



Skin Microbiome—The Next Frontier for Probiotic Intervention

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Abstract

The skin is the largest organ in the human body, and it orchestrates many functions that are fundamentally important for our survival. Although the skin might appear to present a relatively inhospitable or even hostile environment, a multitude of commensals and also some potentially pathogenic microorganisms have successfully adapted to survive and/or thrive within the diverse ecological niches created by the skin's topographical architecture. Dysbiosis within these microbial populations can result in the emergence and pathological progression of skin diseases. Unsurprisingly, this has led to a new focus of research both for the medical dermatology and cosmetic industries that is concerned with modulation of the skin microbiome to help address common microbially mediated or modulated conditions such as acne, body odour, and atopic dermatitis. This review presents an overview of our current understanding of the complex relationship of the skin with its microbiome and then introduces the concept of probiotic intervention for the management of microbial dysbiosis within the skin ecosystem.

Keywords Skin microbiome · Probiotics · Skin · Dysbiosis

Introduction

The skin comprises around 15% of the total adult human body weight and on average has a surface area of 1.5–2 m² [1]. A primary function of the skin is to act as a physical barrier to pathogenic microbes and toxic substances, and indeed, it can be considered to be one of the body's key first lines of defence against infection, along with the innate and adaptive immune systems [2]. Its other functions include preventing transepidermal water loss (TEWL), thermoregulation, structural support, and production of vitamins, all of which help to sustain a healthy body [2–4]. From a microbiological viewpoint, the surface of the skin can be considered to provide an overlapping spectrum of specialized ecosystems, each comprised of its own menagerie of bacteria, fungi, viruses, and skin mites, and as for all of the other anatomical sites in the body, the skin-adapted organisms and viruses have specifically evolved and adapted to inhabit a highly specific ecological niche. The numbers of bacteria

on the skin are considerably lower in comparison with those present in the gut: some estimates ranging from an average of 1 million (10⁶) per cm² [5] compared to more than 1 trillion (10¹²) microorganisms in the large intestine [6]. The composition of the skin microbiota varies widely in different body sites (Table 1) with the differences mediated by a multitude of factors including tissue-specific topographical considerations, internal host-mediated factors, and the external environment [7]. The diversity of bacteria within a particular body site and interpretation of the potential implications of variations between different sites can be studied in terms of alpha and beta diversity. “Alpha diversity” is a measure of bacterial diversity within a sample, whereas “beta diversity” is a measure of bacterial diversity between different regions [8]. Major organs, including the gut, skin, and oral mucosa, harbour high levels of alpha diversity, compared to the low levels of alpha diversity in the vaginal mucosa. An interesting example in which both beta and alpha diversity exist within a single region is the oral cavity, which comprises a variety of hard and soft surfaces, differing atmospheres, and exposure to a heterogeneous supply of dietary nutrients [9].

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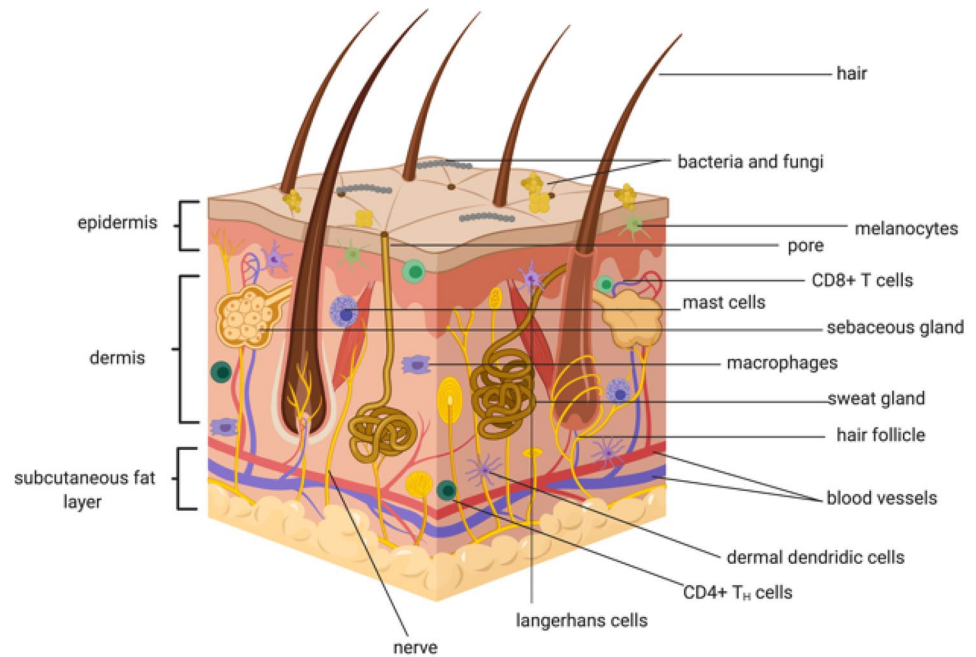
Structure of the Skin

The skin comprises three main layers: epidermis, dermis, and subcutaneous layer (Fig. 1). Each layer contributes to

Table 1 The composition of the skin microbiota varies widely in different body sites

Bacteria	Location/skin site	Function	References
<i>Staphylococcus epidermidis</i>	Mainly in moist areas but can appear in dry and exposed regions like the palms and forearms. Some anaerobic strains can survive in anoxic environments, e.g. hair follicles.	Maintains healthy skin by improving the water and lipid content of the skin, decreasing inflammation, promoting tissue repair, and suppressing the levels of undesirable bacteria. Exerts selective antimicrobial action against pathogenic <i>S. aureus</i> and <i>S. pyogenes</i> . Modulates TLR-3-dependent inflammation Produces bacteriocins and other antimicrobial factors	[4, 26–28]
<i>Staphylococcus hominis</i>	Inhabits many regions of the body including the axillae, legs, and arms.	Produces antimicrobial peptides (AMPs) against pathogenic bacteria, e.g. <i>S. aureus</i> . AMPs also inhibit the growth of microorganisms normally residing on the skin.	[28, 29]
<i>Staphylococcus aureus</i>	Lesioned and un-lesioned atopic dermatitis skin sites. Found in 1/3 individuals and can be described as an opportunistic pathogen.	Skin commensal, but opportunistic Abundance of <i>S. aureus</i> is implicated in atopic dermatitis and other superficial skin conditions.	[4, 27, 30, 31]
<i>Cutibacterium acne</i>	Oily areas of the skin and pilosebaceous glands	Produces short-chain fatty acids (SCFA) which disrupt the development of non-indigenous bacteria on the skin surface, e.g. <i>S. pyogenes</i> . Skin commensal bacteria, but certain phylotypes are associated with acne.	[4, 26, 32]
<i>Micrococcus luteus</i>	One of the most abundant species found associated with human skin. Found predominantly on head leg and arms	One of the most abundant species in the human skin microbiome. Broad spectrum bacteria that help to control acne, eczema, psoriasis, impetigo, athletes foot, methicillin-resistant <i>S. aureus</i> (MRSA), and body odour Adds further protection within the skin microbiome.	[29]
<i>Candida albicans</i>	Mucocutaneous surfaces of the mouth, skin, female reproductive tract, and gastrointestinal tract	Commensal yeast in healthy hosts. Opportunistic in immunocompromised individuals, microbial dysbiosis, and disturbed epithelial surfaces.	[33]

Fig. 1 Physical structure of the skin with corresponding immune cells, bacteria, and appendages that inhabit each layer (adapted from “Anatomy of the Skin”, by BioRender.com (2020). Retrieved from <https://app.biorender.com/biorender-templates>)



help provide a barrier between the exterior environment and the internal body and each may contain additional “sub” layers [2]. The epidermis is composed of four distinct layers: stratum corneum, stratum granulosum, stratum spinosum, and stratum germinativum (from the outermost to innermost). Keratinocytes make up 80% of the epidermis layer and provide structural support, aid in sustaining the microbiota, and help counter pathogens through modulation of the innate immune system [10]. The structure of the stratum corneum contributes to the skin’s remarkable barrier function, helps prevent water loss, regulates the synthesis of epidermal DNA and lipids, and also aids defence against pathogen penetration [11]. Other cells present in the epidermis include Langerhans and T epidermal cells, which contribute to the detection of antigens in the epidermis for the innate and adaptive immune system; melanocytes, which synthesize the pigment melanin; and Merkle cells, which act as slow-adapting mechanoreceptors that respond to stimuli on the skin [12, 13].

