Comprehensive wet and dry experiments reveal the anti-aging effects of yeast fermentation extract by influencing the skin microbiome

Yang Fan[1]*; Liu Zhi[2]; Yang Qianqian[2]; Wang Hua[1]; Miao Guo

[1] Mageline Biology Tech Co., Ltd., Wuhan, Hubei, China

[2] Department of Biotechnology, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China

[*] Yang, Fan, 20th Floor Block A Wandazun Universal International Center, Tel: 0086-15201458605, E-mail: yangfanfenix@outlook.com

Abstract

The skin microbiota plays a pivotal role in maintaining skin homeostasis and barrier function. Previous studies have suggested that yeast fermentation extract contributes to slowing down skin aging, yet its underlying mechanisms remain elusive. This study aims to investigate the impact of yeast fermentation extract on facial skin of Chinese women through clinical trials and metagenomic sequencing, as well as its influence on the skin microbiome. By identifying key microbial strains affected by yeast fermentation extract and further analyzing the correlation between skin microbiota and skin physiological parameters, we seek to elucidate the potential mechanisms through which yeast fermentation extract may delay skin aging.

Keywords: yeast fermentation extract; skin aging; skin barrier; skin microbes; metabolomics; cultureomics

Introduction

The skin, being the body's largest organ, primarily serves as a protective barrier, facilitates sweating, and senses cold, heat, and pressure variations. Enveloping the entire body, the skin

shields various tissues and organs from physical, chemical, and pathogenic microbial threats[1]. The skin microbiota constitutes a complex system composed of diverse microorganisms, epidermal cells, various secretions, and microenvironments. Together, they establish the skin's initial biological barrier, playing crucial physiological roles[2]. Skin microbiota serves as a crucial component of the cutaneous ecosystem. These microorganisms metabolize lipids secreted by sebaceous glands, inhibiting the growth of pathogenic microbes. Simultaneously, they degrade skin metabolites, nourish the skin, slow the aging process, and reduce wrinkles. Furthermore, skin microbiota can produce or induce the host to generate antimicrobial peptides, hindering the proliferation of pathogenic microorganisms. They also break down free fatty acids derived from sebum, purifying the skin environment. Collectively, skin microbiota establishes a mutually stable and harmonious biological barrier on the skin surface[3, 4].

Previous studies have shown that the yeast broth can help delay skin aging and improve facial skin conditions[5]. Yeast fermentation extract is a key ingredient in many commercial skincare products, such as the popular SK-II Facial Treatment Essence, which incorporates a filtrate of a pseudoalteromonas ferment extract, bestowing whitening, moisturizing, and antioxidant properties. Estée Lauder's yeast fermentation extract, the second fermentation yeast extract, represents a premium yeast essence used for skincare, delivering effects such as whitening, anti-aging, and skin nourishment. The yeast fermentation extract utilized in this study is a filtrate of yeast/rice fermentation product, enriched with over 90 natural skin-nourishing components like polysaccharides, minerals, and small-molecule amino acids. It serves as an exceptional all-inclusive skin tonic. Presently, research on this yeast fermentation extract has delved into its efficacy on a cellular level, focusing on whitening, skin enhancement, anti-inflammation, anti-aging, and barrier repair. Its crucial component, Alpha-KG, can activate cell proliferation, promoting skin hydration and barrier function[5]. Furthermore, our previous research has demonstrated that in clinical trials, skincare water containing this type of yeast fermentation extract can enhance skin barrier function and reduce extrinsic photoaging. This

yeast fermentation extract represents a raw material for cellular-level skin cosmetic efficacy, presenting as a promising anti-aging cosmetic ingredient. Nevertheless, there is scarce research and reporting on the impact of yeast fermentation extract on skin microbiology.

This study explored the influence of yeast fermentation extract on skin microbiota and its role in delaying skin aging, unveiling potential mechanisms through which skin microbiota may contribute to retarding aging. This serves as a crucial avenue for a deeper understanding of the anti-aging mechanisms of yeast fermentation extract and may offer further insights into finding superior anti-aging methodologies.

Materials and Methods

Subject recruitment and acquisition of skin physiological parameters

A total of 83 healthy subjects were recruited in this study. All subjects were divided into two groups: test group and control group in a 2:1 ratio. The test group used the facial skin intervention for 12 weeks, and the control group used the facial skin intervention for 12 weeks. Skin clinical parameters were evaluated for all participants participating in the study at these 4 time points before the intervention, 4 weeks after the intervention, 8 weeks after the intervention, and 12 weeks after the intervention. Briefly, skin moisture content was measured in the subjects using Corneometer instrument, percutaneous moisture loss data were collected using Tewameter, skin elasticity testing using Cutometer@MPA580, density and thickness using skin ultrasound instruments Ultrascan UC22. The research involving human subjects conformed to the ethical principles for medical research as stated in the Declaration of Helsinki, and all subjects had given their informed consent to participate.

Sample collection

Participants' microbiome was collected based on previous reports[6]. In brief, sterile swabs were washed with 50 mM Tris of buffer (1 mM EDTA [pH 8.0] and 0.5% Tween-20) with a left

skin area ~2*2 cm^2 at least 50 times. The obtained samples were then centrifuged at 13,000 rpm for 10 min at 4℃. The supernatant was collected and the value was 80℃ stored for skin metabolite detection and analysis and the precipitate for skin microbial gene sequencing.

