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## ***“A Paradigm Shift in Skin Microbiome Enhancement: Leveraging Skin Lipidomics and Probiotic Delivery Systems”***

**Jihoon Ha<sup>\*</sup> <sup>1</sup>, Sung Eun KIm<sup>1</sup>, YounGyun Jung<sup>2</sup>, Ikwhan Kim<sup>3</sup>, DA-Ryung Jung<sup>3</sup>, Jin Mo Kim<sup>1</sup>, Jin Young Kim<sup>1</sup>, Sang Guen Han<sup>1</sup>, Yeon Gyun Jung<sup>3</sup>, Jae-Ho Shin<sup>3</sup>, Yoon Soo Cho<sup>2\*</sup>**

<sup>1</sup> Kolmar Korea, Seoul, Republic of Korea

<sup>2</sup> Hallym University College of Medicine, Seoul, Republic of Korea

<sup>3</sup> Department of Integrative Biology, Kyungpook National University, DAEGU, Republic of Korea

### **1. Introduction**

The skin, the largest organ of the human body, serves not only as a physical barrier against environmental stressors but also as a dynamic ecosystem that hosts a diverse and site-specific microbiome. This complex microbial community, collectively known as the skin microbiome, includes bacteria, fungi, viruses, and archaea, and plays a crucial role in maintaining cutaneous homeostasis and immunity [1,2]. Increasing evidence has demonstrated that the skin microbiome is not merely a passive resident, but an active participant in regulating host skin physiology, including barrier integrity, inflammation modulation, and resistance to pathogenic colonization [3].

Importantly, the composition and function of the skin microbiome evolve with intrinsic aging and environmental exposures such as ultraviolet (UV) radiation, pollution, and personal hygiene practices [4]. Age-related shifts in microbial populations are often associated with a decline in skin health, including increased transepidermal water loss (TEWL), reduced hydration, and the appearance of wrinkles and pigmentation [5]. Notably, aging skin tends to exhibit a reduction in the abundance of beneficial commensals, such as *Cutibacterium acnes* subgroups, and an increase in opportunistic or inflammation-associated species [6]. These alterations suggest that the skin microbiome can serve as both a biomarker and modifiable factor in skin aging.

Among emerging strategies to modulate skin microbiomes, topical probiotics and postbiotics have gained significant attention. In particular, strains of *Lactobacillus*, widely known for their beneficial effects in gut health, have been repurposed for dermatological applications due to their antimicrobial peptides, anti-inflammatory metabolites, and capacity to strengthen the skin barrier [7,8]. Our previous work, presented at the 2023 IFSCC Congress, demonstrated that certain *Lactobacillus*-derived exosomes were capable of selectively suppressing aging-associated bacteria while promoting microbial balance and reducing skin senescence markers.

Building on these findings, the current study explores a novel skin microbiome intervention framework that integrates optimized probiotic delivery systems with lipidomics-based analysis. Lipidomics—the comprehensive profiling of skin lipids—offers a sensitive readout of skin condition, as lipids such as ceramides, free fatty acids, and cholesterol are closely tied to microbiome stability and epidermal barrier function [9]. By correlating microbiome modulation with key lipidomic changes and physiological markers (e.g., TEWL, hydration, pigmentation, and wrinkle depth), this study provides an in-depth view of how targeted probiotic formulations can rejuvenate aging skin.

Furthermore, we employed advanced formulation technologies to improve stability, permeability, and targeted delivery of the probiotic components to specific skin layers. This enables a mechanistic understanding of how surface-applied microbiome modulators interact with deeper skin biology, offering insights for next-generation cosmetic therapeutics aimed at microbiome-guided skin rejuvenation.

This study not only underscores the importance of the skin microbiome in aging but also proposes a scientifically grounded, multi-omics-informed intervention strategy to actively improve skin health through microbiome modulation.

