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Clinical Evidence of Effects of *Lactobacillus plantarum* HY7714 on Skin Aging: A Randomized, Double Blind, Placebo-Controlled Study

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The beneficial effects of probiotics are now widely reported, although there are only a few studies on their anti-aging effects. We have found that *Lactobacillus plantarum* HY7714 (HY7714) improves skin hydration and has anti-photoaging effects, and in the present study, we have further evaluated the anti-aging effect of HY7714 *via* a randomized, double blind, placebo-controlled clinical trial. The trial included 110 volunteers aged 41 and 59 years who have dry skin and wrinkles. Participants took 1×10^{10} CFU/day of HY7714 (probiotic group) or a placebo (placebo group) for 12 weeks. Skin hydration, wrinkles, skin gloss, and skin elasticity were measured every 4 weeks during the study period. There were significant increases in the skin water content in the face ($p < 0.01$) and hands ($p < 0.05$) at week 12 in the probiotic group. Transepidermal water loss decreased significantly in both groups at weeks 4, 8, and 12 ($p < 0.001$ compared with baseline), and was suppressed to a greater extent in the face and forearm in the probiotic group at week 12. Volunteers in the probiotic group had a significant reduction in wrinkle depth at week 12, and skin gloss was also significantly improved by week 12. Finally, skin elasticity in the probiotic group improved by 13.17% ($p < 0.05$ vs. controls) after 4 weeks and by 21.73% ($p < 0.01$ vs. controls) after 12 weeks. These findings are preliminary confirmation of the anti-aging benefit to the skin of *L. plantarum* HY7714 as a nutricosmetic agent.

Keywords: Anti-wrinkle, *Lactobacillus plantarum*, skin elasticity, skin gloss, skin hydration

Introduction

Skin aging has intrinsic and extrinsic components. Intrinsic aging is related to genetic factors and is a set of physiologic processes related to the passage of time that includes thinning of epidermal and dermal skin layers and increasing dryness [4, 25]. Extrinsic aging is caused by environmental factors such as UV-radiation, or toxins such as cigarette smoke. The extrinsic skin-aging process is characterized by coarse wrinkles, loss of elasticity, epidermal thickening, dryness, laxity, rough appearance, and pigmentation disorder [4, 24]. The most marked age-related changes occur on the face, neck, forearm, and dorsal hands [27]. Extrinsic and intrinsic aging signs are combined with the passage of time and accelerate the aging process mainly at these areas. Although intrinsic and extrinsic aging are triggered by different factors, both involve similar molecular mechanisms [18, 25, 27]. The benefits of probiotics on gut health have been extensively researched [3]. Probiotics alter the composition of the intestinal microbiome, produce antimicrobial substances, and stimulate the body's immune response [16]. There is now accumulating evidence to suggest that probiotics are also able to regulate protective mechanisms in the skin [11]. Recent clinical trials have shown protective effects of dietary supplements containing *Lactobacillus johnsonii* alone [17] or combined with carotenoids

[2] against early UV-induced skin *via* regulation of immune cells and inflammatory cytokines. Other trials have shown that atopic dermatitis and dry skin are relieved by probiotic supplements [6, 9, 12, 20]. Recent experiments in hairless mice have suggested that in addition to regulating immune responses in the skin, orally administered probiotics may exert anti-aging effects by suppressing wrinkle formation and increasing skin elasticity [22, 23]. Furthermore, our recent experiments in hairless mice have shown that oral administration of *L. plantarum* HY7714 (HY7714) exerts anti-photoaging effects through reduction of wrinkle formation and suppression of epidermal thickening [14] and that skin hydration increases in association with increasing ceramide level *via* regulation of serine palmitoyltransferase and ceramidase expression in the mice skin [19]. Based on these findings, in this study, we have evaluated the anti-aging effects of HY7714 in humans *via* a randomized controlled clinical trial. Changes in parameters, including dryness, wrinkles, gloss, and elasticity, were compared in a group of Korean women aged 41 to 59 years with wrinkles and dry skin.