DNA extraction and library preparation

Genomic DNA was extracted from as-treated skin samples using the QIAamp PowerSkin Pro DNA Kit (QIAGEN, USA, 51804). The quantity of purified DNA samples was detected by a Qubit 3.0 fluorometer (Thermo Fisher, USA, Q33217) using the Qubit dsDNA HS Assay Kit (Thermo Fisher, USA, Q32854). The integrity of DNA samples was assessed by electrophoresis on 1% agarose gels. After DNA extraction, 300 ng of high-quality DNA sample was added into a new PCR tube and mixed with KAPA Frag Enzyme and KAPA Frag buffer (KAPA Biosystems, USA, KK8514). The tube was incubated in a thermocycler for 10 mins at 37 °C and proceed immediately to the next step. In the same tube in which enzymatic fragmentation was performed, end repair and A-tailing reaction mix was assembled. After incubated for 30 min at 65 °C, adapter stock, ligation buffer and DNA ligase were added into the tube and incubated for 15 min at 20 °C. Post-ligation cleanup and size selection were performed using the VAHTS DNA Clean Beads (Vazyme, China, N411-03), and the clear supernatant was transferred to a new tube. After library amplification and post-PCR cleanup, the final DNA library was transferred to a new tube for further QC steps: a) the size distribution of the libraries was analyzed by Agilent 2100 High Sensitivity DNA kit (Agilent, USA, 43513) on an Agilent 2100 bioanalyzer (Agilent, USA, G2939BA), b) the libraries were quantified using the StepOnePlus RT PCR System (Thermo Fisher, USA, 4376600).

Metagenome sequencing and data preprocessing

Whole genome shotgun sequencing was carried out on the Illumina Novaseq 6000 platform (Illumina, USA) to obtain 150 bp forward and reverse paired-end reads. Trimmomatic v0.39[7]

was used to preprocess the raw data and get the clean data. The processing steps are as follows: 1) Remove the low-quality reads which contain more than 35bp 'N' bases (default quality threshold value ≤ 15); 2) Remove reads which shared the overlapped sequences above a certain portion with adapter (default length of 10 bp). Then, clean data were blast to the human genome reference database GRCh38 using Bowtie2[8] to filter out the reads that originate from host. The parameters are as follows: --end-to-end, --more-sensitive, -I 200, -X 500. Species abundance information was obtained from species annotation using metaphlan4[9], and metabolic pathway abundance information was obtained by functional annotation using humann3[10].

Diversity analysis

The diversity analysis of microbiome was performed on the species level respectively[11]. α-diversity was evaluated by the Shannon index, Simpson Index, Richness index, Pielou index through R package vegan. The richness was evaluated by the number of species, the evenness was calculated through Shannon index divided the logarithm base 2 of richness. For analysis the microbiome β-diversity, R package vegan was used to perform the principal coordinate analysis (PCoA) and permutational multivariate analysis of variance test (PERMANOVA, 999 tests) based on Bray-curtis distance.

Identification of key facial microbiota characteristics

We used the rank sum check analysis of the bacteria with significant differences before and after the intervention, and calculated the change multiple of the relative abundance of microorganisms before and after the intervention, and finally found the skin bacteria with | log2 (fold change) |> =1 and P value <0.05. For the bacteria found, we calculated the pearson correlation coefficients for bacteria and skin physiological parameters with significantly increased abundance after the intervention.

Statistical analysis

Statistical analysis was performed by using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set as $P < 0.05$.

Results

Changes in the clinical skin parameters

To investigate the influence of yeast broth on facial skin aging and the skin microbiome, we designed a clinical trial involving a total of 83 participants, with 81 completing the trial. All participants were divided into two groups, one undergoing a 12-week intervention (addition group of 55 individuals) and the other using standard yeast wash (non-addition group of 28 individuals). Skin physiological parameters were collected at four time points: pre-intervention, 4 weeks post-intervention, 8 weeks post-intervention, and 12 weeks post-intervention.

We employed a corneometer to measure the skin moisture content of the participants. As illustrated in Figure 1, we observed the skin moisture content at W4, W8, and W12 compared to W0 (Figure 1A); no differences were found between W0, W4, W8, and W12 (Figure 2A). This outcome indicates that skincare products with and without the addition of yeast broth can both improve the skin moisture content of the participants, with the yeast broth yielding better improvement, as evidenced at the 8-week mark post-intervention. By collecting percutaneous water loss data, we found that both the added group and the W0 group; there was no difference in the W0 group (Figure 1B); and the percutaneous water loss in the W4, W8 and W12 during the added group (Figure 2B). This result indicates that both skin care products with and without yeast fermentation broth could reduce percutaneous water loss in subjects, but that the yeast fermentation broth improved better, and this difference was reflected in week 4 after intervention.

The skin elasticity test probe Cutometer@MPA580 was used to determine the elastic performance of the skin. Two indexes were collected. R2 is the total elasticity, and F4 is the