The dermis is the second major layer of the skin. It is around 2–5 mm thick and contains connective tissue, a network of nerves, and vascular structures as well as additional skin appendages including hair follicles as well as a variety of eccrine, sebaceous, and apocrine glands. Immune cells, including macrophages and dendritic cells, are also present, and these help initiate innate immune responses within the skin. Dermal collagen and elastic fibres provide pliability, tensile strength, and elasticity to the skin, whereas nerve and vasculature networks maintain thermoregulation and allow for the recruitment of immune cells and the detection of stimuli on the skin surface [10].

The third and innermost layer is the subcutaneous fat layer which provides the skin with its characteristic buoyancy and functions as an energy storehouse [10].

Skin Microbiome

The human skin microbiome is the community of microorganisms (i.e. the microbiota) which inhabits the human skin together with its “theatre of activity” (i.e. the associated microbial structural elements such as proteins, lipids, polysaccharides, and nucleic acids). The skin microbiota comprises bacteria, fungi, viruses, and skin mites [14]. The four main bacterial phyla identified on the skin are Actinobacteria (52%), Firmicutes (24%), Proteobacteria (17%), and Bacteroidetes (7%) [14]. Predominant genera include *Corynebacterium*, *Propionibacterium*, and *Staphylococcus* [4, 15]. Colonization within the human microbiome is initiated at birth, and the composition of the pioneer communities is strongly influenced by the route of delivery [7, 16]. The composition of the skin microbiota is then determined by a multitude of internal and external host factors generating inter- and intrapersonal variations. However, a core set of microbial species are present across all individuals. Rare and transient species of microbes account for interpersonal variations which can be attributed to host lifestyle and environmental and genetic factors [2]. Intrapersonal variation is frequently seen on the forearms and palms of the hand, and this can be attributed to the specific niche, lifestyle factors, hygiene rituals, and cosmetic products (e.g. hand creams) used in these areas, e.g. [8]. Characteristic microbiota differences have

also been detected between males and females in certain regions of the body such as the axilla [2].

Types of Skin

Skin type can be broadly classified into three main categories: oily, moist, and dry with each type hosting a distinctive microbial community (Fig. 2).

Oily skin can be found commonly on areas such as the forehead and nose, forming the T-zone. These areas contain a high density of pilosebaceous units which produce sebum, a lipid-rich substance that gives this skin an oily composition. Sebum secreted by the sebaceous glands act as a moisture barrier that prevents the skin from desiccation and supplies the contiguous microbiota with nutrients. *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), a common commensal of the skin, is particularly abundant in sebaceous environments within the pilosebaceous units. *C. acnes* has adapted to thrive in an oily, anaerobic environment, accessing sebum as a source of nutrients through the action of the enzyme lipase which degrades sebum and releases free fatty acids, thereby contributing to the acidic nature of the surface of the skin [16, 19]. The

resulting acidic environment supports the growth of characteristic commensal bacteria whilst inhibiting proliferation by opportunistic pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes* [2, 20].

Moist skin is typically found in unexposed areas of the body and includes the armpits, skin folds such as the elbows, between toes, and groin areas. Increased moisture in these areas is due to the increased production of sweat. Moist environments favour a more diverse community of Gram-negative and Gram-positive commensal and pathogenic bacteria [21] with a predominance of *Staphylococcus* spp. and *Corynebacterium* spp. [22]. Some pathogens, such as the ubiquitous *Pseudomonas aeruginosa*, have also adapted to thrive in these conditions [21].

Dry skin sites such as the forearms, hands, and parts of the feet harbour a vast community of microbes, the principal phyla being the Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes. Several fungal species are also commonly present and these especially include *Malassezia* spp., *Aspergillus* spp., *Cryptococcus* spp., *Rhodotorula* spp., and *Epicoccum* spp. *Malassezia* spp. are particularly common, sometimes accounting for up to 80% of the entire fungal community [18, 19].

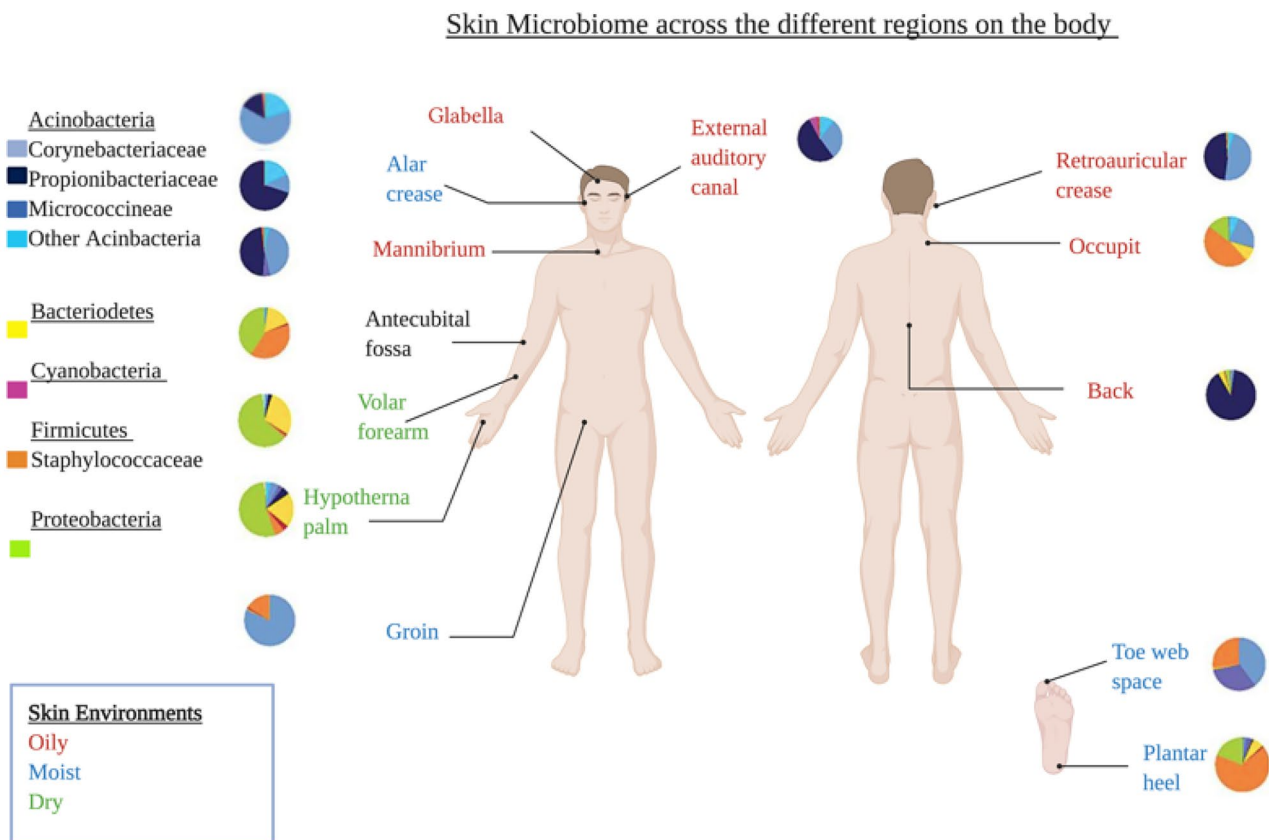


Fig. 2 Difference in composition of bacteria across different human skin types: oily, moist, and dry skin. Information derived from Belkaid and Segre [17], Dréno et al. [18], Grice and Segre [2], and Schommer and Gallo [4]

Stability of Skin Microbiome

The stability of the microbiome is influenced by the skin environment and the phylogeny of colonization. The stability of microbial niches is inversely proportional to their microbial diversity; the higher the microbial diversity, the less stable is the community composition [3]. Oily environments harbour more stable microbial niches than dryer sites due to the high perturbation and exposure to external stimuli [3]. Factors which can further affect this stability include exposure to antimicrobial treatments such as soaps and shampoos, application of skin care products, and changes to lifestyle factors including relocations to new environments, e.g. urban to rural, diet, immunosuppressive drugs, and illness. Changes in the stability of the microbiome suggest that there is microbial-host intercommunication which maintains a stable equilibrium [18].

