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REVIEW

The Role of the Skin Microbiome in Modulating Wellness in Epidermolysis Bullosa

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Abstract: Epidermolysis bullosa (EB) represents a group of rare genetic skin disorders marked by extreme skin fragility, leading to blistering, delayed wound healing, and increased susceptibility to infections. Emerging research highlights the vital role of the skin microbiome in maintaining skin integrity, preventing pathogenic colonization, and supporting tissue repair. In EB, microbial dysbiosis, characterized by reduced microbial diversity and dominance of pathogenic species such as Staphylococcus aureus, has been linked to worsened clinical outcomes. Conversely, commensal bacteria like Staphylococcus epidermidis and Cutibacterium acnes contribute to skin homeostasis and wound healing. This review explores the current understanding of the microbiome-EB relationship, drawing from multiple studies and databases, and evaluates the potential of microbiome-targeted interventions, including probiotic therapies and microbiome transplantation. Strategies that restore microbial balance, avoid broad-spectrum antibiotics, and incorporate advanced wound care hold promise for improving outcomes and quality of life for individuals living with EB. These insights may guide the development of novel treatments, including advanced wound dressings and microbiome-based therapies, to enhance the care of EB patients.

Keywords: microbiome, epidermolysis bullosa, genetics, inherited skin disorders.

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1 Introduction

Epidermolysis bullosa (EB) is a rare inherited skin condition characterized by friable mucous membranes and skin. Blistering and erosion can be triggered by even mild mechanical trauma. It is caused by mutations in genes that encode proteins essential for maintaining skin integrity. Despite variability in severity, all EB subtypes share the hallmark feature of trauma-induced blister formation [1]. EB is classified into four major subtypes based on the skin layer affected: epidermolysis bullosa simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (KS). Each subtype results from distinct genetic mutations affecting key structural proteins [2]. EBS, the most common and mildest form, involves intraepidermal blistering due to mutations in keratin genes, weakening cytoskeletal stability. Patients typically develop blisters on friction-prone areas such as hands, feet, and joints. These lesions are often painful but heal without scarring. Severity ranges from minor heat-induced blisters to more frequent lesions that impair quality of life [3,4]. JEB is more severe, with blisters forming in the lamina lucida between the dermis and epidermis [5]. It can affect mucous membranes of the oral cavity, pharynx, and respiratory tract, causing nutritional issues due to painful oral lesions and delayed wound healing [6]. DEB involves sub-lamina densa blistering due to mutations in COL7A1. Dominant DEB causes widespread but less scarring blisters, while recessive DEB leads to severe scarring, joint contractures, pseudosyndactyly ("mitten deformity"), and heightened risk of aggressive squamous cell carcinoma (SCC) in young adulthood [7,8]. Kindler syndrome, the rarest form, is due to FERMT1 mutations encoding Kindlin-1, a protein involved in cellular adhesion. Unlike other subtypes, blister depth varies by age and trauma severity. SCC risk is also elevated, similar to severe

DEB cases [9,10]. The skin microbiome is vital for protecting against infection, modulating immunity, and supporting wound healing. In EB, chronic wounds, repeated trauma, and extensive topical antibiotic use disrupt microbial homeostasis, leading to dysbiosis. This imbalance promotes colonization by pathogenic bacteria such as Staphylococcus aureus and Pseudomonas aeruginosa, as shown in Figure 1 and Figure 2 [11]. These organisms perpetuate chronic inflammation, delay healing, and can lead to severe complications like sepsis. Dysbiosis in EB wounds contributes to prolonged tissue injury and impaired healing. This review explores the role of the skin microbiome in EB pathophysiology and highlights innovative therapeutic approaches targeting microbial restoration.

