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# Oral Sodium Hyaluronate Moisturizes Skin in Healthy Adults: An 8-Week, Randomized, Double-Blinded, Placebo-Controlled Study

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## Abstract

Objective: Few studies have evaluated the effect of oral sodium hyaluronate (SH) ingestion on the moisture content of the superficial stratum corneum. This study aimed to assess whether oral SH ingestion improves the moisture content of the upper layer of the stratum corneum, which is susceptible to changes in environmental humidity, using the Skicon 200EX. Design: Randomized, double-blind, placebo-controlled, parallel-group study. Participants: One hundred healthy Japanese men and women aged 20 - 64 years. Interventions: Oral ingestion of one 119-mg SH or dextrin (placebo) capsule once daily for 8 weeks. Evaluations: Measurement of water content in the superficial stratum corneum of the face and upper extremities using the Skicon 200EX. Results: Overall facial stratum corneum water content changes were significantly higher at 8 weeks in the SH group compared to the placebo group. Conclusions: In healthy Japanese adults, oral SH ingestion improved skin moisture by increasing the stratum corneum water content. Clinical Trial Registration: The study protocol was preregistered with the Clinical Trials Registry System (registration no. UMIN000053322, January 11, 2024).

## Keywords

Hyaluronic Acid, Hyaluronan, Ingestion, Moisturize

## 1. Introduction

Sodium hyaluronate (SH), a glycosaminoglycan ubiquitously found in the connective tissue of vertebrates [1], has a short half-life ranging from 1 to 4 days and

is most abundantly found in skin, which contains 50% of all SH in the body [2]. SH has striking moisturizing properties, and therefore, is a key factor in maintaining skin moisture [3]. Studies show that the SH content of skin gradually declines with age. One study reported that the skin SH content was 25% lower in 75-year-old individuals than in 19-year-old individuals [4]. SH is also used as a cosmetic material to maintain skin moisture, and for anti-aging purposes, and topical SH use has been demonstrated to improve moisturization, wrinkles, and skin elasticity [5] [6]. SH is also used as an ingredient in face masks, exerting its efficacy in a short duration of <25 min [7]. Conversely, prolonged use of face masks may increase skin fragility due to the excessive impairment of skin transpiration [8]. Therefore, cosmetics and face masks are expected to provide temporary moisturization, whereas sustained supplementation of functional ingredients from within the body is a critical approach to maintaining skin health. Besides SH, collagen peptides are also used as functional food ingredients for skin moisturization and need to be consumed in relatively high amounts of up to 10,000 mg/d, which may be a burden in the context of continuous daily consumption [9]. Studies and meta-analyses reveal that the effective SH dose range in humans is relatively low and that the ingestion of 120 mg/d or more SH achieves a skin-moisturizing effect [10]-[14].

In previous studies investigating the efficacy of SH in skin moisturization, the water content of the stratum corneum was measured with a corneometer. The water content of the stratum corneum can be determined with various approaches, such as electrical impedance and skin conductance, measured using high-frequency current, measurement of skin surface resistance to direct current, and measurement using attenuated total-reflectance infrared spectroscopy [15]-[17]. Among these devices, corneometer and Skicon are commercially available, commonly used high-frequency current methods [18]. Kumasaka *et al.* reported that Skicon was more sensitive than corneometer in detecting the degree of skin hydration and that corneometer was valuable in measuring dehydrated skin, such as that experienced by patients with psoriasis [19]. Skicon can detect hydration in layers closer to the skin surface, whereas corneometer can evaluate hydration in layers deeper than the upper layer of the stratum corneum [20]. Previous studies reported that oral SH ingestion led to an increase in water content within the deep layers of the stratum corneum based on evaluation with a corneometer.

Therefore, we conducted a randomized, double-blind, placebo-controlled, parallel-group study including healthy adults to determine the moisturizing function of SH administered via oral ingestion over 8 weeks by measuring the stratum corneum water content near the upper layer of the stratum corneum, which is susceptible to environmental moisture and to horny moisturizing purpose, using Skicon.

