



Microbioma in Aging Skin

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Abstract

Microbiota is inseparable to the skin. Just as in the gastrointestinal tract, the skin microbiome reflects the health of the organ where it resides. It contributes to skin barrier function and ensures its homeostasis. However relatively stable over time, microbiome composition and number may be influenced by various aging -related changes – dryness, blemish, wrinkles and alteration of sebaceous gland activity impacting the skin ecological conditions – and vice versa. Several generations have been reported to promote the process while others may play a more protective role in this regard.

Introduction

Skin has different 'skin environments': moist, oily and dry areas provide a good ecosystem for various types of microbiota and support the survival of certain microorganisms. The skin microbiota may be more diverse than the gut microbiota. The skin creates an ecological environment or *niche* that hosts many microorganisms with different densities and compositions (Wahyuni, 2021). Many of these microorganisms are commensal, function in skin barrier homeostasis, and participate in the skin's immunological processes against pathogens. Each microorganism occupies a suitable skin environment (Siahaan, 2024). The diversity of microorganisms on the skin is called skin microbiota, while what is meant by skin microbiome is all microorganisms with their habitat in that organ, including the genome, microorganisms and environmental conditions. Skin microbiota includes viruses, bacteria, archaea, fungi and lice (Saragih et al., 2023; Pistone et al., 2021; Yang et al., 2022).

Skin aging is mainly characterized by a decrease in sebum and moisture levels resulting in changes in its physiology and appearance (Nur & Adah, 2021). The appearance of facial aging due to hormonal changes, gravity, reduced muscle mass, reduced subcutaneous fat, collagen degradation, as well as extrinsic factors (exposure to ultraviolet light, pollution, cigarette smoke, etc.) causes the face to lose volume, sag, the pores are more visible, becomes rougher and wrinkled (Naviri, 2013; Blanchard, 2023). These changes cause environmental changes that shift the composition of the microbiota. On the other hand, dysbiosis is also a predisposing factor for the skin aging process. Uniquely, some microbiota are actually reported to play a protective role in this process (Berniyanti, 2023).

Methods

The literature review was conducted by searching for scientific publications from the period 2014-2024 using the PubMed database and Google Scholar. In the PubMed database, entering keyword 1 "microbiome" resulted in 169,556 articles. Keyword 2 "skin" found 959,227

articles. Keyword 3 "aging" found 643,597 articles. Combining the keywords 1, 2, and 3 "microbiome AND skin AND aging" yielded 187 articles. After searching for articles, limiting the publication dates to the period 2014-2024 resulted in 132 articles. After removing duplicate articles, 98 articles remain. These titles were then filtered for relevance and citations, leaving 73 articles. A review of the abstracts was conducted, and a complete study was carried out based on the research objectives of the remaining 54 articles that were considered to be suitable and had complete texts available for review for this literature review.

Result and Discussion

Skin Microbiome

Skin is an ecosystem with various topographic characteristics, including folds, invaginations and niches that support the life of various micro organisms. On the skin there is colonization of various microorganisms including bacteria, fungi, viruses and mites according to certain topography. Much of the skin microbiota is harmless, vital for humans, and protects the skin against invasion by pathogenic organisms. Microorganisms also play a role in the development of T cells, preparing the immune system to respond to pathogens.

Skin and skin adnexa as a habitat for microbiota

Certain physical and chemical characteristics of each area of the skin form a habitat for each microorganism. Habitat is determined by skin thickness, folds, density of hair follicles, and glands. Structurally, the epidermis is a skin barrier that resists the penetration of microorganisms and toxins while retaining moisture and nutrients. Sweat glands (eccrine and apocrine), sebaceous glands, and hair follicles also have unique microbiota habitats. (Grice & Segre, 2011). Sebaceous glands are relatively anoxic and support the growth of the facultative anaerobic commensal bacterium *Cutibacterium acnes*. Research reports on the full sequencing of the *C. acnes* genome discovered genes degrading skin lipids from sebum. *Cutibacterium acnes* obtains nutrition by hydrolyzing triglycerides present in sebum and releasing free fatty acids into the skin. Bacteria attach to the free fatty acids and colonize the glands, while the free fatty acids then contribute to the acidity of the skin surface (Rini & Jamilatur, 2020). This acidity inhibits pathogenic bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes*, but encourages the growth of micrococci and corynebacteria.

