The influence of cosmetics on the bacterial flora of the skin

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Abstract

The human microflora is already formulated in the first minutes after birth as a result of the rapid colonization of microorganisms from the mother's birth canal and those living in the external environment. The human skin is inhabited by a huge amount of microorganisms that constantly take part in the processes taking place on its surface. The number and impact of microflora is influenced by such factors as: humidity, temperature, pH, sebum content, diet, use of antibiotics, pro/pre /synbiotics, vitamins and other supplements. The skin has a number of mechanisms to protect it against pathogens: exfoliation, regulation of drying and release of inhibiting substances. Bacteria existing on the surface of the skin colonize it unevenly, therefore their individual populations have chosen their specific niches such as sebaceous glands, hair follicles and skin appendages. The use of appropriate cosmetics leads to blocking the imbalance between species of skin microflora.

Key words:

skin, cosmetics, skin microbiom, dysbiosis

Intoroduction

The surface of the skin is the habitat of many species of bacteria, fungi and viruses. The composition of these organisms depends on the properties of the skin, such as humidity and temperature, the concentration of sebaceous glands, as well as on the host's genetics and exogenous environmental factors. Metagenomic studies revealed a huge variety of skin microorganism ecosystems and contributed to a new look at commensal organisms that play a much greater role in immune regulation and health [1]. The skin is constantly exposed to endogenous and exogenous factors that may affect its protective function at the physical, mechanical, immunological and microbiological level. These factors can potentially initiate or exacerbate skin inflammation, especially those associated with impairment of its protective function. The skin as a protective barrier depends on the symbiotic relationship between the microorganisms colonizing on it and the host tissues. Interspecific symbiosis results from complex interactions associated with both innate and acquired human immune responses [2]. Indicate that commensal skin bacteria reduce inflammation during wound healing [3], while activating innate immunity and proinflammatory cytokines [4]. The majority of skin microbes populate the stratum corneum, the outermost layer of the skin. Stratum corneum has a thin texture in the facial region with some unique functional characteristics to provide hydrated skin surface with relatively poor barrier function. However, there are differences in properties of the stratum corneum and also of biophysical properties on the forehead, cheek, nose and perioral regions [5]. The normal microbial counts using culture methods typically range from 10^3 to 10^4 organisms per square centimeter with counts reaching a high of 10^6 per square centimeter in the most humid areas such as the groin and axilla. Washing the body with soap and water temporarily reduces the microbial count by an order of magnitude and removes transient microorganisms that may be potential pathogens from the skin surface. Based on traditional culture methods, the predominant bacteria are *Propionibacterium acnes* and *Staphylococcus* spp. in oily sites, *Corynebacterium* spp. and *Staphylococcus* spp. in moist sites, and a significant presence of members of the phyla *beta-Proteobacteria* and *Flavobacteriales* in the dry sites [6].

Each person has their own private- like composition, structure, balance and types of skin microflora. This microorganisms are distributed in all skin layers, which is lifelong qualitatively stable. Dermal microbiota is important and basic for the skin living processes as homeostasis and participates to the immune and protect functions. The cosmetics impact on host' skin and their microorganism with benefits like the rebalancing, the probiotic- like and the antimicrobial effects.

Skin as a habitat for microorganisms

Each of the single square centimeter of human skin can contain up to a billion micro-organisms. Various organisms of bacteria, fungi, mites and viruses can lead to exacerbation of skin lesions, cause disease and delay wound healing [7].