Skin Microbiome The skin microbiome refers to the complex group of microorganisms on the skin, including bacteria, fungi, viruses, and protozoa. The skin bacterial microbiome has been revolutionized with the employment of next-generation 16sDNA sequencing, where whole bacterial populations can be analyzed extensively and on a massive scale (figure 2). The skin bacteriome has four main categories of bacteria: Actinobacteria, Firmicutes, Bacteroidetes, and Proteobacteria. The most frequent and regularly appearing bacteria from these categories were Brevibacterium, Corynebacterium, Micrococcus, Propionibacterium, Streptococcus, and Staphylococcus. There are three main environments of human skin: moist, dry, and oily (sebaceous) [12]. Bacteria of the same skin types had very similar populations. The dry skin has a more complex group of bacteria compared with moist and oily areas. The volar forearm (medial surface of the forearm) has a very extensive amount of bacterial operational taxonomic units (OTUs) and, therefore, has one of the more even and complex populations of bacteria. A "core" skin microbiome for every location of the human body, however, cannot be established because of the variety of bacteria on the dry skin [13]. To exemplify, more Betaproteobacteria and Flavobacteriales were identified on the volar forearm in a study, and Betaproteobacteria, Firmicutes, and Actinobacteria in equal numbers were identified on similar regions in another study. The bacterial community on the volar forearm showed limited long-term stability, indicating that it changed over time. However, the bacteria on one person's skin tend to stay more similar over time than those on someone else's skin. Studying the differences between healthy and diseased skin microbiomes can help us to understand the causes of autoimmune diseases and infections. However, it remains challenging to define what a "normal" skin microbiome is because of its complexity and diversity [14,15]. Many bacterial species residing on the skin surface can either promote or suppress the growth of invading pathogens. The presence of specific disease states in certain bacteria has recently been implicated in current literature. Psoriatic lesions have a relatively higher abundance of Firmicutes and a relatively lower abundance of Actinobacteria and Proteobacteria than healthy skin [16]. The process of skin microbiome workflow has been demonstrated in Figure 3. In this inflammatory skin disorder, the progression of disease in patients with atopic dermatitis correlates with a decrease in overall microbial diversity and an abundance of staphylococci, including S. aureus and S. epidermidis. These studies suggest that changes within the skin microbiome, more specifically, the loss of protective bacteria and the colonization and proliferation of disease-causing bacteria, are connected to a range of skin conditions. Role of microbiome in skin health Within minutes after birth, the skin surface becomes colonized and develops dynamically during the first couple of years of life. It appears that the skin surface of newborns who are delivered conventionally is preferentially colonized by microorganisms common in the female urogenital tract, such as Lactobacillus, Prevotella, and Candida, whereas the skin surface of infants who were delivered via cesarean section is preferentially colonized by skin commensals such as Streptococcus, Staphylococcus, and Propionibacterium. Although the mode of delivery leaves long-lasting marks, its effects on the future composition of the skin microbiome remain unknown [19]. The diversity of microbial communities expands during the first weeks of life and begins to acquire site specificity according to dry, moist, or lipid-rich niches. This stimulation of sebaceous gland secretion at puberty through hormones greatly changes the physicochemical characteristics of the skin surface and thus encourages the development of lipophilic taxa such as Corynebacterium and Propionibacterium [20]. The skin microbiome of an adult remains relatively stable unless there are changes in surrounding factors. Despite the remarkable inter-individual variability, this suggests that even among bacterial species often regarded as opportunistic pathogens, mutualistic and commensal relationships do exist among microbes and between microbes and the host. Most bacteria in healthy skin are mutualistic or commensal organisms. These