Skin topography

Certain skin topographies favor different microorganisms. Some areas of partially occluded skin, including the groin, armpits, and between the fingers, are more moist than other areas, thereby encouraging the growth of microorganisms that thrive in such conditions, including Gram-negative bacilli, *Corynebacterium*, and *Staphylococcus aureus*. Areas rich in sebaceous glands, including the face, chest and back, encourage the growth of lipophilic microorganisms (eg *Cutibacterium* spp. and *Malassezia* spp.). The skin on the arms and legs is relatively dry and experiences temperature fluctuations because of its large surface area, so that the skin microbiota in these areas is smaller than in damp areas. The microbiota of this area mainly consists of *Proteobacteria* (41%), *Actinobacteria* (28%), and *Bacteroidetes* (14%). Figure 1 shows the distribution of microbiota at various skin locations.

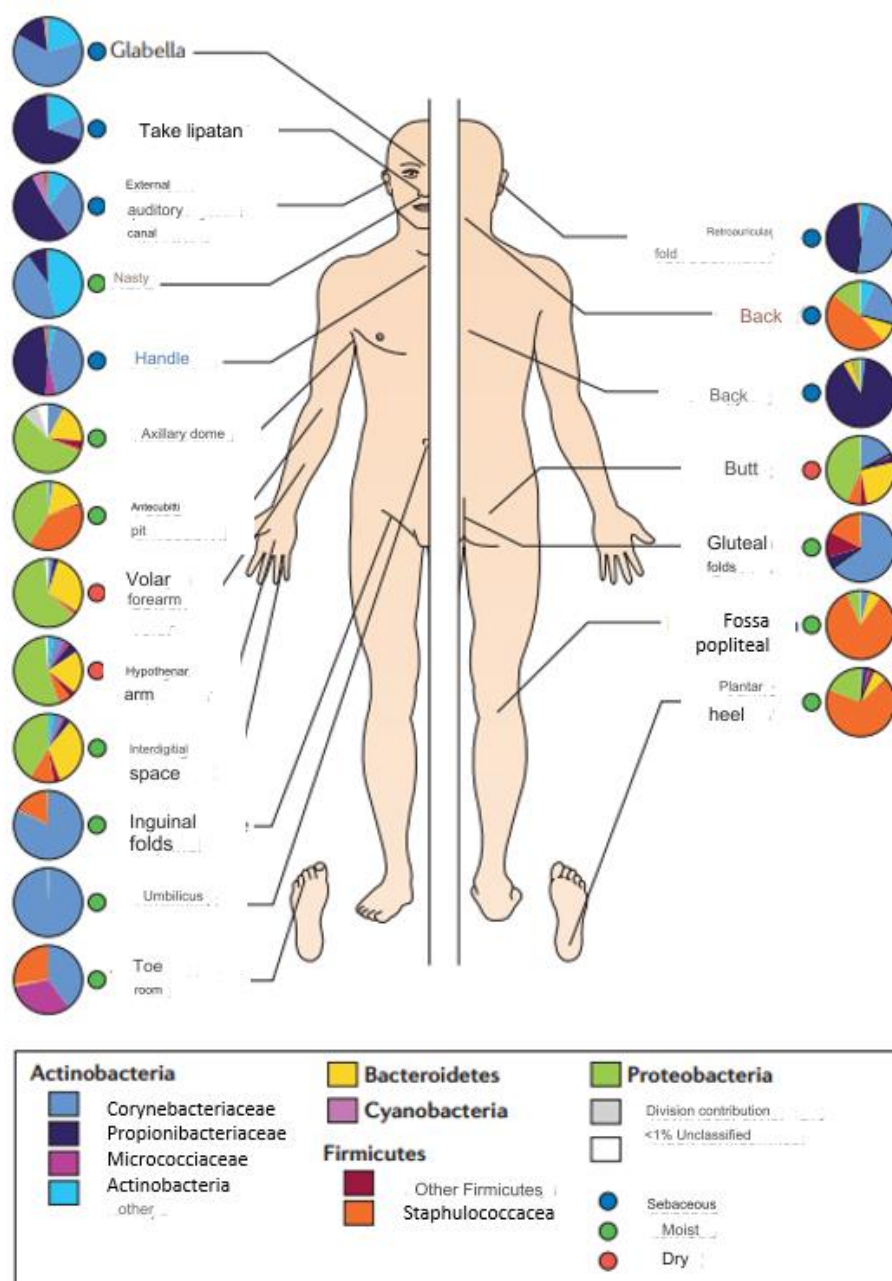


Figure 1 . Distribution of Microbiota Based on Skin Topography ^a

The skin microbiome depends on the microenvironment. Sebaceous-rich areas (blue circles) are dominated by *Propionibacteriaceae*, moist areas (green circles) are dominated by *Corynebacteriaceae* and *Staphylococcaceae*, and dry areas (red circles) are dominated by *Proteobacteria*.

^a adapted from Grice & Segre (2011)

Microbiome variations based on skin location

The majority (>90%) of bacteria in the human skin microbiome are classified into four types: *Actinobacteria* (52%), *Firmicutes* (24%), *Proteobacteria* (16%), and *Bacteroidetes* (6%). Coagulase negative staphylococci, especially *Staphylococcus epidermidis*, *S. hominis*, anaerobic *Cutibacterium acnes*, *Corynebacterium*, *Micrococcus*, *Streptococcus*, and *Acinetobacterium* were the dominant species. The genera *Cutibacterium*, *Staphylococcus*, and *Corynebacterium*, are isolated from almost all areas and may constitute 45 to 80% of the entire

skin microbiome. The average number of microorganisms isolated using traditional culture methods from the skin surface ranges from 10^3 to 10^4 CFU/cm², but in the most humid places, such as the groin, armpits and nostrils, this value exceeds 10^6 CFU/cm².

Bacterial colonization depends on the location of the skin. Specific bacteria were associated with the character of the microenvironment: moist, dry, or sebaceous-rich (Figure 1). In general, bacterial diversity was lowest in sebaceous-rich locations, indicating selection against certain subsets of bacteria that can tolerate the conditions in these areas. Sebaceous-rich locations containing low phylotype diversity include the retroauricular fold, as well as the back and alar fold. *Cutibacterium spp.* is the dominant organism in this and other sebaceous-rich areas.