## 2. Materials and Methods

### 2.1. Study Design

The study was conducted under the supervision of a physician in a medical clinic

between January and April 2024. One hundred participants were randomly allocated into two groups using the block randomization method to avoid age or sex bias. The allocation information was strictly concealed from the study participants, investigators, test supplement providers, and outcome assessors from the completion of allocation to the end of the study. The placebo and SH groups received one capsule daily for 8 weeks. The stratum corneum water content was assessed before and at the end of 8 weeks after the study initiation. This study was conducted per the Declaration of Helsinki and the Ethical Guidelines for Biological Sciences and Medical Research for Human Subjects (Ethical Guidelines for Medical and Health Research Involving Human Subjects (MEXT·MHLW·METI, Japan). The study was approved by Ethics Committee of Miura Clinic, Medical Corporation Kanonkai (approval number: R2305, approval date: December 21, 2023), and the study protocol was preregistered with the Clinical Trials Registry System UMIN-CTR (UMIN000053322).

Participants included 100 healthy Japanese adult males and female participants, including 39 males and 61 females, with a mean age of 42.1 ± 1.1 years. All participants were confirmed to be healthy by an internal medicine specialist and dermatologist fulfilled the inclusion and exclusion criteria. The inclusion criteria were as follows: 1) Healthy males and females aged 20 - 64 years; 2) Individuals who were aware of dry skin; 3) Those who volunteered and agreed to participate in the study by expressing a good understanding of the purpose and the content of the study after being provided the full explanation. The exclusion criteria were as follows: 1) Individuals with skin diseases such as atopic dermatitis; 2) Those with serious diseases such as diabetes mellitus; 3) Individuals who had undergone gastrointestinal surgery; 4) Individuals with diseases currently being treated; 5) Individuals who are allergic to foods and drugs; 6) Women who wished to become pregnant or were breastfeeding during the study period; 7) Individuals with habitual engagement in strenuous sports and those on a diet; 8) Individuals with extremely irregular sleeping or eating habits; 9) Individuals with excessive exposure to ultraviolet light and daily sunlight during the study period, such as mountain climbing; 10) Individuals attending cosmetic salons for skin care during the study period; 11) Individuals who were unable to discontinue the consumption of health foods or designated quasi-drugs; 12) Individuals who were continuously undergoing some form of medical treatment of the skin affecting the skin conditions, such as laser treatment; 13) Individuals who were considered to be inappropriate for the study by the investigators. The main subject adherences were 1) Lifestyle habits such as diet, drinking, exercise, bedtime, smoking, and use of cosmetics (moisturizing-related cosmetics) before participating did not change significantly during the study period; 2) Excessive exercise, eating, and overeating that deviate from the range of daily life were avoided; 3) The consumption of pharmaceuticals (including topical preparations) and health foods was prohibited; 4) Cosmetics used were prohibited from being changed before participating in the study and during the study period; 5) Attending a cosmetic salon for skin care

purposes was prohibited during the study period; 6) Drinking alcohol and excessive exercise were prohibited until the examination on the day before the examination was completed. Participants who provided written informed consent after a thorough explanation of the study details were enrolled. Sample sizes were determined based on similar prior studies [12]. Briefly, with an $\alpha$ of 0.05 and a power $(1 - \beta)$ of 80%, the required sample size was 84. The sample size was calculated using the Cancer Research and Biostatistics Statistical Tools software (https://stattools.crab.org/).

### 2.2. Study Treatments

In the present study, SH [Hyabest® (S) LF-P; Kewpie Corporation, Japan] and dextrin (Matsutani Chemical Industry, Japan), which was used as placebo based on studies demonstrating its lack of impact on skin moisturization, were administered as capsule supplements with equal taste and appearance (Aliment Industry, Japan). Each SH capsule contained 119 mg SH, confirmed by quantitative analysis using high-performance liquid chromatography.