The dominating dermal species of bacteria are: *Actinobacteria*, *Proteobacteria*, *Firmicutes* and *Bacteroidetes* [8]. Human skin is characterized by topographic variability of the population of bacteria inhabiting it depending on the niche of their existence. There is a high variability between skin microorganisms and the time of being within the same person [9]. The most numerous types of bacteria that are found on the skin seem to be relatively stable, with rarer, less abundant types of bacteria responsible for the variability of the entire population of microorganisms. *Staphylococcus*, *Propionibacterium* and *Corynebacterium* are varied in terms of the amount depending on the location on the skin [10;11]. Microorganisms and mites live both on the surface of the skin and deep in the hair and glands of the skin. On the skin surface, bacteria such as *Proteobacteria* and *Staphylococcus* spp. form colonies that are deeply related to each other and other microorganisms. Commensal fungi such as *Malassezi*a spp. grow as both branched mycelium and single cells. Viruses live both freely or inside bacterial cells. Skin mites, such as *Demodex folliculorum* and *Demodex brevis*, are among

the smallest arthropods that live in hair follicles or in their vicinity [12]. Very diverse bacterial groups comprising as many as 734 genera were identified from the facial cheek skin. However, only seven genera (*Propionibacterium*, *Corynebacterium*, *Ralstonia*, *Burkholderia*, *Cupriavidus*, *Pelomonas* and *Staphylococcus*), accounting for <1% of the total number of bacterial genera identified from the facial cheek skin, were identified as cammon bacterial groups in all participants. This was very low in comparison to a previous study stating that 6.6% of total genera were identified as common bacterial groups in forearm skin [13]. Natural healthy human skin surface pH is on average 4.7, lower than currently assumed (pH 5.4–5.9). Skin with pH <5.0 is in better condition than skin with pH >5.0. Growth of *S. epidermidis*, under in- vitro acidic pH conditions (pH 4.7) and in the presence of lactate, is enhanced when compared with neutral pH, whereas growth of *S. aureus* is strongly inhibited under these acidic conditions. An acid pH seems to preserve the resident bacterial flora, whereas an alkaline pH causes dispersal from the skin [14].

Scientific research justifies the previously unknown physical interaction that commonly occurs between commensal bacteria and skin cells. The interaction of skin microorganisms is particularly surprising in the deep layers of the skin and superficial adipose tissue, areas that were thought to be free of microbes in the absence of skin damage. Therefore, bacterial products, including DNA encoding 16S rRNA genes, bacterial specific antigens and ribosomal bacterial RNA, have been widely detected in the subcutaneous regions of human skin. This is evidence of physical interaction between commensal bacteria and living skin cells in its deep layers [15]. Live bacteria colonize or inhabit the dermis. However, the research methods used are not able to distinguish between live and dead microbial cells. Microorganisms do not have to be viable to influence the host's immune system. Bacterial components or products, including LTA, commensal microbial DNA, ATP and polysaccharide A, can affect host cells [16]. Different microbial signals impact on skin barrier organ function and the interdependency between resident microflora and pathogenic microorganisms. Commensal and pathogenic *Staphylococci* differ in their ability to induce expression of antimicrobial peptides/proteins (AMPs) and activate different signaling pathways in human primary keratinocytes. Whereas secreted factors of skin commensals induce expression of the AMPs HBD-3 and RNase7 in primary human keratinocytes via Toll-like receptor (TLR)-2, EGFR, and NF-κB activation, those of pathogenic *Staphylococci* activate the mitogen-activated protein kinase and phosphatidylinositol 3-kinase/AKT signaling pathways and suppress NF-κB activation. Interestingly, commensal bacteria are able to amplify the innate immune response of human keratinocytes to pathogens by increased induction of AMP expression and abrogation of NF-κB suppression, suggesting that the two activation pathways can act in a synergistic way [17].

Current research on skin infectious diseases and microbial virulence factors aims to eliminate these harmful organisms. Some pathological microbes may also play an opposite role under the influence of environmental changes, protecting the host. Complex interaction on the host- microorganism and microorganisms- microorganisms line occurring on the surface of human skin, confirm that the skin microflora is beneficial, like the intestinal microflora. Microbes are involved in inflammatory diseases, but they do not always cause infections. For a clinician, understanding these principles should help in the proper use of available systemic and topical antibiotics [18].