Materials and Methods

Dietary Supplements

HY7714 was isolated from the breast milk of healthy women, and a dietary supplement with 1×10^{10} CFU per packet HY7714 was used as the probiotic agent. The placebo comprised the same product without HY7714.

Study Volunteers

We recruited 129 healthy women aged 41 to 59 years. Inclusion criteria were corneometer-confirmed dry skin (readings below 48 arbitrary units and crow's feet greater than grade 4, as described in the standard operating procedures of Dermapro Ltd., Seoul, Korea). The clinical trial was conducted in accordance with good clinical practice guidelines, and was approved by a local ethics committee (Dermapro Ltd. Institutional Review Board) (DICN14001). All study participants gave written consent to participate in the study after they had been informed of the purpose of and the expectations from the study. Of 129 healthy female volunteers who were initially included in the trial 110 completed the study and were included in the final analysis.

Exclusion Criteria

1. Pregnancy, possible pregnancy, or lactating
2. Medication or a medical history that may affect the skin's response
3. Any active skin disease that may interfere with the study's aim
4. Taking oral or topical steroid medication within 6 months of the start of the study
5. The use of anti-inflammatory, corticoid, retinoid, or laser therapies within 3 months of the start of the study
6. Participation in a previous study without an appropriate intervening period between the studies
7. The presence of a chronic disease, including diabetes, asthma, and high blood pressure
8. The presence of serious renal disorders or hepatic dysfunction
9. The presence of damaged skin in or around the measurement sites, including sunburn, uneven skin tones, tattoos, scars, or other forms of disfiguration
10. History of excessive exposure to sunlight or UV radiation

Study Design

This randomized, double blind, placebo-controlled clinical trial was accepted and conducted by Dermapro Ltd. (Seoul, Korea). This trial was conducted with study participants divided into probiotic ($n = 61$) and placebo ($n = 49$) groups. Participants in the probiotic group consumed 2 g daily of a powder containing HY7714 (1×10^{10} CFU) for 12 weeks. The participants ($n = 49$) in the placebo group consumed an identical powder without HY7714 for 12 weeks. The skin condition of each subject was assessed by dermatologists at baseline and at 4, 8, and 12 weeks after initiation of the study. All participants washed their face and then rested for 30 min in a climate-controlled waiting room (temperature 22 ± 2°C, relative humidity 50 ± 5%) prior to each skin examination in order to maintain homogeneous environmental and measurement conditions as much as possible.

Skin Hydration

Skin hydration was measured in the stratum corneum of the cheek (using the intersection of a vertical line from the corner of the eye and a horizontal line from the tip of the nose as the sampling point), the forearm, and the hand using a corneometer (CM825; Courage and Khazaka Electronic GmbH, Cologne, Germany). This device measures the variation in the electrostatic capacity, which is dependent on the moisture content in the stratum corneum. Measurements are reported in arbitrary units of the electrostatic capacity. Transepidermal water loss from the face, forearm, and hand were measured using a vapometer (SWL4001, Delfin, Finland). This device has a humidity sensor in a cylindrical measurement chamber that records changes in relative humidity inside the chamber during the measurement and automatically calculates transepidermal water loss (g/m^2h). All hydration and water loss measurements were performed three times at each point and the averages were used in the analysis.

Three-Dimensional Imaging for Analysis of Facial Skin Wrinkles

Facial wrinkles were measured using a 3D skin imaging system (PRIMOS Premium; GFMesstechnik GmbH, Teltow, Germany) that makes optical 3D measurements based on digital stripe projections using digital micromirror device technology. This system permits a quantitative analysis of wrinkles at the skin

Table 1. Definition of skin wrinkle parameters.

Parameter	Definition
Ra	Arithmetic average value of profile peaks within the total measuring length
Rmax	Maximum of all peak-to-valley values Rt, measured over the assessment length
Rp	Maximum profile peak height
Rv	Maximum profile valley depth
Rz	Average maximum height of the profile

surface. Skin wrinkles were measured at the outer corners of the left or right eye and analyzed in terms of the parameters described in Table 1.

