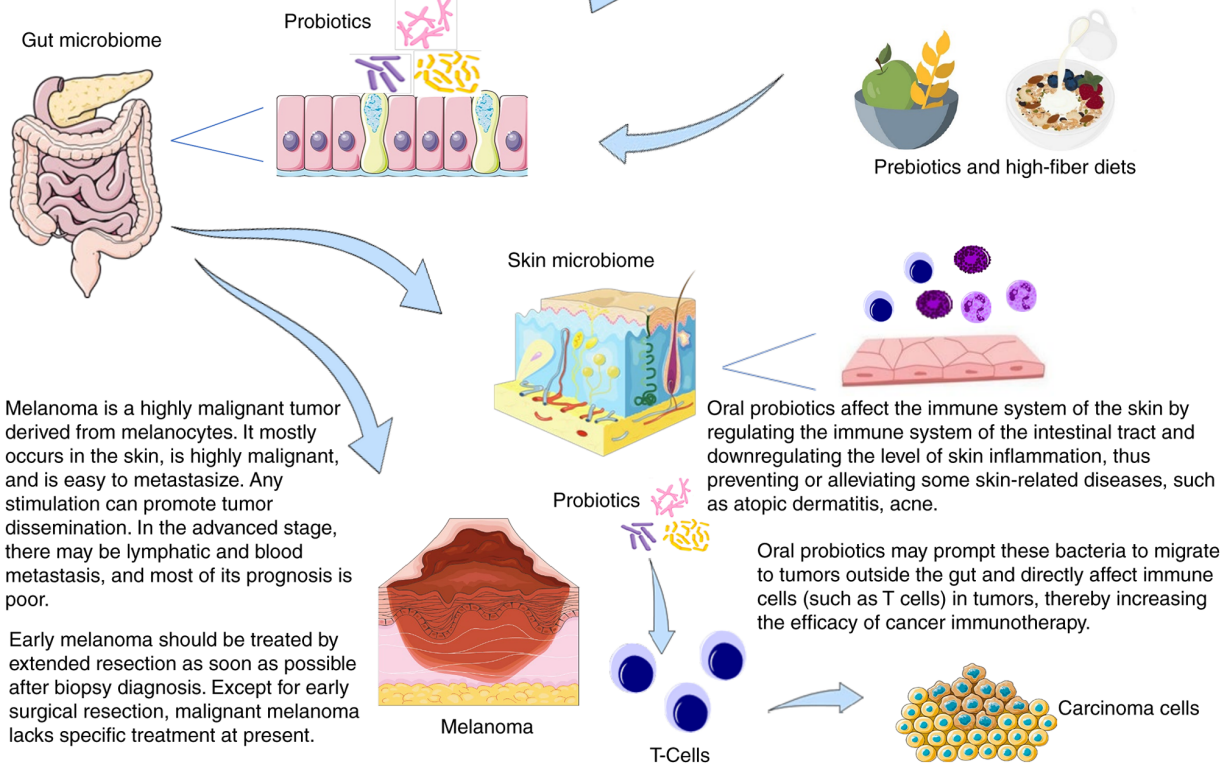


Figure 2. Implications of the gut microbial-skin axis, i.e., the bi-directional interaction between the gut and skin, and certain applications. (A) Next-generation sequencing enables taxonomic profiling, while multi-omics integration (metagenomics, metabolomics) facilitates functional annotation of microbial pathways. (B) Gut dysbiosis alters systemic levels of microbial metabolites (e.g., tryptophan derivatives), triggering skin inflammation. Conversely, cutaneous inflammation impairs intestinal barrier function, shifting the gut microbial composition. (C) The process of FMT, including donor screening, fecal slurry preparation and recipient delivery. Application in dermatology targets microbial reconstitution in conditions like AD. (D) Microbiota-derived metabolites may influence histological characteristics of early melanoma and clinical manifestations of advanced melanoma through direct or indirect immunomodulatory effects. AD, atopic dermatitis; FMT, fecal microbiota transplantation; TMAO, trimethylamine N-oxide.