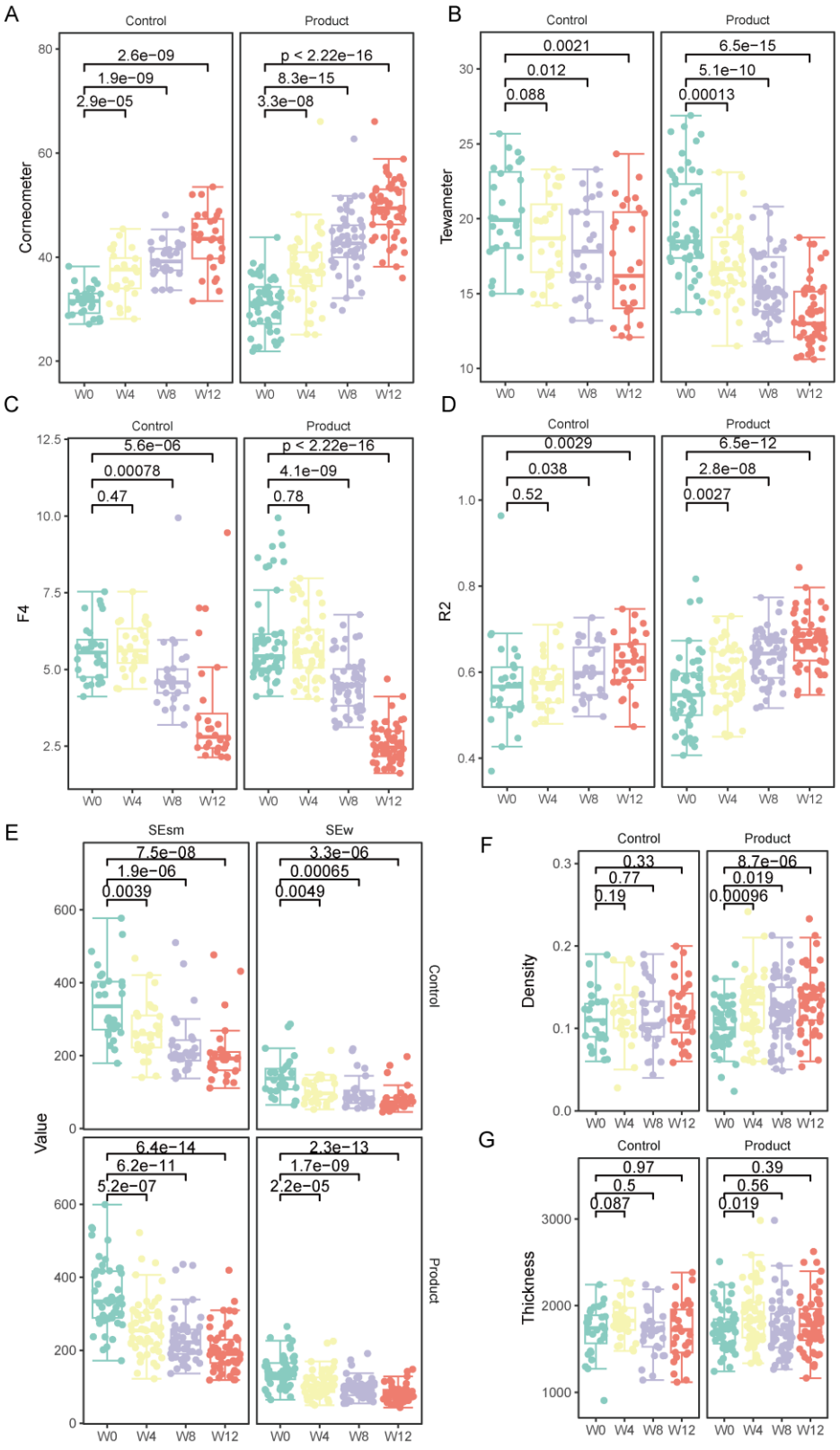

Figure 1: Changes in clinical skin parameters over time. A, skin moisture content; B,

percutaneous moisture loss; C, changes in skin firmness F4; D, changes in total skin elasticity R2; E, skin indicates changes in texture; F, changes in skin density; G, changes in skin thickness. Control: No added group; Product: Add group; W0: before intervention; W4:4 weeks after intervention; W8:8 weeks after intervention; W12:12 weeks after intervention.

firmness index. The closer the R2 data is to 1, the better the elasticity is, and the smaller the F4 value, the better the firmness is. The results showed that the skin elasticity R2, except no difference in W4 (Figure 1D); there was no difference in skin elasticity R2 in W8 and W12 (Figure 2D). For skin firmness, those in the group decreased significantly except for skin elasticity F4 in W0, W4 and W8 (Figure 1C); in W12, skin elasticity F4 decreased significantly compared with W4 without the added group (Figure 2C). This result indicated that skin care products with and without yeast broth could both improve the skin elasticity performance of the subjects, but the yeast broth improved better, and this difference was reflected in week 8 post-intervention.

In addition, we used the skin indication texture test VisioScan VC20 to analyze the skin surface texture, and collected two indicators. SEw is the skin wrinkle index. The larger the data, the more obvious the wrinkles are, and SEsm is the skin smoothness index. The larger the value, the smoother the skin is. The results showed that the skin wrinkle index SEw, compared with the W0 period, there was no difference between W0, W4, W8 and W12 (Figure 1E). For skin slip index SESm, SESm decreased significantly compared with W0; similarly, there was no difference between SESm with and without W0, W 0, W4, W8 and W12 (Figure 2E). The results indicate that skincare products with and without the addition of yeast fermentation extract can both improve the subjects' skin texture, but the enhancement effect of yeast fermentation extract is suboptimal.

Furthermore, using the Ultrascan UC22, we measured skin density and thickness. We found no significant difference in skin density between the non-addition group and the addition

group at the start of the trial (W0); however, there was a notable increase in skin density at W4, W8, and W12 compared to W0 in the addition group as well as no difference in skin density between W0, W4, W8, and W12 in the non-addition group (Figure 1F, G). This outcome suggests that only skincare products containing yeast fermentation extract can elevate the subjects' skin density.