### 2.3. Measurement of Skin Hydration

A Skicon 200EX device (Yayoi, Japan) was used to assess the stratum corneum water content. Measurements were performed in a room with a constant temperature of 21˚C ± 1˚C and humidity of 50% ± 5%, following the acclimation of the participants in a resting state for 20 min. Two sites were used for baseline and end-of-study measurements, including the cheek and medial forearm. The cheek represented a site with exposed skin, and the forearm represented a site without exposed skin. Seven readings were obtained from each session from each site, and the average of five readings was recorded as the measured value after omitting the minimum and maximum values. Averages of the cheek and forearm values were used to calculate the overall stratum corneum water content.

### 2.4. Statistical Analysis

Data were presented as means ± standard error of the mean, and a P-value of $<0.05$ was considered to indicate statistical significance. After confirming normal distribution using the Shapiro–Wilk test, comparisons of the changes in the stratum corneum water content between the two groups were evaluated using analysis of covariance, with the initial value as the covariate, and paired Student's t-test was used for comparisons of the change in the stratum corneum water content between baseline and the end of the study. The SPSS Statistics software version 29.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

## 3. Results

Participants of the study were enrolled and randomized (**Figure 1**) During the study, two participants in the placebo group and one participant in the SH group dropped out due to personal reasons. Additionally, eight participants had

excessive ultraviolet radiation and daily sun exposure during the study period, including five and three participants in the placebo and SH groups, respectively. Therefore, the complete analysis set included 89 participants, including 44 and 45 participants in the placebo and SH groups, respectively, per protocol set exclusion from the analysis based on the exclusion criteria in the study protocol.

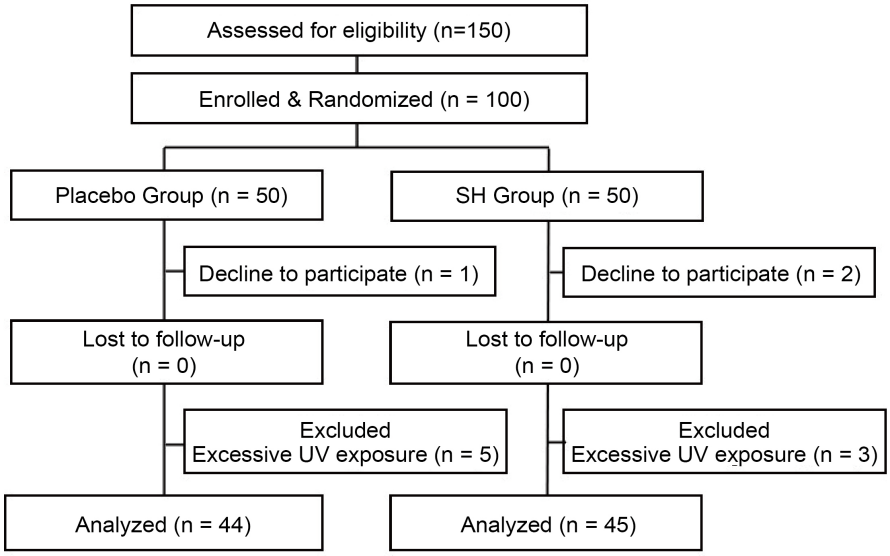


**Figure 1.** Flowchart of subject recruitment and assignment to the study groups.

Table 1 summarizes the background characteristics of the study participants. Age and sex did not significantly differ between the placebo and SH groups. The ingestion rate of the tested compounds, including the SH and placebo capsules, was 98.9%. The dietary and lifestyle habits were comparable between the placebo and SH groups and did not change during the study period.

**Table 1.** Background of the subjects.

| | Placebo<br>Mean ± SE | SH<br>Mean ± SE | P-value |
|---|---|---|---|
| Number of participants | Male: 18<br>Female: 26 | Male: 16<br>Female: 29 | 0.603 |
| Age (y) | 41.5 ± 1.73 | 42.6 ± 1.71 | 0.652 |

P-value of participants is Chi-squared test, and other items are unpaired t-tests.