## 2. Materials and Methods

### 2.1 Subject Recruitment and Sample Collection

This study investigated age-related changes in skin microbial communities and the correlation between *Cutibacterium acnes* abundance and skin biomechanical properties. Sixty healthy Korean adults were recruited in Seoul and divided into two age groups: younger (20–29 years, n=30) and older (60–75 years, n=30). Female participants' hormonal status was controlled by measuring estradiol levels, and only those within normal reference ranges were included. Exclusion criteria included recent steroid or antibiotic use, chronic skin conditions, pregnancy, and lactation. Participants arrived without makeup or skincare products and acclimatized under controlled conditions (22 ± 2°C, 50 ± 5% RH). Skin swabs were collected from the nasolabial fold using sterile swabs with preservatives and stored at -80°C until DNA extraction.

### 2.2 Measurement of Skin Biomechanical Characteristics

Skin physiological properties were measured at the same site as microbiome sampling. Parameters including melanin, erythema, sebum, pH, transepidermal water loss (TEWL), extensibility, and elasticity were evaluated using devices such as the Mexameter®, Tewameter®, Cutometer®, and E-CUBE 7® ultrasound system. Wrinkle depth and pattern were assessed using skin replica analysis with the Skin-Visioline VL 650®.

### 2.3 DNA Extraction and Metagenomic Sequencing

Genomic DNA was extracted from swab samples using the DNeasy PowerSoil Pro Kit with modified protocols for increased yield. DNA was amplified via multiple displacement using the REPLI-g Single Cell Kit. DNA quality and quantity were confirmed using Qubit and NanoDrop systems. Sequencing libraries were prepared with the MGIEasy FS kit and sequenced using the DNBSEQ-G400RS platform, targeting ~12.5 million paired-end reads (100 bp) per sample.

### 2.4 Taxonomic and Functional Profiling

Low-quality reads and host DNA were removed using SOAPnuke and Bowtie2, respectively. Taxonomic classification was performed using Kraken2 and Bracken, while functional gene annotation and pathway mapping were conducted using HUMAnN 3.0 with the UniRef90 and KEGG databases.

### 3. Results

This study revealed significant age-related differences in the composition and function of the skin microbiome, with a particular focus on *Cutibacterium acnes* (*C. acnes*). In the younger group (ages 20–29), *C. acnes* showed higher relative abundance (83.1%) compared to the older group (60.6%,  $p = 0.007$ ), and was the sole biomarker species identified. Conversely, the older group exhibited increased bacterial diversity and enrichment of 22 other species, including *Staphylococcus aureus* and *Streptococcus salivarius*.

Biomechanical assessments showed that the older group had significantly lower skin elasticity (gross, net, and biological elasticity, all  $p < 0.001$ ) and more pronounced wrinkles (depth, length, and area, all  $p < 0.001$ ). Notably, *C. acnes* abundance was positively correlated with skin elasticity ( $r \approx 0.40$ ,  $p < 0.01$ ) and negatively correlated with wrinkle parameters ( $r = -0.26$  to  $-0.38$ ,  $p < 0.05$ ), indicating its protective role in maintaining youthful skin structure.

Functional analysis revealed that *C. acnes* was associated with beneficial metabolic pathways such as zeatin and biotin biosynthesis, and cofactor/vitamin metabolism. These pathways were diminished in the older group, which instead showed increased lipid metabolism and environmental stress response functions. Network analysis demonstrated that the microbial ecosystem in younger individuals was more connected and resilient, while the older group exhibited higher modularity, indicating community fragmentation and functional specialization.

### 5. Conclusion

This study demonstrates that aging is associated with a decline in *C. acnes* abundance and an increase in microbial diversity, leading to alterations in skin biomechanical properties and functional pathways. The loss of *C. acnes* appears to disrupt skin homeostasis, reducing elasticity and promoting wrinkle formation, potentially through decreased production of beneficial metabolites such as short-chain fatty acids and antioxidants.

These findings suggest that *C. acnes* plays a crucial role in preserving skin health and delaying the aging process through its microbial and metabolic functions. Targeted modulation of the skin microbiome—by enhancing *C. acnes* abundance or restoring youth-associated microbial functions—may represent a promising strategy for microbiome-based anti-aging skincare interventions.

### 6. Reference

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