Trompette *et al* (37) demonstrated that gut-derived butyrate enhances skin barrier function by modifying mitochondrial metabolism in keratinocytes. Fang *et al* (38) reported that *Bifidobacterium longum* produces indole derivatives that alleviate AD via the tryptophan pathway. Tryptophan metabolites (e.g., indoleacetic acid) are critical for maintaining intestinal and systemic immune homeostasis (39) (Fig. 2B).

The gut microbiota modulates both systemic and skin-specific immunity (16). Through arginine-induced barrier changes, it influences skin differentiation, immune activation and homeostatic balance (40) (Fig. 2B). Disrupted gut-immune crosstalk compromises skin barrier integrity, increasing susceptibility to inflammatory skin conditions. Marrs *et al* (41) associated a greater *Clostridium* abundance in infant guts with AD, suggesting that gut microbiota evolution during infancy affects immune tolerance development. Intestinal commensal bacteria prime innate immunity; dysbiosis may alter local immune responses via Toll-like receptor pathways or inflammasomes, promoting systemic inflammation (42).

Evidence of association between skin health and gut microbiome. Bidirectional interaction between the gut microbiome and skin health is central to the gut-skin axis theory. While most evidence highlights gut microbes influencing skin health, Dokoshi *et al* (43) demonstrated that skin injury directly remodels the gut microbiome (Fig. 2B), providing experimental support for bidirectional signaling and indicating that skin damage may impair gut immune homeostasis. Long *et al* (44), in a two-sample Mendelian randomization study, established a causal relationship between gut microbiota and four common inflammatory skin diseases: Eczema, acne, psoriasis and rosacea.

4. Gut microbiology in the treatment of skin diseases

Advances in clinical research: Gut microbial regulation and skin diseases. Understanding gut microbiota-skin interactions offers novel mechanistic insights for managing dermatological conditions. Clinical evidence reveals frequent comorbidity of skin and intestinal disorders, such as enteropathic acrodermatitis (zinc malabsorption causing dermatitis, alopecia and diarrhea) (45), and celiac disease (associated with eczema, psoriasis and urticaria) (46).

Restoring gut microbiota balance enhances intestinal barrier integrity and regulates immune responses (47). This involves upregulating immunomodulatory cytokines (e.g., IL-10) (48) and suppressing pro-inflammatory mediators (e.g., TNF- α) (49). Clinical interventions include probiotics, prebiotics, synbiotics and fecal microbiota transplantation (FMT) (50).

FMT in the treatment of skin diseases. FMT involves transferring processed stool from healthy donors to patients to rebuild gut microbiota. Initially used for digestive diseases (51-53), FMT's efficacy depends on donor and recipient factors (immune status, genetic diversity, gut microbial composition) and treatment protocols (stool amount, number of infusions, delivery route and adjuvant therapy) (54) (Fig. 2C).

While most FMT research focuses on gastrointestinal disorders, recent trials suggest it may modulate systemic immune responses, including in skin cancers like melanoma.

Kim *et al* (55) showed that FMT improved AD symptoms in mice by restoring gut microbiota. FMT enhances immunotherapy efficacy in cancer patients by modulating gut microbiota (56). Melanoma, the most common and prognostically worst skin cancer, is increasing globally (57). Baruch *et al* (58) observed that FMT induced favorable changes in immune cell infiltration and gene expression in intestinal and tumor microenvironments. Liu *et al* (59) demonstrated that FMT is effective for moderate to severe AD in adults, altering gut microbiota composition and function. However, FMT carries risks; Eshel *et al* (60) found that while FMT capsules rarely transmit bloodstream pathogens directly, they may indirectly promote bacterial translocation via gut inflammation, potentially compromising intestinal barrier integrity and increasing infection risk. Further in-depth studies are required to ascertain the efficacy and safety of FMT in treating other skin diseases.

Advances in the use of probiotics and prebiotics to modulate gut microbial composition in the treatment of skin diseases. Prebiotics are indigestible food components that selectively stimulate beneficial bacteria (e.g., *Bifidobacterium*, *Lactobacillus*) while inhibiting pathogenic overgrowth, thereby improving intestinal microecology (61). Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits through intestinal colonization (62). These interventions show promise beyond gastrointestinal and cardiovascular diseases (63,64) with emerging applications in dermatology.

