

Effect of Gut Microbiome and Outcome of Gut Dysbiosis on Skin Health: Gut-Skin Axis

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Abstract

Recent advances in metagenomics and immunology have revealed the gut-skin axis, a bidirectional communication where the gastrointestinal microbiota influences skin homeostasis and immune response. This axis operates through systemic circulation of microbial metabolites such as short chain fatty acids (SCFAs), neuroendocrine signaling and modulation of systemic inflammation. The skin and the gut represent two of the body's most significant ecological niche, hosting complex and dense microbiomes. Any disruption in the normal gut microbiome termed dysbiosis can impair the skin health. Dysbiosis can alter gut barrier permeability (leaky gut) and allow pathogens and its metabolites to enter the blood stream. The proinflammatory cytokines that enter systemic circulation migrate to the skin, where they alter the cutaneous environment and trigger or exacerbate several inflammatory pathologies, psoriasis, atopic dermatitis (AD), acne vulgaris (AV) and rosacea. Although multiple studies have demonstrated an association between gut dysbiosis and various skin dermatoses, the underlying mechanisms by which these alterations influence skin health remain incompletely understood. This review summarizes existing data on microbial ecology and its functional contribution to host health and homeostasis. While exploring potential mechanisms links between gut-skin axis and associated diseases. Furthermore, we review current and emerging interventions targeting and modulating gut microbiomes, and discuss their therapeutic potential in skin disorders.

Introduction

The human gastrointestinal system plays a crucial role in maintaining host immunity and health. Composed of a diverse community of bacteria, archaea, and eukaryotes, and they widely reside in the human gastrointestinal tract. Similarly, skin serves as an anatomical barrier and has commensals which play a major role in innate immunity. Both skin and gut actively work in maintaining homeostasis with the immune system. They are constantly exposed to an external environment and several pathogens every day. The intestines and skin are remarkably similar. Both harbor extensive microbiomes, rich vascularization, innervation and their interaction with the immune system. Gut and skin having labile cells, have a high cell turnover rate and are constantly replaced to maintain integrity of skin and gut barrier respectively. The digestive tract and skin are both densely populated with microbiota, with the skin hosting approximately 10^{12} microbial cells and the gut containing around 10^{14} microbial cells. Microbiome is the key regulator in the normal functioning of the immune system. Thus, a dysbiosis in skin or gut commensals can alter immune response and cause skin diseases. Not only is the skin microbiome altered, but also surprisingly many skin diseases are accompanied by an altered gut microbiome leading to various dermatoses like atopic dermatitis (AD), psoriasis, acne vulgaris (AV), rosaceae and chronic urticaria (CU). This review highlights the normal functioning and factors influencing gut microbiome, bidirectional

communication of gut-skin axis and dysbiosis associated with skin pathology. In addition, the review discusses intervention based approaches aimed at modulating gut microbiota.

Methods

This study was designed as a narrative review to consolidate and critically summarize current evidence relating relationships between gut microbiota, probiotics, and dermatological conditions. A systematic search of peer-reviewed articles was performed using electronic databases including PubMed, Scopus, Web of Science, and MDPI journals, covering publications available up to January 2026. Search terms included a combination of controlled vocabulary and free-text keywords such as *gut microbiota*, *skin microbiome*, *probiotics*, *prebiotics*, *synbiotics*, *postbiotics*, *atopic dermatitis*, *psoriasis*, *acne vulgaris*, and *chronic urticaria*. Boolean operators were applied to broaden and refine retrieval of relevant studies.

Both original research and review articles were included to capture current knowledge on the gut–skin axis and interventions involving probiotics, prebiotics, synbiotics, and postbiotics. Studies focusing exclusively on animal models were included only if they provided mechanistic insights relevant to human skin conditions.

Titles and abstracts were screened to remove duplicates and irrelevant studies. Full texts of potentially relevant articles were retrieved and assessed for eligibility. Data extracted included study type, population characteristics, microbial interventions, outcomes on skin conditions, and reported mechanisms of action. The findings were then synthesized qualitatively to summarize current evidence on the interactions between gut microbiota and skin health.

Skin and gut ecology

The skin is the largest organ of the human body and provides multiple niches for colonization by diverse microbial communities, such as the stratum corneum, hair follicles, and sebaceous glands. Healthy human skin harbors >1,000 bacterial species, mainly within the genera *Brevibacterium*, *Propionibacterium*, *Micrococcus*, *Staphylococcus*, *Streptococcus*, and *Corynebacterium*, and *Malassezia* is the main fungal genus. Neonates born vaginally initially carry a skin microbiota signature closely resembling their mother's vaginal bacteria, predominately featuring *Lactobacillus* spp. Conversely, infants delivered by cesarean section often display lower skin microbial diversity, being mainly colonized by environmental microorganisms and those from their mother's skin, including *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species. Like skin, human gut is a home to innumerable amounts of microbes. A number of gut bacteria (e.g. *Lactobacilli*, *E. coli*, *Bifidobacterium*, *Streptococcus thermophilus*, *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, *Fusobacteria*, *Tenericutes*, *Spirochaetes*, *Cyanobacteria* and *Saccharibacteria*) contribute to maintenance of human health state, whereas others (e.g., *Clostridium difficile*, *Campylobacter*, *Enterococcus faecalis*, *Helicobacter pylori*) are more prevalent in disease states. Humans acquire maternal microbiomes mainly from the birth canal and microbial diversity changes over time and infants microbiota are derived from breast milk, and a reduction in the diversity of the intestinal microbiota has been reported in infants fed a milk-replacement mixture.

Site specific ecology

Studies have shown that the skin of each body part, driven by the hair follicle and gland composition resulting in distinct niches for bacterial growth, exhibits different microbe compositions. Sebaceous sites such as the glabella and back, are dominated by lipophilic *Cutibacterium* species. Moist areas, such as

elbow and knee bends and toe webs, are mostly colonized by *Staphylococcus* and *Corynebacterium* species, as well as *beta-Proteobacterium*. *Cutibacterium acnes* (*C. acnes*) and *Corynebacterium* species primarily invade dry regions, such as the volar forearm. *Malassezia* species predominates on the core body and arms that play a complex dual role in the skin microbiome as both commensal and potential pathogen. Similarly, based on chemical composition and physical state, the GI tract is divided into distinct sections. The upper GI tract, stomach, and small intestine have comparably small numbers of microbial species because of a low pH levels and shorter transition period. The colon is the most colonized region of the GI tract. Fungal diversity, in contrast, is relatively limited in the human gut. The prevalent fungal genera are *Saccharomyces*, *Candida*, and *Cladosporium*. An increase in *Candida*, *Aspergillus*, *Fusarium*, and *Cryptococcus* in the gut may have a pathogenic effect on the host. For example, children with type I diabetes have high numbers of *Saccharomyces* and *Candida* yeasts in their gut.

