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Collagen peptide supplementation improves skin aging parameters and modulates the gut–skin microbiota: a randomized, double-blind, placebo-controlled trial

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ABSTRACT: Collagen peptides (CP) have been reported to stimulate dermal collagen synthesis through modulation of the gut microbiota in animal studies, but human evidence remains limited. This study aimed to comprehensively evaluate the clinical efficacy and multi-omics effects of oral CP in humans, integrating skin, gut, and metabolomic analyses. In this 8-week randomized, double-blind, placebo-controlled trial, 70 healthy women (39.2 ± 8.8 years) received CP, a collagen–elastin peptide mixture (MP), or placebo. Significant improvements from baseline were observed in facial wrinkle, texture, hydration, and elasticity in the CP and MP groups (wrinkle: 12.00% and 14.83%; texture: 15.21% and 16.87%; hydration: 4.36 and 4.48 units; elasticity: both 0.10 units), whereas no significant improvements were detected in the PL group ($P < 0.05$). No significant differences were observed between the CP and MP groups, while more pronounced improvements were detected in women older than 40 years. CP supplementation increased the abundance of *Cutibacterium* and Lactobacillus in the skin microbiota, and altered skin metabolite profiles, characterized by elevated N-undecanoylglycine and Pro-Pro. CP also increased the abundance of gut Roseburia and *Faecalibacterium*, enhanced the Gut Microbiome Wellness Index, and enriched amino acid metabolism. Skin improvements correlated with the abundance of *Roseburia intestinalis*, indicating a gut–skin link. These findings indicate that oral collagen peptides represent a promising strategy for improving skin aging by modulating gut–skin microbiota and metabolomic profiles.

Keywords: Skin aging; Collagen peptides; Elastin peptides; Skin microbiota; Skin metabolome; Gut microbiota

1. Introduction

Skin aging has garnered increasing attention in recent years, particularly among women, due to its significant impact on physical appearance, self-esteem, and overall quality of life[1]. In women, this process is generally considered to begin around the age of 30, with early signs such as reduced elasticity and the emergence of fine wrinkles[2]. Skin aging has been reported to accelerate after the age of 42, resulting in more

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noticeable dermatological changes, and tends to plateau around 47 years of age[3]. Given these age-related changes, there is a growing need for evidence-based skincare strategies tailored to middle-aged women. The development of effective interventions to improve skin condition during this critical life stage is therefore of notable public health significance.

Among potential anti-aging interventions, collagen peptides (CP) have gained considerable interest as functional dietary ingredients[4]. CP are known to improve skin elasticity and reduce wrinkle formation by promoting dermal collagen synthesis. Beyond their direct dermal effects, emerging evidence suggests that CP may influence skin physiology through the gut–skin axis, a bidirectional communication network involving the gut microbiota[5]. Notably, CP have been proposed to exert prebiotic-like effects, modulating gut microbial composition and metabolic activity[6]. Our previous work demonstrated that CP not only directly enhanced collagen synthesis but also activated the TGF-β signaling pathway via gut microbiota modulation[7]. However, due to fundamental differences between the intestinal microbiota of rodents and humans, findings from animal models may not fully translate to human physiology[8,9]. Consequently, validating CP-induced microbiota changes in human populations is essential for confirming their biological relevance and underlying mechanisms of action.

In addition to collagen degradation, skin aging is also characterized by a progressive decline in elastin content[10]. Reduced elastin levels contribute to skin sagging, diminished elasticity, and increased fragility. Recent studies have shown that elastin-derived peptides, obtained through enzymatic hydrolysis of elastin, can improve wrinkle appearance and enhance skin hydration[11]. Importantly, collagen and elastin are the two most abundant and functionally complementary structural proteins within the dermal extracellular matrix. Collagen primarily provides tensile strength and structural support, whereas elastin confers elastic recoil and tissue resilience[12,13]. During skin aging, the synthesis of both proteins declines concomitantly, while their degradation and structural disorganization increase, resulting in cumulative impairments in skin firmness, elasticity, and overall mechanical stability[14,15]. Although supplementation with collagen peptides or elastin-derived peptides alone has been shown to improve specific skin parameters, strategies targeting a single extracellular matrix component may not sufficiently address the multifactorial deterioration of dermal architecture associated with aging. From a biological standpoint, the concurrent targeting of collagen and elastin degradation may therefore represent a more comprehensive approach to improving age-related skin changes. However, whether combined supplementation with collagen and elastin peptides provides additive or complementary benefits beyond collagen peptides alone remains largely unexplored, particularly in human intervention studies.

Concurrently, increasing attention has been directed toward the skin microbiota, which plays a critical role in maintaining skin barrier integrity and immune homeostasis[16]. Changes in the skin microbiota may reflect alterations in skin physiological status, and the overgrowth of certain potentially pathogenic taxa has been implicated in skin aging–related processes[17]. Beyond microbial composition, the skin metabolome, comprising bioactive small molecules, plays a central role in linking host physiology to microbial function

and maintaining skin homeostasis[18]. These metabolites not only reflect the biochemical environment of the skin but also actively participate in antioxidant defense, immune modulation, and barrier maintenance[19]. Together, the skin microbiota and metabolome form an intricate, interactive network that critically shapes skin health and aging trajectories.

In this study, we aimed to comprehensively evaluate the effects of oral supplementation with collagen peptides alone or in combination with elastin peptides, with the aim of determining whether the combined supplementation offers complementary benefits on skin condition and related microbial and metabolic profiles in healthy adult women. By integrating assessments of skin physiological parameters with multi-omics analyses, including the skin microbiome, skin metabolome, and gut microbiota, this study sought to elucidate the potential mechanisms underlying the observed dermatological improvements and to identify key microbial and metabolic mediators associated with skin aging–related changes.

2. Methods

2.1 Study design and ethical approval

This study was designed as a randomized, double-blind, placebo-controlled clinical trial conducted at the Institute of Nutrition and Health, Qingdao University, from March to May 2023. All participants provided written informed consent before undergoing any study-related procedures. The study protocol was reviewed and approved by the Ethics Committee of the Medical Department of Qingdao University (Approval No. QDU-HEC-2022168) and registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR2300069162).

2.2 Eligibility criteria

Eligible participants were healthy Chinese women aged 30–55 years who agreed to comply with the study protocol throughout the intervention and had no history of dermatological conditions listed in the exclusion criteria.

Exclusion criteria included: presence of acute or chronic skin diseases in the test area (such as eczema, psoriasis, or atopic dermatitis); known allergy to study ingredients; planned or ongoing exposure to intense ultraviolet radiation (e.g., outdoor work, tanning); major systemic or immune-related diseases; use of systemic or topical medications affecting skin physiology (such as corticosteroids or retinoids) within 30 days; consumption of nutritional supplements or cosmetics with skin-active ingredients within 14 days before the study; tattoos, cosmetic procedures, or topical treatments near the test site; injectable aesthetic treatments (e.g., hyaluronic acid, collagen, botulinum toxin) within the past two years; or a history of severe allergic reactions to cosmetic or dermatological products.