### 3.1. Skin Hydration

The changes in stratum corneum water content between the baseline evaluation and the end of the study (Δ stratum corneum water content) in the face and upper extremities and the overall change, determined by averaging the facial and upper extremity measurements, are shown in Table 2. Briefly, the overall Δ stratum corneum water content was significantly higher in the SH group than in the placebo group (P = 0.036). In the SH group, the overall stratum corneum water

content significantly increased after 8 weeks of ingestion compared with the baseline ($P < 0.001$). Conversely, a significant change was not observed in the placebo group. Regarding the face, the Δ stratum corneum water content was significantly higher in the SH group than in the placebo group ($P = 0.013$). Compared with the baseline, the facial stratum corneum water content significantly increased after 8 weeks of SH ingestion ($P < 0.001$) but not after eight weeks of placebo ingestion. Conversely, the Δ stratum corneum water content in the upper extremities was not significantly different between the SH and placebo groups. Compared with the baseline, the stratum corneum water content in the upper extremities significantly increased after 8 weeks of SH ingestion ($P = 0.030$), which was not observed in the placebo group.

**Table 2.** Changes from baseline on stratum corneum water content after 8-week ingestion of placebo or SH.

| | | Week 8<br>Mean ± SE | P-value a | P-value b |
|---|---|---|---|---|
| Overall (μS) | Placebo (n = 44) | 10.6 ± 8.81 | 0.036* | 0.236 |
| | SH (n = 45) | 36.7 ± 8.17 | | <0.001††† |
| Face (μS) | Placebo (n = 44) | 7.41 ± 14.2 | 0.013* | 0.606 |
| | SH (n = 45) | 57.5 ± 13.4 | | <0.001††† |
| Arm (μS) | Placebo (n = 44) | 13.7 ± 7.73 | 0.852 | 0.083 |
| | SH (n = 45) | 15.9 ± 7.10 | | 0.030† |

a. P-value (ANCOVA), compared with SH and placebo groups; *p < 0.05 vs. placebo groups; b. P-value (paired t-test) compared with baseline. †p < 0.05, †††p < 0.001 vs. baseline.

### 3.2. Safety

During the study period, no adverse events were reported due to the ingestion of SH or placebo.

## 4. Discussion

In this randomized, double-blind, placebo-controlled, parallel-group study, we found that the daily oral ingestion of 119 mg SH for 8 weeks improved skin moisture in healthy Japanese men and women aged 20 - 64 years based on the change in stratum corneum water content from baseline determined using Skicon.

Impact of oral SH ingestion on skin moisturization was assessed using a corneometer in previous studies, including randomized controlled trials, which demonstrated that SH ingestion led to a significant increase in the stratum corneum water content compared to placebo ingestion [10]-[14]. Corneometer has been known to help determine the dryness of extremely dry skin, such as that occurs in patients with psoriasis [19]. However, the Japanese foods with function claims system prohibit the enrollment of patients with diseases such as atopic dermatitis and require the enrollment of healthy adults. Our findings support

previous studies by revalidating that the improvement in skin moisture with oral SH ingestion could be assessed by determining the stratum corneum water content of healthy skin using Skicon 200EX. Skicon detects hydration near the skin surface, whereas corneometer detects hydration in deeper skin layers [20]. Previous studies confirmed increased stratum corneum water content with corneometer assessments. In the present study, the use of Skicon allowed us to determine that the oral ingestion of SH enhanced skin moisturization in not only the relatively deeper layers but also the upper layer of the stratum corneum, which is susceptible to environmental moisture and its horny moisturizing function. In the present study, the amount of stratum corneum water was increased overall and in the face after 8 weeks; however, the changes, especially those observed in the face, significantly differed between the SH and placebo groups. The observed difference in the Δ stratum corneum water content between the face and upper extremities might be partially due to the anatomically distinct sites and differences in the distribution of sebaceous glands and skin-resident bacteria [21].