Cosmetics vs skin biofilm changes

Cosmetics play an important role in the life of every person who uses them. People use many different cosmetic products every day, such as soap, shampoo, toothpaste, deodorant, perfumes or make-up cosmetics. The current trend among consumers is striving to use natural ingredients of cosmetic products, as many of these products show equal, better or additional benefits compared to chemical products [19]. Host-specific factors such as age, place of residence and sex contribute to the variability of the bacterial flora of the skin. The age having a significant impact on the microenvironment of the skin, determines the amount of colonizing microflora [20]. In

the mother's uterus, the fetus' skin is sterile and its colonization occurs immediately after birth, during delivery through the birth canal or shortly after birth via caesarean section [21]. The topic of scientific research is to investigate how the bacterial flora of the skin and other places is colonized and stabilized in the first years of life. The newborn learns about his environment by contacting the microbes that stimulate the maturation of his immune system [22]. During puberty, the changes in the production of sebum correspond to the level of lipophilic bacteria on the skin, as observed in studies based on their culture [23]. The clearly occurring physiological and anatomical differences in the skin environment between men and women, such as sweat, tallow and hormone production, are partially explained by differences in the micro-organisms between the sexes. In a recent study of the human epidermis following skin barrier disruption, women showed a significant greater microbial diversity on their hands than men, and this was linked to their less acidic skin surface and use of make-up [24]. The most important bacteria present in the armpits are *Corynebacterium*, *Staphylococcus*, *Betaproteobacteria*, *Clostridiales*, *Lactobacillus*, *Propionibacterium* and *Streptococcus* species. It has been shown that the bacteria living in the armpits are very variable organisms [24]. Greater variability of the microflora was observed after the use of antiperspirant. It could be argued that aluminum is toxic to soil bacteria and interacts with bacterial DNA. On the other hand, aluminum salts have a different effect on two of the most numerous species in the axillary region-*Firmicutes* and *Actinobacteria* [25]. *Actinobacteria* were less susceptible to aluminum compared to *Firmicutes*. In some cases, the *Actinobacteria* type was able to gain more dominance. Strengthening *Corynebacterium* spp. In the axillary region may lead to the development of increased body odor [26]. The use of antiperspirants modifies groups of axillary bacteria, making them more rich species. Since antiperspirants have been used since the last century, it is supposed that the species of bacteria they favor are not commonly found in human armpits. Regardless of whether these species can interfere with the beneficial skin symbiotes, they contribute to the generation of antibiotic resistance genes [27]. The composition of the skin microbiome is predicted to play a role in the development of conditions such as atopic eczema and psoriasis [28,29]. In addition, the relative abundance of *Propionibacterium* and KEGG (Kyoto Encyclopedia of Genes and Genomes) categories of carbohydrate metabolism, membrane transport, and metabolism of cofactors and vitamins that were statistically more abundant in facial skin of high than low hydration group before cosmetic use decreased in a statistically manner after cosmetic use. Metabolic gene categories (cell motility and lipid metabolism) that were more abundant in low than in high hydration group before cosmetic use were still statistically more abundant after cosmetic use than before cosmetic use, suggesting that skin bacterial communities of low hydration group did not shift to being similar to those of high hydration group after cosmetic use, although hydration levels and biophysical parameters of low hydration group were restored to resemble those of high hydration group by cosmetic use. These results suggest that bacterial communities in dry skin do not shift to those in normal skin just by the increase in skin hydration level using basic cosmetics and skin hydration level may not be a critical factor in determining the composition of skin microbial communities [30]. There are significant differences between the hydration, melanin index, and elasticity of different age groups. Regarding the locations, forehead had the highest melanin index, where as palm had the lowest value. The mean values of erythema index and melanin index and transepidermal water loss (TEWL) were significantly higher in males and anatomic location [31]. For the attention deserve the concept of a single-molecule probiotic as a "natural" method of treatment of infections caused by *S. aureus* in order to eradicate and prevent infections, as in the case of therapy that restores bacterial flora after *Clostridium difficile* infection [32]. The relative abundance of typical skin bacterial groups including *Propionibacterium*, *Staphylococcus*, and *Corynebacterium* decreased after use of the basic cosmetics, which might be due to growth of other skin bacteria utilizing components of the basic cosmetics, or inhibition by the cosmetics of growth of the typical skin bacterial groups, or changed environmental conditions. Interestingly, after use of the basic cosmetics, is

observed a statistically significant decrease in *Propionibacterium*, known as a lipophilic and predominant resident in sebaceous environments, and a statistically significant increase in *Ralstonia*, not a core human skin bacterial group, in facial cheek skin regardless of high (HHG) and low hydration group (LHG) [30].