2.3 Randomization and blinding

Participants were randomly assigned to one of three groups in a 1:1:1 ratio using a computer-generated randomization list created with SPSS software (v23.0) by an independent laboratory technician not involved

in the study. The study products were coded and packaged identically by an independent coordinator to ensure allocation concealment. Both participants and study investigators were blinded to group assignments throughout the intervention period. The randomization code was kept confidential until all data collection and analyses were completed.

2.4 Sample size estimation and study procedures

Based on previous literature[20], we anticipated mean wrinkle improvement rates of 2%, 8%, and 11% across the three groups. Assuming a pooled standard deviation (σ) of 7.8%, a one-way analysis of variance with $\alpha = 0.05$ and statistical power $(1-\beta) = 0.80$ yielded a required sample size of approximately 15 participants per group (total n = 45). To account for an expected dropout rate of ~20%, the target enrollment was increased to approximately 19 participants per group. Ultimately, 75 participants were randomly assigned into three groups (n = 25 per group): placebo group, CP group, and mixed peptides (MP) group.

Participants were instructed to consume the assigned product twice daily, once in the morning and once before bedtime, on an empty stomach, with one packet per dose. The test product was dissolved in warm water prior to consumption. Throughout the 8-week intervention, they were also instructed to maintain their habitual diet, skincare routines, and physical activity levels without major changes. No interim analyses were planned or conducted, and no formal stopping guidelines were specified, as the intervention was of short duration and considered minimal risk. Assessments were conducted at baseline and at week 8 under standardized environmental conditions (22 ± 1 ℃; 45–55% relative humidity) following a 10-minute acclimatization period. Skin parameters were measured, and samples including cheek swabs, tape-stripped stratum corneum films, and fecal specimens were collected for further analysis.

2.5 Product composition

All test products, including the collagen peptide preparation, the mixed peptide preparation, and the placebo, were provided by Fine (Hunan) Biotechnology Co., Ltd. (China), a food-grade manufacturer operating in accordance with national food safety regulations. Routine food safety and quality inspections were conducted prior to use (inspection certificates: 080901GTYL, 080902GTYL, 080903GTYL), confirming that all products met the required standards. Each was formulated as a solid beverage powder with identical appearance, taste, and texture, achieved by using the same excipients to standardize sweetness and flavor profiles across groups, thereby maintaining blinding integrity throughout the trial. The collagen peptide preparation contained 1 g of tilapia-derived collagen peptide per packet. The mixed peptide preparation consisted of 1 g of tilapia collagen peptide and 45 mg of bonito-derived elastin peptide per packet. The placebo contained 1 g of maltodextrin as the primary ingredient. Based on previous human studies in which daily collagen peptide intake in the range of 1.65–2.5 g and elastin peptide intake of approximately 100 mg have been reported[11,21-22], the daily dose of collagen peptides was set at 2 g in the present study, and the mixed peptide formulation provided 90 mg of elastin peptides per day.

2.6 Safety assessment

To evaluate the safety of collagen peptide supplementation, venous blood samples were collected from participants in a fasting state (after an overnight fast) at baseline and after the 8-week intervention. Hematological parameters were measured using the Sysmex XT-4000i automated hematology analyzer, while clinical chemistry, hepatic, and renal function markers were assessed using the Hitachi 7180 automated biochemical analyzer. In addition, participants were instructed to report any adverse events throughout the study, and their health status was monitored at each study visit to ensure the safety and tolerability of the intervention.

2.7 Baseline data collection

Before the intervention began, all participants completed a series of study-related questionnaires and assessments. The questionnaires collected basic demographic information, including age, frequency of late-night sleeping, and exercise habits. To evaluate subjective skin conditions, participants performed a self-assessment using a Visual Analog Scale (VAS) questionnaire, rating various aspects of their skin quality. Additionally, body weight, skeletal muscle mass, and other physiological parameters were measured using the Beijing Donghuayuan Body Composition Analyzer (DBA-510).

2.8 Measurement of skin hydration, sebum, and elasticity

Skin hydration, sebum, and elasticity were measured at both baseline and after the 8-week intervention period. Assessments were performed on both the left and right cheeks, and the mean values were used for analysis to ensure representativeness and reduce site-specific variability. All measurements were conducted using devices from Courage+Khazaka Electronic GmbH (Cologne, Germany). Specifically, skin hydration was measured with the Corneometer® CM 825, sebum secretion was assessed using the Sebumeter® SM 815, and skin elasticity was evaluated with the Cutometer® Dual MPA 580. For elasticity, the R7 parameter, representing biological elasticity, was used as the key indicator. This parameter is calculated as the ratio of immediate retraction to total deformation (Ur/Uf), reflecting the skin's ability to return to its original shape after deformation. In this study, R7 was selected as the representative index of skin elasticity due to its sensitivity to aging and hydration status. All measurements were performed in a controlled environment, as described above. Participants were instructed to avoid washing their face or applying any skincare or cosmetic products for at least 12 hours prior to each measurement session. Additionally, measurements were scheduled at the same time of day for each individual to reduce the effects of circadian variation and enhance intra-subject consistency across timepoints.

2.9 VISIA skin analysis

Facial skin characteristics were assessed using the VISIA®-6 skin analysis system (Canfield Scientific, USA) at both baseline and after the 8-week intervention. Standardized digital images of the participants' frontal facial region were captured under controlled conditions, including consistent lighting, camera distance,

and head positioning. Each participant's chin and forehead were stabilized using the built-in positioning apparatus to ensure image consistency across timepoints. The VISIA system quantitatively evaluates 8 key parameters relevant to facial skin condition: spots, wrinkles, texture, pores, ultraviolet (UV) spots, brown spots, red areas, and porphyrins. These measurements provide a comprehensive profile of facial skin condition, including both surface-level and subsurface features. All assessments were conducted under the same environmental and procedural conditions as described before.

2.10 Collection of skin and fecal samples

Skin and fecal samples were collected at both baseline and after the 8-week intervention. To minimize external interference, participants were instructed not to wash their face or apply any skincare or cosmetic products on the morning of sample collection. For skin microbiota analysis, sterile swabs pre-moistened with phosphate-buffered saline were gently rubbed over both cheeks for 10 seconds with consistent pressure and frequency. For skin metabolite analysis, D-Squame® adhesive tapes (Clinical & Derm, USA) were applied to the cheek with a pressure applicator for 5 seconds, and two tapes per side were collected using sterile forceps. Both swabs and tapes were transferred into sterile centrifuge tubes and stored at −80 ℃ until analysis. Fecal samples were collected by participants using sterile fecal collection tubes and also stored at −80 ℃ for gut microbiota analysis.