Skin Gloss

Facial skin gloss was measured by a glossmeter (Delfin Technologies, Kuopio, Finland). This device consists of a 635 nm red semiconductor diode laser and a mirror in a chamber. When the chamber is placed on the skin, skin gloss is measured by the degree of specular or light scattering. Skin gloss was measured three times at the left or right cheek at the point where a vertical line from the pupil meets a horizontal line from the end of the nose, and the average values of the measurements were used in the analysis.

Skin Elasticity

Skin elasticity was measured by using a cutometer (MPA580; Courage and Khazaka Electronic GmbH). The measuring principle is based on suction and elongation. The device generates 450 mbar of negative pressure, and the skin is drawn into the aperture of the probe under constant negative pressure for 2 sec (on-time). The negative pressure is switched off for 2 sec to allow the skin to return to its original shape (off-time). Each measuring cycle consists of three repetitions of on-time/off-time. Skin elasticity was measured at the left or right cheek using the point marked by the intersection of a vertical line from the outer corner of the eye and the horizontal line from the tip of the nose and the R2 value (gross elasticity; Ua/Uf) was analyzed.

Statistical Analysis

All statistical analyses were performed using the SPSS Package Program (IBM, USA). Normality of the distribution of data was assessed using kurtosis and skewness, and prior homogeneity was analyzed using an independent *t*-test. The statistical significance of the differences between two groups was determined using repeated measures ANOVA. A *p*-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 110 (49 placebo group, average age 48.57 ± 4.52 years; 61 probiotic group, average age 49.82 ± 4.96 years) of 129 female volunteers who were included in the study completed it. Of the 19 volunteers who were excluded from the final analysis, 12 were eliminated before the beginning of the study (9 due to laboratory abnormalities and 3 due to personal circumstance) and 7 dropped out after 4 weeks (3 due to personal circumstance, 2 lost to follow-up, and 2 for violation of protocol). Comprehensive questionnaire surveys of the baseline skin characteristics were completed for all volunteers (Table 2). We next evaluated the prior homogeneity between probiotic and placebo groups through statistical analysis of skin parameters (hydration, transepidermal water loss, wrinkle quality, skin gloss, and skin elasticity) at baseline, using an independent *t*-test. As a result, there was no statistically significant difference between the groups, exerting homogeneity of the placebo and probiotic groups (Table 3).

Skin Hydration

To evaluate the effect of HY7714 on skin hydration, we first measured the water content of the face, forearm, and hand of subjects using a proprietary device called the Corneometer CM825. As shown in Fig. 1A, the water content in both groups was significantly increased ($p < 0.001$) from baseline at weeks 4, 8, and 12, and the rates of retention of water content in the face and hand were significantly higher in the probiotic group than in the placebo group ($p < 0.01$, face; and <0.05, hand) at week 12 (Figs. 1B, 1C, and 1D). We used a proprietary device called the Vapometer SWL4001 to measure transepidermal water loss at the same locations. Water loss was significantly decreased from baseline in both groups at weeks 4, 8, and 12 ($p < 0.001$) (Fig. 2A). The magnitudes of the decrease in transepidermal water loss from the face and forearm were significantly larger in the probiotic group compared with the controls at weeks 4 and 12 (face) and weeks 8 and 12 (forearm) (Figs. 2B, 2C, and 2D).

Skin Wrinkles

We examined the effect of HY7714 on facial skin wrinkles

Table 2. Skin characteristics of subjects in the probiotic (n = 61) and placebo (n = 49) groups.