Rahmayani *et al* (65) showed that oral probiotics increased serum IL-10 levels in patients with acne vulgaris (AV). IL-10 cytokines curtail excessive inflammation, enhance innate immunity and promote tissue repair, offering therapeutic potential for inflammatory diseases (66). Probiotic supplementation improves gut microbiota balance, inflammatory markers and quality of life in patients with psoriasis (67).

In oncology, gut microbiome modulation may enhance immunotherapy efficacy. Specific probiotics influence T-cell-mediated therapies (e.g., anti-programmed cell death 1, chimeric antigen receptor-T) (68), though strain-specific effects require further validation. Bender *et al* (69) demonstrated that *Lactobacillus reuteri* translocates to melanoma sites in mice, secreting indole-3-aldehyde to activate CD8⁺ T-cell receptors and potentiate immunotherapy. Such mechanisms hold potential for future immunomodulatory strategies pending resolution of delivery challenges and dose optimization.

5. Study of the 'gut microbe-skin axis' in specific skin diseases

Psoriasis. Psoriasis is an immune-mediated skin disease characterized by abnormal keratinocyte proliferation and differentiation, posing significant physical and psychological burdens (70). Previous studies suggested gut microbiota dysbiosis in patients with psoriasis, but the relationship remained vague (71). Zang *et al* (72) used bidirectional Mendelian randomization to identify *Pasteurellaceae*, *Brucella* and *Methanobrevibacter smithii* as potential pathogenic contributors, suggesting microbial targets for therapy (Table I). Zhao *et al* (73) demonstrated through metabolomics

Table I. Current status of intestinal microbiota modulation therapy in dermatological treatment.

Study (authors, year)	Disease	Analytical method/study type	Research conclusions	(Refs.)
Zang <i>et al</i> , 2023	Psoriasis	Two-sample Mendelian randomization	<i>Pasteurellales</i> , <i>Pasteurellaceae</i> , <i>Blautia</i> , <i>Methanobrevibacter</i> and <i>E. fissicatena</i> group are nominal risk factors for psoriasis	(72)
Zhao <i>et al</i> , 2023	Psoriasis	Metabonomics	<i>Bifidobacterium CCFM16</i> and <i>Lactobacillus plantarum</i> <i>CCFM8610</i> alleviate AD symptoms; probiotics mitigate antibiotic side effects and enhance acne therapy	(73)
Fang <i>et al</i> , 2020	AD	Metabonomics	Probiotic supplements can reduce the side effects of systemic antibiotics (minocycline) and work in concert with them to treat inflammatory acne	(82)
Eguren <i>et al</i> , 2024	AV	Randomized clinical trial	<i>Lacticaseibacillus rhamnosus</i> (CECT 30031) and <i>Arthrosira</i> <i>platensis</i> (BEA_IDA_0074B) were effective and well- tolerated in acne vulgaris treatment	(91)
Wang <i>et al</i> , 2020	CSU	Combined microbiome and metabolome analysis	Patients with CSU showed increased <i>Enterobacteriaceae</i> and decreased <i>Bacteroides</i> , <i>Faecobacterium</i> , <i>Bifidobacterium</i> and <i>Ruminococcaceae</i> ; serum metabolomics revealed altered docosahexaenoic acid, arachidonic acid, glutamic acid and succinic acid, suggesting disrupted unsaturated fatty acid and butyrate metabolism	(102)
Luo <i>et al</i> , 2022	CSU	Combined microbiome and metabolome analysis	Gut microbiota changes (increased <i>Firmicutes</i> , decreased <i>Bacteroides/Proteobacteria</i>) and altered fatty acid metabolism may contribute to immune dysregulation in CSU pathogenesis	(103)
Fu <i>et al</i> , 2024	Urticaria	Meta-analysis	Oral probiotic regimens have a significant therapeutic effect on urticaria, but the therapeutic effect of multiple probiotic combinations and the safety of probiotic therapy are not obvious	(104)
Bi <i>et al</i> , 2021	CU	Randomized clinical trial	Yimingjia® (main component is Five <i>Lactobacillus</i> strains and one <i>Bifidobacterium</i> strain) is safe and effective in adjuvant treatment of chronic urticaria in children for 4 weeks	(105)
Ni <i>et al</i> , 2020	Vitiligo	Combined microbiome and metabolome analysis	Patients with vitiligo show gut dysbiosis featuring <i>Corynebacterium type 1</i> , <i>Ruminococcus type 2</i> , <i>Actinobacillus</i> and <i>Psychrophilic Bacillus</i> , with distinct serum metabolite profiles (e.g., taurochenodeoxycholic acid, L-NG-monomethylarginine) vs. healthy controls	(111)
Luan <i>et al</i> , 2023	Vitiligo	Metagenome sequencing and bioinformatics analysis	The gut microbiota and genetic function of patients with vitiligo are different from those of healthy controls. The identified gut microbial markers may be useful for early diagnosis and therapeutic targets	(112)
Mrázek <i>et al</i> , 2019	Melanoma	Combined microbiome and metabolome analysis	Melanoma tissue and healthy skin, as well as MeLiM and control piglet fecal microbiota, showed significant diversity differences in 8-12-week-old piglets	(118)
Spencer <i>et al</i> , 2021	Melanoma	Multimiomics sequencing	Low-fiber diets and specific probiotics suppress intratumoral IFN- γ T cells, impairing anti-tumor immunity in mice	(123)
Routy <i>et al</i> , 2024	Melanoma	Combined microbiome and metabolome analysis	FMT partially overcomes immune checkpoint inhibitor resistance in refractory melanoma, is safe as first-line therapy and improves response rates in advanced cases	(124)
Kamal <i>et al</i> , 2025	Oral lichen planus	Randomized clinical trial	The combination of probiotic mixtures containing <i>Lactobacilli</i> with topical corticosteroids results in a significant reduction in the symptoms of oral lichen planus	(140)