The proposed mechanism of action of skin moisturization with oral SH ingestion includes the degradation of SH to 2 - 6 sugars by Enterobacteriaceae, allowing for its partial absorption through the small intestine and subsequent distribution to tissues, including the skin [22]-[24]. Enterobacteriaceae, such as *Prevotella*, which produce hyaluronidases, are ubiquitous in the gut of individuals in Asian and Western countries [25]-[27]. The resorption of SH should not be significantly different among individuals from other races, given the presence of bacteria with hyaluronan-degrading ability in the gut microbiota regardless of race. Furthermore, studies have demonstrated the moisturizing function of SH following its oral ingestion in Italian, Chinese individuals [11]-[13]. Therefore, the findings of our study, including Japanese participants, can be extrapolated to individuals of other races.

In the epidermis of patients with atopic dermatitis, inflammatory cytokines, such as interleukin (IL)-4, IL-13, and IL-25, are highly expressed, whereas the gene expression of filaggrin, which is critical in maintaining epidermal barrier function, is reduced, suggesting that skin moisturization and epidermal inflammation are closely related [28]-[30]. The present study included healthy adults without atopic dermatitis. However, SH has been reported to inhibit inflammation by binding to the intestinal toll-like receptor four and promoting the expression of suppressor of cytokine signaling-3 and the production of IL-10; therefore, suppression of inflammation with SH may improve tight junctions in the skin to have a beneficial impact on the moisturizing function of the skin even in healthy adults [31]. Additionally, studies demonstrating the association between skin inflammation and colitis and that between epidermal hyaluronan metabolism and intestinal immunity [32,33] raise the possibility that the inhibition of inflammation by SH may also impact the intestinal environment, mutually affecting skin health. Previous studies have reported that SH ingestion also affects transepidermal water loss and skin elasticity, suggesting a functional effect on the skin's stratum corneum [12].

The epidermis turnover is approximately 28 days [34], highlighting the need for long-term continuous ingestion of SH to achieve skin moisturization. This study confirms the SH effect during 8 weeks of intake since the epidermis was replaced at least once during this study, which is considered to be long enough for the study period.

The present study has several limitations that should be acknowledged. First, we evaluated the skin-moisturizing function of SH in healthy adults; however, its efficacy and safety in individuals with diseases such as atopic dermatitis or diabetes is yet to be determined. Skin conditions are also intricately associated with various elements, including diet, sleep, fatigue, hormonal balance, sun exposure, dry air, and the epidermal microbiome [35]-[38]. The present study did not fully consider the extent to which the observed effects of SH ingestion were associated with these confounders. Future studies should explore the relationship of the skin-moisturizing function of SH with the skin properties and lifestyle habits of the participants.

In summary, in the present study, we confirmed that oral SH ingestion for 8 weeks increased the water content of the superficial layer of the stratum corneum, which is susceptible to its horny moisturizing function, in healthy Japanese men and women aged 20 - 64 years. These findings suggest that the oral ingestion of SH should be considered a functional food that contributes to maintaining healthy skin.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Fraser, J.R.E., Laurent, T.C. and Laurent, U.B.G. (1997) Hyaluronan: Its Nature, Distribution, Functions and Turnover. *Journal of Internal Medicine*, **242**, 27-33. https://doi.org/10.1046/j.1365-2796.1997.00170.x

[2] Laurent, T.C. and Fraser, J.R.E. (1992) Hyaluronan. *The FASEB Journal*, **6**, 2397-2404. https://doi.org/10.1096/fasebj.6.7.1563592

[3] Papakonstantinou, E., Roth, M. and Karakiulakis, G. (2012) Hyaluronic Acid: A Key Molecule in Skin Aging. *Dermato-Endocrinology*, **4**, 253-258. https://doi.org/10.4161/derm.21923