		Probiotic group		Placebo group	
Item	Classification	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Skin type	Dry	39	63.93	27	55.10
	Normal	20	32.79	18	36.73
	Oily	1	1.64	0	0.00
	Dry and oily	1	1.64	4	8.16
	Problematic	0	0.00	0	0.00
Hydration	Sufficient	0	0.00	0	0.00
	Normal	29	47.54	19	38.78
	Deficient	32	52.46	30	61.22
Sebum	Glossy	1	1.64	4	8.16
	Normal	37	60.66	28	57.14
	Deficient	23	37.70	17	34.69
Surface	Smooth	14	22.95	10	20.41
	Normal	45	73.77	32	65.31
	Rough	2	3.28	7	14.29
Thickness	Thin	18	29.51	14	28.57
	Normal	39	63.93	32	65.31
	Thick	4	6.56	3	6.12
Time of UV exposure	Less than 1 h	25	40.98	13	26.53
	1–3 h	29	47.54	31	63.27
	More than 3 h	7	11.48	5	10.20
Sleeping hours	Less than 5 h	8	13.11	2	4.08
	5–8 h	49	80.33	38	77.55
	More than 8 h	4	6.56	9	18.37
Irritability	Yes	2	3.28	2	4.08
	No	59	96.72	47	95.92
Stinging	Yes	0	0.00	0	0.00
	No	61	100.00	49	100.00
Adverse reaction	Yes	0	0.00	0	0.00
	No	61	100.00	49	100.00

over time using a 3D skin imaging system. The results showed improvement from baseline in all wrinkle parameters (Ra, Rmax, Rp, Rv, and Rz) in both groups (Fig. 3). By week 12, decreases in the parameters were 43.48% (Ra), 65.22% (Rmax), 7.80% (Rp), 106.82% (Rv), and 30.75% (Rz). Decreases in Ra, Rmax, and Rv were significantly larger (Ra, Rmax, $p < 0.05$; Rv, $p < 0.01$) in the probiotic group vs. the placebo group at week 12. Representative digital and 3D images of facial skin following week 12 are shown in Fig. 4.

Skin Gloss

We used a proprietary device called the GlossMeter to evaluate the effect of HY7714 on skin gloss. The result showed that skin gloss improved in both groups during the study period, but that the rates of improvement were much better (16.54%, $p < 0.05$) in the probiotic group by week 12 (Fig. 5).

Skin Elasticity

We used a proprietary device called the Cutometer MPA580 to measure skin elasticity. As shown in Fig. 6, skin elasticity increased gradually in both groups during the study period, but the degree of improvement at week 4 (13.17%, $p < 0.05$) and week 12 (21.73%; $p < 0.01$) was significantly higher in the probiotic group compared with the placebo group.

Table 3. Statistical analysis of skin parameters by independent *t*-test.

Item	Site	Levene's test for equality of variances		*t*-Test for equality of means				
		F	Sig.	t	df	Sig.[a]	Mean difference	Std. error difference
Hydration	Face	6.231	0.014	-0.863	94.944	0.390	-0.354	0.410
	Forearm	0.056	0.814	-0.538	108.000	0.592	-0.388	0.721
	Hand	5.365	0.022	-1.816	107.771	0.102	-1.515	0.834
TEWL	Face	2.330	0.130	-0.858	108.000	0.393	-0.309	0.360
	Forearm	0.831	0.364	0.722	108.000	0.472	0.160	0.221
	Hand	2.079	0.152	1.995	108.000	0.109	0.628	0.315
Skin wrinkle	Ra	3.360	0.070	0.297	108.000	0.767	0.193	0.652
	Rmax	0.468	0.495	0.958	108.000	0.340	4.447	4.641
	Rp	1.148	0.286	0.299	108.000	0.765	0.520	1.737
	Rv	0.018	0.893	1.333	108.000	0.185	4.455	3.341
	Rv	1.644	0.203	0.472	108.000	0.638	1.494	3.169
Skin gloss		1.963	0.164	0.001	108.000	0.999	0.001	0.617
Skin elasticity		2.222	0.139	-1.589	108.000	0.115	-0.112	0.007

[a]$p > 0.1$: significant homogeneity between two groups.