Functions of skin and gut microbiome

The gut microbiota maintains a symbiotic relationship with the gut mucosa and does metabolic, immunological, gut protective functions and pathogen resistance. Many factors influence gut health and microbiota, with nutrition and diet being a major part. Metabolic functions include nutrient metabolism where fermentation of indigestible carbohydrates by bacteria yields short chain fatty acids (SCFAs) like butyrate, propionate and acetate for host energy and influencing glucose homeostasis. These SCFAs create a low pH medium within the gut not allowing pathogens to proliferate, and showing antimicrobial activity. They also exhibit extensive anti-inflammatory properties through interacting with immune cells. SCFAs have also been found in maintaining the tightness of the intestinal barrier by promoting the production of mucin glycoproteins responsible for creating intestinal integrity and inhibiting the buildup of potentially harmful metabolic by-products, such as D-lactate.

Synthesis of vitamin K and B, cortisol, gamma-aminobutyric acid (GABA), tryptophan, serotonin, dopamine, bile acid conversion, protein and gas metabolism are its other metabolic functions. Gut microbiome plays an important role in protection and immunity of the host against pathogens. Microbes induce antimicrobial peptides (AMP) from epithelial cells of the gut and the most abundant AMP is human defensin. They are crucial components of immunoreactive substances and affect the innate immunity system. AMP modulates the immune system in response to pathogens. Interaction between immune cells and gut microbiota also influences immune response, for example, *B. fragilis* enhances phagocytic function of macrophages. Gut microbe derived metabolites regulate Th1 and Th2 cell functions and modulate Th17 cell immunological function and differentiation. They also could promote B cell maturation and enhance specific IgA antibody response. Immune tolerance towards dietary and environmental antigens is modified by gut commensals which also protect against pathogens. Overall, the gut microflora induces maturation of the innate and acquired immune system and maintains immune homeostasis. Similarly skin microbiome and skin barrier are symbiotically related and affect each other in physical, chemical and immunological ways. The commensals also directly interact with pathogens encountered on the skin surface. Firstly, the skin acting as anatomical barrier against external invasions has keratin. Keratin, which is present in the stratified squamous epithelium of the skin, makes the skin resistant to weak acids and bases, bacterial enzymes and toxins. Microbiota is essential for maintaining epithelial barrier integrity and function of skin barrier. In skin damage, microbes produce metabolites that activate the epidermal keratinocytes, promoting epithelial differentiation and supporting the epithelial integrity. Another function of the microbiome is producing substances that contribute to the formation of the skin's lipid barrier. A study

using a mouse model reported that *S. epidermidis* secretes a sphingomyelinase that helps the host to acquire essential nutrients for the bacteria and produce ceramide. Ceramide being a key component of skin barrier prevents water loss of damaged skin and prevents dehydration and aging. Secondly, the chemical barrier is made of numerous lipids and acids secreted by the epidermis and the microbiota. Sebum from the sebaceous glands acts as a seal for hair follicles and includes numerous antibacterial compounds. *C. acnes* and *Corynebacterium* are abundant in the sebaceous regions that secrete lipases that hydrolyse triglycerides to free fatty acids in sebum. These free fatty acids maintain a low pH, inhibiting the growth of pathogens and enhancing skin immunity by stimulating the secretion of human β -defensin 2, one of the most abundant antimicrobial peptides (AMPs) in human skin. Lastly, like the gut, skin also stimulates a range of innate immune responses and maintains the immune barrier. For example, *S. epidermidis* modulates the innate immune system by activating $\gamma\delta$ T cells and upregulating perforin-2, β -defensin and cathelicidins which inhibit the growth of harmful bacteria and fungi while recruiting immune cells to infection sites. They not only enhance skin defence but also prevent excessive inflammation and promote development of regulatory T cells (Tregs). In addition to microbe-host relationship, microbe-microbe relationship also acts as a barrier against proliferation and colonisation of pathogens. While these relationships are not very well understood, coagulase-negative *Staphylococcus* (CoNS) species for *S. aureus* have been well studied. Among the most prevalent microorganisms in the skin microbiome are CoNS species, such as *S. epidermidis*, *S. capitis*, *S. caprae*, *S. hominis*, *S. lugdunensis*, and *S. haemolyticus*. CoNS secretes AMPs to inhibit *S. aureus*. In individuals with atopic dermatitis (AD), for instance, certain strains of *S. hominis* release antibiotics that prevent *S. aureus* colonization. Furthermore, lugdunin, a powerful anti-*S. aureus* AMP, is produced by *S. lugdunensis* in the nasal cavity. Therefore, both the intestine and the skin host diverse bacterial, fungal, and viral species that maintain symbiosis with the human habitat and maintain immune homeostasis and effectively respond to environmental stimuli. They produce metabolites that mediate host microbe-communication, promoting tissue integrity and repair and prevent invasion of pathogenic organisms. They also regulate inflammatory pathways and maintain the anti-inflammatory state. Disruption of this balance might lead to an impaired barrier function and a pro-inflammatory state in skin and GIT.