In moist areas, including the umbilicus, axillary basin, inguinal fold, gluteal fold, soles of the feet, popliteal fossa and antecubital fossa, the most dominant organisms are *Staphylococcus* and *Corynebacterium spp.* *Staphylococcus* occupies the aerobic area and may use the urea in sweat as a nitrogen source. Processing of apocrine sweat by *Corynebacteria* and *Staphylococcus* (along with other axillary microorganisms) produces the characteristic odor of human sweat.

The skin area with the most diverse microbiome is the dry area, with its representation from the phyla *Actinobacteria*, *Proteobacteria*, *Firmicutes*, and *Bacterioidetes*. These locations include the forearms, outer buttocks and hands. A surprising fact is the large number of Gram negative organisms at those locations discovered by molecular analysis; This microbiota is usually thought to rarely colonize the skin, and is only a contaminant from the gastrointestinal tract.

Host or intrinsic factors in the formation of the skin microbiome

Age, ethnicity, and gender, contribute to microbiota variability (Figure 2). Age has a big effect on the skin microenvironment, thus influencing the type and number of microbiota that colonize. The fetal skin is sterile in the womb; colonization occurs immediately after birth, during labor or a few minutes afterward. During puberty, the increase in sebum production is directly proportional to the number of lipophilic bacteria; the opposite occurs in elderly skin. Physiological differences between male and female skin, for example in sweat secretion, sebum and hormone production, also influence differences in the microbiota of the two sexes. The microbiota in the axilla of women is dominated by the *Staphylococcus* group, while in men the *Corynebacterium* group is more common. Li et al found that the microbial composition of East Asians was different from Caucasians and Hispanics. East Asians have higher levels of bacteria, especially proteobacteria. The distribution of *Corynebacterium variabile* species was found exclusively in the Hispanic group, whereas *C. kroppenstedtii* was detected only in the East Asian group. Brandwein et al concluded that body mass index (BMI) influences the skin microbiome. Beta diversity and skin microbiota composition are associated with BMI; *Corynebacterium* relative abundance was significantly correlated with *overweight/ obese individuals*. Beta diversity is defined as the diversity of species composition among samples taken in a certain area.