In relation to skin thickness, we observed a substantial increase in skin thickness at W4 compared to W0; this upward trend continued between W4, W8, and W12. Interestingly, there was no difference in skin thickness between the addition group and the non-addition group at W0, W4, W8, and W12 (Figure 2F, G). This result indicates that the skin care products did not improve the skin thickness of the subjects. Overall, the intervention with the addition of a yeast fermentation fluid can be effective in improving the aging of the facial skin, especially in terms of skin moisture content, transcutaneous moisture loss, skin elasticity, and skin firmness.

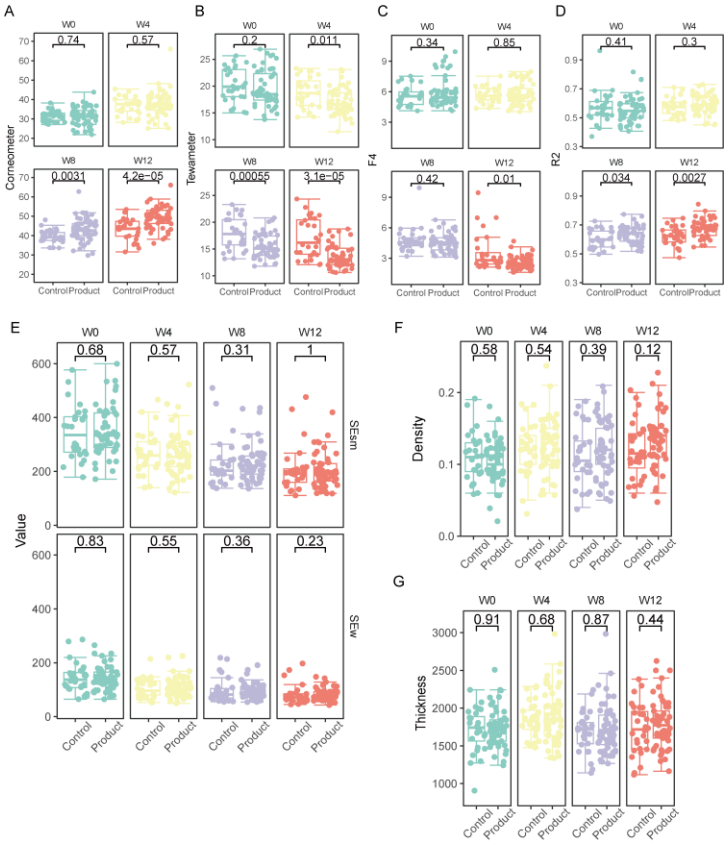

Figure 2: Changes in clinical skin parameters between the added and no added groups. A, skin

moisture content; B, percutaneous moisture loss; C, changes in skin firmness F4; D, changes in total skin elasticity R2; E, skin indicates changes in texture; F, changes in skin density; G, changes in skin thickness. Control: No added group; Product: Add group; W0: before intervention; W4:4 weeks after intervention; W8:8 weeks after intervention; W12:12 weeks after intervention.

Changes in the skin microbiome

Initially, we compared the changes in skin microbiome diversity at two time points. The results reveal that there was no significant difference in α-diversity between the addition group and the non-addition group at pre-intervention and at 12 weeks post-intervention (Figure 2A). However, β-diversity demonstrated significant differences between pre-intervention and 12 weeks post-intervention (Figure 2C). Furthermore, we compared the changes in skin microbiome diversity at the same time points between the different groups. Prior to the intervention and at 12 weeks post-intervention, there was no significant difference in α-diversity between the addition group and the non-addition group (Figure 2B). Additionally, no significant difference in β-diversity was observed between the addition group and the non-addition group at pre-intervention and 12 weeks post-intervention (Figure 2D). Both interventions significantly affected the skin microbiome's β-diversity, but had no significant impact on α-diversity.