Gut-skin communication

Gut-skin communication occurs through immuno-cross linking between the gut and the skin. Recent studies indicate a significant association between the composition and functionality of gut microbiome and various skin disorders. The gut microbiota modulates both systemic and skin specific immunity, thereby the regions colonized by commensals such as skin and the gut has a considerable amount of immune cells. Several rodent studies have been documented to show beneficial effects of gut bacteria on skin health, for instance, a study with mice which received *Lactobacillus reuteri* supplementation showed increased dermal thickness, enhanced folliculogenesis and increased sebocyte production which manifested as thicker and shinier fur. Microbial dysbiosis refers to an imbalance between normal residing commensals and pathogenic organisms. A dysbiotic gut microbiota negatively impacts the skin. There is a bidirectional interaction between gut microbiome and skin health, for example, Skin exposure to ultraviolet B (UVB) and therefore indirectly to serum vitamin D levels increase the α and β diversity of the gut microbiome. Gut microbiota-derived metabolites mediate skin interactions through short-chain fatty acids, tryptophan metabolites and amine derivatives (e.g., trimethylamine N-oxide), which exert systemic effects via specific receptors. SCFAs, as mentioned earlier, have anti-inflammatory properties

which prevents growth of harmful bacteria on skin and improves T cell function and development. On the skin, antiinflammatory action is mediated through regulatory T cells (Tregs), which is reduced in certain inflammatory skin disorders. The gut has a 'mucosal firewall' which comprises gut epithelial barrier, mucus layer, T cell, IgA and dendritic cells (DCs). It is a multi-layered defense system that protects the body from pathogens, toxins, and excessive immune activation while maintaining tolerance to harmless commensals and nutrients. The mucosal firewall limits the shift of commensal bacteria to the gut associated lymphoid tissues (GALTs) thus preventing inflammation of gut and the skin. GALTs are mucosa associated lymphoid tissue (MALTs) in small intestine, including Peyer's patches, isolated lymphoid follicles of intestine, appendix and mesenteric lymph nodes along with diffuse lymphoid tissue in lamina propria and intraepithelial lymphocytes, which play a crucial role in maintaining gut barrier integrity. Healthy GALT supports IgA production and tolerance, potentially improving skin microbiome balance and reducing allergic skin disorders. Innate immune cells of GALT recognise nonspecific infections and activate both the innate and adaptive immune response. Dysregulated GALT responses can promote Th2/Th17 imbalance that exacerbates skin barrier dysfunction via circulating cytokines and immune cells. Therefore, gut barrier integrity maintained by action of mucus, immune cells, IgA and antimicrobial peptides (AMPs) produced by epithelial cells enhanced by gut microbiome prevents bacteria from entering blood stream thus no systemic inflammation and cytokines ultimately maintaining skin homeostasis. The role of neurotransmitters produced by gut microbes such as GABA, acetylcholine, dopamine and serotonin also play a role in skin health. These neurotransmitters modulate skin function through the nervous system and also produce systemic effects by entering the bloodstream through intestinal epithelium. For example, an experiment conducted on inbred mouse line employed as a human AD model led to the conclusion that by increasing the production of serum IgE and splenocyte IL-4, GABA balances Th1 and Th2 levels, keeping Th1 predominant, which effectively diminishes AD-like skin disorders in human. GABA also increases human type 1 collagen by suppressing type 1 collagen degrading enzyme matrix metalloproteinase-1 (MMP-1) and maintains skin elasticity. Though fully not yet explored, the link between skin health and immunological responses caused by the gut microbiome is still largely unclear and requires further research.

Factors affecting gut microbiome

As discussed earlier, it is important that gut microbiome homeostasis is maintained in the gut in order to maintain gut barrier integrity and skin health. There are several factors that influence the health of the gut with diet and dietary components playing the major role. Diet can positively as well as negatively impact the skin health through alteration of gut microbiome.

Diet

Dietary fiber and the gut microbiome

Dietary fibers are non digestible carbohydrates and are parts of plant-based foods. They are further classified as soluble and insoluble fiber. Dietary fibers such as pectin, wheat bran, oats, barley and resistant starch escape digestion and are fermented by gut flora producing SCFAs. It is very well known that SCFA butyrate, acetate and propionate have anti inflammatory properties. Studies show that when dietary fiber intake was reduced, SCFA production was also reduced and thereby increased systemic inflammatory markers and altered gut flora.

Polyphenols and flavonoids

Polyphenols and flavonoids play a major role in gut flora composition and function. They are secondary metabolites produced by plants and have health promoting effects such as antioxidant, anti-inflammatory, antibacterial, anti-adipogenic and neuroprotective properties. They are abundant in fruits, vegetables, berries, tea, wine and pomegranate. These compounds upregulate beneficial bacteria in the gut.

Source	Beneficial bacteria	Pathogen inhibition
Red Wine Flavonoids	↑ Bacteroides, Prevotella, Bifidobacterium	↓ E. coli, Enterobacteriaceae
Grape Polyphenols	↑ Bifidobacterium, Lactobacillus	↓ Clostridium, Bacteroides
Berry Anthocyanins	↑ Akkermansia, Lactobacillus	↓ Ruminococcus
Pomegranate Ellagitannins	↑ Bifidobacterium, Lactobacillus	↓ Proteobacteria

Table 1: Polyphenols and Flavonoids sources and their effect on gut bacteria

(Data from Beam A, Clinger E, Hao L. Effect of Diet and Dietary Components on the Composition of the Gut Microbiota. *Nutrients* 2021;13(8):2795.)

Western and high fat diet

A typical western diet is composed of high consumption of red and processed meat, containing high levels of carnitine and choline. Trimethylamine (TMA) is a compound produced from carnitine and choline by the gut bacteria Firmicutes and Proteobacteria, which is then transported to the liver and converted into trimethylamine N-oxide (TMAO). TMAO is associated with systemic inflammation and insulin resistance. Trans fatty acids (TFAs) primarily arise from industrial partial hydrogenation of vegetable oils. Diet rich in trans fatty acids such as processed foods increase the number of harmful microbes such as Desulfovibrionaceae and Proteobacteria while suppressing beneficial flora e.g. members of Bacteroidetes, Lachnospiraceae, and Bacteroidales. They cause inflammation of the gut which then manifests on the skin. When beneficial bacteria are reduced there is an increase in lipopolysaccharides. This leads to loss of mucosal firewall function and is associated with delayed skin wound healing due to systemic inflammation and oxidative stress which may be exacerbated by a high fat diet and alcohol. Moreover, a diet rich in fish oil and olive oil has been associated with reduction in skin inflammation due to their high levels of omega 3 and mono-unsaturated fatty acids.