AD, atopic dermatitis; AV, acne vulgaris; CSU, chronic spontaneous urticaria; CU, chronic urticaria; FMT, fecal microbiota transplantation.

that gut microbiota transplantation from severely affected mice exacerbated skin inflammation in mild cases, while a phosphodiesterase-4 inhibitor alleviated symptoms and restored the gut microbiota, providing a theoretical basis for gut microbiota-skin axis-based psoriasis treatment (Table I).

AD. AD is a common chronic inflammatory skin disease characterized by persistent itching and eczematous rash (74). It increases the risk of comorbidities like food allergies, asthma, allergic rhinitis and mental health disorders (75). The pathogenesis involves hereditary immune dysregulation, skin barrier dysfunction and environmental factors (76). The gut microbiota modulates immune system development, implying a key role in AD (77).

First-line AD treatment includes topical corticosteroids and calcineurin inhibitors (e.g., pimecrolimus, tacrolimus). For moderate to severe cases, ultraviolet phototherapy is used adjunctively (78). Probiotic supplementation is increasingly used, particularly in children, to modulate gut microbiota and regulate immune responses (79,80). Meta-analyses indicate certain probiotics reduce Scoring Atopic Dermatitis indices in adults (81). Fang *et al* (82) showed that *Bifidobacterium* CCFM16 and *Lactobacillus plantar* CCFM8610 specifically improve AD by altering gut microbiota composition and function (Table I).

AV. AV is a chronic inflammatory skin disease affecting sebaceous units, characterized by comedones, papules, pustules, nodules and scars, typically on the face, upper trunk and extremities (83). The global prevalence is estimated at 8.96% in men and 9.81% in women (84). The pathogenesis involves multifactorial mechanisms, with pubertal sebum hypersecretion being a key factor. AV often persists into adulthood with distinct features (85). Androgens and testosterone regulate sebum production, explaining why males often experience more severe symptoms (86).

Gut dysbiosis may exacerbate AV through upregulated insulin-like growth factor 1 signaling, insulin resistance and systemic pro-inflammatory cytokines (87). First-line treatments include topical retinoids, azelaic acid and benzoyl peroxide (88). The role of gut microbiota modulation via probiotics in improving AV is underexplored. Jung *et al* (89) found that probiotic-antibiotic combination therapy synergistically reduced inflammation and antibiotic side effects. Fabbrocini *et al* (90) showed that *Lactobacillus rhamnosus* SPI (LSP1) probiotic normalized skin insulin signaling gene expression. Eguren *et al* (91) conducted a 12-week trial with *Lactobacillus rhamnosus* and *Arthrospira* in patients with AV aged 12-30 years, finding the probiotic adjunct safe and effective (Table I).