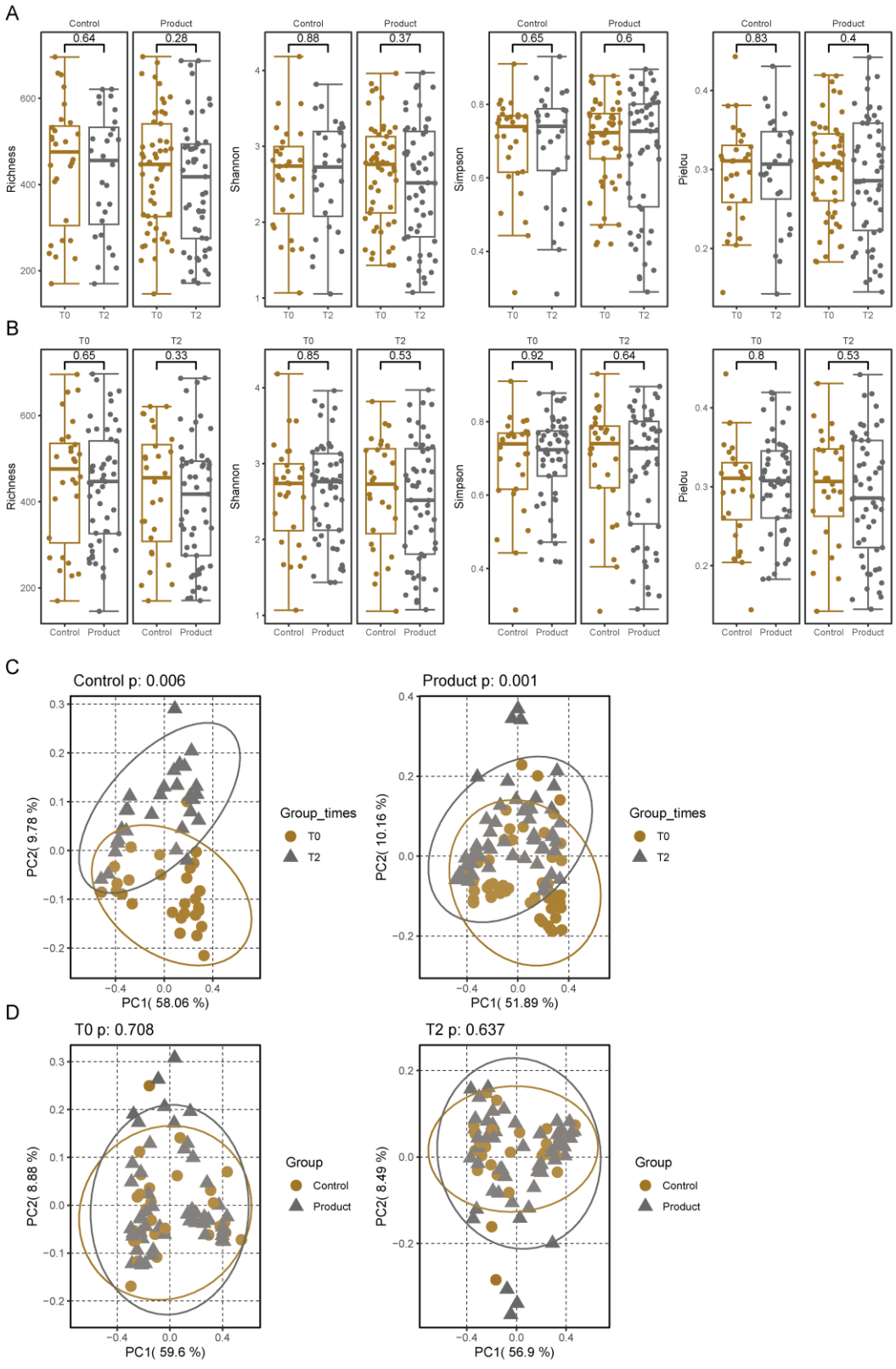

Figure 3: Changes in the skin microbiome diversity. A, changes before and after the α diversity

intervention; B, changes in α diversity in the added and no added groups; A, changes before and after the β diversity intervention; B, changes in β diversity in the added and no added groups.

Moving forward, we delved into the variations in species composition at the phylum, genus, and species levels. At the phylum level, the predominant phyla observed were Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes. There were no significant changes in species composition observed before and after the intervention (Figure 4A, B). On the genus level, the primary genera identified were Cupriavidus and Nocardia. Before and after the intervention, there was an increase in the relative abundance of Propionibacterium, while a decrease was noted in the abundance of this genus (Figure 4C, D). At the species level, the key species included Propionibacterium acnes, Nocardia xinjiangensis, Nocardia vagus, and Nocardia kunmingensis. Our findings revealed that post-intervention, there was an increase in the relative abundance of Propionibacterium acnes and a decrease in the abundance of Propionibacterium acnes in both the addition and non-addition groups (Figure 4E, F).