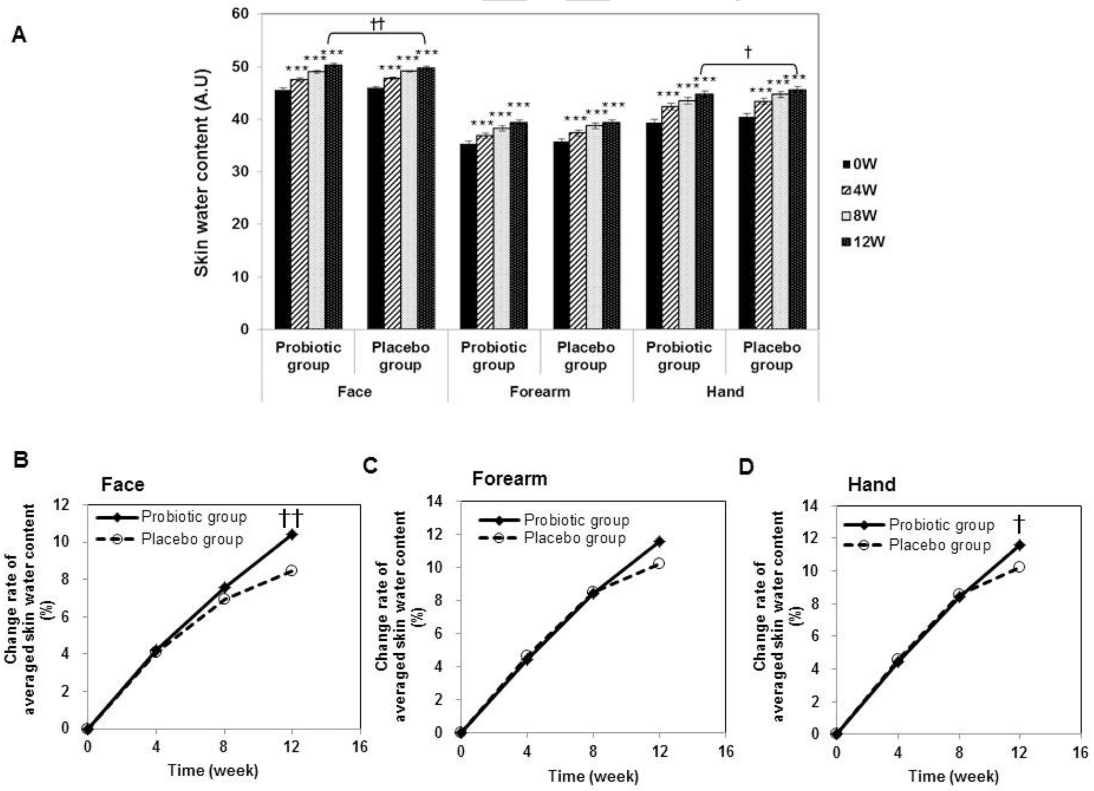

Fig. 1. Changes of skin water content after 12 weeks.

(**A**) The skin water content was measured at three areas (face, forearm, and hand) every 4 weeks from baseline to week 12. (**B**), (**C**), and (**D**) show the average rates of change in water content in the face, forearm, and hand, respectively, in the placebo and probiotic groups. Results are expressed as the mean ± SEM for all subjects. ***$p < 0.001$ vs. baseline; $^{\dagger\dagger}p < 0.001$, $^{\dagger}p < 0.05$ probiotic vs. placebo group.