Environmental or extrinsic factors in the formation of the skin microbiome

Environmental factors, including work, place of residence, clothing, pets, lifestyle, and use of antibiotics and probiotics, influence the skin microbiota (Figure 2). Differences were reported between the skin of humans living in rural and urban environments, and between groups living with or without pets. Cosmetics, soap, hygiene products and moisturizers also have the potential to contribute to variations in skin microbiota. Some cosmetic compounds, for example preservatives, are useful in preventing the growth and formation of biofilms by pathogenic *S. aureus* or *C. acnes*, but they are also involved in inhibiting the survival of commensal bacteria.

Regarding the use of antibiotics, SanMiguel et al showed that topical antibiotics can change the composition of skin bacteria and have implications for reducing the population of *Staphylococcus spp.* commensals, which compete with *S. aureus* pathogens to colonize, although this conclusion is still controversial and needs further investigation. Zhang et al showed that oral vancomycin decreased bacterial populations and changed their composition in skin wounds, which may have contributed to delayed closure in mice.

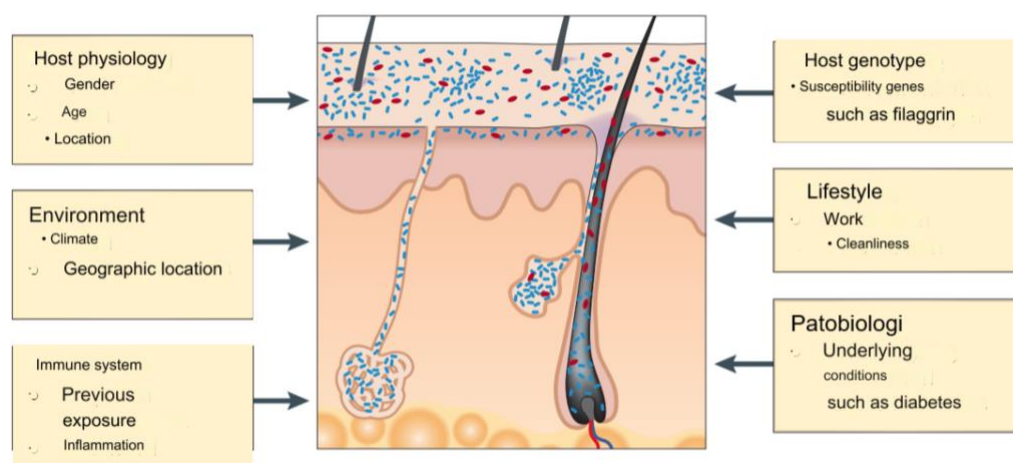


Figure 2 . Intrinsic and extrinsic factors that contribute to variation skin microbiome . ^a

The intrinsic factors of age, genetics, disease, gender, skin location contribute to variations in the skin microbiome, as do extrinsic factors, namely the environment and lifestyle. ^a adapted from Grice & Segre (2011).

Populations living in areas with high temperatures and high humidity have higher numbers of bacteria on the back, armpits and feet compared to those in low humidity. High humidity and low temperature were associated with higher numbers of Gram-negative bacteria on the back and legs. Extreme environmental conditions disrupt the stability of skin microbiome diversity ; Air pollution has also been shown to reduce it.

The Relationship between the Gut and Skin Microbiome and Aging

The gut microbiome and aging

The gut microbiome functions to maintain host health, homeostasis, mediate inflammation, and modulate the immune system through a good balance between commensal and pathogenic bacteria . However, the gut microbiome can change due to lifestyle, food intake, bacterial infections, antibiotics, surgical interventions, and inflammatory conditions. These changes result in dysbiosis , which is characterized by a decrease in species diversity and a decrease in the number of commensal bacteria. Disorders of intestinal microflora and their consequences can influence the pathology of various diseases and aging.