Side effects of skin cosmetics

The skin is the largest multifunctional organ in the body. It functions as a protective physical barrier by absorbing ultraviolet radiation and preventing microorganism invasion and chemical penetration. The skin also controls the passage of water and electrolytes and has a major role in the thermoregulation of the body, in addition to its immunological, sensory, and autonomic function. Understanding the physiological, chemical, and biophysical characteristics of the skin helps us develop a proper approach for the management of skin diseases. However, the influence of genetic and environmental factors on the skin is also critical to consider [33]. Human, as a host for the organisms that make up the skin microflora, has many structures, molecules and mechanisms that limit temporary commensals. They include local skin anatomy, hydration, availability of nutrients and inhibitors of various types. Constantly living microflora is beneficial in settling niches, regulating transient states that may have harmful and infectious effects [34]. Increased density (chronic dermatitis), reduced diversity (psoriasis), increase in the number of commensal organisms causing disease and/ or co-infections (acne) and changes in the environment and colonization of unique species (chronic wounds) can contribute to skin diseases in many ways [7]. Although members of the genus *Propionibacterium* have the ability to metabolize triglycerides, they may not utilize the oil components of the basic cosmetics in skin. Instead of *Propionibacterium*, other bacteria such as *Ralstonia* may be able to metabolize the oil components of the basic cosmetics. Because a member of the genus *Propionibacterium*, *P. acnes*, is known to be associated with acne [35]. The use of basic cosmetics may be helpful to diminish the development of acne in facial skin by decreasing *Propionibacterium*. Although the order *Burkholderiales* of the class *Betaproteobacteria* possibly including the genus *Ralstonia* was prominent in subepidermal compartments containing high lipid content [36], the dominance of *Ralstonia* in the human skin microbiome was not reported until now, suggesting that the dominance of *Ralstonia* in facial cheek skin can be used as an indicator for the use of basic cosmetics. Along with the growing knowledge that microflora associated with humans is an element of health and many disease processes, medical strategies targeting microorganisms are being introduced. Research is carried out to identify probiotic strains and prebiotics that may be beneficial to skin microorganisms and, hence, to the health of the host [17]. *S. epidermidis* as a member of the skin microbiota has a protective effect on *S. aureus* skin colonization. This effect, however, depends on the integrity of the epithelial barrier and is reversed by epithelial barrier disruption, which is often associated with skin inflammation. On the basis of our previous results, with which we showed that *S. epidermidis* amplifies the innate immune response in human skin [37], in healthy skin the microbiota creates a protective environment by immune conditioning of the epithelial surface toward a protective immune response. However, barrier disruption generates an inflammatory environment, which itself promotes pathogen colonization and infection leading to suppression of the protective mechanism of skin commensals. This adverse effect of microbiota might be a general phenomenon in several inflammatory skin diseases such as atopic dermatitis. Further studies will elucidate the signaling pathways involved in *S. epidermidis*-induced modulation of the immune response toward *S. aureus* skin infection and also the bacterial factors that trigger both the protective and the adverse effects [38]. The role of skin microflora in skin aging remains unclear and is an area where care based on skin microflora can be promising. It is presumed that certain metabolites produced by cutaneous microflora may be beneficial by regulating an anti-inflammatory response similar to that shown in the gastrointestinal tract [39]. This is particularly important in conditions where the protective barrier dysfunction may occur, such as: dry, sensitive and reactive skin, exposure to aggressive cosmetic or hygienic treatments, after aesthetic procedures or while taking medications, including antibiotics and corticosteroids. Research suggests that the inclusion of prebiotics, eg.

