

Exploring the Nexus of Microbiota, Aging, and Skin Health: A Comprehensive Review on Probiotic and Its Topical Applications

Faris Dary Utama^a, Damayanti^{b*}, Atika^c, Afif Nurul Hidayati^b

^aMedical Study Program, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

^b Department of Dermatology and Venereology, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

^c Department of Public Health Sciences - Preventive Medicine, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.

* Corresponding author: damayanti@fk.unair.ac.id

Abstract

The human microbiome, a unique entity in mammals, hosts a diverse ecosystem on the skin, playing a pivotal role in maintaining homeostasis. Key bacterial phylum, including *Firmicutes*, *Actinobacteria*, *Bacteroides*, and *Proteobacteria*, are prevalent on the skin, with dynamic variations observed across different life stages. Notably, dysbiosis in the skin microbiome has been associated with chronic skin disorders such as dermatitis atopic and psoriasis. This literature review delves into the intricate interplay between microbiota, aging, and skin health, with a particular focus on the role of probiotics and their topical applications. In the aging process, significant shifts in the skin microbiome occur, with changes in bacterial density and diversity. Metagenomic studies reveal distinctions between young and old skin, suggesting implications for overall skin health. Furthermore, the review explores the unique crosstalk between the gut and skin microbiomes, emphasizing the gut-skin axis. This two-way communication pathway underscores the vulnerability of the balance system as age progresses, contributing to skin dysfunction. The literature extensively covers various probiotic strains, predominantly *Bifidobacterium* and *Lactobacillus*, commonly found in probiotic products. Topical probiotics have proven effective in addressing skin issues like acne, atopic dermatitis, and rosacea. The historical use of topical bacteriotherapy, dating back to 1912, is highlighted, showcasing its potential in treating skin diseases. The review concludes by emphasizing the therapeutic potential of probiotics topical in skincare, presenting a comprehensive overview of their impact on aging and skin health.

Keywords: Skin Aging, Probiotic, Sensitive Skin, Human and Health

1. Introduction

The relationship between microbiota, aging, and skin health has become a focal point in scientific inquiry, with probiotics emerging as key players in this dynamic interplay. The human microbiome, an ecosystem of microorganisms residing on and within the body, is particularly unique in its manifestation on the skin. Comprising an array of bacteria, viruses, and fungi, the skin microbiome plays a crucial role in maintaining a delicate balance that is integral to overall health. Among the prominent bacterial phylum found on the skin are *Firmicutes*, *Actinobacteria*, *Bacteroides*, and *Proteobacteria*, each contributing to the complex and dynamic nature of the skin's microbial inhabitants (Boyajian et al., 2021).

Throughout the life course, the skin undergoes significant changes in its microbiome, a phenomenon that is closely tied to the aging process. In the womb, the skin is a sterile environment, but during and immediately after birth, it becomes colonized, setting the stage for a dynamic and evolving microbiota. Metagenomic studies utilizing RNA 16S sequencing have enabled a deeper understanding of the bacterial populations present on the skin. Dysbiosis, characterized by alterations in the skin microbiota, has been implicated in various chronic skin conditions, including dermatitis atopic and psoriasis. As individuals age, distinct shifts occur in the composition and diversity of the skin microbiome. Notably, during puberty, there is an increase in the density of lipophilic bacteria on the skin, corresponding to heightened sebum levels. Conversely, older individuals exhibit lower bacterial density, reflecting a more nuanced relationship between the aging process and the skin microbiota. Metagenomic analyses have revealed differences in the overall structure of the microbiota between young and old skin, with a decrease in *Actinobacteria* observed in older skin. Despite these variations, there is a notable increase in species diversity on older skin, highlighting the complexity of the aging-microbiome relationship (Olejniczak-Staruch et al., 2021).

Beyond the skin's surface, an intriguing connection exists between the microbiomes of the gut and the skin, known as the gut-skin axis (Olejniczak-Staruch et al., 2021). This two-way communication pathway underscores the vulnerability of the balance system, particularly susceptible to disruption as age progresses. The hygiene hypothesis posits that excessive cleanliness and antimicrobial practices during childhood may interfere with the development of the immune system, including the skin, potentially increasing the risk of allergies. Furthermore, skin dysbiosis has been associated with various skin disorders, prompting exploration into topical bacteriotherapy as a therapeutic avenue. Historical records dating back to 1912 showcase the utilization of topical probiotics, such as *Lactobacillus bulgaricus*, in addressing conditions like acne vulgaris and dermatitis seborrheic (Olejniczak-Staruch et al., 2021).