Immune Modulation

Intercommunication between host and the microbiome helps to maintain a stable microbiota through modulation of the innate immune system [18]. For example, keratinocytes interact with microbes through pattern expression receptors (PRR) on the cell surface, constantly sampling the skin microbiota [2]. Recognition by PRRs can result in the release of antimicrobial peptides (AMPs), cytokines, and chemokines in response to microbial growth to help control the skin microbiota, reduce skin dysbiosis, and educate the immune system [2]. PRRs become desensitized when exposed to long-term commensal microbes like *Staphylococcus epidermidis*, which can help the skin distinguish between commensal and pathogenic microbes [20]. Skin appendages such as the pilosebaceous unit and eccrine secretions have immune modulation abilities [18]. Pilosebaceous units release AMPs in response to Gramme-positive bacterial activity, and the presence of free fatty acids provides antimicrobial effects. Eccrine secretions contain dermcidin, a weak AMP, providing further control over the microbiota [19].

The skin surface engages in symbiosis with diverse microbial niches working together to improve the overall innate immune response. Commensal bacteria contribute greatly to this relationship via the production of AMPs, selective bacteriocins, and phenol-soluble modulins which selectively inhibit the growth of pathogenic bacteria without harming themselves [19]. AMPs are important chemical modulators continuously released from cells in a controlled manner. In the presence of a pathogen, their concentration increases signalling to the immune system that something is wrong, and thus, they are a vital component of microbial-host communication [18].

Microbiome Analysis

Microbial Sampling Methods

Invasive and non-invasive techniques are involved in the collection of microbial samples from the skin (Fig. 3). Non-invasive techniques known as “flock sampling” require a cotton swab, to be rubbed against the skin surface to remove skin and bacterial cells. To collect samples from deeper layers of the skin, keratin tape or super glue has been found to be useful [18]. A punch biopsy is an invasive technique; however, due to its nature, it is used only to identify infections and to inform their appropriate antibiotic treatment.

Analytical Tools and Techniques

Swab Culture

A traditional approach to microbiota analysis involves the enumeration of the microbes present in swab samples using selective agar-based growth media. This technique is simple and does not require sophisticated equipment so it can be replicated in many laboratories. However, it is very species-specific and time-consuming. There are also limitations to the range of microbial species that can be cultured. For example, *Staphylococcus* spp. are relatively easily cultivated when compared with *Cutibacterium* and *Corynebacterium* species potentially resulting in inaccurate representations of their numbers in samples [7, 16].

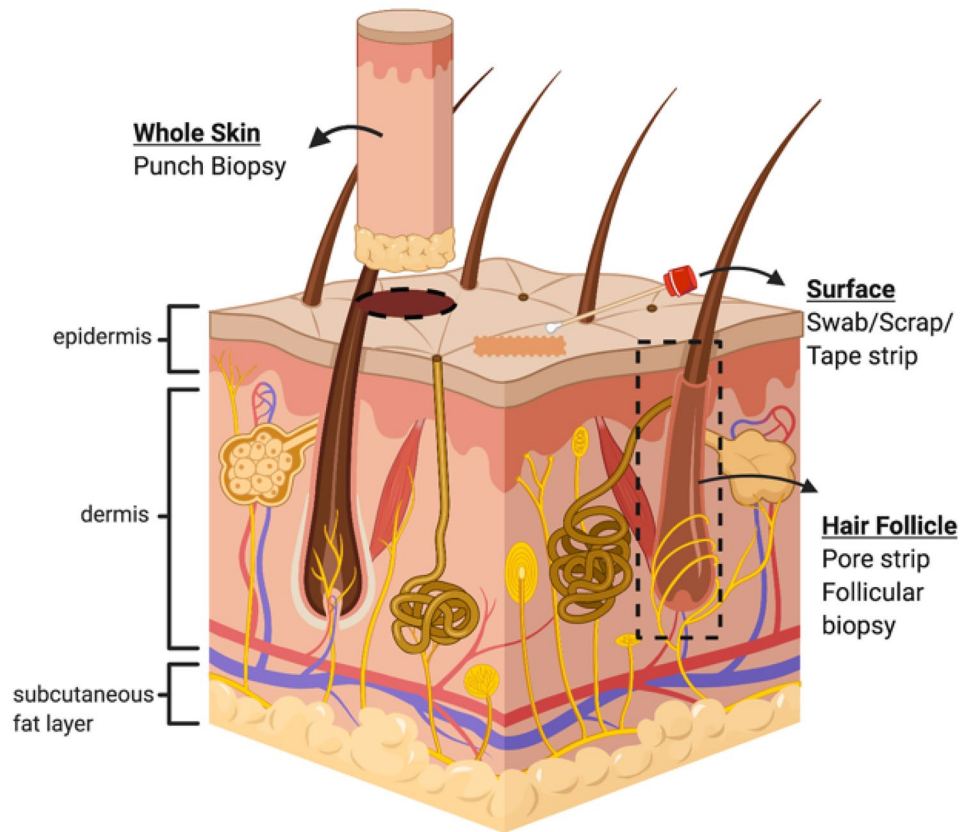
DNA Amplicons

DNA amplicon sequencing allows for the specific regions of genomic material to be amplified. For bacteria, the highly conserved 16S rRNA primer is used to amplify certain regions, whereas in fungi, ITS1 is preferred [18]. The 16S rRNA primer is universal and found in almost all prokaryotes, aiding in assessing the complexity and diversity of microbial communities [18]. This method is limited, however, by its short-read lengths, sequencing errors, and its ability to distinguish between related species within the same phyla due to limited resolution [23]. This method also provides no information concerning microbe-host interactions or whether the organism is dead or alive at the time of sequencing. It is also expensive and time-consuming [18, 23].

Shot Gun Sequencing

Shot gun sequencing is a technique used to target the entire genomic material of a microorganism rather than a specific section. Whole genome sequencing involves breaking the

Fig. 3 Potential methods for sampling the skin microbiome: skin swab, tape strip, and punch biopsy (adapted from “Anatomy of the Skin”, and “Skin Biopsy” by BioRender.com (2020). Retrieved from <https://app.biorender.com/biorender-templates>)



DNA into segments of various sizes and then cloning the fragments into vectors [24]. This method offers a global view of microbial communities, allowing for better assessment of phylogenetic diversity regarding species and strains within phyla and the actions they are responsible for [16]. Limitations to this technique include the requirement for large DNA samples, which is difficult with normal skin swabs as they typically harvest only a relatively small biomass of microbes [24]. The requirement for analysis of large quantities of genomic information results in incomplete genomic analysis for some microbial populations [7].

Skin Commensal Bacteria

Commensal microbes inhabit different regions of the skin and contribute to symbiosis in various ways (Table 1). Something important to note is the switch from a homeostatic state to a disease state that can be affected by microorganisms. It is not fully understood what initiates this process and if it is microbe-dependent or environmentally triggered. Potential effectors include physical damage to the mucosa, disruption of the indigenous microbiota with antimicrobials,

expression of specific virulence factors, and access to the site by excessive numbers of pathogens [7, 25].