Rosacea. Rosacea is a chronic recurrent inflammatory skin condition affecting the central face (forehead, nose, cheeks, chin) (92). It is classified into erythematotelangiectatic, papulopustular, phymatous and ocular subtypes (93).

Gastrointestinal disorders are common comorbidities (94) and rosacea is linked to inflammatory bowel disease (95,96). While mechanistic studies are limited, microbiota modulation shows therapeutic potential. Manzhali *et al* (97) showed that oral *Escherichia coli* Nissle 1917 increased beneficial bacteria

(*Bifidobacterium*, *Lactobacillus*) and improved mucin barrier function, resolving rosacea symptoms. Fortuna *et al* (98) reported a case of scalp rosacea treated with doxycycline and probiotics (*Bifidobacterium breve* BR03, *Lactobacillus salivarius* LS01), with significant improvement. These findings support further investigation into gut microbiota-targeted rosacea management.

Urticaria. According to 2021 guidelines, urticaria is classified as acute (lasting <6 weeks) or chronic urticaria (CU). CU is a common inflammatory skin disorder involving mast cell-mediated allergy and autoimmunity, characterized by recurrent wheals, angioedema and itching lasting ≥6 weeks (99). Pathophysiology involves immune dysregulation, inflammatory cascade imbalance and coagulation-fibrinolytic activation (100). CU subtypes include chronic spontaneous urticaria (CSU) and chronic inducible urticarial (101).

Research links the gut microbiota to urticaria. Wang *et al* (102) found reduced *Bacteroidetes* and *Proteobacteria* in patients with CSU, with butyric acid metabolism alterations (Table I). Luo *et al* (103) observed decreased *Bacteroidetes*, *Ruminococcus*, *Megasphaera* and anaerobic bacilli in CSU, with altered serum metabolites (e.g., unsaturated fatty acids, purines), suggesting immune dysregulation (Table I). Few studies exist on gut microbiome-modulating therapies for urticaria. Fu *et al* (104) reported that probiotics reduced symptom scores (Table I). Bi *et al* (105) showed that probiotic mixtures were safe and effective adjuncts for childhood CU (Table I). These preliminary findings require larger validation studies.

Vitiligo. Vitiligo is a depigmentation disorder affecting 0.5-2% globally, with a genetic component (106). It presents as white, scaleless patches (107). Pathophysiologically, vitiligo is an autoimmune condition where melanocytes are sensitive to oxidative stress, triggering inflammatory cytokine release and innate immune activation. CD8⁺ T cells destroy melanocytes, driven by IFN-γ. Oxidative stress may induce gut dysbiosis, promoting autoimmunity. IFN-γ blockade therapies temporarily reverse depigmentation but relapse occurs upon cessation (108). The chronic course of vitiligo affects patients' appearance and psychological well-being; Kussainova *et al* (109) reported a 35.8% anxiety prevalence, higher in women.

Current evidence on the gut-vitiligo link is limited. Emerging studies suggest gut microbiome involvement. Hadi *et al* (110) reported vitiligo-inflammatory bowel disease comorbidity. Ni *et al* (111) documented a *Firmicutes/Bacteroidetes* ratio reduction in patients with vitiligo (Table I), while Luan *et al* (112) observed decreased microbial alpha diversity with altered cysteine/galactose metabolism (Table I). These findings support the gut-microbiota-skin hypothesis but require further investigation for therapeutic applications.

Skin cancer (mainly melanoma). Skin cancer is the fifth most common cancer globally, with its incidence rising (113). It arises from genetic defects or DNA mutations in skin cells, primarily due to ultraviolet exposure (114). Skin cancers are

classified as malignant melanoma (MM) or non-melanoma skin cancer (NMSC). MM originates from melanocytes, while NMSC (e.g., squamous cell carcinoma, basal cell carcinoma) arises from epidermal cells (115). Treatments include cryotherapy, radiotherapy and photodynamic therapy, but novel approaches are needed (116).

MM is highly metastatic, has a poor prognosis and is the leading cause of death among patients with skin cancer (117). Mrazek *et al* (118) found compositional differences between melanoma and healthy skin microbiomes, with elevated *Fusobacterium* and *Eubacterium* in tumors (Table I). Mekadim *et al* (119) demonstrated distinct gut and skin microbiome profiles in melanoma models, addressing knowledge gaps (Table I).