During the transition from adulthood to old age, the gut microbiota undergoes significant changes . Compared with adults, microbial diversity decreased and variation in microbiota composition between individuals was greater in elderly people (>65 years). These different microbial compositions are associated with aging and inflammatory processes. Theravanjan et al found a decrease in intestinal anti-inflammatory bacterial species in aged mice. Longevity was positively associated with increased abundance of short-chain fatty acid-producing microbiota, such as *Clostridium cluster XIVa*, *Ruminococcaceae*, *Akkermansia*, and *Christensenellaceae* . There is research cited by Ratanapokasatit et al which shows that 116 microbial genes are significantly correlated with aging, and identified as signs of aging. More diverse phyla were found in the gut microbiome of centenarians compared with other groups. " Good " bacteria related to intestinal health, namely *Akkermansia* , *Christensenellaceae*, and *Lactobacillus* are more commonly found in groups of people who live longer. The

disappearance of *Lactobacillus* and *Faecalibacterium*, as well as the increase in the abundance of the genera *Oscillibacter* and *Alistipes* along with the family *Eubacteriaceae* is associated with general condition susceptibility in the elderly population. Frail elderly people also have more pro-inflammatory commensal *Bacteroidetes* bacteria.

The production of various bioactive metabolites is also important in the relationship between gut microbiota and host aging and health. Short chain fatty acids or *short chain fatty acids* (SCFA) such as butyrate, propionate and acetate, are products of fiber fermentation by the gut microbiota and have been shown to provide anti-inflammatory and immunomodulatory effects. Vaiserman et al demonstrated a dramatic decrease in the *Firmicutes* phylum and an increase in the *Bacteroidetes* phylum occurring from adulthood to old age, resulting in a decrease in the *Firmicutes-to-Bacteroidetes* (F/B) ratio. The F/B ratio is important for SCFA production. A study on old mice, as quoted from Ratanap okasatit et al, found the gut microbiome is associated with markers of cellular aging and inflammatory factors, known as *senescence-associated secretory phenotype* (SASP). *Clostridiales*, *Staphylococcus*, and *Lachnospiraceae* were positively correlated with SASP, whereas *Coriobacteriaceae* and *Akkermansia* were negatively correlated with this marker. The relationship between cellular aging and microbial composition suggests that dysbiosis occurs in aging.

Leakage of pro-inflammatory microbial products due to intestinal dysbiosis occurs through impaired intestinal permeability. This product moves into the bloodstream, causing systemic effects by increasing the effects of SASP through *upregulation* of various inflammatory molecules, including *tumor necrosis factor-alpha* (TNF- α), *interferon-gamma* (IFN- γ), IL-1, IL-6, *matrix metalloproteinases* (MMPs), and others, thus contributing to a chronic proinflammatory or inflammatory state. It can be said, the consequences of dysbiosis are *inflammaging* and *reduced immunity* *surv e illness* which promotes aging.

The gut-skin axis and aging

The gut-skin axis and skin aging illustrate the bidirectional communication pathways between the gut microbiome and the integumentary system that occur in aging. The increase in intestinal permeability by dysbiosis leads to the accumulation of bacterial metabolites in the skin, leading to decreased epidermal differentiation and skin integrity. The exact mechanisms underlying gut-skin microbial interactions have not yet been fully elucidated, however research which was quoted from Ratanap okasatit showed oral probiotics to be beneficial in improving signs of skin aging, oxidative stress, *photodamage*, and barrier dysfunction. Research on *Lactobacillus plantarum* HY7714 and *Bifidobacterium breve* B-3 in a mouse model shows that bacterial metabolites *lipoteichoic acid*, peptidoglycan, and SCFA in the skin-gut axis may exert anti-inflammatory effects on *both* organs, as well as suppress *reactive oxygen species* (ROS) in UV radiation, thereby being photoprotective. Which has antiaging effect. Administration of *Lactobacillus plantarum* HY7714 is thought to limit wrinkles and increase elasticity within 12 weeks.