Microbial Imbalance

Dysbiosis

Dysbiosis is a state of microbial imbalance within areas of the body sometimes impacting on the vitality and health status of those areas. Illness is thought to be associated with dysbiosis due to a loss of microbial diversity and an increase in the relative numbers of pathogenic bacteria [27]. Dysbiosis can be induced and influenced by a wide variety of factors including the route by which a baby is born, hormonal shifts, undue stress, hygiene practices, personal care products, medicine use, nature, and food [4, 34]. Gender-linked differences may be based on physiological and anatomical differences such as hormone production, sebum production, soaps, fragrances, and personal care products that contain harsh preservatives and synthetic ingredients that can influence the microbiome by altering the pH of the skin [4, 34]. Many human skin disorders and diseases have been linked to changes within the skin microbiome, including acne, atopic

dermatitis, and psoriasis [4, 27, 30, 31]. However, it is generally not established whether dysbiosis is the cause of these condition or the consequences.

Putative Inducers of Dysbiosis

Antibiotics

Antibiotics are one of the greatest medical discoveries of all time, having transformed the treatment of many previously incurable conditions. However, the long-term adverse effects of antibiotic administration have relatively seldom been given scientific consideration, including their effect on the body's microbial composition, which can take many years to re-equilibrate [4, 35]. Antibiotics are the most common type of medication prescribed to children in the Western World [35]. In the USA alone, antibiotics account for 25% of all prescriptions for paediatric populations, with amoxicillin, azithromycin, and amoxicillin/clavulanate most commonly utilized [35]. The type and duration of antibiotic treatment differentially alter microbial communities by targeting and eradicating susceptible taxa [35, 36]. This can affect the microbiome in many ways such as contributing to the elimination of key commensal taxa and a generalized loss of biodiversity which can contribute to specific health issues [27, 36]. Communities of bacteria that have been eradicated from their specific niches leave these areas open for pathogenic species to colonize and flourish in, further disrupting microbiota homeostasis. Long-term therapy with topical antibiotics to treat acne has led to the development of resistant bacterial strains, decreasing clinical improvement of acne lesions [37]. A wide variety of health consequences including increased risk of excessive weight gain, asthma, allergies, and autoimmune diseases have been associated with early childhood antibiotic exposure [35, 38]. However, the literature is limited in directly implicating microbial dysbiosis as the link between childhood antibiotics and conditions later in life as there are a multitude of confounding factors including genetic predisposition and immune interactions [36].

Hygiene Hypothesis

The hygiene hypothesis proposes that exposure to environmental microorganisms and parasites is important for healthy development and maintenance of the immune system [35]. Within the Western world, there has been a cultural shift towards more stringent application of hygiene measures. One consequence of over-cleansing and increased antimicrobial use has been the relatively reduced exposure in early childhood to potentially pathogenic microbes, thereby reducing natural immune development and predisposing

to the development of atopic conditions [39]. A study conducted in the USA looked at the effect of a farming environment on microbial exposure [40]. It was shown that farm children are exposed to a higher diversity of environmental bacteria and fungi. Dust collected in Amish communities who adhere to a traditional type of farming, with minimal changes in the last 2 centuries, prevented airway hyper-responsiveness, a trademark sign of asthma, whereas dust from farming communities that had industrialized with the times did not [40]. The concept behind over-cleansing has been fostered by the notion that all bacteria are bad bacteria. Increased hygiene not only causes changes within the taxa comprising the human microbiota, but it is also hypothesized to be one of the factors responsible for a rapid increase in the prevalence of atopic dermatitis (AD) over the past two decades [41].

Birth

In utero, a child's skin is sterile, with colonization occurring during the birthing process, whilst over time, a complex ecosystem forms made up of primitive and transient microbes [5, 26]. Caesarean (C) section birth greatly affects the variety and composition of microbes colonizing the neonate as these babies are not directly exposed to the mothers vaginal and faecal microbiota [34, 42]. Instead, they immediately come in contact with the mother's skin microbiota, as well as microbes shed by the hospital staff or present in the operating room. Microbes acquired by infants that are associated with vaginal delivery include *Lactobacillus*, *Prevotella*, and *Candida albicans* as compared to infants born via C-section that are predominantly colonized by maternal commensal skin bacteria: *Staphylococcus*, *Streptococcus*, and *Cutibacterium* [36, 42–44]. C-section delivery has the potential to interrupt the "normal" colonization by skin microbes that is achieved during labour and vaginal delivery [44]. The lack of exposure to maternal vaginal and faecal bacteria results in different microbial communities on the skin of the infant [45]. A study conducted by Chu looked at the differences in microbial communities on infant skin at birth and 6 weeks of age [28]. At birth, the microbial composition of neonates was influenced by the mode of delivery; however, these differences were absent at 6 weeks of age once the infants had been exposed to similar conditions, e.g. breastfeeding and cuddling with the parents [43]. Interestingly, studies show that neonates born via C-section who were swabbed with the mother's vaginal secretions were more microbially like infants born vaginally versus those who experienced the standard C-section birth [46].

C-section delivery impinges not only on the microbiota but also on immune development. Labour induces immune responses within the uterine cavity that are absent in the case of elective C-sections, which affects the immune

environment of the neonate [47]. Levels of cytokines have been shown to be reduced in C-section delivery, cells which are vitally important in initiating and maintaining the immune response [42]. Differences in microbial colonization patterns are important as they not only impact upon the final composition of the microbiota but they also influence the development of the infant’s immune system in the first months of life. Given that the first few months of life represent a vital time window in the ontogenesis of the immune system, including establishing tolerance, C-section delivery may impact on the lifelong risk of developing immune disease [42, 47]. Immune disorders known to be impacted via C-section delivery include type I diabetes and allergen development [46, 48]. A large meta-analysis detected a 19% increase in type I diabetes in children born by C-section after controlling for confounders such as gestational age, maternal age, and birth weight [47]. Researchers speculate that initial alterations in the microbiome of infants following C-section birth may play some role in the association between chronic disease and route of birth; however, not all findings are conclusive [46]. The influence of the microbiota hence highlights the importance of the development in early life and how it can impact upon individuals later in life.