2.11 16S rRNA amplicon sequencing of skin and gut microbiota

The procedures for microbiota analysis, including DNA extraction, PCR amplification, and sequencing, are detailed in the Supporting Information. Raw sequencing data have been deposited in the NCBI Sequence Read Archive under the following BioProject accession numbers: PRJNA1348445 for the skin microbiome and PRJNA1268169 for the gut microbiome.

2.12 Untargeted metabolomics

Untargeted metabolomic analysis of skin samples was conducted by Shanghai Bioprofile Technology Co., Ltd. (Shanghai, China). Metabolites extracted from D-Squame® adhesive tape samples were analyzed using ultra-high-performance liquid chromatography coupled with a Q Exactive™ Plus Orbitrap mass spectrometer (UHPLC-Q Exactive™ Plus MS; Thermo Fisher Scientific, USA). Detailed procedures, including sample preparation, chromatographic conditions, and data processing, were provided in the Supporting Information.

2.13 Statistical analysis

Descriptive statistics were conducted to summarize baseline demographic characteristics and lifestyle factors across the three groups. Categorical variables were presented as frequencies and percentages. The Chi-square test was used for comparisons, while Fisher’s exact test was applied when expected frequencies were small. Continuous variables were expressed as medians and interquartile ranges (IQRs) and compared using

the Kruskal–Wallis test. These analyses were used to assess the baseline comparability among groups. Given the low attrition rate (< 10%) and the assumption that missing data were completely at random, a complete-case analysis was performed without imputation. Sensitivity analyses confirmed the robustness of the results. Inferential statistical analyses were conducted using GraphPad Prism 9.3 and SPSS. For comparisons between two groups, the Wilcoxon signed-rank test was used for paired samples. For comparisons involving three groups, the Kruskal–Wallis test followed by pairwise Mann–Whitney U tests was applied, with p-values adjusted using the Benjamini–Hochberg false discovery rate (FDR) method. A p-value of < 0.05 was considered statistically significant. Subgroup analyses were performed using the dplyr R package (v1.1.4). Microbiota analyses, including alpha and beta diversity assessments, were conducted using the microeco R package (v0.3.3)[23]. The Gut Microbiome Wellness Index (GMWI) was calculated using the GMWI-webtool (https://gmwi-webtool.github.io/)[24]. GMWI uses two predefined sets of microbial taxa, classified as health-prevalent and health-scarce, which were established based on large-scale human gut microbiome datasets. For each sample, the collective relative abundance of health-prevalent taxa (ψMH) and health-scarce taxa (ψMN) was computed, and GMWI was calculated as: GMWI = log10(ψMH / ψMN). Untargeted metabolomic profiling was carried out with the Integrated Platform for Metabolomics Data Mining 2.0 (IP4M)[25]. Spearman's rank correlation was used to explore associations among variables, performed with the psych R package (v2.4.3). For microbiota and metabolomic data, as well as correlation analyses, p-values from univariate comparisons were adjusted for multiple testing using the FDR method.

3. Results

3.1 Recruitment of trial participants and baseline characteristics

Among the 117 individuals screened, 75 met the eligibility criteria and were enrolled in the study, and 70 female participants completed the intervention and were included in the final analysis (age = 39.2 ± 8.8 years, Fig. 1). No significant differences in anthropometric measurements or basic information were observed among the three groups at baseline (Table 1).

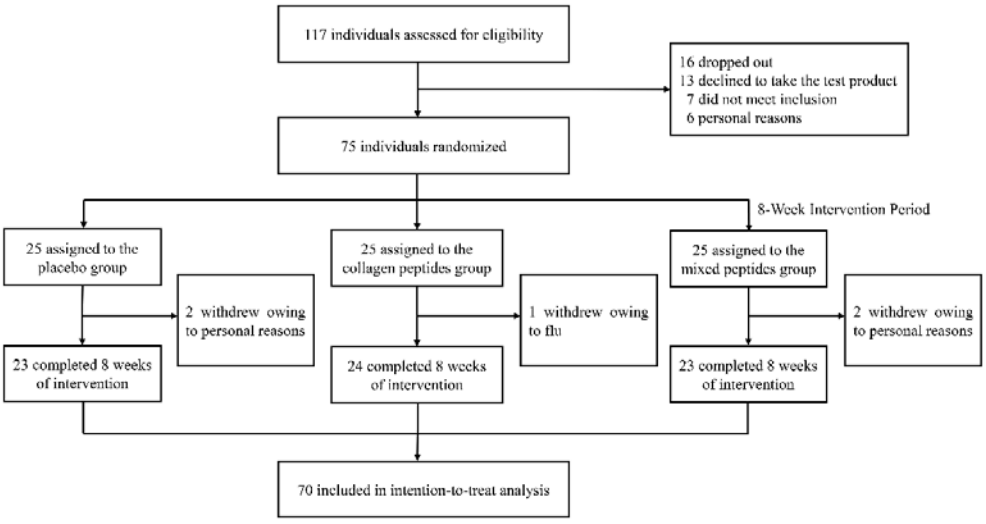


Fig. 1. Flow chart of subject recruitment.

Table 1 Baseline characteristics of the volunteers

Items	PL (n = 23)	CP (n = 24)	MP (n = 23)
Age (years)	38.00 ± 13.00	37.00 ± 9.50	37.00 ± 9.00
Weight (kg)	60.60 ± 9.60	59.40 ± 8.28	61.50 ± 10.90
BMI (kg/m2)	22.50 ± 3.30	21.70 ± 3.90	22.00 ± 3.40
SMM (kg)	22.90 ± 2.00	22.25 ± 3.25	23.60 ± 3.20
Frequency of alcohol consumption			
Never	16 (69.57%)	16 (66.67%)	17 (73.91%)
Once a week	7 (30.43%)	8 (33.33%)	6 (26.09%)
Frequency of intake of foods with added sugar			
Hardly	2 (8.70%)	3 (12.50%)	4 (17.39%)
Once or twice a week	13 (56.52%)	13 (54.17%)	12 (52.17%)
Three to four times a week	3 (13.04%)	3 (12.50%)	2 (8.70%)
Five to six times a week	4 (17.39%)	2 (8.33%)	4 (17.39%)
Almost everyday	1 (4.35%)	3 (12.50%)	1 (4.35%)
Frequency of late bedtimes			
Hardly	2 (8.70%)	2 (8.33%)	3 (13.04%)
Once or twice a week	10 (43.48%)	9 (37.50%)	10 (43.48%)
Three to four times a week	5 (21.74%)	4 (16.67%)	4 (17.39%)
Five to six times a week	3 (13.04%)	4 (16.67%)	2 (8.70%)
Almost everyday	3 (13.04%)	5 (20.83%)	4 (17.39%)
Frequency of physical activity			
Hardly	13 (56.52%)	14 (58.33%)	15 (65.22%)
Once or twice a week	8 (34.78%)	8 (33.33%)	7 (30.43%)
Three or more times	2 (8.70%)	2 (8.33%)	1 (4.35%)

Data are presented as median ± IQR or n (%). PL, placebo group; CP, colla3.2 Safety evaluation of collagen peptides supplementation

Hematological, clinical chemistry, and hepatic and renal function markers in all groups remained within the established clinical reference ranges both at baseline and after 8 weeks of supplementation (Tables S1, S2). No significant differences were observed in baseline values or in the magnitude of change across the three groups. All participants maintained good health throughout the study. Any observed fluctuations in these safety indicators were deemed clinically insignificant. Furthermore, no adverse events were reported by participants during the intervention period, indicating the overall safety and tolerability of peptide supplementation.