Several studies confirmed that the gut microbiota can modulate the response to cancer immune checkpoint blockade therapy (120-122). Spencer *et al* (123) reported improved progression-free survival in ICB-treated patients with higher fiber intake, particularly without probiotics; fiber/prebiotics enhanced antitumor T-cell responses via microbiome modulation (Table I). Routy *et al* (124)'s phase I trial confirmed FMT safety combined with first-line melanoma therapy, though efficacy requires further validation (Fig. 2D) (Table I). Future investigations of the gut-skin axis may yield innovative therapeutic strategies for skin cancer.

Rare skin diseases (AIBD and LP)

Pemphigus and related disorders. Rare dermatoses like AIBD and LP receive limited research due to funding and recruitment challenges (125). AIBD involve chronic immune-mediated blistering, with fragile cutaneous/mucosal vesicles rupturing into erosions. These include pemphigus vulgaris (PV), bullous pemphigoid (BP) and mucous membrane pemphigoid (126). PV subtypes include vulgaris, foliaceus, IgA pemphigus and paraneoplastic pemphigus. BP, the most common pemphigoid, features tense, rupture-resistant subepidermal blisters, often involving the oropharyngeal and ocular mucosa. It primarily affects adults aged >50 years but can also occur in younger individuals (127).

Pemphigus has a long course and poor prognosis, severely affecting patients' quality of life, with most deaths due to uncontrollable secondary infections (128). The pathogenesis involves Th1/Th2 and Th17/Treg imbalances, leading to IgG autoantibodies that target epidermal/mucosal antigens, causing loss of cell adhesion and blister formation (129).

Huang *et al* (130) reported reduced *Lachnospira/Coprococcus* and elevated *Aspergillus* in PV fecal samples, with negative correlations between *Lachnospira/Coprococcus* and IL-17A suggesting T-cell modulation. Han *et al* (131) found a divergent gut microbiota in patients with PV vs. BP, implicating autoantibody and gut-barrier pathways.

LP. LP is a chronic inflammatory disease presenting as violaceous pruritic papules on skin, mucosa or nails. Subtypes include cutaneous LP (CLP) and oral LP (OLP), with possible esophageal, genital or nail involvement (132). The prevalence of LP ranges from 0.22 to 1%, with OLP about five times more common than CLP (133). Genital subtypes have been reported (134), and concurrent subtypes complicate diagnosis (135). The pathogenesis of CLP involves cell-mediated immune responses against basal keratinocytes (136).

Georgescu *et al* (137) reported an oxidant-antioxidant imbalance in patients with LP, suggesting oxidative stress plays a role.

Few studies have focused on the role of the 'gut microbe-skin axis' in rare skin diseases such as LP and pemphigus (22). Li *et al* (138) observed a distinct gut microbiota in patients with active pemphigus, with *Prevotella* spp. and *Coriobacteriaceae* abundance correlating with autoantibodies. Roy *et al* (139) reviewed intestinal microecological dysregulation in several rare diseases, including LP, and highlighted the complexity of host-microbiota interactions, emphasizing knowledge gaps, the need for improved study designs, and the promise of microbiome-based therapeutics. Kamal *et al* (140)'s trial on 60 patients with OLP showed a greater reduction in pain and Thongprasom scores with combined clobetasol/probiotic therapy vs. clobetasol alone. Despite research challenges, such as scarce pathogenic data and small cohorts, elucidating microbiota-skin interactions could yield novel diagnostics and therapies for rare dermatoses.

6. Challenges and prospects for preclinical and clinical research

Methodological advances and challenges: Data collection and analysis techniques. Despite progress, translating gut microbiome research into clinical applications remains challenging. Methodological limitations in data collection, representativeness and analysis are key barriers. Resources like GMrepo (<https://gmrepo.humangut.info/home>) and gutM-Gene (<https://bio-computing.hrbmu.edu.cn/gutmgene/#/home>) provide valuable data, but heterogeneity due to geographic, demographic and lifestyle factors complicates sampling and standardization (Fig. 2A). The lack of a consensus definition for 'healthy gut microbiota' impedes benchmark establishment (141,142).