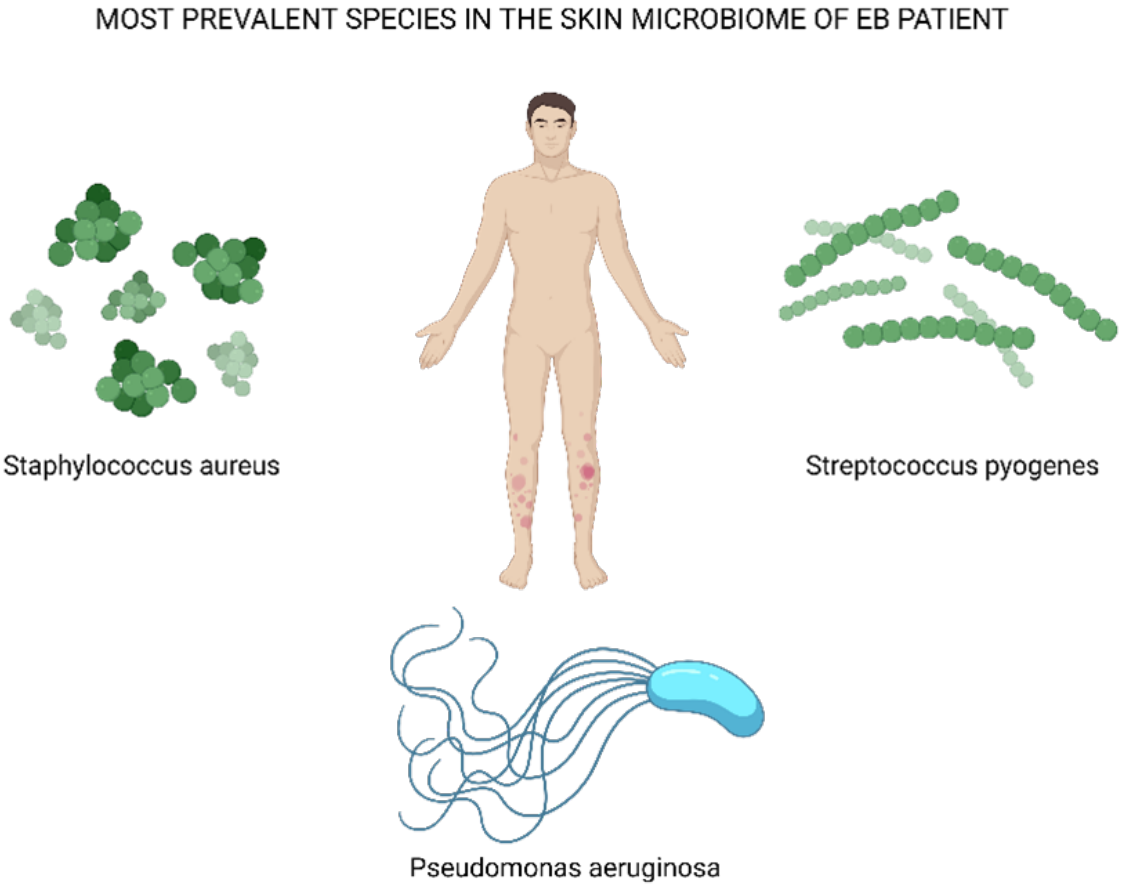

Figure 1. Different bacterial species in the microbiome of EB patients: Diagram illustrating the dominant microbial species in EB patients compared to healthy individuals. Shows increased pathogenic bacteria and reduced beneficial microbes in EB wounds.

microbes use multiple strategies to prevent the overgrowth of opportunistic parasites, such as the induction of innate immune factors. IL-1 secretion and antimicrobial peptides from keratinocytes. Commensal microbes also contribute to healthy skin barrier homeostasis and immune system regulation. Both the skin barrier and the microbiome protect the body against external invaders [21]. There is a balanced interaction between the host and the resident or transitory bacterial populations. The composition of the skin microbial communities of a host and the function of the skin barrier of the host is continuously influenced by extrinsic and intrinsic factors. Dysbiosis is a condition in which balance is disrupted. Such dysbiosis-altering diversity and abundance of commensal species compromise the skin barrier function and exacerbate chronic skin diseases, including psoriasis and acne [22]. This dysbiosis may be due to the underlying pathobiology or genetic variation in the properties of the stratum corneum. For instance, Staphylococcus epidermidis is a skin commensal but can also act as an opportunistic pathogen in immunocompromised hosts, while Staphylococcus aureus, though considered a resident microbe, also contributes highly to being a pathogen in cases of overcolonization of the skin [23]. Another example is the fact that Propionibacterium acnes makes the skin uninhabitable for pathogens such as S. aureus and Streptococcus pyogenes, but allows the growth of less virulent Staphylococci strains such as S. epidermis and Corynebacteria [24]. However, dysbiosis does not occur only between bacteria; disequilibrium between bacteria and commensal fungal strains on the scalp has also been observed in subjects prone to dandruff. Host skin cells continually survey the colonizing microbes of the epidermis and dermis using PRRs. The degree to which the immune response is triggered and how changes are regulated distinguishes commensal organisms from potential pathogens. Examples of typical commensal species that regulate the outgrowth of pathogens and maintain stability in the resident cutaneous community include P. acnes and S. epidermis. Both play a role in the growth control of pathogens, such as S. pyogenes and S. aureus. P. acnes has also been shown to hinder the growth of methicillin-resistant

Table 1. Role skin microbiome in health and disease [26,27]

Concept	Details	Examples	Research Findings
Dominant Phyla	Major groups include Actinobacteria and Firmicutes, influencing skin health and disease.	Actinobacteria, Firmicutes	Diversity in Actinobacteria linked to skin health.
Key Genera	Important genera like Propionibacterium and Staphylococcus play roles in skin health and disease.	P. acnes, S. epidermidis	Increased S. aureus is associated with dermatitis severity.
Micro-ecosystems	Skin areas differ: moist zones host different microbes than dry or sebaceous regions.	Armpits (moist), Forearm (dry)	Moist areas show lower diversity; dry areas have more variety.
Diversity in Skin Sites	Diversity varies by location; dry areas tend to have more microbial variety than moist areas.	Forearm (dry), Scalp (sebaceous)	Higher diversity in dry skin can be protective.
Microbiome Implications	Newborn microbiomes are influenced by delivery method and environment; adults maintain stability unless disrupted.	Vaginal vs. C-section microbiome	C-section delivery linked to lower microbial diversity in infants.
Dysbiosis Impact	Skin conditions like psoriasis and acne are associated with shifts in microbial balance.	Psoriasis, Atopic dermatitis, Acne	Treatment can improve outcomes by modulating the microbiome.
Protective Functions	Beneficial bacteria produce antimicrobial compounds that protect against infections.	S. epidermidis, P. acnes	S. epidermidis has been shown to reduce infection rates.
Disease Associations with Microbiome	Conditions like psoriasis and atopic dermatitis are linked to microbiome changes; treatments focus on restoring balance.	Treatment of psoriasis, eczema management	Microbiome-targeted interventions show promise in reducing symptoms.