[4] Longas, M.O., Russell, C.S. and He, X. (1987) Evidence for Structural Changes in Dermatan Sulfate and Hyaluronic Acid with Aging. *Carbohydrate Research*, **159**, 127-136. https://doi.org/10.1016/s0008-6215(00)90010-7

[5] Ito, A. (2014) The Effects of a Hyaluronan Lotion with a Molecular Weight of around 50-110 kDa on the Aged Atrophic Skin. *Journal of Cosmetics, Dermatological Sciences and Applications*, **4**, 150-155. https://doi.org/10.4236/jcdsa.2014.43021

[6] Jegasothy, S.M., Zabolotniaia, V. and Bielfeldt, S. (2014) Efficacy of a New Topical Nano-Hyaluronic Acid in Humans. *Journal of Clinical and Aesthetic Dermatology*, **7**, 27-29.

[7] Wang, Y., Cao, Y., Huang, X., Zhang, M., Hu, J., Li, L., *et al*. (2024) Short-Term Skin Reactions and Changes in Stratum Corneum Following Different Ways of Facial Sheet Mask Usage. *Journal of Tissue Viability*. https://doi.org/10.1016/j.jtv.2024.06.012

[8] Hafeez, Z.H., Zhai, H. and Maibach, H.I. (2006) Hydration Injury. In: Chew, A.-L. and Maibach, H.I., Eds., *Irritant Dermatitis*, Springer-Verlag, 393-396. https://doi.org/10.1007/3-540-31294-3_42

[9] Asserin, J., Lati, E., Shioya, T. and Prawitt, J. (2015) The Effect of Oral Collagen Peptide Supplementation on Skin Moisture and the Dermal Collagen Network: Evidence from an *ex Vivo* Model and Randomized, Placebo-Controlled Clinical Trials. *Journal of Cosmetic Dermatology*, **14**, 291-301. https://doi.org/10.1111/jocd.12174

[10] Kawada, C., Yoshida, T., Yoshida, H., Sakamoto, W., Odanaka, W., Sato, T., *et al*. (2015) Ingestion of Hyaluronans (Molecular Weights 800 K and 300 K) Improves Dry Skin Conditions: A Randomized, Double Blind, Controlled Study. *Journal of Clinical Biochemistry and Nutrition*, **56**, 66-73. https://doi.org/10.3164/jcbn.14-81

[11] Feng, N., Shi, Y., Guo, F. and Guo, X. (2016) Improving Effect of Oral Hyaluronan on Skin Moisture and Its Antioxidation Function *in Vivo*. *Food and Drug*, **18**, 386-390.

[12] Hsu, T., Su, Z., Hsieh, Y., Wang, M., Oe, M., Matsuoka, R., *et al*. (2021) Oral Hyaluronan Relieves Wrinkles and Improves Dry Skin: A 12-Week Double-Blinded, Placebo-Controlled Study. *Nutrients*, **13**, Article No. 2220. https://doi.org/10.3390/nu13072220

[13] Michelotti, A., Cestone, E., De Ponti, I., Pisati, M., Sparta, E. and Tursi, F. (2021) Oral Intake of a New Full-Spectrum Hyaluronan Improves Skin Profilometry and Ageing: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *European Journal of Dermatology*, **31**, 798-805. https://doi.org/10.1684/ejd.2021.4176

[14] Sun, Q., Wu, J., Qian, G. and Cheng, H. (2022) Effectiveness of Dietary Supplement for Skin Moisturizing in Healthy Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Nutrition*, **9**, Article ID: 895192. https://doi.org/10.3389/fnut.2022.895192

[15] Tagami, H., Ohi, M., Iwatsuki, K., Kanamaru, Y., Yamada, M. and Ichijo, B. (1980) Evaluation of the Skin Surface Hydration *in Vivo* by Electrical Measurement. *Journal of Investigative Dermatology*, **75**, 500-507. https://doi.org/10.1111/1523-1747.ep12524316