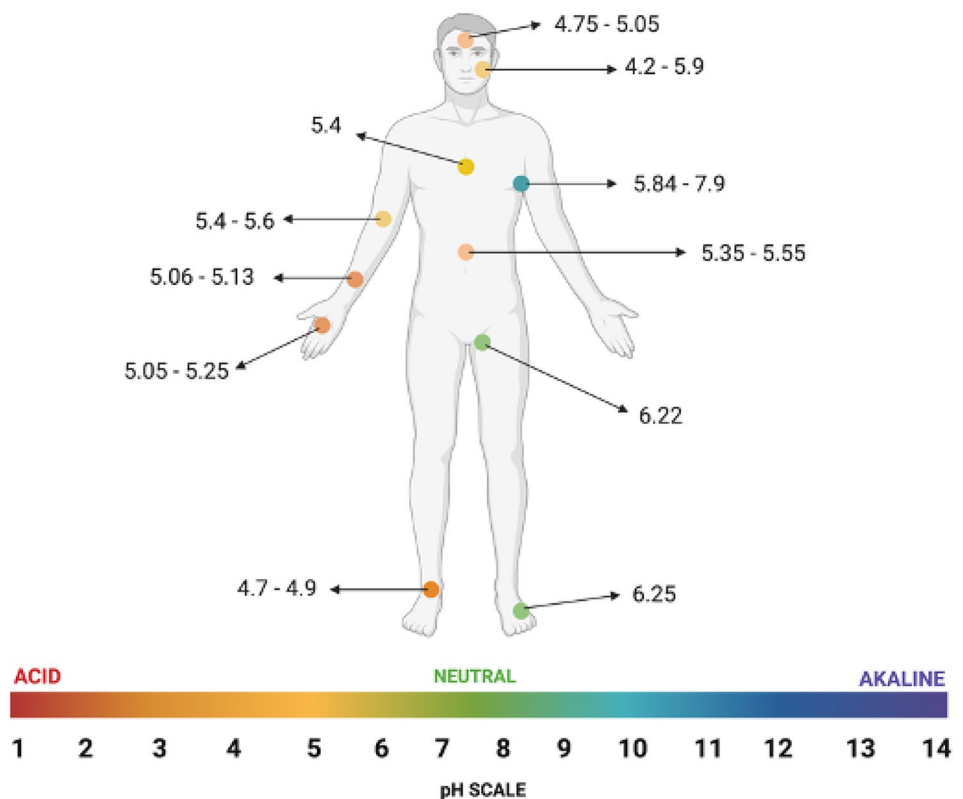
Personal Care Products

Studies show that the exposure of normal, western skin to commonly used cosmetics, soaps, steroids etc. alters the natural skin microbiota, especially in the developed world [2, 49]. Cosmetic products that contain preservatives (e.g. izothiasoline in makeup, moisturizers), alcohols (e.g. propylene glycol in deodorants and antiperspirants), and paraffins and fragrances (in moisturizers, soaps, and perfumes) can non-selectively kill or inhibit the growth of commensal skin bacteria alongside pathogenic ones, disturbing the equilibrium and creating dysbiosis [50]. Therefore, it is important to choose products that contain ingredients that benefit not only the host but also the microorganisms existing symbiotically with the host. However, there is a lack of research into what ingredients disrupt specific species of bacteria and the effects of this disruption. More research is needed to generate more conclusive findings.

Skin Surface Acidity

The pH of the skin surface, known as the acid mantle, changes to suit the needs of the specific region and protects the skin against certain pathogens (Fig. 4) [27]. The acidity of the skin’s surface is important for maintaining a healthy ecosystem, skin barrier support, optimal conditions for physiological processes, and the growth of skin microbes

Fig. 4 Differing pH across different regions of the skin to suit the needs of the microorganisms and physiological functions (adapted from “Adult Male”, by BioRender.com (2020). Retrieved from <https://app.biorender.com/biorender-templates>)



[18, 51]. The acidic environment is established through microbial metabolites, appendageal secretions, free fatty acid production, local generation of protons in the lower stratum corneum, and production of urocanic acid [11]. The pH of the skin ranges between 4.7 and 5.75. Low-exposure, higher occluded regions like the axilla have higher pH values ranging as high as 7.9 and are considered to be anomalies sometimes referred to as “holes in the mantle” [18].

The topographical environment of the skin is important in determining microbial colonization at each site. Hair density, occlusion level, and the presence of specific gland appendages contribute to the acidity of the skin [52]. There is a positive relationship between lower pH values and preservation of the skin microflora, with a pH of 5 recognized as an optimal level [18]. Lower pH environments favour hydrophobic and electrostatic attractions between microbes and the skin, lowering overall bacterial dispersal rates from the skin [18]. Despite the skin's harsh landscape, the acidic mantle has allowed for many different types of bacteria to thrive [52]. For example, the acidity of the skin favours the growth of *Staphylococcus epidermis*, a skin commensal bacterium whilst inhibiting the growth of the relatively pathogenic *S. aureus* and *S. pyogenes* [18, 22].

Conditions Arising from Dysbiosis

Factors influencing the skin microbiome either alone or in combination result in several skin disorders and diseases. These skin anomalies affect people of different age groups, gender, and race and require symptomatic and therapeutic interventions. Some of the common skin ailments have an underlying microbial element leading to overpopulation of pathogenic bacteria or fungi and contributing to infection and dysbiosis.

Acne

Acne vulgaris is a chronic skin condition involving hair follicles and sebaceous glands that affects up to 80% of adolescents [26, 53]. The microbiome of acne sufferers is characterized by a diverse group of microorganisms, but *C. acnes* and *Malassezia* have been linked to the development of acne lesions [53]. *C. acnes*, an anaerobic Gramme-positive bacterium, influences the development of acne via sebum commensalism, comedone formation (whiteheads and blackheads), hyperproliferation of keratinocytes, and aggravating inflammation in the skin [54]. *C. acnes* lesions create an anaerobic microenvironment that aids the growth of *C. acnes* further [54]. *Malassezia* are lipophilic fungi associated with sebum-rich areas of skin [4].

Initially increased sebum production is related to a change in hormones which first occurs around puberty; hence,

teenagers can be the initial sufferers of acne [54]. It is also the important trigger that provides optimal living conditions for the *C. acnes* to thrive [27]. Whilst there are bacteria that contribute to the formation of acne, there are also some that work in favour of the host including *S. epidermidis*. *S. epidermidis* antagonizes *C. acnes* by fermenting glycerol which creates zones of inhibition to repel overgrown colonies of *C. acnes* [34, 55]. *C. acnes* is a commensal in healthy, unaffected skin, yet it is unknown what triggers the bacteria to be implicated in the disease state and become pathogenic [49]. Acne is classically treated with topical and oral antibiotics, commonly macrolides, clindamycin, and tetracyclines. Treatment of acne with antibiotics has caused high levels of resistance to occur which raises serious issues across multiple areas of medicine. For example, resistance towards the antibiotic clindamycin has increased from 4% in 1999 to 90.4% in 2016 [53]. Not only does it result in increased resistance rates but the amount of *C. acnes* on the skin also increases and it remains longer which can manifest as a re-occurrence of acne.

Atopic Dermatitis

Atopic dermatitis (AD) is a condition resulting in dry, red, and itchy skin. Eczema is thought to develop due to barrier disruptions in the upper skin layers leading to the loss of water through the skin layers known as transepidermal water loss (TEWL) causing dryness [55]. AD is a chronic condition that usually manifests in childhood but then sometimes flaring up periodically in adulthood [56]. It is commonly accompanied by asthma and food allergies, a collective of conditions sometimes referred to as the atopic march. Prevalence has increased over the past decade with 15–20% of children now affected and 2–10% of adults [30]. There is no current cure for AD, only supportive medications to help deal with symptoms, including the application of topical corticosteroids and hydrating moisturizers. Although the exact cause of eczema is unknown, *S. aureus* colonization is typically present in eczema lesions [56]. Ninety percent of AD patients are colonized with *S. aureus* on both lesioned and non-lesioned skin compared with less than 5% of healthy individuals [5, 9]. Genetic and environmental factors contribute to the disease, with skin barrier dysfunction being critical for the pathogenesis of *S. aureus* infection [30]. Dry skin and hyperkeratinization, characteristic features of AD, act as adherence factors for *S. aureus* [57]. Bacteria that reside on normal skin provide some protection against *S. aureus* whereas the relative absence of competitive bacteria on the skin of subjects with AD and decreased bacterial diversity in these populations was strongly associated with increased colonization by *S. aureus* [28, 44]. The administration of specifically selected bacteria to reduce the abundance of *S. aureus* is inherently superior to the use of

current pharmaceutically derived antibiotics because they do not disrupt cutaneous homeostasis by nonspecific killing of the indigenous microbiota [28]. For example, the common skin commensal *S. hominis* was found to significantly decrease the relative abundance of *S. aureus* when applied to the forearm of individuals with AD compared to the use of classical treatments, e.g. lotion [28, 58].

Psoriasis

Psoriasis vulgaris (PV) is a chronic inflammatory skin condition characterized by rapid proliferation of keratinocytes and infiltration of immune cells with formation of plaques of thickened skin giving the appearance of scales [59]. It is a non-communicable disease affecting around 2% of the world's population [4] and can affect individuals of any age [55]. Not only does psoriasis impact upon an individual physically but it can also adversely influence a patient's quality of life and emotional status. The aetiology of PV is not well-understood but it is known to be the product of a complex interplay between an individual's genetic predisposition and environmental factors. Bacteria characteristically found on the skin of individuals with PV include Firmicutes, Actinobacteria, and Proteobacteria [4]. Additionally, *Staphylococcus* and *Streptococcus* spp. have been detected more frequently in lesioned skin [59]. In other studies, *S. aureus* has been found at significantly higher levels on diseased skin whereas *S. epidermidis* and *C. acnes* are more commonly detected on non-diseased skin, an observation taken to indicate that the skin microbiota may have a role in PV pathophysiology [55]. Treatment aims to remove scales and halt the rapid growth of skin cells and this is usually done via the application of topical corticosteroids, vitamin A derivatives, phototherapy, and the management of lifestyle factors which may contribute to flare ups. In the future, the dysregulated skin microbiota may become a novel therapeutic target, whilst restoration of symbiosis may increase the efficacy of already established medical treatments [60].