Staphylococcus aureus (MRSA). Both are known to produce various compounds with antimicrobial action: P. acnes releases fatty acids from sebum lipids, which tend to impede the growth of bacteria on the skin surface and favor the growth of lipophilic yeasts, including Malassezia species, while S. epidermidis stimulates microbial lipid membrane leakage, which then cooperates with the production of human host antimicrobial peptides to reduce the number of such bacteria. Antimicrobial peptides (AMPs) also represent key communication molecules between the innate host immune system and microbiota [25]. The skin's microbiota can influence the cells of the body and induce immunity. Staphylococcus epidermidis, for example, can trigger the production of AMPs, such as β-defensins 2 and 3, which strengthen the body's defense against Staphylococcus aureus. It also triggers mast cells' anti-viral response, regulates inflammation

when wounds are being healed, stimulates AMP production, and supports the production of skin T-cells. All of these processes act in synergy with the defense of the body and natural AMPs for protecting the skin. The microbiome also acts as a filter, interacting with chemicals that enter into, pass, and interact with the skin. The immune response, under partial genetic influence, has a substantial contribution towards developing the composition of the microbiota. When the microbiota is detected through Toll-like receptors (TLRs) on epidermal Langerhans cells, these cells can guide naïve T cells to develop a Th17 response. This response helps keratinocytes produce AMPs. This shows that epidermal dendritic cells not only assist in innate immunity, but also help guide the adaptive immune system, contributing to the complex interactions that control skin colonization by microbes as depicted in Table 1 [26,27].

Role of microbiome in infections and immune regulation It helps in the prevention of infection and regulation of immune responses, complementary to both the innate and adaptive immune pathways. Skin surface infections mostly occur due to the overgrowth of opportunistic pathogens, including Staphylococcus aureus and Candida albicans, which take advantage of microbiome imbalance to invade tissues and evade immune responses. The virulence of these pathogens is enhanced by the production of toxins, enzymes, and biofilms, which further complicates treatment and results in chronic infections. In addition, commensal microbes delicately balance immune responses, and any disturbance in this interaction can lead to inflammatory skin diseases that are closely associated with immune dysregulation, including Atopic Dermatitis (AD), psoriasis, and acne. In the context of infection, commensal bacteria such as Staphylococcus epidermidis confer protection through AMP production themselves and by inducing signals in keratinocytes for the expression of defensins and cathelicidins that impede pathogen growth [28]. These beneficial microbes also compete for nutrients and adhesion sites with pathogens, thereby limiting their infectious capabilities. On the other hand, dysbiosis is passed on by reduced microbial diversity, which allows pathogenic bacteria to become prevalent. For instance, overgrowth of Staphylococcus aureus is a characteristic of AD and has the potential to induce or initiate an infection with cytolytic toxins that disrupt host epithelia integrity, for instance, α-toxin. Besides, by offering a survival mechanism for pathogens through the protection of bacteria against antibiotics and immune cells, organized microbial communities such as biofilms possess distinctive characteristics because they live in an extracellular matrix and are involved in chronic infections such as bacterial infection of wounds and diabetic ulcers [29]. Some other fungal infections of the skin are seborrheic dermatitis and pityriasis versicolor, due to an excess of Malassezia species in sebaceous-gland-dense areas of the body. The skin microbiota is also crucial for the regulation of immune responses at the local and systemic level. Innate skin immune responses are strongly influenced by commensal microbes through the stimulation of the production of keratinocytes and immune cells that maintain basal levels of inflammation and 'priming' of the skin tissues for effective responses to invading pathogens [28,29]. Staphylococcus epidermidis can activate PRRs, such as TLRs, on keratinocytes, leading to the production of AMPs and pro-inflammatory cytokines. Furthermore, commensal antigens play a role in regulating adaptive immune responses by influencing T cell differentiation. During a healthy state of the microbiome, this interaction causes immune tolerance, which is induced by a balanced Treg response. However, this is compromised when dysbiotic status occurs and is characterized by aberrant immune responses. Immune-mediated diseases such as atopic dermatitis, psoriasis, and acne are strongly associated with microbial imbalance and immune dysfunction [44]. In AD, dysbiosis promotes the overgrowth of S. aureus, enhancing inflammation through the release of toxins and inducing a shift toward Th2-mediated immune responses, characterized by elevated levels of IL-4, IL-5, and IL-13 [30]. It is further postulated that such Th2 dominance disrupts the skin barrier, thus creating a self-sustaining cycle of inflammation and recurrent infection. In psoriasis, there is a decrease in microbial diversity, and some bacterial types, such as Streptococcus, can be considered flare triggers. IL-17 and IL-23 signaling are highly expressed in psoriatic lesions; these cytokines are produced by Th17 cells and contribute to chronic inflammation [31]. Even acne vulgaris was associated with overgrowth of the bacterium Cutibacterium acnes, which directly stimulates TLRs on immune cells, thereby recruiting neutrophils and releasing mediators of inflammation, such as IL-1β. This cascade contributes to pustule, nodule, and comedone formations [32]. Biofilm formation by microbes confers added complexity to infections and host immune responses. Biofilms formed by bacteria, such as S. aureus and Pseudomonas aeruginosa,