Intestinal dysbiosis, impaired senescence cell elimination, and SASP accumulation can affect skin function and integrity, leading to a premature aging phenotype (Figure 3). An increase in a number of *matrix metalloproteinases* (MMP) which are included in SASP is a factor causing age-related changes in the appearance of the skin. MMP reconstructs the extracellular matrix by degrading the proteins collagen, fibronectin, elastin, and proteoglycans resulting in wrinkles, sagging, and skin weakness.

Skin microbiome and aging

The skin microbiome plays an important role in maintaining homeostasis and contributes to barrier function to protect the body from the environment and pathogenic bacteria. Commensal bacteria compete for nutrients and space, and inhibit the reproduction of competitors through the production of antimicrobial peptides (AMP), thereby inhibiting the growth of pathogens.

Skin microbes secrete various enzymes involved in barrier homeostasis ; Protease plays a role in renewal of the stratum corneum, lipase in breaking down the surface of the lipid film , and urease in urea degradation. Other roles include bacteriocin and biofilm production, quorum sensing, pH regulation by sebum , as well as the production of free fatty acids. Quorum sensing is a communication mechanism between bacteria in the form of gene expression as a response to cell population density. Interactions between host tissues and the microbiome generate complex signals involved in innate and adaptive immune responses.

Skin aging is characterized by a decline in sebum, sweat, and immune function, resulting in significant changes in skin surface function . Skin dryness , collagen fragmentation, and reduction in the total amount of collagen and elastin influence the skin ecology that shapes the skin microbiome. Skin immunity weakens with age, increasing skin infections and susceptibility to cancer.

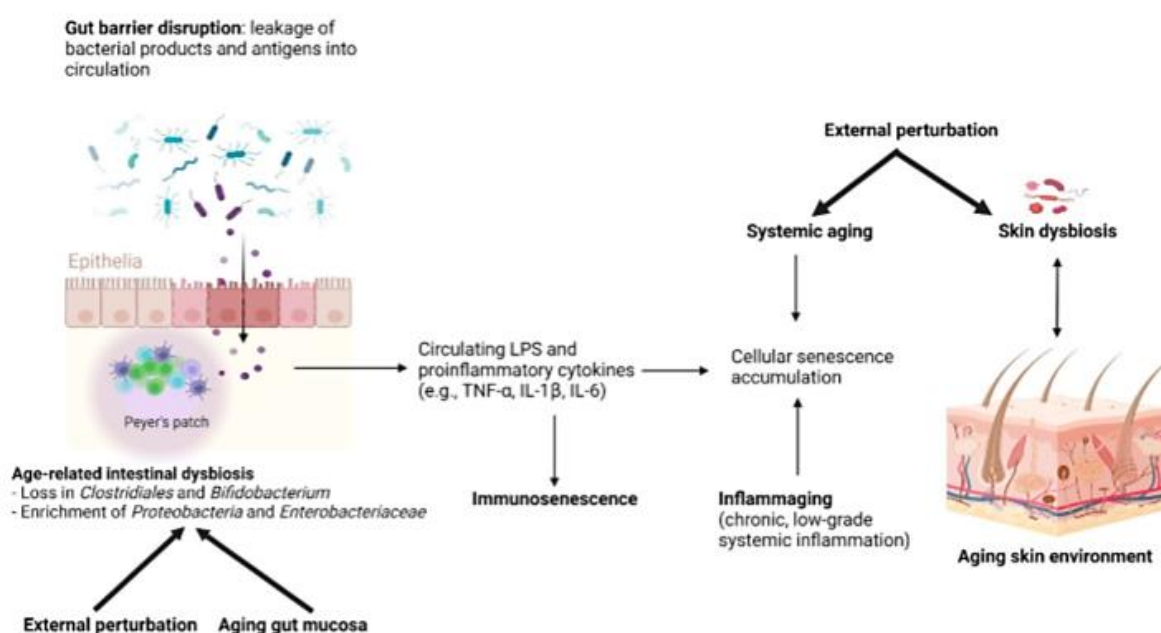


Figure 3. Age-related gut dysbiosis. ^a

Dysbiosis in the intestine with age is generally characterized by a decrease in short chain fatty acid production and an increase in proinflammatory proteobacteria . Intestinal dysbiosis causes “leakage” described by increased mucosal permeability, thereby allowing small but periodic translocation of bacterial antigens and proinflammatory cytokines into the systemic circulation. Both causes a cumulation of cellular senescence and immunosenescence . Chronic low-grade systemic inflammation called *inflammaging* also causes the accumulation of cellular senescence . ^a reproduced from Ratanapokasatite