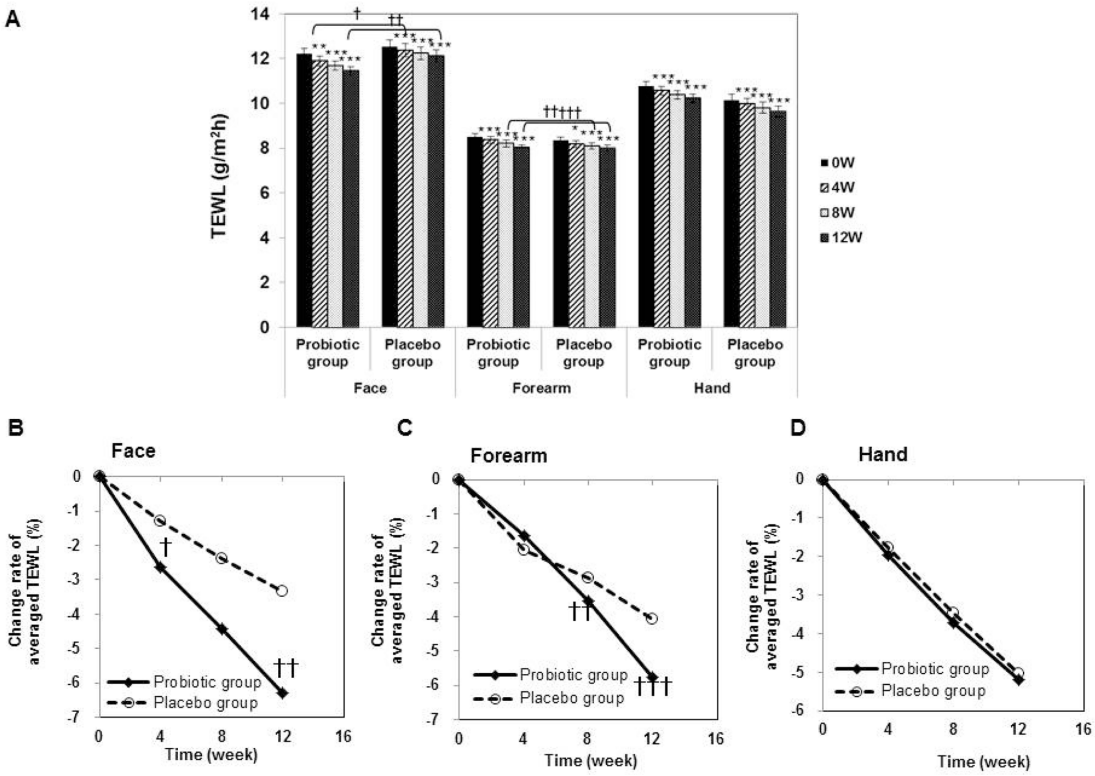

Fig. 2. Changes in transepidermal water loss (TEWL) after 12 weeks.
(**A**) TEWL was measured at three points (face, forearm, and hand) every 4 weeks from baseline to week 12 and average rates of change for the face, forearm, and hand (**B**, **C**, and **D**, respectively) were compared between placebo and probiotic groups. Results are expressed as the mean ± SEM. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ compared with baseline; $^{\dagger\dagger\dagger}p < 0.001$, $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$ probiotic vs. placebo group.

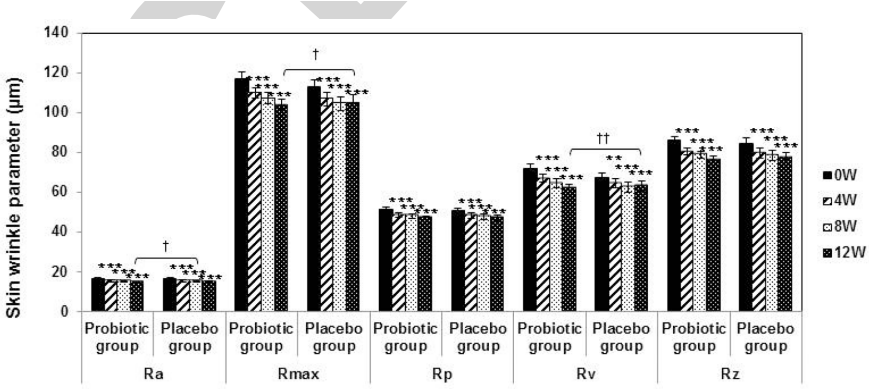

Fig. 3. Changes in skin wrinkle measurements after 12 weeks.
Facial skin wrinkles were measured every 4 weeks from baseline to week 12. Results are expressed as the mean ± SEM for all subjects. ***$p < 0.001$, **$p < 0.01$ vs. baseline; $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$ probiotic vs. placebo group.