Table 2. Different types of EB and the major microbiome findings [41-42]

Type of EB	Symptoms	Prominent Microbial Species	Major Microbiome Findings
EB Simplex (EBS)	Blistering primarily on hands and feet, triggered by heat and friction.	Staphylococcus aureus in open lesions. Candida spp. in moist, damaged areas.	Generally lower microbial diversity in blistered areas. Higher abundance of Staphylococcus spp., due to repeated barrier breakdown.
Junctional EB (JEB)	Severe blistering at birth affecting skin, respiratory, and digestive tract. Chronic wounds in oral cavity, increased susceptibility to infections. Enamel hypoplasia.	Pseudomonas aeruginosa in chronic wounds. Staphylococcus aureus in open wounds.	Decreased commensal diversity, with frequent dominance of Pseudomonas and Staphylococcus. Reduced populations of Cutibacterium acnes and other beneficial skin microbiota.
Dystrophic EB (DEB)	Widespread blistering, often leading to mitten-like hand deformities. Oral and esophageal blistering and scarring. High risk of squamous cell carcinoma (SCC) in adulthood.	Streptococcus spp., Staphylococcus aureus, Corynebacterium spp. in chronic, open wounds.	Enrichment of pathogenic microbes (Staphylococcus, Streptococcus, Corynebacterium). Decreased beneficial microbiota like Staphylococcus epidermidis.
Kindler Syndrome	Blistering on trauma-exposed areas, poikiloderma, photosensitivity. Progressive skin atrophy, increased risk of SCC on sun-exposed areas.	Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli in non-healing lesions and moist wounds.	Dysbiosis with Staphylococcus dominance, reducing overall skin resilience.

protect the microbial community from immune recognition and increase resistance to different classes of antibiotics. This is particularly problematic in wound and ulcer infections, because the biofilm matrix is barely penetrated by the immune system. Chronic infection may be associated with sustained immune activation that depletes immune resources and fosters additional tissue injury [33]. Role of dysbiosis in EB The EB Clinical Characterization and Outcomes Database (EBCCOD), a repository of clinical data from multiple centers in the United States and Canada, is a valuable resource for investigating bacterial colonization of EB wounds. The objective of this study was to conduct an analysis of a large number of EB patients' wound cultures with a perspective towards identifying the trends of bacterial colonization and antibiotic resistance [34]. This is a retrospective study that analyzed 739 wound cultures taken from 158 EB patients across 13 centers over 2001-2018. Bacterial species in the wound cultures were analyzed with particular interest in the distribution between Staphylococcus aureus (SA), Pseudomonas aeruginosa (PA), and Streptococcus pyogenes (GAS). Resistance patterns of methicillin and mupirocin for SA-positive cultures were also analyzed to compare antibiotic resistance trends. Of 152 culture-positive patients, the most common isolate was Staphylococcus aureus, which was detected in 131 patients (86%). Pseudomonas aeruginosa occurred in 56 patients (37%), and Streptococcus pyogenes in 34 patients (22%). Methicillin-sensitive SA was isolated from 68% of SA-positive patients, and 47% had methicillin-resistant SA (MRSA). Eighteen patients were infected with both methicillin-susceptible and methicillin-resistant organisms at various intervals. Of 15 mupirocin-resistant patients tested, 11 were mupirocin-susceptible SA and 6 were positive for mupirocin-resistant SA (2 patients had resistant and susceptible strains). Of 23 patients diagnosed with SCC, 10 were found to have documented wound cultures positive for SA, PA, and Proteus species in 90%, 50%, and 20% of the cases, respectively [35]. Pseudomonas aeruginosa and Staphylococcus aureus were the most common bacterial isolates in EB wound cultures. The occurrence of methicillin-resistant SA (MRSA) in 47% of patients and mupirocin resistance