This literature review aims to comprehensively explore the roles of microbiota, aging, and probiotics in skin health. With a particular emphasis on the evolving landscape of the skin microbiome throughout the life course and the therapeutic potential of probiotics in addressing age-related skin conditions, this review provides a foundation for understanding the complex interplay that governs skin health in the context of microbiota and aging.

2. Review Content

2.1 Skin Aging

The process of skin aging is a physiological process that cannot be avoided and is a concern for society due to the fact that the skin is the part of the body most frequently exposed to external factors. Skin aging is the first thing that is visible when an individual interacts with others, and it greatly affects their quality of life. Skin aging in an individual is a combination of intrinsic and extrinsic aging processes (Zahrudin & Damayanti., 2018). Both intrinsic and extrinsic aging processes result in the same outcome, which is a decrease in the skin's physiological function, manifested clinically as skin aging. Extrinsic aging accelerates the appearance of these manifestations, while intrinsic aging progresses at a normal, slower pace as a person ages. According to the definition, aging is the accumulation of molecular changes that manifest as macroscopic clinical alterations. The morphological and biophysical characteristics of the skin are known to change due to significant environmental variables. The term "aging variables" refers to various factors that accelerate the accumulation of molecular changes, including ultraviolet (UV) radiation, air pollution, injuries, infections, trauma, anoxia, cigarette smoke, and hormonal conditions (Cinque et al., 2017). Skin aging is a physiological process that primarily affects the elderly. It is characterized by a decrease in skin protection, reduced sebum production, and a slow rate of epidermal cell regeneration. Symptoms of skin aging include dry skin, hyperpigmentation, loss of firmness, elasticity, and smoothness due to these issues (Nabila et al., 2021). Skin

aging is a complex biological issue influenced by a combination of extrinsic and intrinsic factors. The fact that healthy and beautiful skin reflects "well-being" and mirrors human "health" has led to the development of various anti-aging therapies. The three main structural components of the skin, namely dermis, collagen, elastin, and Glycosaminoglycan (GAGs), are the subjects of the majority of anti-aging therapies. Anti-aging therapy aims to achieve healthy, smooth, blemish-free, and resilient skin (Ganceviciene et al., 2012).

It is a common knowledge that skin aging is accompanied by increased wrinkles and sagging. However, when examining the causes of these changes, it is important to distinguish between the effects of genuine biological aging (intrinsic aging) and environmental influences, such as sun exposure (extrinsic aging). Molecular changes brought about by photoaging are usually seen as an augmentation and amplification of molecular changes caused by skin aging over time (Fisher et al., 2002). Skin aging is a complex process involving multiple changes and many molecules in terms of its biochemical and molecular processes (Cinque et al., 2017).

2.1.1 Factors Influencing Skin Aging

Skin aging is influenced by two main factors: external factors and internal factors, and these factors interact with each other. Internal factors include ethnic influences, hormonal effects, variations in skin anatomy, and the suspected role of gene expression affecting the skin's deoxyribonucleic acid (DNA) involved in skin aging (Farage et al., 2008; Russell-Goldman and Murphy, 2020). External factors consist of 1) sunlight radiation: ultraviolet radiation, visible light, and infrared radiation, 2) air pollution, 3) cigarette smoke, 4) nutrition, and 5) other miscellaneous factors. These factors collectively affect the structural and physiological changes in each layer of the skin, especially in areas exposed to sunlight. Sunlight consists of an electromagnetic spectrum with different wavelengths, ranging from short, high-energy ultraviolet (UV) radiation to visible light (VL) and long, low-energy infrared radiation. Most of the sunlight spectrum reaches the skin. Ultraviolet radiation accounts for 5% of the total sunlight spectrum and is divided into three groups in order of decreasing wavelength; ultraviolet C (UVC) (100–280 nm), which does not reach the skin due to ozone filtering, ultraviolet B (UVB) (280–315 nm), and ultraviolet A (UVA) (315–400 nm). The UVA group comprises the majority of UV radiation that penetrates the skin (Krutmann et al., 2017).