ceramides, niacinamide or selenium-rich thermal water from the thermal springs may increase the effectiveness of moisturizing agents, acting on the skin's microflora [2]. The last 75 years have been the time of a sharp increase in the number of food allergies and skin allergies, in which the rate of deterioration has accelerated in the last 5-10 years [40]. It is suggested that there are many environmental factors behind this, more and more often associated with synthetic substances contained in cosmetics [41]. It is likely that the exposition of normal European skin to the hygiene and cosmetics of the 21st century [42] has changed the natural environment of cutaneous microflora, especially in developed countries. The use of synthetic chemical components in modern cosmetics is considered to be a cause of skin microflora damage. Biodiversity of human skin microorganisms is currently one of the most reliable indicators of its health [43]. The skin properties can be influenced by changing altitude because different altitudes have different environments such as air temperature, humidity, UV radiation, and so on, and it is also necessary to investigate the factors which can influence with perceived skin condition such as skin type and skin concerning [44]. Skin protects itself against infection through a variety of mechanisms. Antimicrobial peptides (AMPs) are major contributors to cutaneous innate immunity, and this system, combined with the unique ionic, lipid, and physical barrier of the epidermis, is the first-line defense against invading pathogens. However, recent studies have revealed that our skin's innate immune system is not solely of human origin. *Staphylococcus epidermidis*, a major constituent of the normal microflora on healthy human skin, acts as a barrier against colonization of potentially pathogenic microbes and against overgrowth of already present opportunistic pathogens. Our resident commensal microbes produce their own AMPs, act to enhance the normal production of AMPs by keratinocytes, and are beneficial to maintaining inflammatory homeostasis by suppressing excess cytokine release after minor epidermal injury [45].Chemicals used in cosmetics must interact with the enzymes for their consumption after entering our bodies. The area at which the interaction realizes on the enzyme is known as the active center. This center is three dimensional and optically active. Considering the properties of the active regions, it is believed that the determination of the geometric properties of the chemicals may contribute to the safety evaluation of the chemical products. Obtainment of toxicological data of chemicals is a long and difficult process. It is an impossible process as the animal experiments have been prohibited. Since there are large number of chemical compounds available, it is not possible to conduct toxicological evaluation on all of them. Therefore, it is important to estimate whether chemicals are toxic through using molecular formulas [46].

It is not plausible to expect synthetic products to reduce biodiversity, a scenario only likely if these products happened to be particularly powerful. However, they were both very commonly used products. Crucially, this suggests that as soon as the skin's exposure to synthetic ingredients was decreased, the microbial diversity and richness increased. This could be the beginning of a link between exposure to chemicals and a repressed skin microbiome [43].

Therefore, we need to investigate many other factors including cosmetic components, climate, and change in study conditions, particularly because preservatives such as methylparaben, one of the ingredients of cosmetics, have high influence on skin microbiome [32].

Summary

The human skin is inhabited by a permanent, transient or temporary microflora. Constantly living microorganisms are in a dynamic balance with the host tissue, and the microflora can be considered as an integral component of the skin. The vast majority of these microorganisms is gram-positive and located on the surface of the skin [33]. Cosmetics that are formulated to reduce microbial abundance such as deodorants or germicidal soaps may differ in their impact on the numbers and diversity of the skin microbiota by site of application, whereas moisturizers that help retain the water content may support the skin microbiota and reduce skin cell shedding. A more complete understanding of the interaction of cosmetics with the microbiota may improve skin care [47]. The main goal of scientific research will be to understand the components of microorganisms

and their impact on homeostasis and predisposition to diseases [48]. The possibilities of research and experiments broaden our horizons to consider the concept of a "cosmetic microbiome" that can affect the skin-intestine-brain relationship [49], thereby leading to the design of innovative cosmetics and percutaneous medications. The cosmetics potential of the future can create a satisfying look and improve the well-being of consumers [47]. This can be used in the future to check the effectiveness of cosmetics or their ingredients for skin health [43].