[16] Campbell, S.D., Kraning, K.K., Schibli, E.G. and Momii, S.T. (1977) Hydration Characteristics and Electrical Resistivity of Stratum Corneum Using a Noninvasive Four-Point Microelectrode Method. *Journal of Investigative Dermatology*, **69**, 290-295. https://doi.org/10.1111/1523-1747.ep12507517

[17] Potts, R.O., Guzek, D.B., Harris, R.R. and McKie, J.E. (1985) A Noninvasive, *in Vivo* Technique to Quantitatively Measure Water Concentration of the Stratum Corneum Using Attenuated Total-Reflectance Infrared Spectroscopy. *Archives of Dermatological Research*, **277**, 489-495. https://doi.org/10.1007/bf00510068

[18] Takahashi, M. (2000) Non-Invasive Techniques to Measure Physiological Properties of the Skin and Their Application to Efficacy Test of Skin Care Products. *Journal of Society of Cosmetic Chemists of Japan*, **34**, 5-24. https://doi.org/10.5107/sccj.34.5

[19] Hashimoto-Kumasaka, K., Takahashi, K. and Tagami, H. (1993) Electrical Measurement of the Water Content of the Stratum Corneum *in Vivo* and *in Vitro* under Various Conditions: Comparison between Skin Surface Hygrometer and Corneometer in Evaluation of the Skin Surface Hydration State. *Acta Dermato-Venereologica*, **73**, 335-339. https://doi.org/10.2340/0001555573335339

[20] Blichmann, C.W. and Serup, J. (1988) Assessment of Skin Moisture. Measurement of Electrical Conductance, Capacitance and Transepidermal Water Loss. *Acta Dermato-Venereologica*, **68**, 284-290.

[21] Arda, O., Göksügür, N. and Tüzün, Y. (2014) Basic Histological Structure and Functions of Facial Skin. *Clinics in Dermatology*, **32**, 3-13. https://doi.org/10.1016/j.clindermatol.2013.05.021

[22] Akazawa, H., Fukuda, I., Kaneda, H., Yoda, S., Kimura, M., Nomoto, R., *et al*. (2023) Isolation and Identification of Hyaluronan-Degrading Bacteria from Japanese Fecal Microbiota. *PLOS ONE*, **18**, e0284517. https://doi.org/10.1371/journal.pone.0284517

[23] Kimura, M., Maeshima, T., Kubota, T., Kurihara, H., Masuda, Y. and Nomura, Y. (2016) Absorption of Orally Administered Hyaluronan. *Journal of Medicinal Food*, **19**, 1172-1179. https://doi.org/10.1089/jmf.2016.3725

[24] Oe, M., Mitsugi, K., Odanaka, W., Yoshida, H., Matsuoka, R., Seino, S., *et al*. (2014) Dietary Hyaluronic Acid Migrates into the Skin of Rats. *The Scientific World Journal*, **2014**, Article ID: 378024. https://doi.org/10.1155/2014/378024

[25] Karlsson, F.H., Nookaew, I. and Nielsen, J. (2014) Metagenomic Data Utilization and Analysis (Medusa) and Construction of a Global Gut Microbial Gene Catalogue. *PLOS Computational Biology*, **10**, e1003706. https://doi.org/10.1371/journal.pcbi.1003706

[26] Kawai, K., Kamochi, R., Oiki, S., Murata, K. and Hashimoto, W. (2018) Probiotics in Human Gut Microbiota Can Degrade Host Glycosaminoglycans. *Scientific Reports*, **8**, Article No. 10674. https://doi.org/10.1038/s41598-018-28886-w

[27] Sato, T., Kamaguchi, A. and Nakazawa, F. (2012) Purification and Characterization of Hemolysin from *Prevotella oris*. *Journal of Oral Biosciences*, **54**, 113-118. https://doi.org/10.1016/j.job.2012.03.002