Body Odour

The frequently stigmatized condition of malodorous body odour is most targeted using a wide array of deodorants and antiperspirants and sometimes a combination of both. There are three types of glands present in the axilla: apocrine, eccrine, and sebaceous. Apocrine glands secrete a hydrophobic mixture that contains fats, steroids, and proteins via hair follicles. Eccrine glands conversely provide water and a hydrophilic mix including salt and lactic acid, which is released straight onto the skin. On the other hand, sebaceous glands secrete sebum, which can be used as a metabolic substrate by certain bacteria [61]. The moist, warm environment provided by the structural anatomy of the axilla

together with the dense coverage of hair fosters bacterial proliferation [53, 61]. Axilla odour represents a complex interplay between specific glands, secreted amino acid conjugates, and the products of certain enzymes associated with microorganisms colonizing the skin [61]. Interestingly, fresh axilla secretions are odourless, only developing their classic pungent scent following contact with skin bacteria which transforms them into volatile odoriferous molecules, known as bacteria-triggered odour release [53]. Common microbiota present in the axilla include members of the genera *Staphylococcus*, *Micrococcus*, and *Corynebacterium* [62]. However, more than 200 species have been identified within this microbial community. The diversity of these populations increases with age as well as the total bacterial numbers with senior subjects (55+) having the highest numbers [53]. Although multiple species have been tested, only members of the genus *Corynebacterium* are known to cause odour [44]. Odour is generated from volatile fatty acids (VFA) via the activity of the corynebacterial enzyme Na-acyl glutamine aminoacylase which acts at Na-acyl-L-glutamine, producing 3-methyl-2-hexenoic acid (3M2H), the source of the characteristic pungent apocrine smell [44, 62]. Bacteria-triggered release is not the only way odour is generated in humans. Reactions with thioalcohols involving bacteria are also known to cause odour, like that of VFA. Deodorants work in one of three ways (1) by blocking bacterial growth via the activity of antibacterials, e.g. triclosan; (2) by using odour-masking fragrances to overpower the malodours; and (3) by reducing perspiration through the activity of various inorganic salts such as aluminium chloralhydrate, which are thought to work by clogging sweat ducts [61]. Changes in microbial diversity have been linked to deodorant use, together with a relative increase of *Corynebacterium*, showing that axillary products can stimulate odour-producing bacteria instead of treating the problem [58]. Deodorant-focused mechanisms are not specific to malodorous bacteria and do not treat the root problem, which highlights the need for further research and product development.

Tinea Pedis

Tinea pedis is a dermatophyte infection particularly affecting the interdigital web and/or the sides of the feet. Its distribution is extensive (> 70% of humans) and occurs independently of subject age, race, and sex [63]. It is most prevalent in the post-pubescent period and can be either a chronic or reoccurring condition [63, 64]. The environment of the skin of the feet is unique and features a large number of sweat glands and a relative absence of sebaceous glands. The wearing of occlusive footwear creates a highly relative humidity and warm conditions, conditions allowing both bacteria and fungi to thrive [64]. Other factors predisposing the development of tinea pedis include sweating, trauma,

an immunocompromised state, and exposure of the feet to communal surfaces [52]. Epidermal samples from patients with tinea pedis have been shown to exhibit increased fungal diversity and decreased bacterial diversity when compared to healthy controls [63, 64]. An increase in *Trichophyton rubrum* (27.26%) was observed in patients with tinea pedis as compared to healthy controls (0.065%) [63]. The most prevalent bacterial phyla in swabbing's from patients with tinea pedis were Firmicutes, Actinobacteria, and Proteobacteria, whilst *Staphylococcus* constituted more than 30% of the bacterial genera. Tinea pedis can be treated with topical or oral antifungals or a combination of both [63]. Topical applications of antifungals are used for 1–6 weeks depending on infection severity and the active ingredient of the antifungal. A topical corticosteroid can also be incorporated into treatment regimens if the area is inflamed. Oral antifungals tend to be reserved for patients with extensive chronic tinea pedis; however, interactions with other medications are common and pose a risk to these patients [63]. It is clear that the composition of the skin microbiota in subjects having tinea pedis is different to that of controls, prompting suggestions that skin dysbiosis may influence the occurrence and development of the disease [64].

Impetigo

Impetigo is a bacterial infection of the epidermis commonly occurring in school children [57, 65]. It is a highly contagious infection, usually transmitted via direct contact. The bacteria responsible for impetigo infections are predominantly either *S. pyogenes* or *S. aureus*, or a combination of both [65]. Depending on the layer of skin that is infected, bacteria that are implicated in impetigo can also cause ecthyma or cellulitis [57]. Both of the primary bacterial agents of impetigo can produce toxins that bypass the immune system and elicit the development of characteristic lesions. The typical presentation of impetigo starts with a singular erythematous blemish which subsequently becomes vesicular or pustular [65]. The vesicles are subject to eruption leaving a “honey coloured” yellow crust over the superficial lesion. Host factors including immunosuppression and tissue damage are important in the pathological process of impetigo [57]. Often, there is a correlation between where the patient's fingernails have scratched the skin and the development of lesions, as generally damage to the skin is required for bacterial infection [48, 65]. Mainstay treatment includes wound care and antiseptic washes such as chlorohexidine and antibiotic therapy. Topical antibiotics including fusidic acid are used in the absence of systemic symptoms. It is however more common for systemic symptoms to present, such as fever and lethargy, thereby prompting the use of systemic antibiotics [57]. There are concerns around the use of antibiotics for *S. aureus* infections largely

prompted by the development and spread of MRSA [57, 65]. *S. aureus* readily acquires antimicrobial resistance, a factor limiting treatment options and contributing to the global proliferation of antimicrobial resistance.

Approaches to Establishing and Maintaining a Beneficial Skin Microbiota

Probiotics and the Current Products on the Market

The development of several key technologies has allowed researchers to evaluate the human microbiome in greater depth and to achieve a better understanding of the connections between specific microbes and a variety of disease presentations, leading to the development of many novel and emerging therapies to treat commonly occurring ailments [49]. Whilst pharmaceutical companies continually assess candidate site-specific bioactive molecules for their capability to improve skin function or to effect amelioration of disease processes, the increased information relating to the skin microbiome has also stimulated probiotic development. The World Health Organization (WHO) 2001 has defined probiotics as “Live micro-organisms which when administered in adequate amounts, confer a health benefit on the host”. The importance of maintaining the balance of good (probiotic) and bad (disease-causing) bacteria has been highlighted for many years in relationship to the gastrointestinal tract and more recently also in the oral cavity and the vaginal tract. The time for the advent of effective skin probiotics is now at hand.

Gut probiotics have now been in use for hundreds of years with early studies utilizing fermented milk dating back to Roman times. Scientist Elie Metchnikoff has been credited with the first successful promotion of the value of probiotics in relationship to his assessing of their role in promoting longevity in impoverished rural Bulgarian communities [66]. His work on phagocytosis, for which he was awarded a Nobel Prize in 1907, led him to theorize that body changes associated with old age were at least in part due to the work of phagocytes transformed by colonic bacteria from being defenders of the gut into tissue destroyers [66]. From this, a large interest in the role bacteria can play in providing beneficial effects on gut health ensued with a focus on their ability to improve digestion, relieve post-antibiotic and traveller's diarrhoea, and generally boost immunity. Microbial homeostasis in the gut is influenced by many factors including diet, physical condition, susceptibility to diseases, hormonal status, and antibiotic exposure. Genera commonly sourced for gut probiotics such as *Bifidobacterium* and *Lactobacillus* function as probiotics through multiple actions including the sequestering of essential nutrients required by undesirable bacteria, outcompeting others for attachment

and production of anti-competitor molecules such as bacteriocins, all of which effectively limits the proliferation of undesirable bacteria and leads to the development of a microbial community rich in beneficial bacteria in the gut.