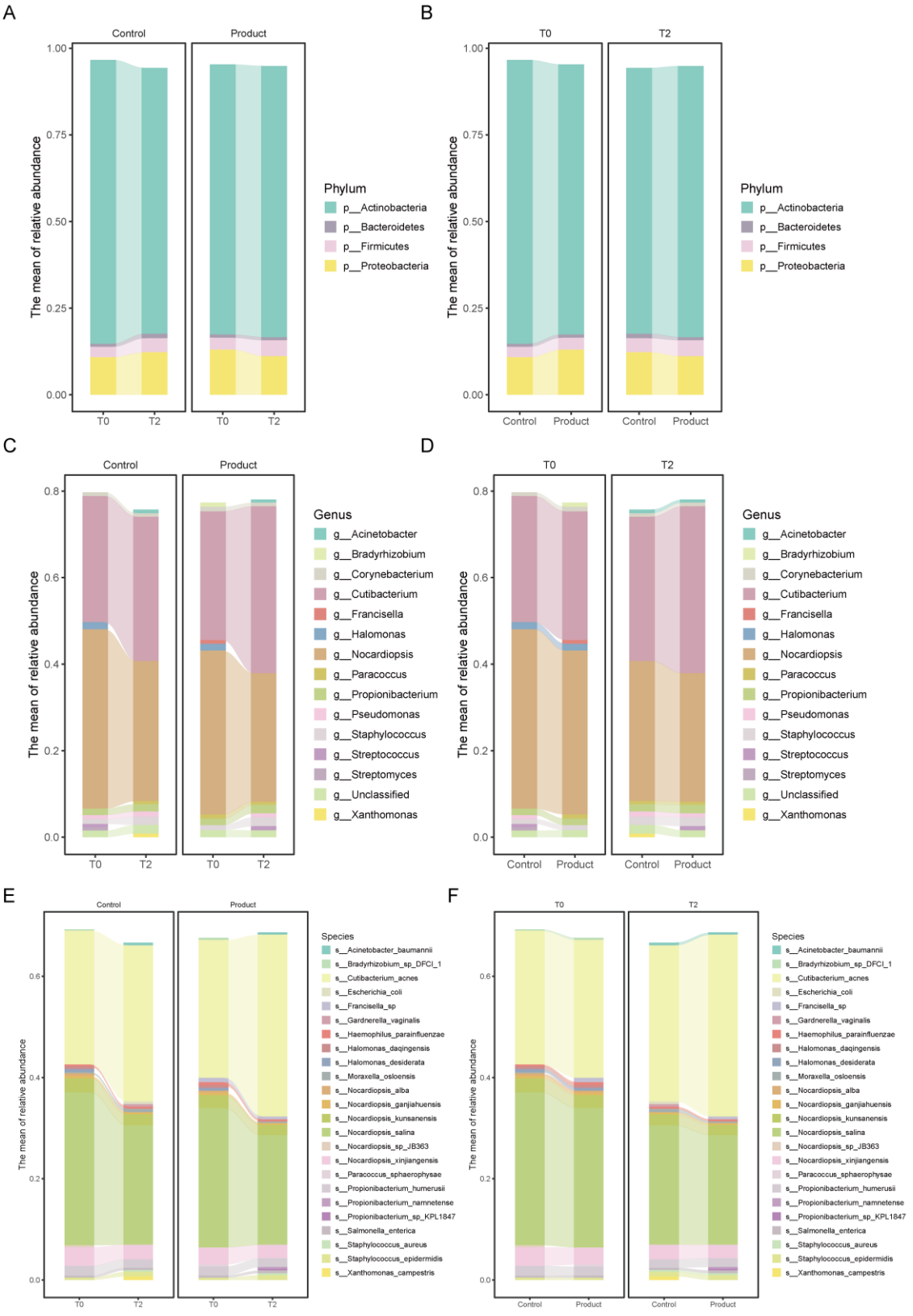

Figure 4: Changes in the skin microbiome composition. A and B, changes in species

composition at phylum level; C and D, changes in species composition at genus level; E and F, changes in species composition at species level.

Furthermore, we also compared the significant changes in bacteria before and after intervention in different groups. In the addition group, we identified a total of 80 bacterial species with |log2(fold change)| >= 1 and a P-value < 0.05. The bacteria with increased relative abundance were Pseudomonas oryzihabitans, Microbacterium sediminis, Thermus thermophilus, Massilia yuzhufengensis, Achromobacter xylosoxidans, and Staphylococcus epidermidis. In all of the bacteria that increased significantly after the intervention, S. epidermidis had the highest relative abundance at the T2 period (Figure 5A). In the non-addition group, we discovered 70 strains with |log2(fold change)| >= 1 and a P-value < 0.05. The bacteria with increased relative abundance were Microbacterium sediminis, Anoxybacillus flavithermus, Massilia yuzhufengensis, Haematobacter massiliensis, Acinetobacter baumannii. In all of the bacteria that increased significantly after the intervention, A. baumannii showed the highest relative abundance during the T2 period (Figure 5B).

Finally, we analyzed the correlation of significantly different bacterial and skin physiological parameters. First, in the addition group, we analyzed the correlation of the 36 bacteria and 12 skin physiological parameters with significantly increased abundance during the T2 period. The results showed that Thermus thermophilus and Thermus scotoductus were significantly associated with Tewameter, Deinococcus wulumuqiensis and Deinococcus radiodurans were significantly associated with SEw, and Brevundimonas naejangsanensis was significantly positively correlated with Density (Figure 6A). In the non-addition group, we analyzed the correlation of 27 bacteria and 12 skin indicators significantly increased during T2, and we found that Acinetobacter ursingii was significantly negatively associated with Tewameter, and Brevundimonas diminuta was significantly negatively associated with SESm (Figure 6B).