Discussion

Daily intake of HY7714 for 12 weeks significantly increased the skin moisture content and reduced signs of facial aging by limiting wrinkles and improving elasticity and skin gloss in women with dry skin and wrinkles. Quantitative and qualitative data supported the multifunctional activity of HY7714. Strain HY7714 was selected on the basis of our earlier studies showing its beneficial effects on skin hydration [19] and its anti-photoaging [14] activities *in vitro*

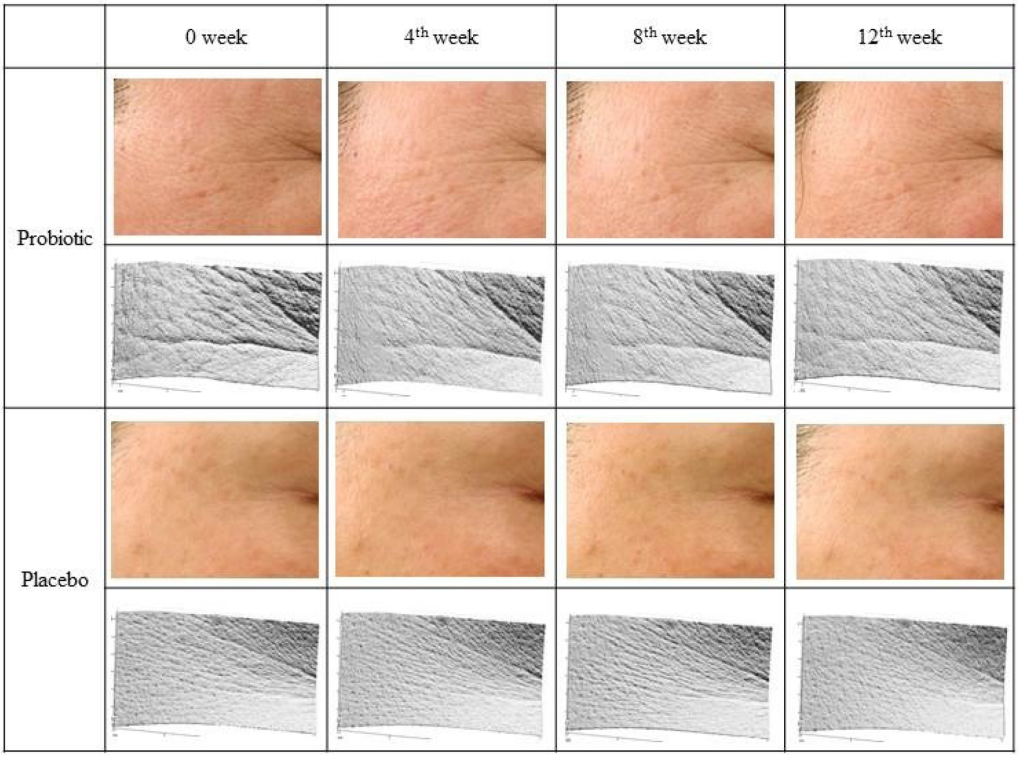

Fig. 4. Images of skin wrinkle changes after 12 weeks.
These images are representative of the overall results in each group. Upper row, digital photographs; Lower row, three-dimensional imaging. The subjects shown are probiotic group Volunteer No. 33 and placebo group Volunteer No. 44.

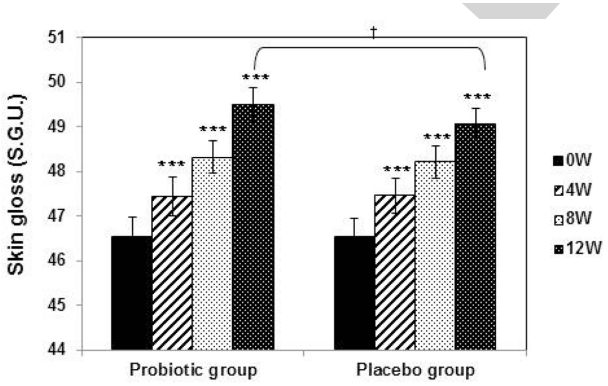

Fig. 5. Changes in skin gloss after 12 weeks.
Facial skin gloss was measured 4 weeks from baseline to week 12. Results are expressed as the mean ± SEM for all subjects. ***$p < 0.001$ vs. baseline; $^{\dagger}p < 0.05$ probiotic vs. placebo group.