A healthy host' microflora may cause minor and transient dermatological problems. Therefore, topical products should have little or no effect on the ecology of the microflora [33]. Scientific research in the future should seek an answer to the question how changing lifestyle, environment and even medical practices affect human microbes. Further research in this area may provide some key information on how changes in microflora contribute to disease progression and symptoms. This creates the prospect of manipulating microflora to develop new therapeutic strategies [7]. Characterization these microbial communities has enhanced our knowledge of the ecology of organisms present in normal skin; furthermore, studies have begun to bring to light the intimate relationships shared between host and resident microbes. In particular, it is apparent that just as host immunological factors and behaviors shape the composition of these communities, microbes present on the skin greatly impact the functions of human immunity. Thus, today the skin immune system should be considered a collective mixture of elements from the host and microbes acting in a mutualistic relationship [52]. Although human skin is constantly exposed to a variety of potential pathogenic microorganisms, it gets only rarely infected [53]. Furthermore, human skin is selectively colonized by commensal bacteria, especially by *S. epidermidis*, whereas *S. aureus* is only rarely found on healthy human skin [54]. Molecular approaches to characterizing microbial diversity have dramatically changed our view of the skin microbiome, subsequently raising many important questions about the host- microorganism relationship and its relevance to skin disease. Although it is now clear that several dominant organisms (that is, *Staphylococcus* and *Propionibacterium* spp.) constitute a large proportion of the skin microbiota, little is understood about the rare or transient organisms making up the balance. It is unclear what factors drive variation in these organisms, and how fluctuation is associated with skin disease. Metagenomic analysis to elucidate the full complement of microbial genes and their functions should provide insight into these questions [50]. Identifying specific microbial community structure patterns of the human skin microbiota associated with disease will identify new potential intervention measures for improving health. It is anticipated that exploration of this new and different approach to human health will provide insights into disease etiology, management, and prevention [51].

The use of appropriate cosmetics leads to proper regulate inbalance between species of skin microflora (dysbiosis). New technologies in microbiological researchs helps to develop substances that have a protective and therapeutic effect on the skin microflora. Such substances are used to treat and minimize the side effects of cosmetic, hygienic and sensitive skin care. Hence, maintaining the right balance between beneficial and pathogenic organisms correlates with the condition and appearance of the skin.

References

1. Chen YE, Tsao H. The skin microbiome: current perspectives and future challenges. J Am Acad Dermatol. 2013;69(1):143-155.
2. Baldwin HE, Bhatia ND, Friedman A, et al. The Role of Cutaneous Microbiota Harmony in Maintaining a Functional Skin Barrier. J Drugs Dermatol. 2017 Jan 1;16(1):12-18.
3. Lai Y, Di Nardo A, Nakatsuji T, Leichtle A, Yang Y, Cogen AL, et al. Commensal bacteria regulate Toll-like receptor 3-dependent inflammation after skin injury. Nat Med. 2009;15:1377-1382.
4. Lai Y, Cogen AL, Radek KA, Park HJ, Macleod DT, Leichtle A, et al. Activation of TLR2 by a small molecule produced by Staphylococcus epidermidis increases antimicrobial defense against bacterial skin infections. J Invest Dermatol. 2010;130:2211-2221.
5. Lee MR, Nam GW, Jung YC, Park SY, Han JY, Cho JC, Suh KD, Hwang JK. Comparison of the skin biophysical parameters of Southeast Asia females:

forehead-cheek and ethnic groups. J Eur Acad Dermatol Venereol. 2013;27(12):1521-6.
6. Noble WC. (1981) Microbiology of human skin, 2nd edn. Lloyd-Luke, London, p 443.
7. Weyrich LS, Dixit S, Farrer AG, Cooper AJ, Cooper AJ. The skin microbiome: Associations between altered microbial communities and disease. Australas J Dermatol. 2015;56(4):268-274.
8. Hannigan GD, Grice EA. Microbial ecology of the skin in the era of metagenomics and molecular microbiology. Cold Spring Harb Perspect Med. 2013;3(12):a015362.
9. Structure, function and diversity of the healthy human microbiome. Human Microbiome Project Consortium. Nature. 2012 Jun 13; 486(7402):207-14.
10. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, Topographical and temporal diversity of the human skin microbiome. NISC Comparative Sequencing Program., Bouffard GG, Blakesley RW, Murray PR, Green ED, Turner ML, Segre JA Science. 2009 May 29; 324(5931):1190-2.
11. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science. 2009 Dec 18; 326(5960):1694-7.
12. Grice EA, Segre JA. The skin microbiome [published correction appears in Nat Rev Microbiol. 2011 Aug;9(8):626]. Nat Rev Microbiol. 2011;9(4):244-253.
13. Gao Z, Tseng CH, Pei Z, Blaser MJ. Molecular analysis of human forearm superficial skin bacterial biota. Proceedings of the National Academy of Sciences, 2007;104:2927–2932. 14.
14. Lambers H., Piessens S., Bloem A., Pronk H., Finkel P. Natural skin surface pH is on average below 5, which is beneficial for its resident flora. Int J Cosm Sci. 2006;28:359–370.
15. Nakatsuji T, Chiang HI, Jiang SB, Nagarajan H, Zengler K, Gallo RL. The microbiome extends to subepidermal compartments of normal skin. Nat Commun. 2013;4:1431
16. Hall JA, et al. Commensal DNA limits regulatory T cell conversion and is a natural adjuvant of intestinal immune responses. Immunity. 2008;29:637-649.
17. Wanke I, Steffen H, Christ C, Krismer B, Gotz F, Peschel A. et al. Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways. J Invest Dermatol. 2011;131:382–390.
18. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence?. Br J Dermatol. 2008;158(3):442-455.
19. Vecino X, Cruz JM, Moldes AB, Rodrigues LR. Biosurfactants in cosmetic formulations: trends and challenges. Crit Rev Biotechnol. 2017;37(7):911-923.
20. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Age-related changes in the resident bacterial flora of the human face. J. Invest. Dermatol. 1975;65:379-381.
21. Sarkany I, Gaylarde CC. Bacterial colonisation of the skin of the newborn. J. Pathol. Bacteriol. 1968;95:115-122.
22. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5:e177.
23. Somerville DA. The normal flora of the skin in different age groups. Br. J. Dermatol. 1969;81:248-258.
24. Giacomoni PU, Mammone T, Teri M. Genderlinked differences in human skin. J. Dermatol. Sci. 2009;55:144-149.
25. Gao Z, Perez-Perez GI, Chen Y, Blaser MJ. Quantitation of major human cutaneous bacterial and fungal populations. J Clin Microb. 2010;48(10):3575-3581
26. Callewaert C, Kerckhof FM, Granitsiotis MS, van Gele M, van de Wiele T, Boon N. Characterization of Staphylococcus and Corynebacterium clusters in the human axillary region. PLoS One 2013;8(8):e50538.
27. Leyden JJ, McGinley KJ, Holzle E, Labows JN, Kligman AM (1981) The microbiology of the human axilla and its relationship to axillary odor. J Invest Dermatol 77(5):413–416.
28. Castelino M, Eyre S, Moat J, Fox G, Martin P, Ho P, Upton M, Barton A. Optimisation of methods for bacterial skin microbiome investigation: primer selection and comparison of the 454 versus MiSeq platform. BMC Microbiol. 2017;17(1):23
29. Urban J, Fergus DJ, Savage AM, et al. The effect of habitual and experimental antiperspirant and deodorant product use on the armpit microbiome. PeerJ. 2016;4:e1605.
30. Lee HJ, Jeong SE, Lee S, Kim S, Han H, Jeon CO. Effects of cosmetics on the skin microbiome of facial cheeks with different hydration levels. MicrobiologyOpen. 2018;7:e557.