The Skin Microbiome of the Elderly

Although the skin microbial composition of healthy subjects remains largely stable over time during adulthood, Age-related physiological changes, especially changes in sebum secretion and immune function, as well as decreased sweating may affect it. The skin microbiome in this group also varied by race (Sarbin et al., 2020). A comparative cohort study of the skin microbiomes of healthy individuals in China by Leung et al revealed that older adults (50–60 years) had lower overall bacterial abundance than young adults (25–35 years). *Enhydrobacter* which is a *Proteobacteria* is considered to be richer in older individuals than in adolescents and adults, especially in the back and nostrils. In contrast, the number of *Cutibacterium* is lower, especially in dry and damp places, as is *S. aureus* compared with children and adults (Nugraha et al., 2022).

Comparison of the skin microbiome at four skin sites between younger (<40 years) and older (≥ 60 years) healthy Japanese women in the Shibagaki et al. (2017) study quoted from Luna,⁴⁶ revealed that species richness or bacterial diversity was higher in the group with older for all skin sites tested although *Actinobacteria* were lower overall (genus *Cutibacterium* predominated), followed by increases in other phyla (*Firmicutes*, *Bacteroidetes*, and *Proteobacteria*) in proportions that varied according to skin site. (Figure 4) The decline in *Cutibacterium* may be related to decreased sebum secretion in aging skin. In contrast, *Corynebacterium*, *Acinetobacter* (*Proteobacteria*), *Streptococcus* (*Firmicutes*), and *Prevotella* (*Bacteroidetes*) were more common in older women (Karneli, 2023).

Dimitriu et al. showed aging as the fourth most important factor influencing variations in the skin microbiome after lifestyle, physiology, and pigmentation. Reduced sebaceous gland activity and reduced sebum production reduce nutrition for commensal bacteria and favor the colonization of opportunistic species, thereby altering the ecological conditions of the skin. Several reports prove that there is a reduction in the genus *Cutibacterium* and an increase in the relative richness of *Corynebacterium* and *Proteobacteria* in the elderly skin group. A cohort study by (Shibagaki et al., 2017) reported significant differences in 38 bacterial species between adults and the elderly at the same skin location. The proportion of the genus *Cutibacterium* was reduced in the cheeks, forearms, and forehead of older adults, *Corynebacterium* was increased in the cheek and forehead areas, and *Acinetobacter* was increased on the scalp. In another study, Jugé et al.⁴⁸ found an increase in *Proteobacteria* populations and a decrease in *Actinobacteria*, as well as a significant increase in *Corynebacterium* and a decrease in *Cutibacterium* on older people's skin (Figure 4). Howard et al reported a decrease in sebaceous gland activity and an increase in natural moisturizing factors (NMF), skin lipids, and AMPs, resulting in a decrease in the relative abundance of *Cutibacterium* and *Lactobacillus* on the face, forearms, and buttocks in the older age group.