in 40% of patients examined highlights the growing problem of antibiotic resistance in EB populations. Besides, evidence has shown that long-term bacterial colonisation can enhance the susceptibility of EB patients to squamous cell carcinoma [36]. Research into the microbic content of the skin of people with EB has also shown them, on average, to be of lower microbic diversity compared with normal people. The use of antibacterial and anti-inflammatory drugs, needed for their use in treating their infections, also reduces the numbers of beneficial microorganisms such as Staphylococcus epidermidis, whose presence under normal conditions protects against invasion of more virulent microorganisms [37-40]. The absence of such protecting microbes subjects people with EB to more frequent and more severe infections and can also reduce the ability of the skin for effective healing. The chronic inflammatory environment of chronic wounds of people with EB, maintained by both the presence of pathogenetic microorganisms and the host's immune response, leads to greater fibrosis and scarring, and contributes to the complexity of treating wounds in such people. In recent years, there has been a growing interest in the contribution of the skin microbiome towards treating EB [41-43]. A normal skin microbiome can be a new treatment approach for reducing the severity of sepsis and infections in patients with EB. Treatments with probiotics, with the aim of repopulating commensal skin flora with beneficial microbes, and approaches towards reducing the use of antibiotics not to promote the growth of resistant microbes are being explored today [44]. Clarification of our understanding of the genetic mutations for causing EB and of the contribution of the skin microbiome towards infection and healing of wounds is critical for identifying novel targets for treatment, such as gene treatment and treatment of the microbiome. These treatment innovations offer hope for improving the quality of lives of patients with this complex disease. The different forms of EB and major microbiome findings for each of them are enlisted in Table 2 [45-47]. Role of dysbiosis in SCC progression Skin microbiome dysbiosis, which is an imbalance, is accountable for the formation of squamous cell carcinoma (SCC) in those patients who have diseases such as bullosa (EB) [48]. EB patients' chronic wounds devastate normal microbial homeostasis, triggering the overpopulation of pathogenic bacteria, i.e., Staphylococcus aureus and Pseudomonas aeruginosa as depicted in Figure 4. These pathogens are accountable for chronic inflammation, hinder wound healing, and enhance tissue damage, thereby creating

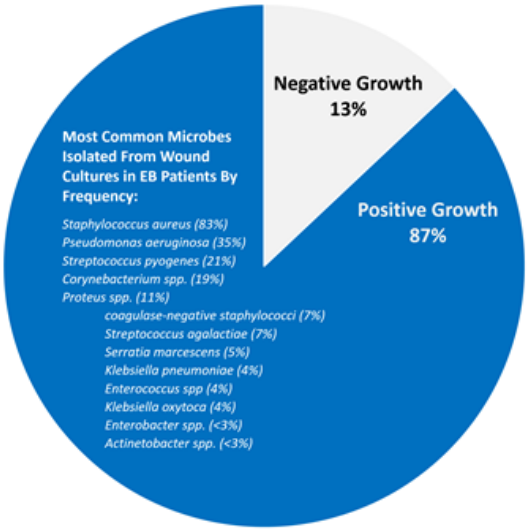

Figure 2. Most common microbes isolated from wound cultures in EB patients: Pie chart showing percentages of Staphylococcus aureus, Pseudomonas aeruginosa, and Candida albicans isolated from chronic EB wounds.

a microenvironment conducive to tumorigenesis [49, 50]. Chronic inflammation and oxidative stress due to infection can cause damage to DNA, promote angiogenesis, and induce proliferation of cancer cells [51]. Furthermore, elimination of benign commensal bacteria that normally regulate the immune response and inhibit pathogenic colonization reduces skin defense mechanisms. This environment favors the unchecked growth of aberrant keratinocytes, thereby increasing the likelihood of SCC development [52, 53]. Clarification of the interplay between dysbiosis and SCC development highlights the need for microbiome-targeted therapies, such as probiotics or microbiota-restoring treatments, to dampen chronic inflammation and reduce the risk of malignancy in at-risk populations [54].

Restoration of Skin Normal Flora Clinical trials have increasingly highlighted the pivotal role that probiotics, prebiotics, and microbiome-modifying treatments play in improving skin health. There is restoration of the skin's microbial equilibrium, enhancing immunity, and alleviating inflammation. With these, numerous dermatological issues can be addressed. The skin microbiome is a complex community of microorganisms surrounding the human body, serving as a barrier from pathogens, immune modulation, and overall skin health. Disruption of this microbial community is known to give rise to various dermatologic conditions like atopic dermatitis (AD) among others. Therefore, there is a need to restore the normal flora of the skin to promote skin health and for the management of these conditions. They can either be topical or