3.3 Effect of CP supplementation on skin quality via VAS scores

Skin quality was self-evaluated by participants using the VAS questionnaire (Table 2). Baseline VAS scores did not differ significantly among the three groups. Following the 8-week intervention, VAS scores showed varying degrees of improvement across all groups. Notably, the increases in elasticity scores in the CP and MP groups were 5.50-fold and 5.00-fold higher than those in the PL group, respectively ($P < 0.05$). Similarly, the increases in firmness scores were 3.38-fold and 4.00-fold greater ($P < 0.01$), while the improvements in wrinkle scores were 4.17-fold and 5.33-fold higher in the CP and MP groups ($P < 0.01$), respectively, compared to the PL group. Moreover, the overall VAS score improvements were 4.67-fold and 5.67-fold greater in the CP and MP groups, respectively, than in the PL group ($P < 0.01$). However, no significant differences were observed in skin hydration and radiance scores among the three groups.

Furthermore, no significant differences were found between the CP and MP groups in the magnitude of improvement across any VAS indicators.

Table 2 Changes in skin quality Visual Analog Scale (VAS) scores

Items	PL (n = 23)	CP (n = 24)	MP (n = 23)	*P* value
Elasticity Score				
baseline	59.00 ± 9.00	59.50 ± 17.00	60.00 ± 12.00	0.97
week 8	63.00 ± 9.00	72.50 ± 11.75	74.00 ± 14.00	
change	3.00 ± 12.00[b]	16.50 ± 20.50[a]	15.00 ± 9.00[a]	< 0.05
Hydration Score				
baseline	50.00 ± 11.00	51.00 ± 17.00	50.00 ± 14.00	0.94
week 8	61.00 ± 10.00	65.50 ± 12.50	66.00 ± 12.00	
change	10.00 ± 16.00	15.50 ± 20.75	14.00 ± 10.00	0.33
Radiance Score				
baseline	53.00 ± 28.00	50.50 ± 20.75	52.00 ± 16.00	0.76
week 8	59.00 ± 8.00	68.50 ± 13.50	69.00 ± 15.00	
change	6.00 ± 26.00	13.50 ± 20.75	18.00 ± 15.00	0.06
Firmness Score				
baseline	54.00 ± 19.00	52.00 ± 21.25	51.00 ± 23.00	0.89
week 8	58.00 ± 12.00	67.50 ± 14.50	68.00 ± 15.00	
change	4.00 ± 15.00[b]	13.50 ± 15.00[a]	16.00 ± 15.00[a]	< 0.01
Wrinkle Score				
baseline	55.00 ± 21.00	54.00 ± 22.50	52.00 ± 24.00	0.91
week 8	58.00 ± 13.00	67.50 ± 14.50	68.00 ± 15.00	
change	3.00 ± 15.00[b]	12.50 ± 13.75[a]	16.00 ± 15.00[a]	< 0.01
Overall Score				
baseline	56.00 ± 23.00	56.00 ± 22.50	54.00 ± 22.00	0.80
week 8	59.00 ± 17.00	71.50 ± 15.50	72.00 ± 14.00	

Data are presented as median ± IQR. PL, placebo group; CP, collagen peptides group; MP, mixed peptides group. Comparisons among the three groups were conducted using the Kruskal–Wallis test. For significant markers, all pairwise comparisons were performed using the Wilcoxon rank-sum test, followed by Bonferroni adjustment. Within each row, values with different letters indicate significant differences ($P < 0.05$). The letter 'a' denotes the highest value in each comparison.

3.4 Effect of CP supplementation on facial skin hydration, elasticity and sebum

Facial skin hydration, elasticity, and sebum were assessed using a Corneometer, Cutometer, and Sebumeter, respectively. At baseline, no significant differences were observed among the three groups for these indicators. Following supplementation, significant increases in facial hydration and elasticity were observed in both the CP and MP groups compared with baseline ($P < 0.05$, Fig. 2A, B). The improvement in facial hydration in the CP and MP groups was 3.23- and 3.32-fold greater than that in the PL group ($P < 0.05$). Similarly, both the CP and MP groups exhibited an increase of 0.10 units in elasticity scores, while no improvement was observed in the PL group ($P < 0.05$). No significant changes in facial sebum levels were observed within any of the three groups from baseline to week 8, and the changes did not differ significantly among the CP, MP, and PL groups (Fig. 2C). Furthermore, no significant difference was observed between the CP and MP groups in the changes of these three indicators.