2.2 Clinical Manifestations of Skin Aging

The intrinsic and extrinsic processes of skin aging together play a role in the occurrence of skin aging in an individual. Both intrinsic and extrinsic aging processes have the same ultimate consequence, which is the decline in the physiological function of the skin, clinically manifesting as skin aging. While the intrinsic aging process occurs more slowly with age, extrinsic aging will contribute to accelerating these manifestations (Hwang et al., 2011). Mechanisms involved in intrinsic skin aging include increased free radicals, decreased formation of the skin's extracellular matrix, and a reduction in the capacity of skin cells to proliferate (Jenkins, 2002). Extrinsic skin aging is also referred to as photoaging, primarily caused by UV radiation, and has main effects such as DNA damage, inflammatory processes, immunosuppression, and intrinsic aging, leading to increased free radicals that reduce synthesis and accelerate damage to the extracellular matrix in the skin (Helfrich et al., 2008; Sjerobabski-Masneć and Situm, 2010).

2.3 Antiaging Therapy

The aging process is an unavoidable biological process. In clinical practice, "looking better" does not necessarily mean "looking younger." It is important to educate patients about their expectations regarding antiaging therapy, considering various available therapy options. Age, previous procedures or surgeries, overall health condition, skin type, lifestyle, and many other factors must be taken into account before determining the choice of antiaging therapy. The desired therapeutic effects of antiaging should be continuous, gradual, combining various methods of skin bio revitalization and rejuvenation, augmentation,

and the restoration of each layer of the skin individually, taking into account other factors such as lifestyle, immune system, genetics, emotions, and overall health conditions (Ganceviciene et al., 2012).

2.4 Definition of Probiotics

Probiotics are microorganisms that provide health benefits to both humans and animals. These microorganisms play a crucial role in maintaining the balance of the gut flora and promoting health. The term "probiotic" has been in use since 1965, coined by Lilley and Stilwell, who first utilized it. Probiotic microorganisms are most commonly found in the genera *Lactobacillus* and *Bifidobacterium*, although they can also be found in the genera *Bacillus*, *Pediococcus*, and yeast (Vandenberghe et al., 2010). Probiotics have long been known to have health benefits, initially in the digestive system, but with advancing knowledge, their use has expanded to other areas of the body, including the skin. The role of probiotics in modulating the immune system involves their participation in the release of regulatory cytokines, which is believed to influence skin homeostasis. The potential use of probiotics in dermatology has been extensively studied, such as in cases of atopic dermatitis (Wu et al., 2017), psoriasis (Olejniczak-Staruch et al., 2021), and acne (Lee et al., 2019). Probiotics are living organisms that can provide beneficial health effects to consumers when consumed in sufficient quantities by improving the balance of intestinal microflora upon entering the digestive tract (Hill et al., 2014; Nagpal et al., 2018).

2.5 Types of Probiotics

Most probiotic products consist of one or more strains of *Bifidobacterium* (*adolescentis*, *animalis*, *bifidum*, *breve*, and *longum*) and *Lactobacillus* (*acidophilus*, *casei*, *fermentum*, *gasseri*, *johnsonii*, *paracasei*, *plantarum*, *rhamnosus*, and *salivarius*) (Hill et al., 2014). The skin microbiota is a diverse population of microorganisms that play a crucial role in innate and adaptive immune responses, as well as serving as a skin barrier. The hygiene hypothesis suggests that a lack of pathogen exposure during childhood due to excessive cleanliness and antimicrobial use can disrupt the development of the immune system, including the skin, and increase the risk of allergies. Skin dysbiosis, changes in skin microbiota, is also associated with several skin conditions such as atopic dermatitis, psoriasis, acne vulgaris, and seborrheic dermatitis. Topical bacteriotherapy, such as the application of one individual's skin microbiota to another, has been used as a treatment for skin diseases since 1912. In this study, the topical application of *Lactobacillus bulgaricus* improved conditions such as acne vulgaris and seborrheic dermatitis on the skin (Lee et al., 2019). Topical probiotics have proven to be effective in addressing skin issues such as acne, atopic dermatitis, and rosacea.