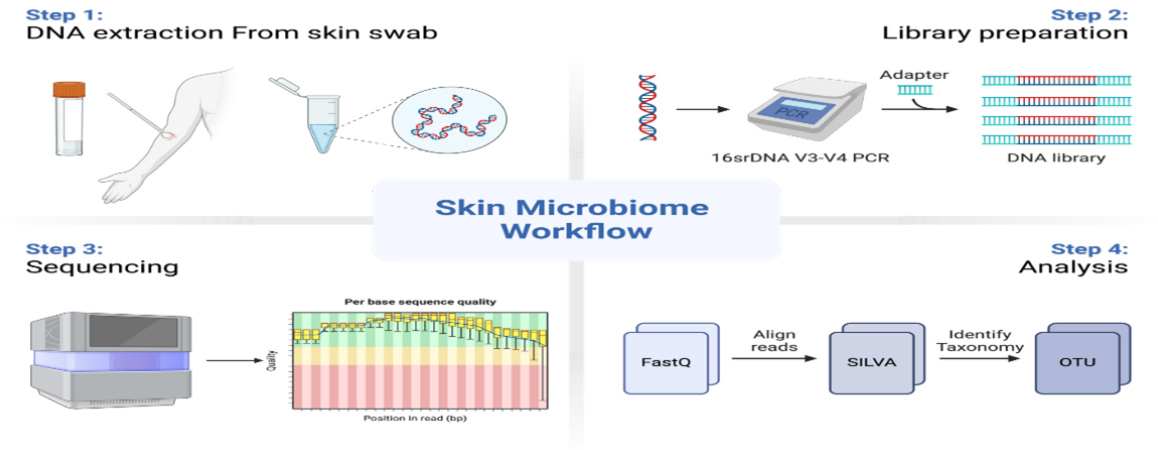

Figure 3. Skin Microbiome Workflow: Flowchart outlining steps from skin sampling to next-generation sequencing and data analysis

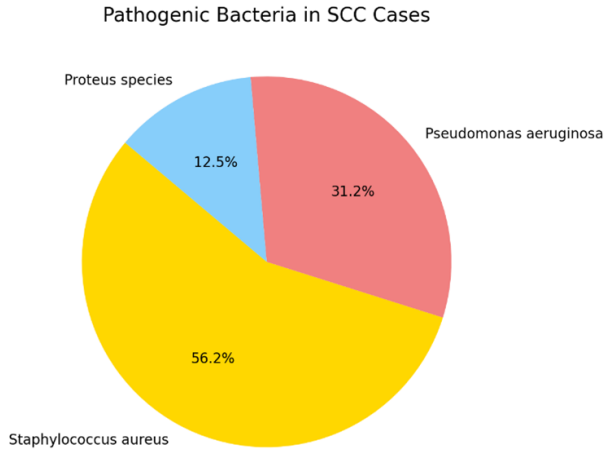

Figure 4. Figure 4: Pathogenic bacteria in SCC cases: The percentages of various bacteria in SCC patients is demonstrated in the pie-chart.

oral preparations of viable beneficial bacteria, which restore this balance by taking probiotics. Evidence from clinical studies indicated that probiotics can relieve symptoms of skin conditions like AD. For example, oral probiotics significantly improved AD symptoms in adults, resulting in lower pruritus and severity scores [55]. This improvement arises from the fact these probiotics help in modulating immune response, reducing inflammation, and inhibiting colonization by pathogenic bacteria. Probiotics are beneficial for the introduction of useful organisms into the ecosystem because they enhance the resilience of the skin to harmful bacteria and promote general skin health.

In addition to their contribution of probiotics, prebiotics also play a major contribution towards skin health. Prebiotics are not digestible foods, and they stimulate beneficial bacteria, encouraging their growth and functioning. Prebiotics, on the basis of research, can be useful for maintaining skin health by reinforcing the barrier of the skin and modifying the immune response [56]. Prebiotics, by providing beneficial bacteria with the requisite nutrition, maintain a balanced skin microbiome, and this balanced skin microbiome contributes towards prevention of infection and the process of curing. This approach also points towards the importance of symbiotic relationship between prebiotics and probiotics towards maintaining natural microbial status of the skin [57,58]. Bacteriotherapy, being a novel approach, consists of directly administering beneficial bacteria on the skin. Bacteriotherapy has been found useful for treating skin disease such as atopic dermatitis by suppressing growth processes and growth of pathogenetic bacteria. To take a specific example, topically administering specific strains of Staphylococcus epidermidis has been found useful for suppressing growth of pathogenetic Staphylococcus aureus, a frequent perpetrator of skin disease and exacerbation of AD [21-26, 59]. This selective approach not only manages disease process of infection but also ensures restoration of natural skin flora, hence, its natural barrier function. Emerging research on skin microbiome transplantation (SMT) offers a new strategy for treating disease-causing skin microbiome imbalances. SMT involves transplanting a normal microbiome into a disease-affected, unbalanced environment of the skin, possibly regrowing the natural composition of microbes and assisting with the process of curing [58]. SMT can be of particular value in disease states where the skin's microbiome has been severely disordered, for example, chronic wounds, and some genetic disease, for example, epidermolysis bullosa (EB). SMT, coupled with other methods altering the microbiome, may be the key to future treatment modalities for regrowing the skin's environment of microbes and for achieving