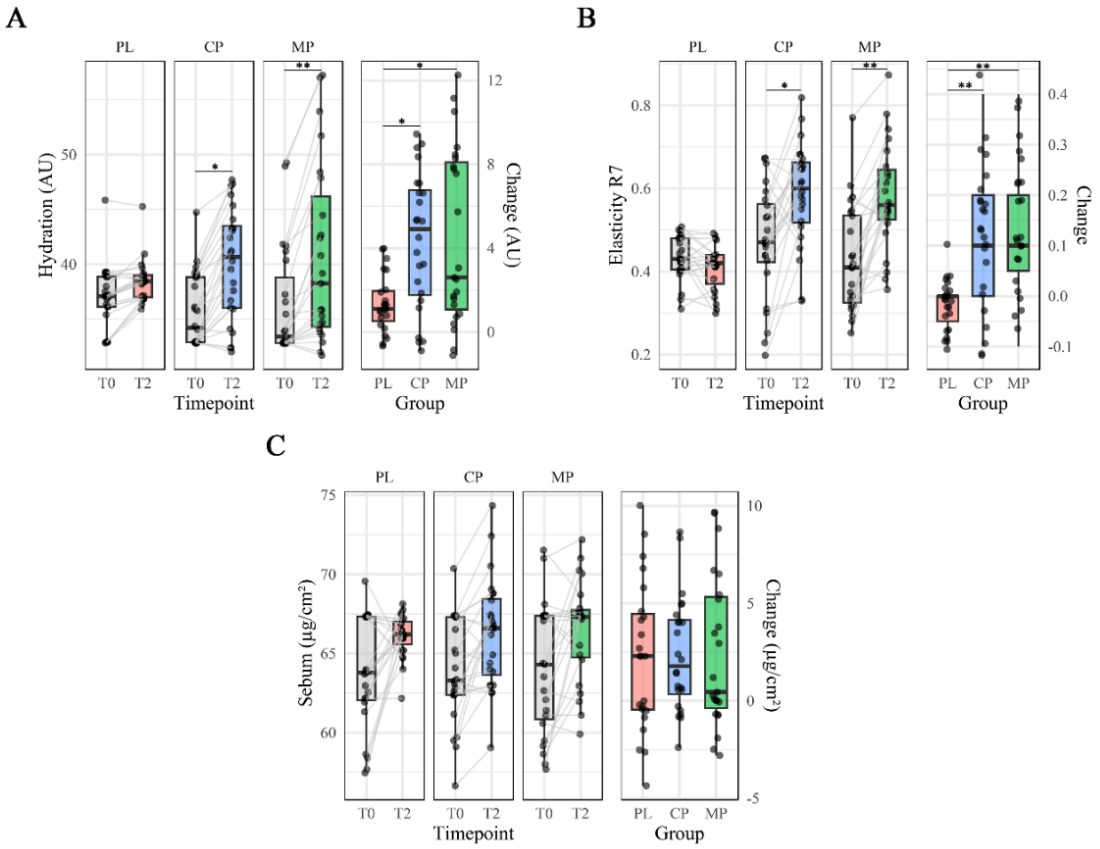


Fig. 2. Changes in facial skin hydration, elasticity and sebum. (A) Hydration. (B) Elasticity (R7). (C) Sebum. T0, baseline; T2, week 8; PL, placebo group (n = 23); CP, collagen peptides group (n = 24); MP, mixed peptides group (n = 23). *P < 0.05 and **P < 0.01 based on the Wilcoxon signed-rank test for within-group comparisons (T0 vs T2), and the Kruskal–Wallis test for between-group comparisons.

3.5 Effect of CP supplementation on VISIA scores of frontal facial skin

Frontal facial skin parameters were assessed using the VISIA system, where higher VISIA scores indicate better skin condition. The intervention effects are shown in Fig. 3A. After 8 weeks of supplementation, participants in both the CP and MP groups exhibited visibly reduced facial wrinkles and smoother skin texture compared with baseline. At baseline, no significant differences were observed among the three groups for any VISIA indicators. Following supplementation, wrinkle and texture scores improved significantly in both the CP and MP groups (P < 0.01, Fig. 3B, C). Specifically, wrinkle scores increased by 12.00% in the CP group and 14.83% in the MP group, whereas the PL group exhibited a 2.78% decrease (P < 0.01). Similarly, texture scores improved by 15.21% and 16.87% in the CP and MP groups, respectively, in contrast to a 5.96% decline in the PL group (P < 0.01). Moreover, the CP and MP groups demonstrated comparable improvements in UV spots and brown spots relative to the PL group (P < 0.05, Fig. 3D, E). However, the within-group changes from baseline following supplementation did not reach statistical significance. No significant differences were observed among the three groups in spot, pore, red area, or porphyrin scores (Fig. S1). Additionally, no significant differences were detected between the CP and MP groups for any of the eight VISIA parameters.

Taken together, 8-week supplementation with CP or MP improved self-reported skin quality and instrumentally assessed hydration, elasticity, wrinkle, and texture compared with placebo, with no significant differences observed between the two intervention groups.

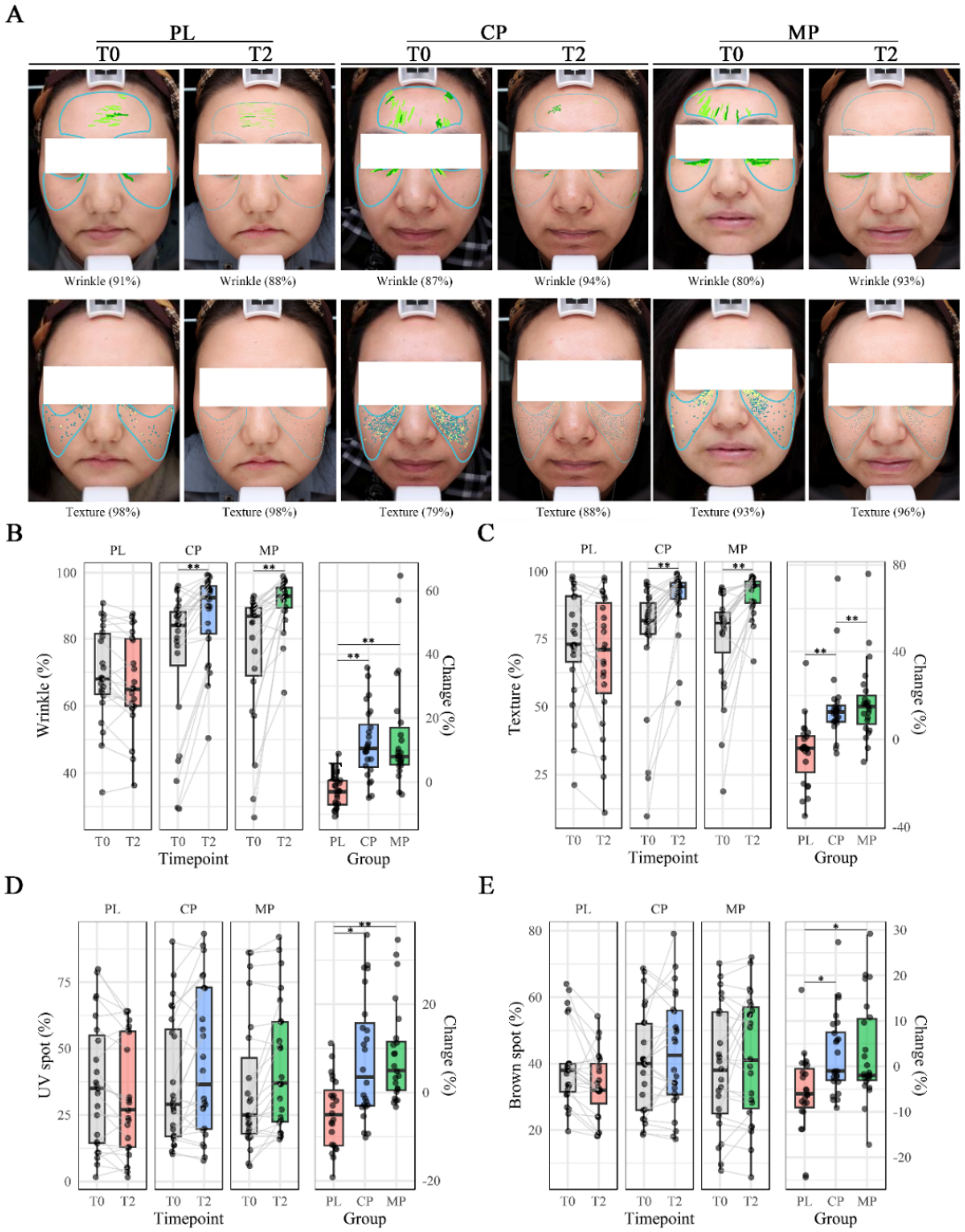


Fig. 3. Changes in VISIA scores of frontal facial skin. (A) Representative VISIA images at baseline and after 8 weeks of supplementation. (B) Wrinkle. (C) Texture. (D) UV (ultraviolet) spot. (E) Brown spot. T0, baseline; T2, week 8; PL, placebo group (n = 23); CP, collagen peptides group (n = 24); MP, mixed peptides group (n = 23). *$P < 0.05$ and **$P < 0.01$ based on the Wilcoxon signed-rank test for within-group comparisons (T0 vs T2), and the Kruskal–Wallis test for between-group comparisons.