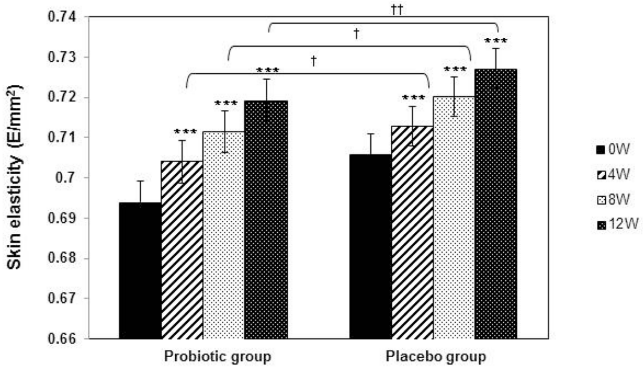

Fig. 6. Changes of skin elasticity after 12 weeks.
Skin elasticity was measured on the face every 4 weeks from baseline to week 12. The results are expressed as the mean ± SEM for all subjects. ***$p < 0.001$ vs. baseline; $^{\dagger\dagger}p < 0.01$, $^{\dagger}p < 0.05$ probiotic vs. placebo group.

and *in vivo*.

Dry skin is caused by an imbalance between the amount of moisture in the stratum corneum and the intercellular lipids, which is a prominent clinical manifestation of the skin-aging process [1]. Because the skin is the outermost part of the body, it is susceptible to effects of environmental factors, including humidity, ultraviolet rays, and temperature. Internal factors such as hormones can also affect skin balance [1, 13]. Since dry skin plays an important role in the formation of fine wrinkles, many people make an effort to moisturize their skin using cosmetics or dietary supplements.

In the present study, we measured both water content and transepidermal water loss at three separate areas (face, forearm, and hand) in order to confirm the probiotic efficacy, and statistically significant improvements were shown in least at two areas (face and hand, water content; face and forearm, water loss). In particular, in the face, water content was significantly increased while the rate of water loss was significantly reduced.

Other changes associated with aging include loss of elasticity, change in skin texture (from smooth to rough), and wrinkles. Wrinkle formation is associated with damage to the structural proteins (collagen and elastin) of the connective tissue of the dermis. Because collagen acts along with elastin to enhance the tensile strength of skin, loss of collagen by attrition or destruction leads to wrinkle formation. There has been much evidence showing that the major alterations in aging skin occur in the dermal extracellular matrix. In young skin (usually under 30 years of age), intact collagen fibrils are abundant, densely packed, and well organized, whereas in very old skin (usually over 80 years), collagen fibers are fragmented and disorganized [7, 8, 18]. Loss of collagen impairs the structural integrity of the skin. Young skin has a reticulated healthy structure, whereas the area of this dense structure is loosened in aging skin [10, 21]. The collagen fibers of the deep dermis become rearranged in parallel with advancing years, which results in deep furrows, skin roughness, and loss of elasticity and skin gloss [15, 21]. In the present study, volunteers in the probiotic group responded positively and noticed subjective reductions in wrinkles during the study period, and the measured parameters of wrinkle formation also showed statistically significant differences between the probiotic group and the placebo group at week 12. Gloss and elasticity were also significantly improved in the probiotic group compared with the placebo group. Taken together, these results suggest that HY7714 reduces skin aging through a variety of pathways.

As we have previously reported, oral ingestion of HY7714 in hairless mice was associated with regulation of the expression of genes related to skin hydration [19]. HY7714 also suppressed UVB-induced signal transduction in fibroblasts [14], which suggests that oral HY7714 may contribute to the molecular control of signaling pathways and gene expression in the skin cells after being absorbed by the intestine. The precise mechanisms of amelioration of skin aging by probiotics should be a topic of continued research in the future.

In conclusion, healthy skin is regarded as an indicator of overall health, and the skin condition is influenced by diet and oral medications [4, 5]. Thus, it is appropriate to consider the potential anti-aging effects of natural dietary supplements [26]. The present study has provided clinical evidence that oral consumption of HY7714 increases skin hydration, alleviates facial wrinkling, and improves elasticity and skin gloss. These results suggest that HY7714 would be a useful anti-aging nutricosmetic agent.

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