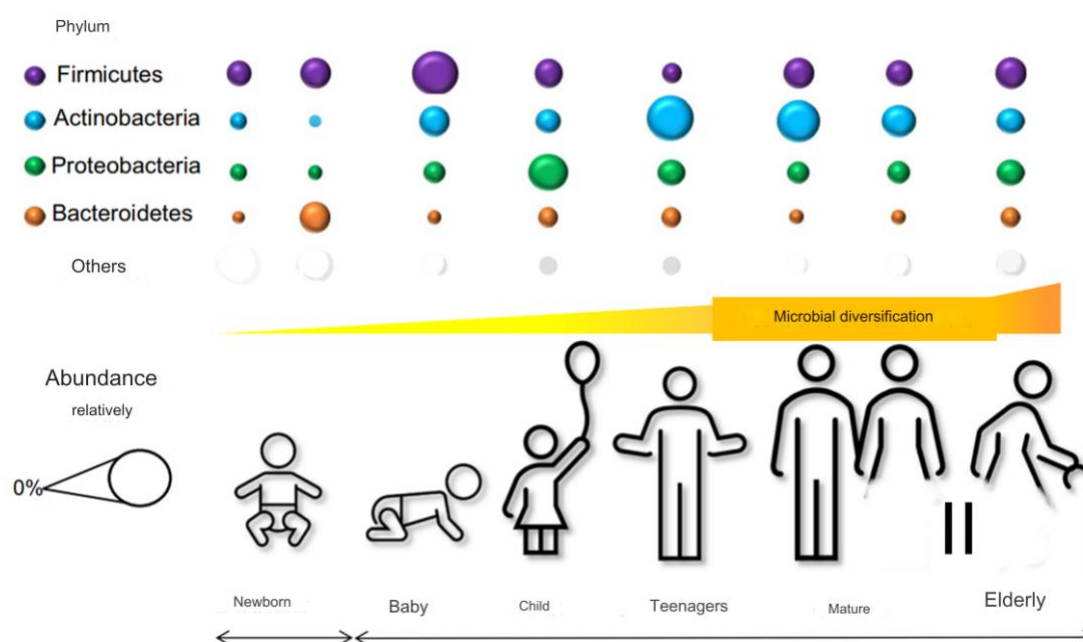


Figure 4. Evolution of the skin microbiome in healthy subjects over time.^a

The graph shows an overview of the relative abundance of the most common bacterial phyla on human skin at life stages as measured from 16S RNA or metagenomic (DNA) approaches. It can be seen in the image that the abundance of microbiome diversity slightly increases in the elderly population. In contrast, the relative abundance of *Actinobacteria* was reduced.^a adapted from Luna

Li et al showed that *Streptococcus* genera were more abundant in the skin of elderly individuals, and were positively correlated with increased pigmentation, wrinkles, texture and porphyrins. The dominant *Streptococcus* species is thought to change the probiotic bacterial community to become pathogenic, thereby becoming an accelerator of aging. In the adolescent to middle-aged group, the number of *Staphylococcus* and *Cutibacterium* was higher. *Staphylococcus* produces several AMPs and proteases that protect the skin from pathogen invasion and maintain microbiota homeostasis. Meanwhile, *Cutibacterium* can mediate immune responses and suppress inflammation to slow the aging process by modulating the formation of conjugated linoleic acid. In the middle-aged group, high levels of *Lactobacillus* provide a protective effect against UV rays by producing various antimicrobial substances and inducing the anti-inflammatory effect of Treg cells, in addition to synergizing with *Staphylococcus* for antibiotic biosynthesis. In the adolescent and middle-aged group, *Staphylococcus*, *Cutibacterium*, and *Lactobacillus* are thought to be able to modulate the host's immunity or defense thereby protecting it against *photoaging*.

Conclusion

On the skin there is a diverse environment, which is a good ecosystem for various kinds of microbiota. The composition of the skin microbiome depends on many factors, including intrinsic factors and extrinsic factors. Natural changes in skin structure and function that accompany the aging process, for example atrophy and decreased sebaceous secretion, affect the environment and subsequently the composition of the skin microbiome, causing dysbiosis. In fact, a number of genera are needed to ward off pathogenic bacteria, protect the body from the effects of ultraviolet, and control inflammation. Interestingly, there is a gut-skin axis that is also disrupted in aging; leakage of inflammatory mediators from unhealthy mucosa causes accumulation of cellular senescence in the skin.

Understanding the skin microbiome opens up ideas about how this knowledge will later become the basis for microbiome-based manipulation and management for skin health. This article is a kind of introduction; details of the pathomechanisms of certain functions, for example impaired control of pathogenic bacteria and modulation of anti-inflammation, require a separate, longer discussion, and can be learned from several articles referenced in the bibliography.

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