Protein rich diet

Ingestion of a diet containing whey and pea protein extracts increases the abundance of Lactobacillus and Bifidobacterium and pathogenic Bacteroides fragilis and Clostridium perfringens is simultaneously decreased. SCFA levels are also increased with consumption of pea proteins which is necessary in keeping healthy gut barriers. A high collagen peptide diet contains high quantities of microbes which protect the

skin from wound healing and promote wound healing. In contrast, a diet containing excessive levels of animal protein can result in production of unfavourable metabolites such as indoxyl sulfate, TMAO and p-cresyl sulfate which is shown to be linked with psoriatic arthritis.

Breastmilk

Breast feeding is the major factor in development of infant's gut flora. Microbial colonisation of the gut is important in order to maintain metabolism, absorption of nutrients, immunologic maturation and proper gastrointestinal development. Human breast milk is rich in oligosaccharides which is necessary for proliferation of *Lactobacillus* and *Bifidobacterium* species. Immunological superiority is another advantage to breast milk, IgA, lactoferrin which protects from *Escherichia coli* and immune defences cells. They also contain growth factors which helps in maturation of intestine and decreases the risk of allergy. Furthermore, formula fed infants or cessation of breast feeding is associated with high opportunistic bacterial colonisation such as *Escherichia coli* and *Clostridium difficile*, while predisposing them to diarrheal, respiratory diseases, hypersensitivity reactions and asthma.

Supplements

Antibiotics

The misuse and prolonged use of antibiotics has detrimental effects on the gut flora. There is reduced species diversity, altered metabolism and development of antibiotic resistant organisms which in turn results in reduced response to therapy, antibiotic associated diarrhoea and recurrent *Clostridioides difficile* infections. These antibiotics have the potential to change the bacterial flora in the gut leading to dysbiosis and consequently skin abnormalities and delayed skin wound healing repair mechanisms. For example, administration of a combination of meropenem, gentamicin, and vancomycin resulted in an increase in the prevalence of *Enterobacteriaceae* and other pathogenic bacteria, and a decrease in *Bifidobacterium* and butyrate-producing species. Additionally, opportunistic fungi like *Candida* species also proliferates in the human gut with use of levofloxacin and moxifloxacin, this increase in *Candida* species manifest as skin redness which in turn accelerates aging. Exposure to antibiotics in infancy is associated with delay in microbiota development and use in childhood has been associated with several negative outcomes like obesity, asthma, allergy and inflammatory bowel disease.

Prebiotics and probiotics

Prebiotics simply contain compounds that promote the growth of microorganisms, and metabolites produced by them are useful to the host. Whereas probiotics are living organisms that, when consumed in sufficient proportions, have health benefits. Although there are many different sources of prebiotics, such as breast milk, soybeans, and raw oats, the oligosaccharides found in plants are the most often used prebiotics, for example fructooligosaccharides, galactooligosaccharides, inulin, polydextrose, lactulose, sorbitol, and xylitol. Prebiotics are not degraded in the upper regions of the gastrointestinal tract and reach the colon intact, where it is degraded by the gut microbiota to produce acetic, propionic, butyric, and lactic acids as well as gasses. In the meanwhile, the most popular probiotics are *Lactobacillus* and *Bifidobacterium* species. *Bacillus*, *Streptococcus*, *Enterococcus*, and *Saccharomyces* are further microbial species that can be utilized as probiotics. Both prebiotics and probiotics influence the gut-skin axis, where gut health improvements indirectly benefit skin by lowering systemic inflammation and enhancing immune responses. Several beneficial effects have been demonstrated, for example, measures of disease

activity were improved in psoriasis patients taking probiotic and prebiotic supplements along with anti-psoriatic local therapy. They restore skin microbiota balance, reducing inflammation in conditions like acne, eczema, and rosacea via strains such as *Lactobacillus* and *Bifidobacterium*, which compete with pathogens and strengthen the skin barrier. For instance, a study evaluated a probiotic therapy on intestinal borne dermatoses, results showed statistically significant improvement in dermatoses such as rosacea and acne, with some participants achieving complete resolution, compared with the placebo group. Also daily consumption of fermented milk containing *Lactobacillus bulgaricus* and *Streptococcus thermophilus* showed clinical improvement of acne over 12 weeks in a clinical study. Children who received probiotic supplements after the neonatal period were found to have a substantially lower risk of developing atopic dermatitis.