3.6 Effect of age on the clinical benefits for skin

To assess whether age influences improvements in clinical skin parameters, a subgroup analysis was performed. In the CP group, 14 participants were under 40 years old and 10 were aged 40 years or older. In the MP group, 13 participants were under 40 and 10 were aged 40 years or older. The analysis focused on skin indicators that showed significant improvement after intervention in both the CP and MP groups, including skin hydration, elasticity, wrinkles, and texture. According to the linear regression model, participants aged

40 years or older showed 1.71-fold and 1.33-fold greater improvements in skin elasticity compared with those under 40 years in the CP and MP groups, respectively, with significant age-by-group interaction effects ($P < 0.05$, Fig. 4A). Similarly, participants aged 40 and above experienced 1.33-fold and 2.04-fold greater wrinkle reduction relative to younger participants in the CP and MP groups, respectively, also with significant interaction effects ($P < 0.05$, Fig. 4B). In contrast, no significant interaction effects were observed for skin hydration or texture (Fig. S2).

These results suggest that participants of different ages responded differently to peptide supplementation, with individuals aged 40 years and above showing more pronounced improvements in skin elasticity and wrinkle reduction, whereas changes in hydration and texture were less affected by age.

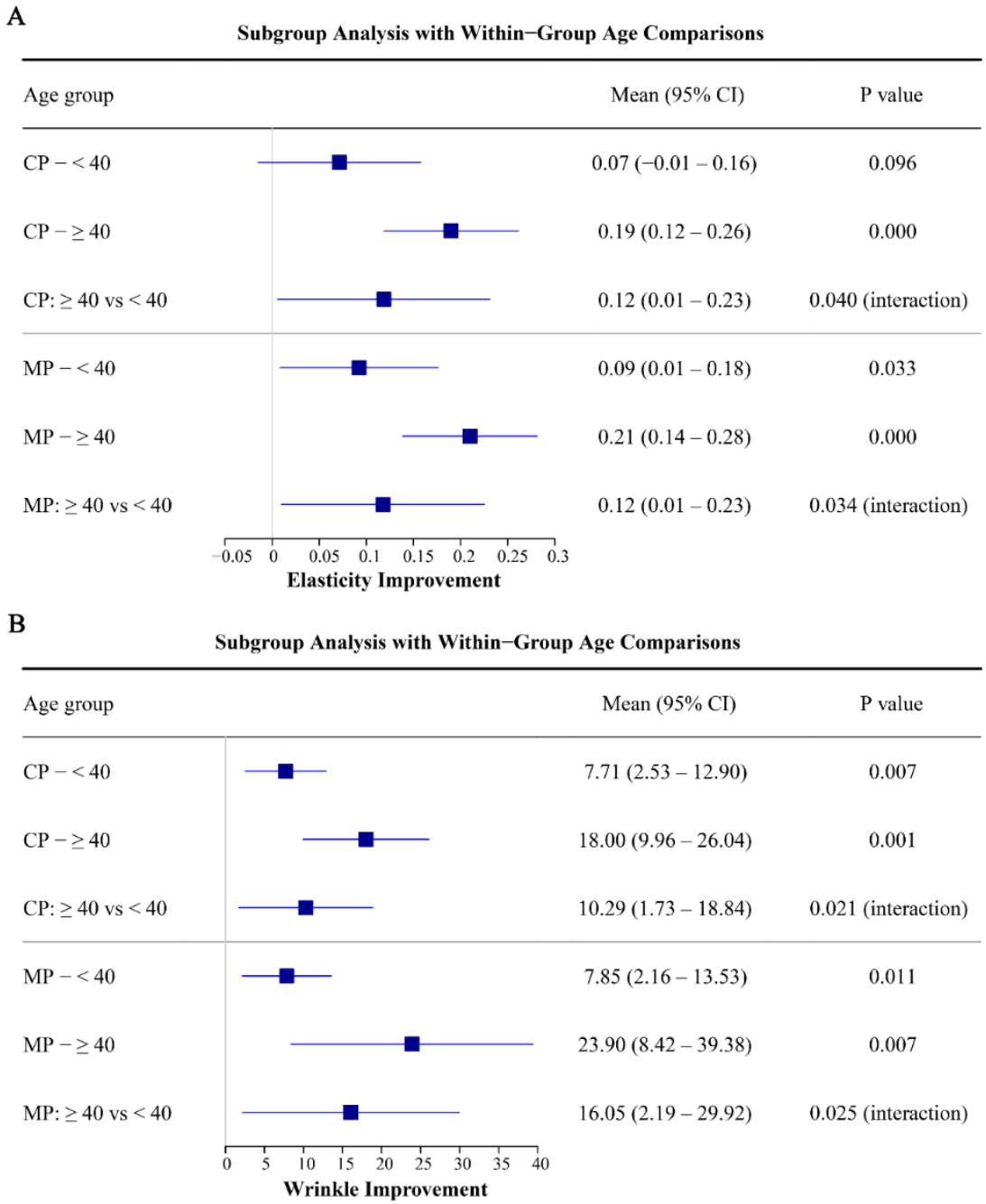


Fig. 4. Subgroup analysis of age-related effects on skin parameters. (A) Elasticity. (B) Wrinkle. Data are presented as mean values with 95% confidence intervals (CI) and were analyzed using a linear regression model. CP, collagen peptides group (< 40 years, n = 14; ≥ 40 years, n = 10); MP, mixed peptides group (< 40 years, n = 13; ≥ 40 years, n = 10).

3.7 Effect of CP supplementation on facial skin microbiota

The composition of the facial skin microbiota was analyzed using 16S rRNA sequencing to evaluate whether collagen peptide supplementation influences the microbial communities on the skin. Due to sample quality control limitations, 20 skin swab samples that met quality standards were randomly selected from each group for analysis. The overall α- and β-diversity of the facial skin microbiota showed no significant changes among the three groups after supplementation (Fig. S3).