As our understanding on the role microbes play on human health progresses, the concept of applying probiotics to other sites of the body evolved with a focus on the vaginal tract and the oral cavity becoming key scientific and commercial targets. Progression of probiotics or probiotic technology (i.e. supernatants, lysates or killed probiotics, or immunozombie biotics) for topical skin applications has only evolved within the past decade. All have a focus on altering the skin microbiome to promote a healthier skin. Prior to this, some research had focused on evaluating the ability of gut-targeted probiotics to also provide beneficial outcomes on the skin [67]. Recent work has evaluated direct topical application of some of these probiotics. There are indications that there is a link between certain skin pathologies and poor gut health and that the taking of high-quality probiotics and the consumption of probiotic-rich foods improve the skin hydration conditions [68]. Although the concept of improving skin health from inside the body is highly commendable, a more logical approach could be of combating skin conditions on the target site, i.e. surface of the skin. Therefore, more recent research is focussing upon developing topical probiotics suitable for maintaining skin health [32, 37, 69].

These topical probiotic approaches are being considered non-antibacterial antibiotic alternatives with potential to relieve and prevent common skin disorders and over time may become established as integral components of an individual's natural skin microbiota. Such organisms may also contribute to the boosting of local skin immunity. To date, however, most of the so-called probiotic products for the skin do not appear to actually contain live bacteria. Instead, their formulations comprise bacterial lysates, extracts, or ferments with only very preliminary data documenting their precise mechanism of action. Considering that these products do not contain any live bacteria and with an array of terminology arising define this, the International Scientific Association for Probiotics and Prebiotics (ISAPP) defined the term “postbiotic” in 2021 [70]. This ensures a clear distinction with live probiotics which can signal in consumer products. Small-scale, poorly designed clinical studies further obscure any clinical efficacy outcomes of the products, and rather, the emphasis is on cosmetic findings that may potentially reflect the action of excipients present in the formulations rather than of the putative probiotic component [71].

Interestingly, for a number of products which do actually contain live bacteria, these probiotics have been derived from sources other than the skin. These so-called probiotic bacteria include a lactobacillus used as a yogurt starter

culture [72]—the ammonia-oxidizing bacterium *Nitrosomonas europaea* [73] and a combination of *Lactobacillus* and *Bifidobacterium* strains [73]. More examples are shown in Table 2. Typically, these bacteria are not considered to be typical members of the natural skin microbiota and their role in benefiting skin disorders has not been established.

Prebiotics

The ISAPP have defined a prebiotic as: “a substrate that is selectively utilized by host microorganisms conferring a health benefit” [76]. Prebiotics can change the microbial composition by stimulating the growth of certain species which can improve host health [34, 76]. Prebiotics are mainly derived from complex carbohydrates known as oligosaccharides, and the objective of their application as nutrients is to selectively support the growth of beneficial bacteria over that of pathogenic bacteria [34]. The human body does not digest prebiotic carbohydrates due to the orientation of their osidic bonds which are able to resist hydrolysis by salivary and intestinal digestive enzymes. Oligosaccharides primarily enhance the growth of and activity of specific *Bifidobacterium* spp. [77]. Their bifidogenic effect varies depending on the type of prebiotic [55]. Breast milk is key prebiotic as it is the first food for infants and provides the initial intestinal microbiota with optimal nutrients for growth [55]. Examples of prebiotics commonly found in the human diet include bananas, grains, honey, and onion. A common prebiotic for skin bacteria is sucrose, which is found in fresh fruit and honey. Sucrose actively feeds *S. epidermidis* but not *C. acnes*, thereby relatively impeding the growth of the pathogenic bacteria in acne-affected skin [34]. A synbiotic is a “synergistic mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and colonization of live beneficial microorganisms in the gastrointestinal tract” [77].

Postbiotics

The development of commercial research containing bacterial metabolites has led to the new term of postbiotics which has been defined by ISAPP as “preparation of inanimate microorganisms and/or their component that confers a health benefit on their host” [70]. This unified term has been proposed to give a clear definition and usurp an array of other commonly utilized terms for the same thing, such as “parabiotics”, “ghost biotics”, “bacterial lysates”, and “tyndallized probiotics” as examples.

Postbiotic efficacy may be attributable to a multitude of factors including “microbial metabolites, proteins, lipids, carbohydrates, vitamins, organic acids, cell wall components, or other complex molecules that are generated in the matrix that is fermented” [77]. The underlying mechanisms

Table 2 Commercial probiotic formulations for skin applications actually contain viable cells

Commercial product, dosage form, and manufacturer	Microbial component	Other key ingredients/excipients	Storage conditions/shelf life (if available)	Effects claimed or other indications
Dead probiotics/extract/ferment lysate				
Probiotic radiance tonic (Edible Beauty, Australia)	<i>Lactobacillus bulgaricus</i> Ferment filtrate	Water aloe leaf juice, birch leaf extract, yarrow extract, emu bush leaf extract, jojoba, seed oil, radish root ferment filtrate, aspen bark extract, sodium hyaluronate	Storage 25 °C	Intensely hydrating, restores skin microbiome, encourages optimal skin health and resistance to acne breakouts
Probiotic serum concentrate (Laflore Probiotic skincare, USA)	<i>Lactococcus</i> ferment lysate and kefir probiotics (a mix of seven different yeast and bacterial strains)	Triphase multibiotics plus a hydrating blend of plant oils and protective antioxidants	Storage below 25 °C or refrigerated	Calms, smooths fine lines, and wrinkles. Boosts the skin's natural defence system
Youthful serum (Galinee, UK)	Dead (heat-killed/tyndallized) <i>Lactobacillus casei</i> and <i>Lactobacillus acidophilus</i> isolated from human gut	Water, maltodextrin, alpha-glucan oligosaccharide inulin lactic acid, <i>Polymnia sonchifolia</i> root juice, <i>Lactococcus</i> ferment lysate, <i>Cyathea cumingii</i> leaf extract	Storage 25 °C	Skin hydration Supports microbiome and skin barrier function, naturally fights against the bad bacteria on the skin Karska-Wysocki showed growth inhibitory activities of <i>L. casei</i> and <i>L. acidophilus</i> against standard MRSA strains [74]
Columbia Skincare Probiotic Concentrate (Columbia skincare, USA)	Ferment lysate of <i>Lactococcus</i> spp. isolated from <i>Malus domestica</i> (apple tree)	Herbal plant stem and root extracts, vitamin C	Storage 25 °C	Enhance skin renewal process
Probiotic hydraglow cream oil (Glowbiotics, USA)	Ferment lysate of <i>Lactococcus</i> spp.	<i>Termanilia ferdinandiana</i> fruit extract, beta-glucan, abyssinian seed oil, <i>Alisma plantago aquatica</i> extract	Storage 25 °C	Stimulates skin renewal process, visibly reduces fine lines and wrinkles Activates and boosts the natural immune functions with peptides whilst reducing inflammation
Superstart Skin renewal booster (Elizabeth Arden, USA)	Ferment lysate of <i>Lactococcus</i> spp. probiotic complex	Sea fennel and flaxseed extracts, glasswort extract	Storage 25 °C	Boosts skin natural defence and ability to renew
Probiotic nutrient moisturizer (Paula's choice, Australia)	<i>Lactobacillus</i> /Rye flour ferment <i>Lactobacillus</i> ferment, <i>Bifida</i> ferment lysate <i>Saccharomyces</i> lysate leuconostoc/radish root ferment filtrate	Water, glucomannan, ceramide, anti-oxidant plant oils, fruit extracts	Storage 25 °C	Moisturizes, soothes, and softens skin Stabilizes and strengthens skin's microbiome. Progressively fortifies against signs of ageing. Maintains healthy bacteria for smooth skin
Redness Solution cream (Clinique, New Zealand)	<i>Lactobacillus</i> ferment	Water, green tea, yellow tea, white tea, red tea leaf extracts, barley, wheat germ <i>Saccharomyces</i> lysate, algae extract	Storage 25 °C	Instantly calms skins with visible redness Sooths and strengthens the skin's barrier Restores microbiome balance
Advanced Genefique Serum (Lancome, Australia)	<i>Bifida</i> ferment lysate	Water, lactobacillus, tocopherol, sodium hyaluronate, yeast extract, <i>Polymnia sonchifolia</i> root juice, salicyloyl phytosphingosine, xanthan gum, alpha-glucan oligosaccharide	Storage 25 °C	Nourishing serum to strengthen the skin barrier Targets inflammation, dull skin, fine lines, uneven tone, and loss of firmness Contains a blend of 3 prebiotic and 4 probiotic fractions Encourages healthy bacteria growth on the skin

of postbiotics are not fully understood, yet they seem to be mediated via interactions between the host and microbial products which stimulate an immune response [77]. Effects

within cells that support this notion include increased adhesion to intestinal cells and secretion of various metabolites [78]. A benefit of postbiotics is their relative tolerance to a