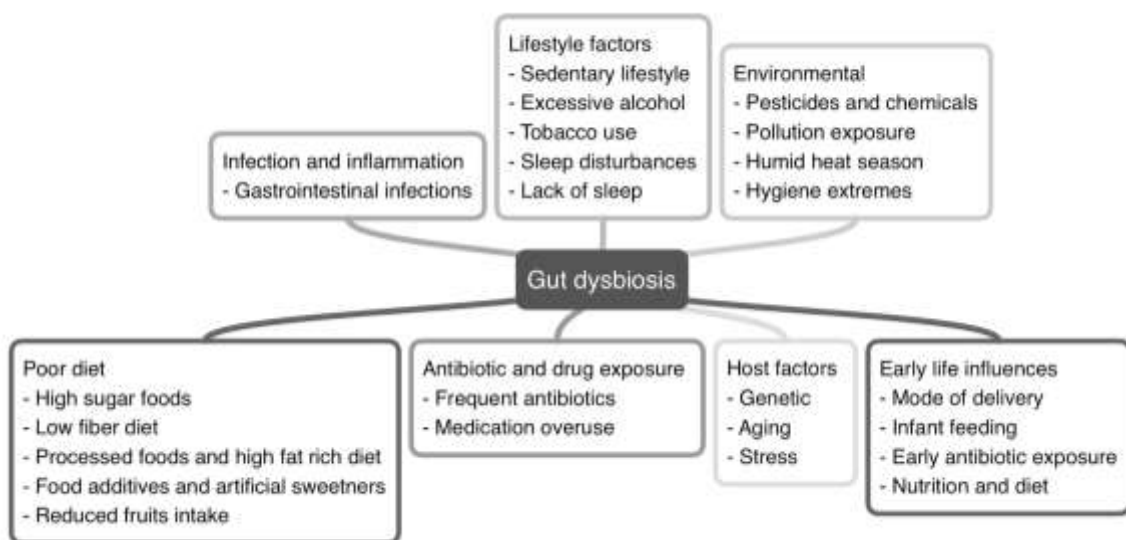


Figure 1- Flow chart illustrating major factors contributing to gut dysbiosis

Gut microbial dysbiosis and its impact on skin diseases

Acne Vulgaris

Acne vulgaris is a common chronic cutaneous inflammatory disorder of the pilosebaceous unit. The disease and its related disruption of the skin microbiome have been associated with specific strains of *Cutibacterium acnes*. The condition commonly manifests as inflammatory lesions such as papules, pustules, or nodules primarily on the face, although it can also affect the upper arms, trunk, and back and as non-inflammatory lesions such as open or closed comedones. It is a multifactorial disease and involves the interaction of several host factors with skin microbiome composition playing a major role. Other factors include the immunological state of the host, hormones, sebum production, genetics, diet, etc. It has been postulated to have a gastrointestinal mechanism, however there is no direct evidence that gut microbial dysbiosis contributes to pathogenesis of acne vulgaris. Possible mechanisms of association:

1. High glycemic and high fat rich diets reduce the levels of helpful gut microbes and increase the concentration of LPS, which leads to development of systemic inflammation and pro-inflammatory cytokines.
2. Latest research shows that the theory of microbiota-gut-brain axis plays crucial role in maintaining optimal neuroendocrine responses, and that changes with gut dysbiosis and affect CNS and hypothalamus pituitary adrenal axis (HAP) eventually influencing the hormonal responses in acne

vulgaris. HAP controls various pathways and hormones involved in the pathogenesis of acne, such as androgens, insulin-like-growth factor, corticotrophin releasing hormones, adrenocorticotrophic hormones and glucocorticoids.

3. An association between acne and reduced gastric acid secretion has been described where low acidity levels allow migration of bacteria to the small intestine, leading to dysbiosis, increased intestinal permeability, and subsequent skin inflammation.
4. Numerous studies have shown that anxiety and depression change gut flora and increase intestinal permeability.

Microbiome profiles:

In 2018, a study showed, higher proportion of Bacteroidetes in patients with acne and there was a decrease in Firmicutes and Clostridial families such as Lachnospiraceae and Ruminococcaceae, which are potentially beneficial. Additionally, in a clinical study, 31 acne patients vs 31 controls demonstrated, acne patients had lower beneficial bacteria like Bifidobacterium, Lactobacillus, Butyricoccus, and higher Proteobacteria which is linked with inflammation and metabolic imbalances. It is also evident that patients after minocycline therapy had an increase in faecal Bacteroidetes and decrease in Firmicutes to Bacteroidetes (F/B) ratio.

Atopic dermatitis

Atopic dermatitis also known as atopic eczema, is a chronic inflammatory skin condition characterised by intense and persistent pruritus, extremely dry skin and erythema. It often begins in infancy or early childhood, following an intermittent course with flares and remissions influenced by genetic, immune, and environmental factors. Primary physical findings include xerosis (dry skin), lichenification (thickening of the skin and an increase in skin markings), eczematous lesions (skin inflammation). The two main hypotheses have been proposed in the disease mechanism, the first suggests a primary immune dysfunction and imbalance between Th1 and Th2 cells with Th2 dominance resulting in IgE sensitisation and allergic inflammation, and a secondary epithelial barrier disturbance. However, while changes in the gut microbiome cannot cause AD, the interaction of certain bacteria with the host immune system, along with other external factors such as dietary habits, may be responsible for the immunopathology. Possible mechanisms of association:

1. Gut microbiome of AD patients had increased Faecalibacterium prausnitzii, had more genes which encoded for molecules that can damage the gut epithelium and had lower levels of butyrate and propionate, which has anti-inflammatory properties. Increased gut permeability, allowing various cytokines, toxins, food antigens and pathogens to access the blood stream. These metabolites eventually reach the skin and induce Th2-type immune response. For instance, Clostridia and Escherichia coli in the intestine might be associated with AD via eosinophilic inflammation.
2. Gluten containing diet impairs the gastrointestinal barrier causing leaky gut and gluten sensitivity is associated with gut microbiome dysbiosis.
3. Research suggests that balance of immune response is responsible for protecting hosts against the development of AD. Thus any disruption of the normal gut microbiota results in altered immune responses.
4. Researchers confirm that early age onset of disease such as in children may begin even before birth, as dysbiosis in pregnant women is associated with poor immune system in offspring.

5. Tryptophan produced by the gut microbiome causes an intense itching in the skin while *Lactobacillus* and *Bifidobacterium* species produce GABA which inhibits the skin itch. Additionally *Escherichia* species and *Enterococcus* species can produce serotonin which causes skin pigmentation.

Microbial profiles:

A study showed increased abundance of *Akkermansia muciniphila* in infants with AD is associated with intestinal barrier dysfunction and skin lesions worsening. Also, higher levels of *Clostridium* and *Escherichia* were found in the gut of atopic infants compared to healthy controls, which contribute to inflammatory state. On the other hand, lower levels of *Bacteroidetes*, and *Bifidobacterium* were found in AD patients. It is important to note that along with *Clostridia* and *Escherichia* species, *Staphylococcus aureus* (*S.aureus*) is also higher in the gut of AD patients.

S.aureus is the most common pathogen grown from AD skin and flares in AD is associated with *S.aureus* superantigens.

Psoriasis

Psoriasis is a chronic, multisystem inflammatory disease with predominantly skin and joint involvement, where the immune system becomes over active causing skin cells to multiply rapidly. Patches of skin become scaly and inflamed, most commonly seen on the scalp, elbows or knees. Symptoms of psoriasis go through cycles, flaring for a period of time followed by remission. Symptoms vary from person to person, but some common ones are, patches of thick, red skin with silvery-white scales that itch or burn, typically on the elbows, knees, scalp, trunk, palms, and soles of the feet, dry, cracked skin that itches or bleeds and thick, ridged, pitted nails. While some patients can present with psoriatic arthritis. Beyond the cutaneous manifestations, patients may also experience numerous co-morbidities such as metabolic disorders, cardiovascular diseases, inflammatory bowel disease and pulmonary infections. It is an immune mediated relapsing inflammatory dermatoses, with its pathogenesis unclear. Though the disease is multifactorial, recent studies have shown the role of gut dysbiosis in the pathogenesis.