31. Firooz A., Sadr B., Babakoohi S., Sarraf-Yazdy M., Fanian F., Kazerouni-Timsar A., Nassiri-Kashani M., Naghizadeh M.M., Dowlati Y. Variation of biophysical parameters of the skin with age, gender, and body region. Scientific World Journal. 2012;2012:386936.
32. Burnham CA, Hogan PG, Wallace MA, et al. Topical Decolonization Does Not Eradicate the Skin Microbiota of Community-Dwelling or Hospitalized Adults. Antimicrob Agents Chemother. 2016;60(12):7303-7312.
33. Rahrovan S., Fanian F., Mehryan P., Humbert P., Firooz A. Male versus female skin: What dermatologists and cosmeticians should know. Int J Womens Dermatol. 2018;4(3):122–130.
34. Holland KT, Bojar RA. Cosmetics: what is their influence on the skin microflora? Am J Clin Dermatol. 2002;3(7):445-449
35. Krutmann J. Pre-and probiotics for human skin. Journal of Dermatological Science, 2009;54:1–5.
36. Nakatsuji T, Chiang HI, Jiang SB, Nagarajan H, Zengler K, Gallo RL. The microbiome extends to subepidermal compartments of normal skin. Nature Communications, 2013;4, 1431.
37. Grice EA. The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease. Semin Cutan Med Surg. 2014;33(2):98-103
38. Burian M, Bitschar K, Dylus B, Peschel A, Schittek B. The Protective Effect of Microbiota on S. aureus Skin Colonization Depends on the Integrity of the Epithelial Barrier. J Inv Derm. 2017;137(4):976-979.
39. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451-455
40. Srinivas G, Möller S, Wang J, Künzel S, Zillikens D, Baines JF, Ibrahim SM. Genome-wide mapping of gene–microbiota interactions in susceptibility to autoimmune skin blistering. Nat. Commun. 2013, 4, 2462.
41. Salverda JGW, Bragt PJC, de Wit-Bos L, Rustemeyer T, Coenraads PJ, Tupker RA, Kunkeler LCM, Laheij-de Boer A-M, Stenveld HJ, van Ginkel CJW, et al. Results of a cosmetovigilance survey in The Netherlands. Contact Dermat. 2013, 68, 139-148
42. Rocha LA, Ferreira de Almeida e Borges L, Gontijo Filho PP. Changes in hands microbiota associated with skin damage because of hand hygiene procedures on the health care workers. Am. J. Infect. Control 2009;37:155-159.
43. Wallen-Russell C. The Role of Every-Day Cosmetics in Altering the Skin Microbiome: A Study Using Biodiversity. Cosmetics 2019;6(1):2-24.
44. Lee M, Jung Y, Kim E, Lee HK. Comparison of skin properties in individuals living in cities at two different altitudes: an investigation of the environmental effect on skin. J Cosmet Dermatol. 2017;16(1):26-34.
45. Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. J Invest Dermatol. 2011;131(10):1974–1980
46. Demir Y, Uckaya M, Demir N. Evaluation of the efficacy in cosmetic products safety: Comparison with biochemical substrates. Regulatory Toxicology and Pharmacology, 2019;104:56-58.
47. Cundel A.M. Microbial Ecology of the Human Skin. Microbial Ecology, 2018;76(1):113-120.
48. Beri K. Skin microbiome & host immunity: applications in regenerative cosmetics & transdermal drug delivery. Future Sci OA. 2018;4(6):FSO302
49. Denda M. Epidermis as the third brain. Dermatol. Sin. 2015;33(2):70-73.
50. NIH HMP Working Group, Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Guyer M, et al. The NIH Human Microbiome Project. Genome research, 2009;19(12):2317–2323.
51. Rosenthal M, Goldberg D, Aiello A, Larson E, Foxman B. Skin microbiota: microbial community structure and its potential association with health and disease. Infect Genet Evol. 2011;11(5):839–848.
52. Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. Seminars in Immunology, 2013;25(5):370-377.
53. Schittek B, Paulmann M, Senyurek I. et al. The role of antimicrobial peptides in human skin and in skin infectious diseases. Infect Disord Drug Targets. 2008;8:135–143
54. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence?. Br J Dermatol. 2008;158:442–455.