Analytical techniques involve sequencing and data analysis (Fig. 2A). Sequencing and analysis methods face several limitations. High-throughput 16S rRNA sequencing offers taxonomic profiling but lacks strain-level resolution and poorly detects archaea/viruses. Whole-genome shotgun metagenomics enables functional insights but requires computational resources for high-dimensional data integration (143). Microbiome-wide association studies link microbial patterns to diseases like obesity and colorectal cancer (144), but cannot establish any causality due to confounders like medications and comorbidities (145). Integrative multi-omics approaches (e.g., metagenomics, metabolomics) and genome-wide association studies provide deeper insights (146,147) but require advanced normalization to address batch effects. Machine learning shows promise for modeling microbial interactions and predicting functional outputs from fragmented data (148). Ma *et al* (149) applied machine learning to identify diagnostic gut microbiome biomarkers for AD, enabling precision management.

Ethical issues and safety considerations. FMT, probiotics and prebiotics present ethical and safety challenges. Al-Bakri *et al* (150) highlighted skepticism among Jordanian medical workers regarding FMT efficacy, influenced by cultural and religious factors. Patients expressed safety

concerns about infection risks. Regulatory complexity arises from divergent global standards; the Food and Drug Administration (FDA) classifies FMT as an investigational drug requiring rigorous oversight. Two microbiota-derived therapeutics are FDA-approved: Rebyota® (RBX2660; Ferring Pharmaceuticals) and VOWST™ (SER-109; Seres Therapeutics) (151).

Patient and provider acceptance barriers persist, especially in culturally conservative settings. Probiotics, though generally safer than FMT, carry risks such as bacteremia in immunocompromised hosts and horizontal gene transfer (152,153). Cases like *Lactobacillus rhamnosus* infections in immunosuppressed individuals underscore the need for further safety research (154-156).

Future directions and prospects. Preclinical gut microbiome research will continue diversifying. International data-sharing collaborations may overcome ethnographic limitations (157). Integrating medicine, biology and informatics could expand the research scope, as seen in machine learning applications for microbial community analysis (158). Current algorithms predict health status and identify disease-microbiome associations through differential abundance analysis (159).

In clinical translation, precision medicine requires refinement. Longitudinal studies with larger cohorts may better evaluate probiotic efficacy across populations, informing targeted microbiome-based interventions using adaptive trial designs (e.g., cluster randomized controlled trials). These frameworks would strengthen disease prevention and treatment strategies.

Emerging technologies like high-intensity ultrasound show potential for enhancing functional food development by improving probiotic stability and bioactivity (160). Future validation studies should assess gut health optimization and personalized approaches (161,162). Beyond dairy probiotics, fermented foods and beverages are demonstrating health benefits (163,164).

7. Conclusions

The following conclusions can be drawn from the present review: i) The gut-skin axis framework highlights the influence of gut microbiota on skin homeostasis, with dysbiosis implicated in psoriasis, AD, acne and AIBD; ii) the gut microbiota modulates skin health through immune regulation, microbial metabolite production (e.g., SCFAs) and systemic inflammation control. FMT, probiotics and prebiotics show promise in restoring microbial balance and reducing inflammation, though larger trials are needed; iii) current evidence primarily establishes correlations, but causal relationships require validation via multi-omics approaches integrating genomics, metabolomics and immune profiling; iv) clinical translation faces challenges including methodological limitations, ethical concerns with FMT and insufficient long-term safety data for probiotics; v) mechanistic insights into rare skin diseases via the gut-skin axis are scarce, warranting targeted investigations; vi) future research should prioritize patient-specific microbiome interventions, machine-learning diagnostics and cross-disciplinary collaboration (e.g., dermatology-gastroenterology-bioinformatics) to advance

precision dermatology; and vii) the gut-skin axis redefines skincare paradigms, emphasizing gut health as integral to dermatological wellness, with breakthroughs in microbiome engineering and Artificial Intelligence-driven interventions offering transformative potential.

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Authors' contributions

YZ performed the analyses and wrote the first draft of the manuscript. CY, JZ, QY, XZ and XZ performed the literature search and discussed and edited the manuscript. XZ and XZ supervised the preparation of the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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