Possible mechanisms of association:

1. *Blautia* species increases the number of regulatory T cells in the gut and encourages biotransformation, *Ruminococcus*, on the other hand, encourages immune activation and the production of cytokines like $\text{TNF-}\alpha$. These two things suggest that psoriasis may be caused by an imbalance in the gut microbiota that affects the immune system.
2. Microbial imbalance in the gut such as increase in *Bacteroides* species and *Prevotella* species promotes systemic immune activation through pattern-recognition receptor pathways, resulting in aberrant activation of Th1/Th17 cells. This leads to elevation of key inflammatory cytokines and factors which disrupt the skin homeostasis, triggering overproliferation of damaged keratinocytes and skin thickening.
3. *Bacteroides* has been shown in multiple studies to synthesize polysaccharide A that activates Tregs, and promotes an anti-inflammatory response. A significant decrease in *Bacteroides* may affect the immune system and cause inflammation in psoriasis.
4. *Bacteroides*, *Akkermansia muciniphila* and *Ruminococcus* produce SCFAs. Therefore, their reduction results in leaky gut and immune activation and subsequent skin inflammation.
5. Certain beneficial bacteria promote anti-inflammatory cytokines such as IL-10 while some pro-inflammatory bacteria stimulate production of proinflammatory cytokines like $\text{IL-1}\beta$ and $\text{TNF-}\alpha$. In

psoriasis, gut microbe dysbiosis alters this balance and amplifies inflammation.

Microbial profiles:

A study showed fecal samples of psoriasis patients had increased *Faecalibacterium* and *Megamonas*. Alterations in gut microbiota were associated with abnormal inflammatory biomarkers in psoriasis patients. In particular, the levels of IL-2 receptors showed a direct association with the abundance of *Phascolarctobacterium* and an inverse association with *Dialister*. Because these two bacteria varied consistently with immune activation, their relative proportions may serve as indicators of disease activity. An investigation of intestinal microbiota by analysing stool samples found a decrease in the abundance of *Akkermansia muciniphila* species among psoriasis patients, compared to controls. Another study was done using Mendelian randomisation (MR), the data inferred that *Lactococcus*, *Ruminiclostridium* and *Eubacterium fissicatena* present in the intestinal microflora were risk factors for psoriasis, while *Odoribacter* showed a protective effect against psoriasis.

Rosacea

Rosacea is a chronic inflammatory cutaneous disorder that mainly affects the centrofacial region, including cheeks, nose, chin, forehead, and eyes. There are four subtypes of rosacea, which are erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and ocular rosacea. Though the etiology is uncertain, a link between gut dysbiosis and rosacea has been hypothesised. *Helicobacter pylori* (*H.pylori*), IBD and small intestinal bacterial overgrowth (SIBO) are associated with pathogenesis of rosacea.

Possible mechanisms of association:

- 1. *Helicobacter pylori*, gram negative, spiral shaped bacteria infecting the gastric and duodenum lining. It can cause a chronic infection that is difficult to eradicate. It is shown that rosacea is associated with *H.pylori* seropositivity and eradication of *H.pylori* reduces rosacea and GIT symptoms.**
 - *H.pylori* causes gastric mucosal infection and inflammation and produces various cytokines and inflammatory mediators such as nitric oxide. These mediators can cause skin inflammation and alter skin physiological processes, including vasodilation and flushing.
 - Another mechanism hypothesized- An autoimmune mechanism involving cross reactive antibodies.
 - *H.pylori* induced production of $\text{TNF-}\alpha$ and IL-8 causes gastric mucosal inflammation and clinical manifestation of rosacea.
- 2. Microbiome mediated inflammation via the innate immune system.**
 - Enhanced Toll-like receptor 2 expression leads to increased cathelicidin production, and aberrant proteolytic processing of cathelicidins results in pro-inflammatory peptides that aggravate clinical manifestations.
 - Elevated levels of cytokines IL-8 and interferon α are also involved in the pathogenesis of rosacea.
 - Increased Pathogen-associated molecular patterns (PAMPs) in the bloodstream and decreased butyrate from beneficial bacteria may cause hyperresponsiveness of B-cells and impaired differentiation of T-cells.
 - Pathogenic bacteria/ pathobionts along with its compounds can reach the skin via the bloodstream and can alter the skin physiology and immune response.

Microbial profiles:

Prevalence of SIBO is increased in rosacea patients. A recent study found higher abundance of Acidaminococcus and Megasphaera and a lower abundance of Peptococcaceae and Methanobrevibacter. Imbalances in skin microbiota have also been implicated such as Cutibacterium acnes, Staphylococcus epidermidis, Bacillus oleronius, and Demodex folliculorum. Additionally, a MR study showed the protective roles of Actinobacteria and the genus Butyrivibrio against rosacea.

Chronic spontaneous urticaria

Chronic urticaria (CU) is a common inflammatory skin disease characterised by pruritic wheals with or without angioedema, and is associated with severe itch persisting for greater than 6 weeks. Chronic urticaria is further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria. CSU is the most common type of chronic urticaria and has no identifiable triggers. Though the pathophysiology of CSU is complex and not well established, researchers have reported the link between CSU and intestinal dysbiosis. CSU is primarily driven by mast cells and its mediators. When mast cells are activated, they degranulate to release histamine, leukotrienes, chemokines and cytokines that bind to histamine receptors causing vasodilation and extravasating fluid from the blood vessel, intense itching eventually allergic inflammation. The role of gut dysbiosis in this inflammation has been studied.