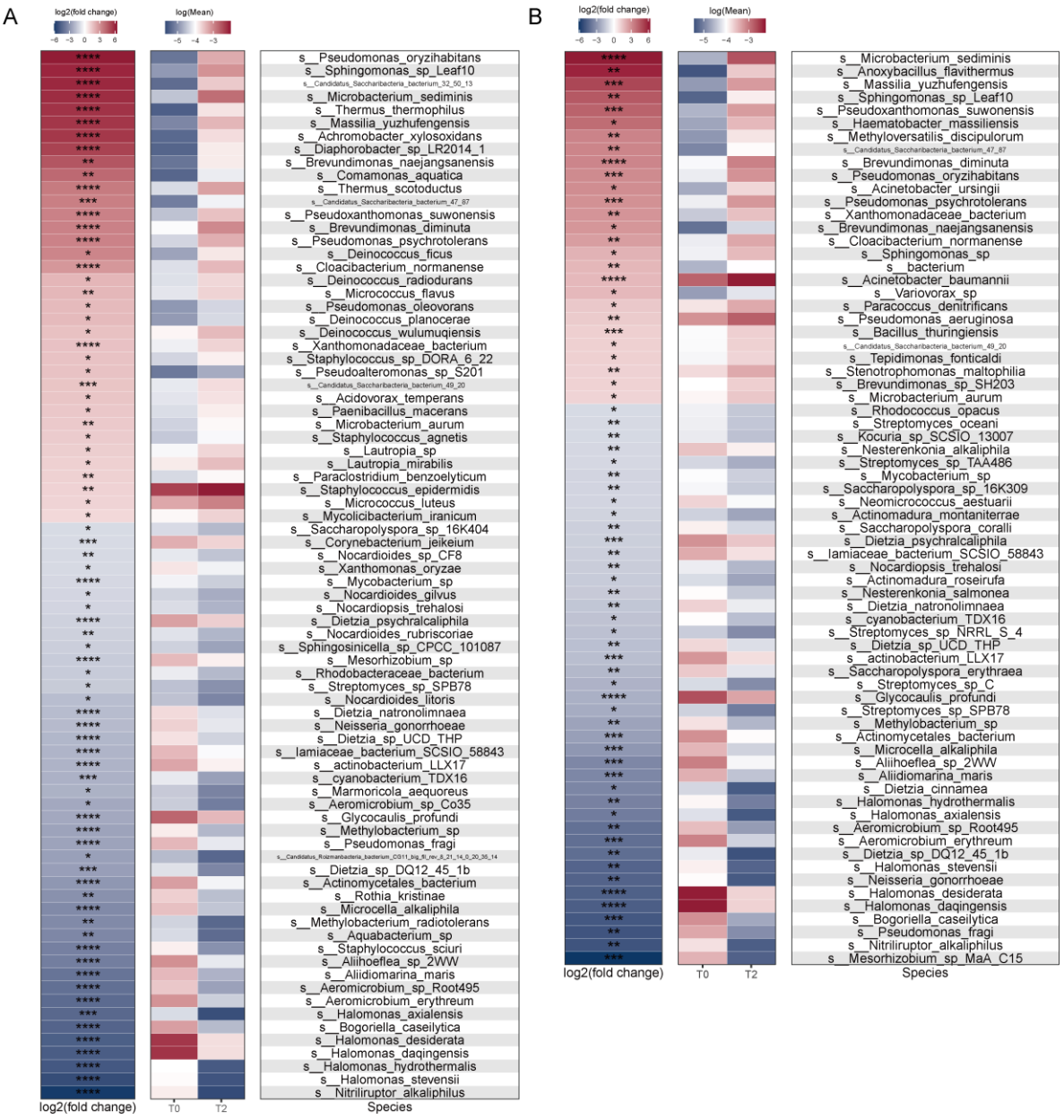

Figure 5: significantly changed skin microorganisms before and after the intervention. A, skin microorganisms that changed significantly before and after the addition group; B, skin microorganisms that significantly changed before and after the addition group. The first column is the fold change, red indicates increased relative abundance in intervention and decrease in blue. The second column is the mean relative abundance of bacteria at the T0 and T12 time points. T0: before intervention; T2:12 weeks after intervention. *，p<0.05；**，p<0.01；***，p<0.001；****，p<0.0001.