Table 3. Microbiome-Based Therapeutic Approaches for Skin Health [55,56,59-61]

Treatment Approach	Mechanism of Action	Examples/Applications	Commercially available drugs
Probiotics	Modulate immune response, reduce inflammation, inhibit pathogens	Oral probiotics improving AD symptoms	BioGaia, Lactinex
Prebiotics	Nourish commensal bacteria, enhance skin barrier function	Support in preventing infections, promoting healing	Inulin, Sunfiber
Bacteriotherapy	Apply beneficial bacteria to suppress harmful microbes	Staphylococcus epidermidis inhibiting Staphylococcus aureus [59]	Gladskin
Skin Microbiome Transplantation (SMT)	Restore microbial diversity by transferring healthy microbiome	Treatment of imbalanced microbiomes in chronic conditions	Roseomonas mucosa, SkinBioTherapeutics
Bacteriophage Treatments	Selectively target and kill specific harmful bacteria	Reducing harmful bacteria without affecting commensals	PhageGuard, AP-SA01

enhanced clinical outcomes. To date, methods directly addressing restoration of normal flora in EB for reducing pathogen colonization and replenishing commensal populations are not widespread. The use of prebiotics and probiotics, however, has substantial potential for this use. Systemic and topically administered probiotics target replenishing beneficial microbes and suppressing harmful ones. The utilization of Staphylococcus epidermidis strains, for example, has been shown to suppress growth of Staphylococcus aureus, a frequent causative microbe of EB-related skin disease, from becoming established on the skin's surface [59]. Through the targeting of disease-causing microbes and encouraging commensal growth, such treatment can increase stability of the skin's microbiome and promote enhanced wound curing.

Prebiotic formulations are also being explored for use in maintaining skin integrity in EB patients. Prebiotics, by supplying selectively beneficial microbes with nutrition, can fortify natural barriers of the skin and barrier function. [60]. The use of prebiotics and probiotics, referred to also as synbiotics, may be a holistic strategy towards restoration of microbial balance and skin health in EB and other chronic skin disease. Antibiotic stewardship, too, is a very critical component of maintaining a balanced skin microbiome. The selective use of antibiotics minimizes disruption of beneficial microbes and reduces the rate of resistance. This approach becomes very critical in disease states such as EB, where recurrent infections lead to use of excess antibiotics and, therefore, disruption of the microbiome. Advanced therapies, such as bacteriophage treatment, offer a viable alternative for traditional use of antibiotics. Bacteriophages are selective affinity and lethal action against specific bacteria, and therefore, offer a useful tool for elimination of harmful bacteria without affecting commensal populations [61]. The selective action of bacteriophages ensures disease-causing bacterium elimination with minimal disruption of beneficial microbes, and therefore, beneficial microbes can be protected and allowed to flourish for maintaining skin health. Bacteriophage treatment, when combined with other interventions affecting the microbiome, has the capacity for revolutionizing treatment of chronic skin disease and achieving improved patient outcomes. Research from Bar et al. suggests that DEB-specific skin microbiome signature may be treated with pathogen-specific treatment, and beneficial bacterium promotion may be useful for improved DEB-patient wound healing [62]. Emerging research into the discipline of microbiota transplantation and synthetic biology has attempted to infuse personalized bacterial populations into the skin with the goal of replacing normal microbials and inducing skin-healing outcomes outlined in Table 3 [55,56, 59-61]. These innovations offer substantial hopes for treating the

challenge of chronic skin disease and re-establishing normal skin flora [63].

2 Conclusion

The importance of the skin microbiome in EB, particularly regarding infection risk, wound healing, and disease progression, is the emphasis of this review. Dysbiosis or imbalance of the microbes is common in EB and can potentially lead to enhanced skin fragility, inflammation, and poor wound healing. Understanding the microbiome dynamics with the skin in EB patients introduces new possibilities to improve care. While traditional care is important, strategies targeting the microbiota have potential to reduce complications and improve skin condition in vulnerable patients. Subsequent studies should characterize the skin microbiome of EB across different disease subtypes and phases. Longitudinal research must determine the association between microbial changes and severity of disease and clinical outcomes. Exploration of the effect of probiotics, prebiotics, and microbiome-modifying treatments in clinical trials may provide insights into new treatments. In addition, new ways to optimize wound healing and reduce the risk of infection in patients are needed. Collaboration between dermatologists, microbiologists, and geneticists will be critical for improving our understanding of these complex interactions. Translating microbiological research into effective clinical interventions.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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