Table 2 (continued)

Commercial product, dosage form, and manufacturer	Microbial component	Other key ingredients/excipients	Storage conditions/shelf life (if available)	Effects claimed or other indications
Live probiotics				
Rescue serum for acne-prone skin, Serum, (Bak skincare, Denmark)	Live cells <i>Lactobacillus plantarum</i> LB356R and <i>Lactobacillus plantarum</i> LB244R isolated from fermented beet and fermented kale, respectively	Jjoba oil, hydrogenated olive oil, rosehip oil, tocopherol	Storage below 25 °C or refrigerated	Suitable for acne-prone skin to reduce pimples and impurities—without irritating, drying, or impairing skin health Brachkova et al. tested <i>L. plantarum</i> 's ability to prevent wound infection in mice with <i>S. aureus</i> and <i>P. aeruginosa</i> . Both bacteria were unable to establish infection [75] Muizzuddin (2012) conducted a pilot study to determine the effects of <i>L. plantarum</i> in acne patients. It was found that the use of the probiotic reduced erythema, repaired the skin barrier, and reduced skin microflora [69]
AO + Mist Live Probiotic Spray (Mother Dirt, USA)	Live cells ammonia-oxidizing bacteria (AOB)— <i>Nitrosomonas eutropha</i> isolated from soil	Water, buffering agents	6 months, refrigerated (2–8 °C)	Restores balance to problem, dry, oily, and sensitive skin Improves skin clarity, smoothness, look, and feel of dry uneven skin
Esse Probiotic + serum (Esse skincare, South Africa)	Live (50 million cfu/drop) <i>Lactobacillus</i> spp. isolated from human gut	Jjoba oil, sesame seed oil, shea butter, vegetable oil, marula seed oil, tocopherol, sunflower seed oil	Storage below 25 °C or refrigerated	Balances skin microbiome, strengthens natural defences, anti-ageing
BLIS Q24 Live probiotic hydration serum (developed by Blis Technologies and marketed by Unconditional Skincare Co., New Zealand)	Live 150 million cfu/dose of freeze-dried <i>Micrococcus luteus</i> Q24 (strain isolated from skin of healthy human adult)	Medium chain triglyceride, silica, Polysorbate 80	Storage 25 °C	Balances skin microbiome, hydrates and restores natural skin condition

range of storage conditions and transportation stringencies as they are not subject to degradation to the same extent that live bacteria are. Safety advantages are also evident, as postbiotics reduce the risk of microbial translocation, infection, and reduce the occurrence and extent of inflammatory responses [78]. The introduction of postbiotics on to the market constitutes a new development in the application of microorganisms in food products and supplements. They provide an important alternative for products where probiotics are damaged, or shelf life viability is minimal as they do not require refrigeration [78].

What Are the Challenges to Topical Probiotic Applications?

Early research has demonstrated that topical applications of probiotics have a potential benefit for skin-related conditions, yet there are still some challenges to their use [79]. The generation of a probiotic requires the isolation and then comprehensive characterization of a bacterium using an exhaustive combination of genotypic and phenotypic tests [80]. There are few probiotic strains on the market that have been selected to be effective in the management of specific maladies. Unfortunately, the embryonic field of commercially developed skin probiotics is at present inadequately

controlled due to the large number of poorly researched products carrying unproven claims that have gained entry to the market. Major issues include failure to establish a complete probiotic profile for the putative probiotic constituents of the product in accord with the specifications of regulatory groups [48]. Since the regulations concerning labelling are often inadequate, false claims concerning putative benefits have also been made, e.g. claims may be made for benefits relating to skin health for a generic gut probiotic [80].

Effective topical delivery of bioactives has proven to be a challenge due to the strict natural and protective barrier function of the skin maintained by the stratum corneum which serves to control the absorption of molecules into the deeper layers of the skin, thereby also limiting therapeutic options [81]. The formulation requirements for topical products containing viable microorganisms differ markedly from those solely containing relatively small molecules due to the requirement to maintain the stability of the microorganisms. Critical factors requiring control for microorganisms include pH and osmolality levels as well as the temperature and humidity levels of storage conditions [82].

A common issue in probiotic therapy is the utility (if any) of non-viable, or inactivated bacteria present in the probiotic formulations. Unfortunately, it appears that relatively few commercial probiotic formulations for skin applications actually contain viable cells (Table 2). This is because live

probiotics are sensitive to heat and moisture, making it difficult to keep them alive in a formulation for skin application (such as aqueous or emulsion-based topical creams, lotions, or sprays). The additional costs required for the inclusion and maintenance of viable probiotic cells in a product in order to increase its efficacy and shelf life impose considerable commercial constraints. Therefore, most companies typically resort to the marketing of products containing heat-killed bacteria or bacterial lysates and extracts. There have been few studies conducted to determine the relative effectiveness of non-viable bacteria as alternatives to probiotics [83].

Wide variations characterize the distribution of individual microbial species within the skin microbiota, reflecting the influence of interpersonal environmental factors, ethnicity, age, and body site-specific parameters. An important question relates to the likelihood of functional efficacy in an epidermal environment of probiotics that are of non-skin origin such as the intestinally derived *Lactobacillus* and *Bifidobacterium* probiotics or non-human origin probiotics. It appears that at present, very few probiotics marketed for epidermal application have actually been sourced from the skin microbiome or are well-documented skin commensals. Exceptions include *Micrococcus luteus* Q24 and *S. hominis* [28]. It is inferred that microbes not naturally found on the skin surface are less likely to survive or colonize efficiently on the skin surface in comparison with common skin commensals. This means that any beneficial activity associated with the topical application of gut probiotics is probably akin to the relatively shorter term benefits mediated by postbiotics or prebiotics and thus is unlikely to be maintained in the manner associated with use of a colonizing probiotic.

Conclusions

The complex interplay between commensal and pathogenic bacteria, as modulated by the various downstream mediators of disease progression, plays a major role in the genesis of many of the common pathologies of the skin. There is as yet only very limited clinical research that is focused upon the topical application and efficacy of probiotics and postbiotic, but the available information highlights the imminent considerable benefits to be obtained from their application as convenient and effective preventative and treatment options for a broad spectrum of skin pathologies. Acne, atopic dermatitis, psoriasis, body odour, tinea pedis, and impetigo all exhibit putative or proven links between dermal-based dysbiosis and the progression of disease. The mechanistic details of the relationship between dysbiosis and pathogenesis have sometimes not yet been fully established. Further study is in some cases required to answer the following questions: what is the specific role of the microbiome in the expression of each disease progression?

Is dysbiosis an etiological factor or a consequence of pathological processes in the skin? What factors trigger previously commensal bacteria to become pathogenic? Hopefully, this timely review now stimulates further carefully controlled research into the potential disease preventative and therapeutic benefits to be derived from the controlled topical application of appropriately certified probiotic or postbiotic agents.

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Declarations

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