[28] Howell, M.D., Kim, B.E., Gao, P., Grant, A.V., Boguniewicz, M., DeBenedetto, A., *et al*. (2009) Cytokine Modulation of Atopic Dermatitis Filaggrin Skin Expression. *Journal of Allergy and Clinical Immunology*, **124**, R7-R12. https://doi.org/10.1016/j.jaci.2009.07.012

[29] Hvid, M., Vestergaard, C., Kemp, K., Christensen, G.B., Deleuran, B. and Deleuran, M. (2011) IL-25 in Atopic Dermatitis: A Possible Link between Inflammation and Skin Barrier Dysfunction? *Journal of Investigative Dermatology*, **131**, 150-157. https://doi.org/10.1038/jid.2010.277

[30] Tazawa, T., Sugiura, H., Sugiura, Y. and Uehara, M. (2004) Relative Importance of IL-4 and IL-13 in Lesional Skin of Atopic Dermatitis. *Archives of Dermatological Research*, **295**, 459-464. https://doi.org/10.1007/s00403-004-0455-6

[31] Asari, A., Kanemitsu, T. and Kurihara, H. (2010) Oral Administration of High Molecular Weight Hyaluronan (900 kDa) Controls Immune System via Toll-Like Receptor 4 in the Intestinal Epithelium. *Journal of Biological Chemistry*, **285**, 24751-24758. https://doi.org/10.1074/jbc.m110.104950

[32] Dokoshi, T., Seidman, J.S., Cavagnero, K.J., Li, F., Liggins, M.C., Taylor, B.C., *et al*. (2021) Skin Inflammation Activates Intestinal Stromal Fibroblasts and Promotes Colitis. *Journal of Clinical Investigation*, **131**, e147614. https://doi.org/10.1172/jci147614

[33] Dokoshi, T., Chen, Y., Cavagnero, K.J., Rahman, G., Hakim, D., Brinton, S., *et al*. (2024) Dermal Injury Drives a Skin to Gut Axis That Disrupts the Intestinal Microbiome and Intestinal Immune Homeostasis in Mice. *Nature Communications*, **15**, Article No. 3009. https://doi.org/10.1038/s41467-024-47072-3

[34] Halprin, K.M. (1972) Epidermal "Turnover Time"—A Re-Examination. *British Journal of Dermatology*, **86**, 14-19. https://doi.org/10.1111/j.1365-2133.1972.tb01886.x

[35] Lee, J., Kim, S., Kim, D., Cho, Y. and Kim, K. (2023) The Influence of Dietary Patterns on Skin Bacterial Diversity, Composition, and Co-Occurrence Relationships at Forearm and Neck Sites of Healthy Korean Adults. *Journal of Applied Microbiology*, **134**, lxad211. https://doi.org/10.1093/jambio/lxad211

[36] Misery, L., Morisset, S., Séité, S., Brenaut, E., Ficheux, A., Fluhr, J.W., *et al*. (2021) Relationship between Sensitive Skin and Sleep Disorders, Fatigue, Dust, Sweating, Food, Tobacco Consumption or Female Hormonal Changes: Results from a Worldwide Survey of 10 743 Individuals. *Journal of the European Academy of Dermatology and Venereology*, **35**, 1371-1376. https://doi.org/10.1111/jdv.17162

[37] Misery, L., Reaux-Le Goazigo, A., Morisset, S., Seite, S., Delvigne, V., Cochener, B., *et al*. (2022) Association of Sensitive Eyes with Sensitive Skin: A Worldwide Study of 10,743 Subjects. *Skin Pharmacology and Physiology*, **35**, 148-155. https://doi.org/10.1159/000522056

[38] Fluhr, J.W., Menzel, P., Schwarzer, R., Kaestle, B., Arens-Corell, M., Praefke, L., *et al*. (2022) Acidic Skin Care Promotes Cutaneous Microbiome Recovery and Skin Physiology in an Acute Stratum Corneum Stress Model. *Skin Pharmacology and Physiology*, **35**, 266-277. https://doi.org/10.1159/000526228