Possible mechanisms of association:

1. A study done using metagenomic sequencing and Metabolomics revealed CSU patients had lower gut bacterial diversity and fewer SCFA producing bacteria. It is a well known fact that SCFA maintains intestinal barrier integrity. Reduced SCFA and elevated LPS in the blood correlated with disease severity. Also fecal microbiota transplantation (FMT) in mice was performed to analyse how gut microbiota affected the disease. Transferring CSU gut microbiota into mice enhanced allergic inflammation while giving mice Roseburia hominis or SCFA supplements reduced inflammation.
2. Lachnospiraceae is a major SCFA producer in the human gut, SCFA have been shown to play an important role in gut homeostasis and immunomodulation. Moreover, SCFA have shown notable results in reducing inflammation in inflammatory dermatoses. Thus a lower abundance of Lachnospiraceae within the gut microbiota correlated with reduced SCFA concentrations may contribute to development of CSU.
3. Researchers used two sample bidirectional MR, the analysis suggested that some gut taxa are genetically linked to CSU risk and some metabolic pathways of gut bacteria are positively associated with CSU risk. One pathway, PWY-7400 partly mediates the effect of Peptococcaceae family on CSU.
4. A study explored vitamin D3 status and microbial balance may influence immune regulation and disease severity in CSU. CSU patients with vitamin D3 insufficiency had higher disease activity, greater systemic inflammation and weak IFN-I immune response. And vitamin D3 insufficiency was associated with altered gut microbiome. For instance, Prevotella 9, Escherichia, Shigella, and Klebsiella were higher while Bacteroides, Faecalibacterium, Agathobacter were lower indicating gut dysbiosis linked with vitamin D₃ status.
5. Another study aimed to explore how the gut microbiome alteration and its serum metabolites contribute to disease mechanisms. CSU patients had lower overall gut microbial diversity versus healthy controls. They also showed altered levels of several metabolites including, Docosahexaenoic acid (DHA), arachidonic acid (unsaturated fatty acids), Glutamate and Succinic acid. These changes

point to alterations in unsaturated fatty acid metabolism and butanoate metabolism, which is a pathway for producing certain SCFA important for immune regulation.

Microbial profiles:

A study found that, at the genus level, individuals with CSU showed higher levels of Bacteroides, Streptococcus, Agathobacter, and Bifidobacterium, while Roseburia, Faecalibacterium, Ruminococcus, Lachnospira, Prevotella, Blautia, Coprococcus, and Subdoligranulum were reduced compared to healthy controls. Additionally, unidentified members of the Enterobacteriaceae family were elevated in CSU patients.

Gut microbiome based interventions

Many research studies have focused on understanding, identification, and prevention of gut dysbiosis linked dermatological diseases. New therapeutic strategies targeting gut dysbiosis to restore normal flora and alleviate skin conditions. Approaches such as probiotics, prebiotics, synbiotics, dietary change and fecal microbiota transplantation (FMT) have shown promising results in clinical studies. Therefore understanding these interventions and their underlying mechanisms provides an insight into microbiome focused dermatological therapies.

FMT is an effective method to directly change the recipient's gut microbiota to restore healthy gut microbiome and gain a therapeutic benefit. It involves transferring of processed stool from healthy donor to patient, providing an ecological niche for colonization of transplanted stool microbiota. While most FMT indications are gastrointestinal disorders, recent trials suggest it may modulate systemic immune responses including skin diseases like AD. A study in a mouse model of AD showed FMT from healthy donors helped restore gut microbiota balance and reduced skin inflammation and skin thickness suggesting a therapeutic benefit. Notably, FMT also had increased Firmicutes to Bacteroidetes ratio and the amount of butyric-producing bacteria (BPB), including Erysipelotrichaceae, Lactobacillaceae, and Eubacteriaceae in AD models, which is a marker of healthy gut microbiota. A study transplanted fecal samples from healthy mice to mice with experimentally induced eczema. After the transplant, the mice showed improvement in skin lesions. FMT increased beneficial gut bacteria and SCFA levels. In addition, it also restored Th1/Th2 balance, modulated Tregs and reduced mast cells, eosinophils, basophils count and IgE levels. Thus restoration of gut microbiota and immunomodulation along with suppression of AD-induced allergic inflammation provides a new approach in treatment of AD.

It is important to note that AD patients have disrupted gut barriers which makes them vulnerable to the risks of FMT. FMT also comprises unidentified bacteria that can exacerbate illness or pose potential risks to the host. It also carries a risk of infectious complications, particularly in immunocompromised patients. Washed microbiota transplantation (WMT) is a refined version of conventional FMT that includes a washing step during preparation for additional safety and microbiota quality control. A clinical study performed on patients with moderate-to-severe AD based on WMT showed significant improvement in clinical scores (e.g., SCORAD, EASI, etc) along with shift in microbial profiles of both skin and gut enhancing clinical recovery through microbiome rebalancing. Post-WMT restoration of gut with beneficial bacteria enriches the gut environment with SCFA producers and controlled immune-regulatory responses which contribute to clinical improvements in AD severity. Despite emerging evidence of benefit, the long term safety of FMT and WMT is an active area of clinical investigation.

As previously mentioned, prebiotics and probiotics into the human diet is favourable for the intestinal microbiome. Many clinical studies have proven the effectiveness of probiotics and prebiotics for treatment of various conditions including cutaneous diseases. In addition, synbiotics have emerged as a therapeutic approach, which are a combination of synergistically acting probiotics and prebiotics. They are products in which a prebiotic component selectively favours a probiotic microorganism and enhances nutrient absorption. This provides an environment that supports the survival of probiotic bacteria in the gastrointestinal tract. The most popularly used synbiotic is a combination of Bifidobacterium or Lactobacillus genus bacteria with fructooligosaccharides. Synbiotics work through a combination of mechanisms and they include:

1. Improved survival and colonization of probiotics.
2. Enhanced fermentation and SCFA production
3. Reduction in concentration of unfavourable metabolites
4. Modulation of microbiota diversity
5. Immunomodulation and support gut immune defence
6. Strengthening the gut barrier.
7. Inhibit growth of opportunistic pathogens

Hence, through these actions, synbiotics strengthen the gut barrier and thereby help maintain skin health. In rat studies, intestinal IgA levels were elevated following introduction of synbiotic containing Lactobacillus rhamnosus and Bifidobacterium lactis, and inulin and oligofructose as prebiotics to the diet. A study revealed optimal synbiotic preparations may achieve better results in AD prevention or treatment than either probiotics or prebiotics alone. Further studies are required to elucidate their role in other skin diseases.