2.6 Relationship between Probiotics and Aging

The human microbiome is a unique entity in mammals. The skin serves as a host to a diverse ecosystem, including up to one million bacteria per square centimeter of skin surface, in addition to viruses and fungi. In the womb, the skin is sterile and becomes colonized during and immediately after birth. After this initial colonization, the microbiome remains dynamic and varies at different stages of life. Metagenomics, specifically RNA 16S sequencing, has allowed the characterization of the skin bacterial population. There are four main bacterial phylum on the skin: *Firmicutes* (including *Staphylococci*), *Actinobacteria*, *Bacteroides*, and *Proteobacteria*, with prevalence varying depending on the location on the body. The microbiome flora largely functions well and can even play a role in preventing infections through the production of antibacterial compounds. Components derived from the microbiome also influence the host's immune system. Research indicates that surface components of *Staphylococcal* cell walls can directly inhibit the host's immune response by modulating cytokine release from keratinocytes. Skin microbiome disruptions have also been implicated in chronic skin disorders such as atopic dermatitis and psoriasis (Russell-Goldman and Murphy, 2020).

There are significant differences in the skin microbiome between young and old populations. For example, during puberty, the density of lipophilic bacteria on the skin increases, corresponding to an increase in sebum

levels, and is lower on the skin of older individuals. Metagenomic studies comparing the skin microbiome of young and old individuals found that the overall structure of the microbiota differs between the two groups, with a decrease in *Actinobacteria* on older skin. Overall, however, there is an increase in species diversity on older skin. Research has found that the increased diversity of the microbiome on older skin is associated with oral flora, a pattern also observed in the microbiome of younger patients with atopic dermatitis. The interaction between the microbiome, skin, and the immune system represents a more vulnerable balance system as age advances (Jugé et al., 2018; Russell-Goldman and Murphy, 2020).

The skin and gut microbiomes have the same purpose and function, acting as the body's main barriers to the external environment, and must be maintained in homeostasis. The skin is highly vulnerable to damage due to frequent exposure to environmental factors such as air pollution, tobacco smoke, nutrition, and skincare products. As a result, premature aging can occur in the skin, accompanied by impaired skin function. Disorders in skin health can lead to systemic damage. Disruptions in the permeability of the skin epidermis will increase the levels of pro-inflammatory cytokines in serum, such as IL-1 and IL-6. Bacterial microbes and their metabolites entering the body's circulation will affect distant organs and tissues, including the skin. There is a two-way communication pathway between the gut microbiome and the integumentary system, known as the gut-skin axis. Increased gut permeability due to dysbiosis leads to the accumulation of bacterial metabolites (such as phenol from aromatic amino acids) on the skin and disturbances in epidermal differentiation and skin integrity. Some aged cells typically accumulate on the skin, triggering inflammation through Senescence-Associated Secretory Phenotypes (SASP) and contributing to various types of skin dysfunction. The unique crosstalk between the gut and skin provides an opportunity to target old skin cells with the hope of resolving skin disorders (Boyajian et al., 2021).

3. Conclusion

In conclusion, this literature review highlights the association between microbiota, aging, and skin health, emphasizing the dynamic nature of the skin microbiome. The shifts observed in microbial composition during aging, coupled with the unique interplay between the gut and skin microbiomes, underscore the vulnerability of the skin's balance system. Probiotics, particularly in topical applications, emerge as promising therapeutic agents in addressing age-related skin conditions, as evidenced by historical practices and contemporary research. Understanding these complexities offers valuable insights for future skincare interventions, with the potential to enhance skin health and mitigate the impact of aging on the skin microbiome.

Acknowledgements

The authors would like to thank all the supervisors, enabling the successful implementation of this study.

References

- Boyajian, J. L., Ghebretatios, M., Schaly, S., Islam, P., & Prakash, S. (2021). Microbiome and Human Aging: Probiotic and Prebiotic Potentials in Longevity, Skin Health and Cellular Senescence. *Nutrients*, 13(12), 4550. <https://doi.org/10.3390/nu13124550>
- Cinque, B., Palumbo, P., La Torre, C., Melchiorre, E., Corridoni, D., Miconi, G., Di Marzio, L., Cifone, M. G., & Giuliani, M. (2017). Probiotics in Aging Skin. In *Textbook of Aging Skin* (pp. 1315–1327). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-662-47398-6_78