At the genus level, the relative abundance of *Cutibacterium* significantly increased in both the CP and MP groups following the 8-week supplementation, with significant differences relative to the PL group ($P < 0.05$, Fig. 5A). Consistently, at the species level, *Cutibacterium acnes* exhibited a significant increase in abundance in the CP and MP groups relative to the PL group ($P < 0.05$, Fig. 5B). Linear discriminant analysis effect size (LEfSe) was employed to identify taxa differentially enriched before and after supplementation in the intervention groups ($P < 0.05$, LDA score > 2, Fig. 5C). Both CP and MP groups showed significant increases in *Lactobacillus* at the genus level, accompanied by corresponding increases in *Lactobacillus crispatus* and *Lactobacillus iners* at the species level. Conversely, the abundance of *Corynebacterium* significantly decreased, along with its representative species *Corynebacterium tuberculostearicum*.

Correlation analysis demonstrated that *Cutibacterium* and *Lactobacillus* were significantly and positively associated with multiple skin health parameters, including texture, elasticity, wrinkle, and hydration, whereas *Corynebacterium* exhibited negative associations with these indices ($P < 0.05$, Fig. 5D). In particular, wrinkle improvement was positively correlated with *C. acnes* ($r = 0.587$), *L. crispatus* ($r = 0.310$), and *L. iners* ($r = 0.243$), but negatively correlated with *C. tuberculostearicum* ($r = −0.249$).

These findings indicate that collagen peptide supplementation promotes a favorable skin microbial balance characterized by increased beneficial taxa and reduced potentially detrimental bacteria, which may contribute to improvements in skin condition.

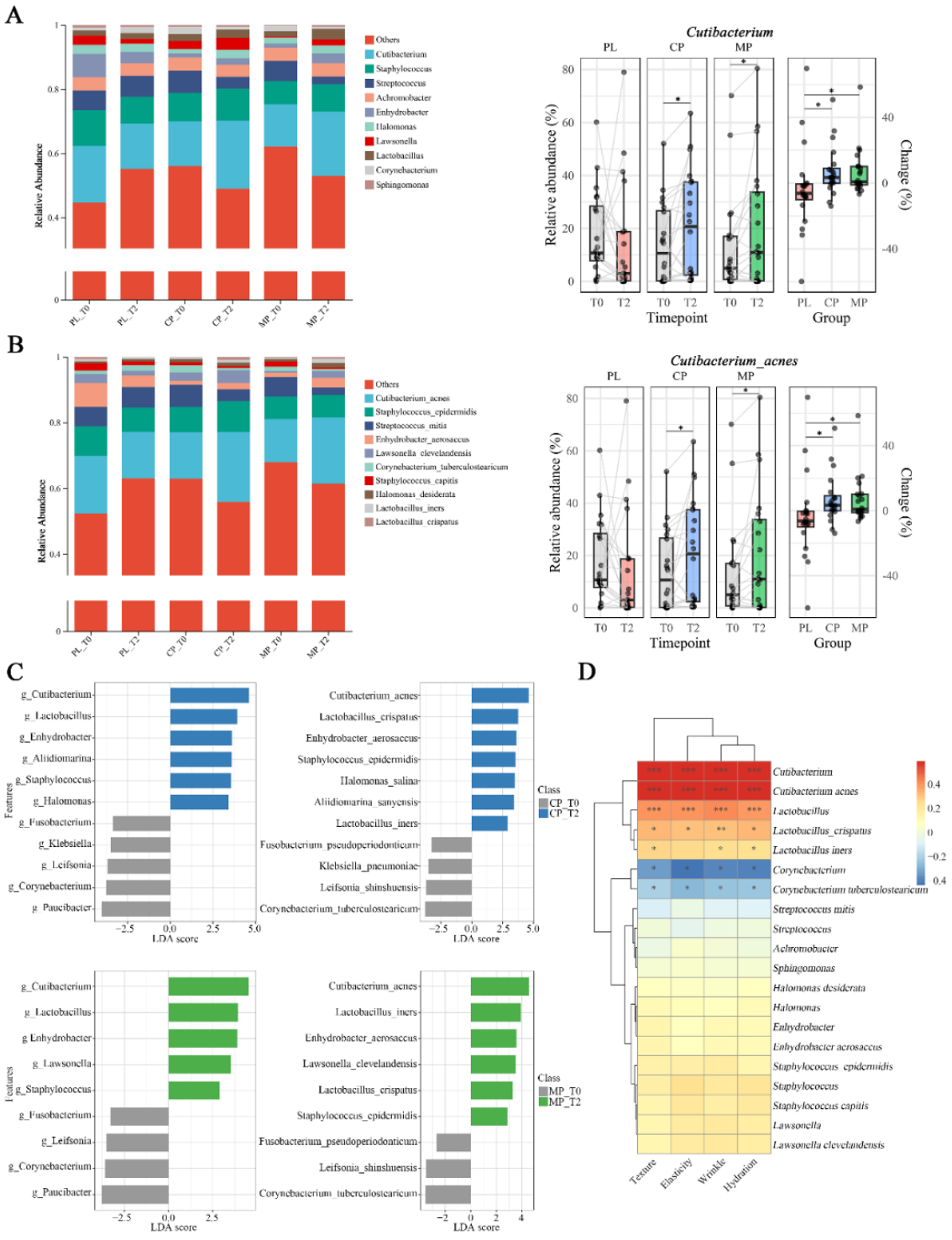


Fig. 5. Changes in skin microbiota composition. (A) Relative abundance of bacterial taxa at the genus level, including *Cutibacterium*. (B) Relative abundance of bacterial taxa at the species level, including *Cutibacterium acnes*. (C) Differentially abundant genera and species identified by linear discriminant analysis (LDA) effect size (LEfSe). (D) Heatmap of Spearman correlation between the skin indices and key skin microbiota. **P* < 0.05, ***P* < 0.01 and ****P* < 0.001. P values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate correction. T0, baseline; T2, week 8; PL, placebo group (n = 20); CP, collagen peptides group (n = 20); MP, mixed peptides group (n = 20). The Wilcoxon signed-rank test was used for within-group comparisons (T0 vs T2), and the Kruskal–Wallis test was used for between-group comparisons.

3.8 Effect of CP supplementation on facial metabolomic profiles

To investigate whether collagen peptide supplementation affects the metabolite profiles on the skin surface, a non-targeted metabolomic analysis was performed to assess changes in facial skin metabolites.

Orthogonal partial least squares discriminant analysis (OPLS-DA) revealed notable alterations in the metabolic profiles of both the CP and MP groups following supplementation (Fig. 6A, B). The robustness and predictive power of the OPLS-DA models were confirmed through validation procedures. Potential biomarkers were identified based on variable importance in projection (VIP) scores > 1 and statistical significance ($P < 0.05$), as visualized in the V-plot (Fig. S4). Metabolite variations were investigated in the CP and MP groups (Table 3, Fig. 6C–M). Pro-Pro, N-undecanoylglycine, Leu-Ser, 6-hydroxymelatonin, chenodeoxyglycocholic acid, 3-hydroxykynurenine, and Asp-Pro were significantly upregulated in both the CP and MP groups after supplementation. Additionally, N-acetylvaline and dopamine were significantly elevated in the CP and MP groups, respectively. Conversely, levels of neopterin, methionine sulfoxide, xanthosine, and aminoadipic acid significantly decreased in both the CP and MP groups. Among these differential metabolites, the increases in Pro-Pro, and N-undecanoylglycine were significantly greater in the CP and MP groups compared to the PL group. Similarly, the reductions in neopterin, xanthosine, and aminoadipic acid were significantly more pronounced in the CP and MP groups relative to the PL group. Correlation analysis showed that Pro-Pro and N-undecanoylglycine were positively associated with skin parameters (r = 0.456 and 0.344 for wrinkle, respectively), whereas aminoadipic acid was negatively correlated (r = −0.359 for wrinkle) (Fig. 6N).