More recently, postbiotics have been introduced as additional products to support the symbiotic host microbe relationship. Postbiotics are non-viable probiotic microbial preparations and/or their components that provide health benefits to the host. They include, physiologically active microbial cellular components (cell wall fragments or enzymes) or functional bioactive substances such as vitamins, SCFAs, proteins. Therefore, postbiotics can be defined as cell-free supernatants without metabolite specification/individualization, cell wall components and/or intracellular compound. These are shelf stable preparations that has antiinflammatory, antioxidant, immunomodulatory, antimicrobial and anti-aging properties. The benefits of both topical and oral postbiotics have been studied. Postbiotics from *L. fermentum*, *L. reuteri*, and *B. subtilis natto*, applied topically with a cold cream, may promote faster wound healing and are under investigation as a new therapeutic strategy. Topical use of *S. thermophiles* lysate containing sphingomyelinase, an enzyme that converts sphingomyelinase to phosphocholine and ceramide shown to increase stratum corneal ceramide levels, improve the lipid barrier and reduce water loss, maintaining hydration. While oral postbiotics consumption has also been shown to restore and improve skin barrier integrity. Oral intake of heat killed *Lactococcus lactis* strain H61 has been shown to improve certain skin properties, including reduced dehydration from seasonal changes and significant enhancement of skin elasticity on the inner forearm. Oral administration of Lactocare[®], a symbiotic formulation, when associated with topical administration of hydrocortisone demonstrated improvement in the psoriasis indexes. A recent trial with a skincare cream containing a bacterial lysate of *L. plantarum* V22, isolated from fecal samples of infants reduced severity of acne in mild to moderate cases. Overall, interventions targeting the gut microbiome have the potential to produce systemic effects, including modulation of

immune responses and improvement of skin health, although mechanisms are not fully understood, but their precise effects are being studied.

Research gaps

Gut dysbiosis has been increasingly associated with chronic inflammatory skin diseases such as atopic dermatitis, psoriasis, acne vulgaris, chronic spontaneous urticaria, influencing immune regulation and skin barrier function. Despite growing evidence, the mechanisms linking gut microbial alterations to skin pathology remain poorly understood. Therefore addressing these gaps is essential for advancing microbiome based therapies in skin health. Firstly, many studies show associations between gut dysbiosis and skin conditions but the exact molecular and cellular mechanisms remain unclear. For instance, we know gut microbes modulate immune responses and metabolites like SCFAs, but how these specific pathways cause skin inflammation or disease progression is not fully understood. Additionally, it remains unclear which microbial metabolic pathway exert protective versus harmful effects on the host.

Results on the specific changes in gut microbial composition linked to skin diseases are consistent across studies, for example, in acne patients, studies have reported decreased Actinobacteria and Firmicutes/Bacteroidetes ratio with more Proteobacteria. But one study reported a high Firmicutes/Bacteroidetes ratio in acne cases before antibiotic treatment. Although gut microbiome dysbiosis has been observed in CSU, the number of available studies is limited and the specific bacterial groups involved as well as the significance of these alterations remains unclear. We know gut and skin are connected through gut skin axis, but we often don't see data showing exactly how the skin microbiome changes in response to gut based therapy, instead researchers tend to measure clinical severity or immune markers. Some studies indicate that oral interventions (probiotics, synbiotics, postbiotics, prebiotics) can demonstrate beneficial changes in skin health by strengthening gut barrier integrity. However, demonstrating clinical improvement without clearly documenting skin microbiome changes may indicate a gap in understanding of how gut targeted interventions influence skin disease. Majority of interventional studies have focused on AD, further studies are required to establish the role of these therapies in diseases beyond AD. Though probiotics and FMT show promising results in clinical studies, their long term safety evidence is sparse. These interventions efficacy vary between individuals. For example, a probiotic strain that improves barrier function in one patient might have no effect in another because their gut already contains similar strains.

Furthermore, much of existing research focuses on children or specific age groups whereas evidence remains sparse in older patients or those with complex comorbidities, e.g., majority of studies focus on infant or childhood AD because its prevalence is highest in early life and have documented reduced beneficial bacteria. But in adults, studies sometimes fail to find significant gut microbiome changes and only report changes in specific taxa. This inconsistency suggests that microbiome changes might be age dependent or influenced by other factors such as diet, medications, environmental factors and lifestyle.

Additionally, most microbiome studies in skin diseases show changes in gut microbial composition correlate with disease but this does not prove that the microbes cause the disease. This may be due to complex interactions, confounding factors, etc., so it's unclear whether dysbiosis is a cause or a consequence. While there are methodological limitations in microbiome research. Many studies rely on 16s rRNA gene sequencing because it is relatively affordable and good for identifying broad bacterial groups. But it has limitations that include, 16S rRNA sequences often cannot distinguish closely related

species or strains, thus studies may report changes at genus level that hide important strain specific information. Besides, this approach fails to include other microbial organisms such as fungi, viruses.

In summary, while the role of gut dysbiosis in skin diseases is increasingly recognised, there is a lack of data to draw definitive conclusions. The interplay between gut microbes, host immunity and skin pathology is complex and not fully understood, and existing interventions have yet to demonstrate their efficacy across populations. Addressing these challenges through detailed studies that examine multiple layers of microbial and host data are needed to develop safe and effective microbiome based interventions while also establishing clear causal relationships.

Conclusions

The gastrointestinal system and the skin is inhabited by a diverse microbial community and is connected via the gut-skin axis, which plays a crucial role in maintaining the host homeostasis. The equilibrium is maintained by the interplay of the gut microbiome and the immune system. Gut microbiota modulates skin health through various complex mechanisms like regulation of immune response, metabolite production, neuromodulation via neurotransmitters and systemic inflammation control through strengthening the gut barrier. Thus any dysbiosis of the gut can directly or indirectly cause skin pathology including atopic dermatitis, acne vulgaris, psoriasis, chronic spontaneous urticaria and rosacea. Through gut microbiome modulation, probiotics, prebiotics, synbiotics, postbiotics, FMT, show promising results in reversing the pathology and reducing the severity of clinical manifestations. Despite extensive research, exact mechanisms underlying gut-skin communication are incompletely understood. Future research should improve our understanding on these complex mechanisms, disease specific research, gut microbiome modulating interventions, other host factors influencing gut microbiota targeted therapy on other organisms, fungi and viruses. Ultimately, further research on microbiome based biomarkers, treatment response, identifying early life microbiome patterns, for offering improved patient outcomes and enabling personalised, predictive, preventive dermatological care and enhanced healthcare practices.

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