- Farage, M. A., Miller, K. W., Elsner, P., & Maibach, H. I. (2008). Intrinsic and extrinsic factors in skin ageing: A review. *International Journal of Cosmetic Science*, 30(2), 87–95. <https://doi.org/10.1111/j.1468-2494.2007.00415.x>
- Fisher, G. J., Kang, S., Varani, J., Bata-Csorgo, Z., Wan, Y., Datta, S., & Voorhees, J. J. (2002). Mechanisms of Photoaging and Chronological Skin Aging. *Archives of Dermatology*, 138(11). <https://doi.org/10.1001/archderm.138.11.1462>
- Ganceviciene, R., Liakou, A. I., Theodoridis, A., Makrantonaki, E., & Zouboulis, C. C. (2012). Skin anti-aging strategies. *Dermato-Endocrinology*, 4(3), 308–319. <https://doi.org/10.4161/derm.22804>
- Helfrich, Y. R., Sachs, D. L., & Voorhees, J. J. (2008). Overview of skin aging and photoaging. *Dermatology Nursing*, 20(3), 177–183; quiz 184.
- Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., Morelli, L., Canani, R. B., Flint, H. J., Salminen, S., Calder, P. C., & Sanders, M. E. (2014). Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology and Hepatology*, 11(8), 506–514. <https://doi.org/10.1038/nrgastro.2014.66>
- Jugé, R., Rouaud-Tinguely, P., Breugnot, J., Servaes, K., Grimaldi, C., Roth, M.-P., Coppin, H., & Closs, B. (2018). Shift in skin microbiota of Western European women across aging. *Journal of Applied Microbiology*, 125(3), 907–916. <https://doi.org/10.1111/jam.13929>
- Krutmann, J., Bouloc, A., Sore, G., Bernard, B. A., & Passeron, T. (2017). The skin aging exposome. *Journal of Dermatological Science*, 85(3), 152–161. <https://doi.org/10.1016/j.jdermsci.2016.09.015>
- Lee, Byun, & Kim. (2019). Potential Role of the Microbiome in Acne: A Comprehensive Review. *Journal of Clinical Medicine*, 8(7), 987. <https://doi.org/10.3390/jcm8070987>
- Nabila, Y. A., Damayanti, D., Handayani, S., & Setyaningrum, T. (2021). The effect of lifestyle on Skin aging. *Berkala Ilmu Kesehatan Kulit Dan Kelamin*, 33(2), 110. <https://doi.org/10.20473/bikk.v33.2.2021.110-115>
- Nagpal, R., Mainali, R., Ahmadi, S., Wang, S., Singh, R., Kavanagh, K., Kitzman, D. W., Kushugulova, A., Marotta, F., & Yadav, H. (2018). Gut microbiome and aging: Physiological and mechanistic insights. In *Nutrition and Healthy Aging* (Vol. 4, Issue 4, pp. 267–285). IOS Press. <https://doi.org/10.3233/NHA-170030>
- Olejniczak-Staruch, I., Ciężńska, M., Sobolewska-Sztychny, D., Narbutt, J., Skibińska, M., & Lesiak, A. (2021). Alterations of the Skin and Gut Microbiome in Psoriasis and Psoriatic Arthritis. *International Journal of Molecular Sciences*, 22(8), 3998. <https://doi.org/10.3390/ijms22083998>
- Russell-Goldman, E., & Murphy, G. F. (2020). The Pathobiology of Skin Aging. *The American Journal of Pathology*, 190(7), 1356–1369. <https://doi.org/10.1016/j.ajpath.2020.03.007>
- Sjerobabski-Masneć, I., & Situm, M. (2010). Skin Aging. *Acta Clinica Croatica*, 49(4), 515–518.
- Vandenberghe, L., Spier, M. R., Bianchi, A., Medeiros, P., De, J., & Lindner, D. (2010). The Potential of Probiotics: A Review Biocatalytic production of 2,5 Furan dicarboxylic acid (FDCA) by using whole cells View project Probiotics View project. In *Article in Food Technology and Biotechnology*. <https://www.researchgate.net/publication/47864067>
- Wu, Y.-J., Wu, W.-F., Hung, C.-W., Ku, M.-S., Liao, P.-F., Sun, H.-L., Lu, K.-H., Sheu, J.-N., & Lue, K.-H. (2017). Evaluation of efficacy and safety of *Lactobacillus rhamnosus* in children aged 4–48 months with atopic dermatitis: An 8-week, double-blind, randomized, placebo-controlled study. *Journal of Microbiology, Immunology and Infection*, 50(5), 684–692. <https://doi.org/10.1016/j.jmii.2015.10.003>
- Zahrudin, A., & Damayanti, D. (2018). Penuaan Kulit: Patofisiologi dan Manifestasi Klinis (Skin Aging: Pathophysiology and Clinical Manifestation). 30 (3), 208–215. <https://doi.org/10.20473/bikk.V30.3.2018.208-215>