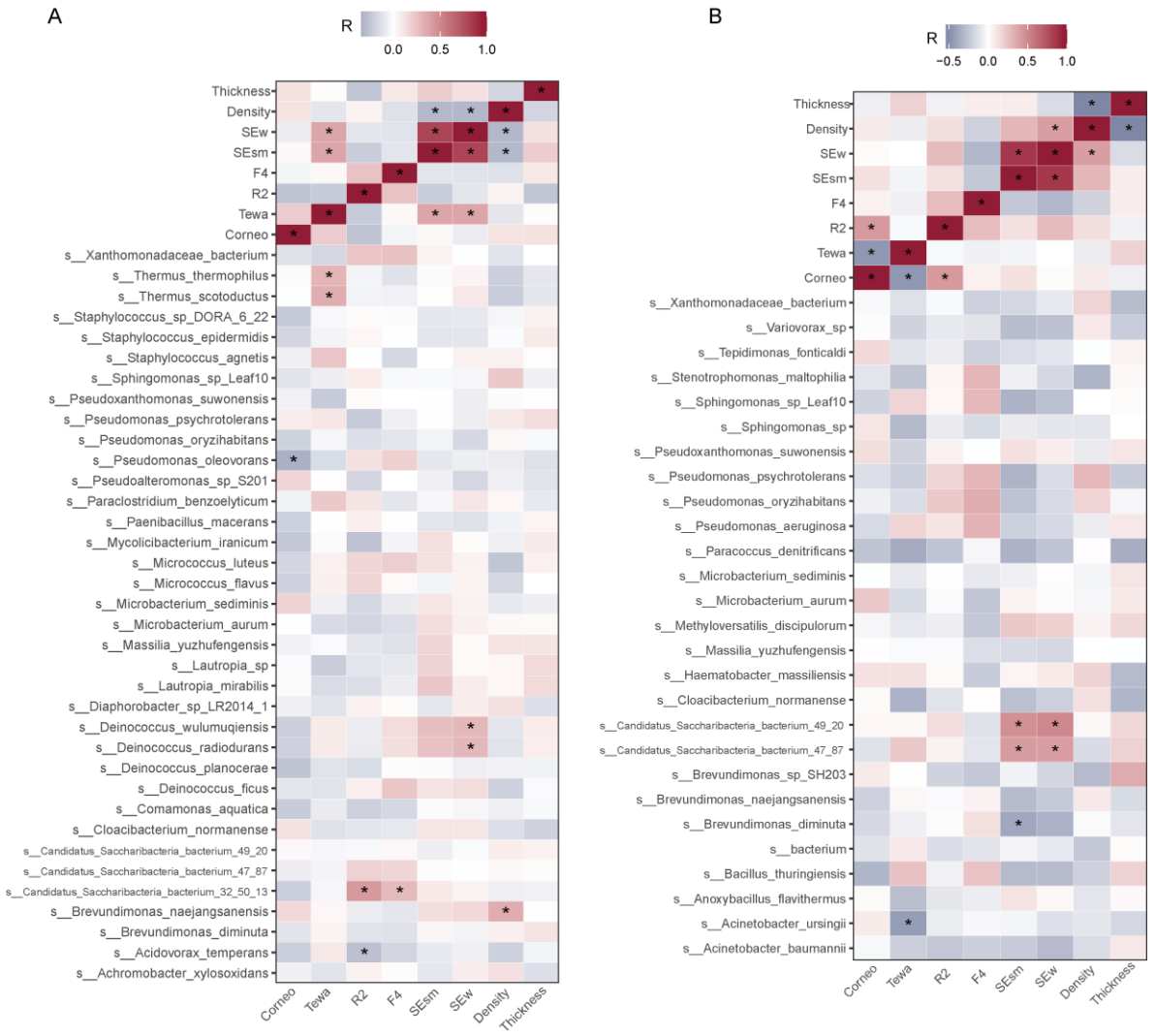

Figure 6: Correlation of significantly increased bacterial and skin physiological parameters after the intervention. A, Correlation of 36 bacteria and 12 skin physiological parameters with significantly increased abundance in the added group; B, 27 bacteria and 12 skin physiological parameters with significantly increased abundance in the non-added group. Red shows a positive correlation and blue is a negative correlation. *, $p<0.05$.

Discussion

Aging is a problem that we have to face. In life, early childhood and old age will show significant skin differences. Both time and environmental factors can cause skin aging[12].

Currently, a variety of methods have been developed to resist the aging of the skin, such as UV protection, topical drugs, injection fillers, and so on[13]. Yeast fermentation filtrate can be incorporated into a variety of skincare products. Our previous research has also indicated that the use of skincare products containing yeast fermentation filtrate can effectively delay skin aging. In recent years, with advancements in the field of the skin microbiome, there has been a growing focus on how the skin microbiome influences human skin health and disease. However, the impact of yeast fermentation filtrate on the skin microbiome remains unclear, and there has been limited research on this subject. This article primarily investigates the effects of skincare products enriched with yeast fermentation filtrate on the skin microbiome.

To explore the effects of yeast fermentation broth on facial skin aging and skin microbiome, we designed this clinical experiment. According to the data of skin physiological parameters, the skin care products supplemented with yeast fermentation broth can effectively improve the state of the facial skin of the subjects, which is consistent with the results of our previous study[5]. Compared to skincare products without yeast fermentation filtrate, those containing it exhibit superior improvements in skin hydration, transepidermal water loss, and skin elasticity. The enhanced outcomes in these skin parameters within the group featuring the addition of yeast fermentation filtrate are likely attributed to the presence of the yeast broth, an essential component in skincare. In future research, we can further focus on the influence of yeast fermentation filtrate on skin hydration, transepidermal water loss, and skin elasticity.

In addition to enhancing facial skin condition, we observed profound alterations in the composition and structure of the skin microbiome regardless of the presence of yeast fermentation filtrate in skincare products. However, the specific skin microbes altered by the intervention differed between the group with the additive and the group without it. In the group with the additive, we noted a significant increase in the abundance of epidermal Staphylococcus after intervention, a change not observed in the non-additive group. Research indicates that epidermal Staphylococcus can modulate immunity, maintain skin barrier function,

and inhibit the colonization of bacterial pathogens[14]. It may be an important factor in regulating facial skin status in yeast fermentation broth. Moreover, Deinococcus wulumuqiensis and Deinococcus radiodurans increased significantly after the intervention, which are known for their ionizing radiation resistance and contain numerous genes involved in natural product synthesis and oxidoreductase activity[15]. Deinococcus wulumuqiensis and Deinococcus radiodurans were significantly and positively correlated with SEw, and both bacteria can be associated with improved skin surface texture, which may be related to their ionising radiation resistance properties. In addition, we found that Brevundimonas naejangsanensis, which was significantly increased after the additive group intervention, was significantly positively correlated with Density. Previous reports of surface Brevundimonas naejangsanensis with the ability of Ochratoxin[16].This holds significant implications for food safety and warrants further investigation into its role in skin aging. In essence, yeast fermentation filtrate exerts a profound influence on skin microbiota, and its intervention enhances the abundance of certain probiotic bacteria in the skin, aiding in their anti-aging effects.

Conclusion

This study validated the efficacy of yeast fermentation filtrate in delaying skin aging among Chinese women through clinical trials. Analyzing skin physiological parameters before and after intervention at different time points, we found that wheat extract effectively improves facial skin hydration, trans-epidermal water loss, skin elasticity, skin surface texture, skin density, and skin thickness, particularly showing notable improvements in skin hydration, trans-epidermal water loss, skin elasticity, and skin density. These findings indicate that wheat extract serves as a beneficial skincare ingredient for skin aging improvement, enhancing the anti-aging effects of the skincare products. Furthermore, the intervention of skincare products also influences the structure and function of the skin microbiota. The results suggest that skincare product intervention significantly impacts the beta diversity of the skin microbiome.

Post-intervention, there was a significant increase in the abundance of specific probiotic bacteria in the group with the additive. In the intervention group, the abundance of epidermal Staphylococcus aureus significantly increased, contrasting with no increase in the non-intervention group. This elevation in the abundance of these probiotic bacteria in the intervention group may contribute to the anti-aging effects of the wheat extract. In sum, this study explored the influence of yeast fermentation filtrate on facial skin aging and the skin microbiota. Further experiments are needed to validate the results of this study. In subsequent research, we will verify the anti-aging effects of different strains and investigate the impact of yeast fermentation filtrate on the in vitro growth of these strains. Furthermore, we aim to further validate the potential mechanisms of the core efficacy strains in in vivo anti-aging experiments. This will aid in further understanding the anti-aging mechanisms of yeast fermentation filtrate, enabling the development of skincare products with superior anti-aging effects.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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