Overall, collagen peptide supplementation reshaped the facial metabolomic profile, favoring increased collagen-related and antioxidant metabolites while reducing metabolites associated with oxidative stress and inflammation, which may contribute to improvements in skin condition.

Table 3 Differential metabolites of skin

No.	Metabolite identification	Rt (min)	m/z	CP_T2/CP_T0			MP_T2/MP_T0			HMDB ID
				VIP	Log_2FC	P	VIP	Log_2FC	P	
1	Pro-Pro	6.08	213.1232	1.97	1.63	0.00	2.15	1.16	0.00	HMDB0011180
2	N-Undecanoylglycine	7.79	242.1738	1.95	1.51	0.00	2.09	1.48	0.00	HMDB0013286
3	Leu-Ser	5.62	201.1234	1.72	1.26	0.00	0.55	0.61	0.04	HMDB0028938
4	6-Hydroxymelatonin	7.18	249.1213	1.55	1.24	0.02	1.28	0.67	0.04	HMDB0004081
5	Chenodeoxyglycocholic acid	10.90	450.3219	1.37	0.50	0.04	1.51	0.59	0.01	HMDB0006898
6	3-Hydroxykynurenine	13.08	223.0713	1.21	0.70	0.02	1.12	0.55	0.01	HMDB0000732
7	Asp-Pro	1.69	231.0978	1.09	1.10	0.03	1.78	0.98	0.04	HMDB0002335
8	N-Acetylvaline	5.18	206.0454	1.09	0.60	0.02	0.37	0.24	0.62	HMDB0011757
9	Dopamine	6.50	152.0687	0.68	0.22	0.29	2.14	0.48	0.00	HMDB0000073
10	Neopterin	8.59	252.0711	2.24	−1.45	0.00	2.38	−3.72	0.00	HMDB0000845
11	Methionine sulfoxide	0.88	166.0536	1.74	−0.77	0.02	1.70	−0.87	0.01	HMDB0002005
12	Xanthosine	4.95	283.0658	1.69	−2.30	0.00	1.50	−1.85	0.01	HMDB0000299
13	Aminoadipic acid	5.07	144.0656	1.40	−0.46	0.04	1.14	−0.42	0.03	HMDB0000510

Rt, retention time; CP, collagen peptides group; MP, mixed peptides group; T0, baseline; T2, week 8; VIP, variable importance in projection; FC, fold change value; HMDB ID, Human Metabolome Database Identifier.

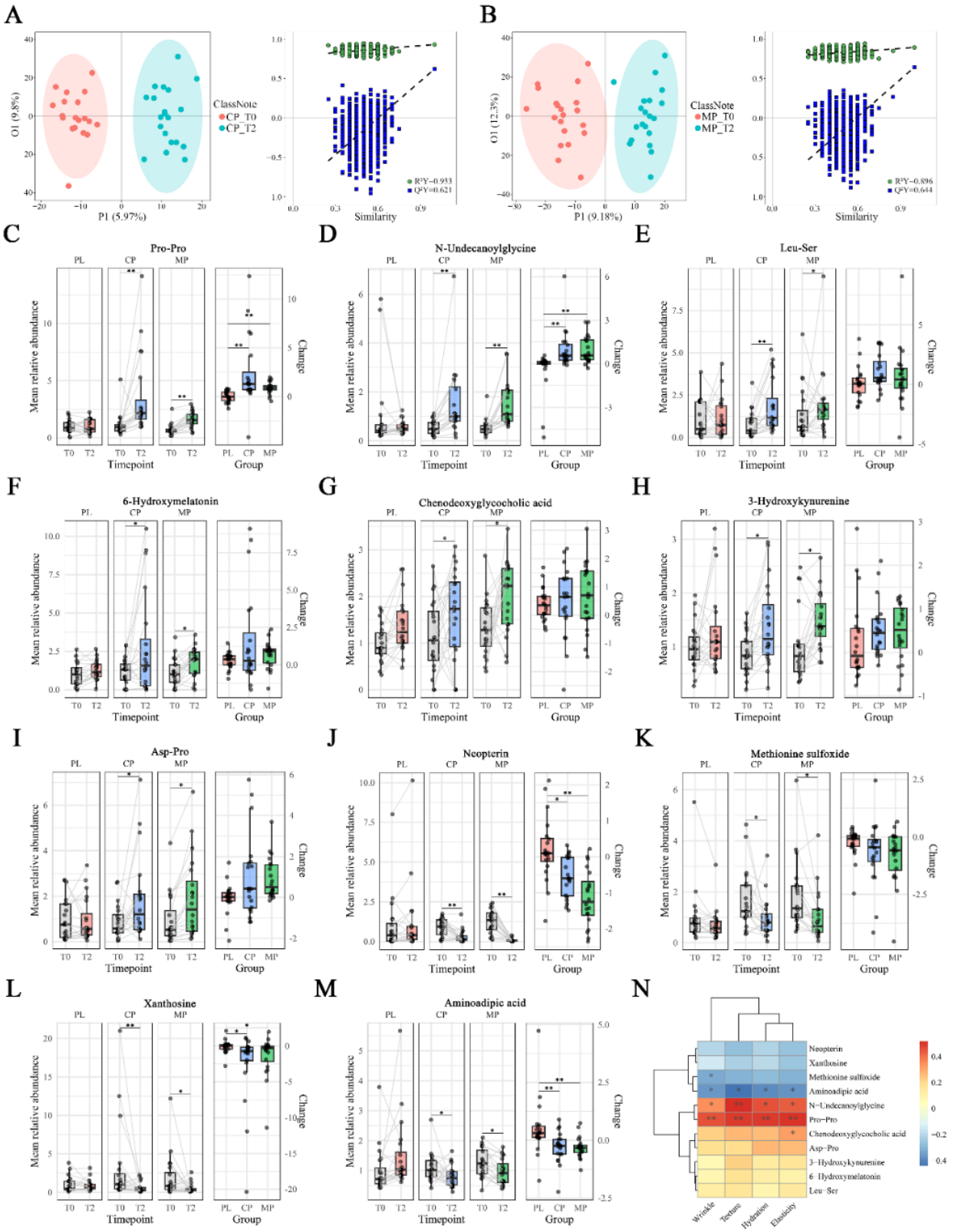
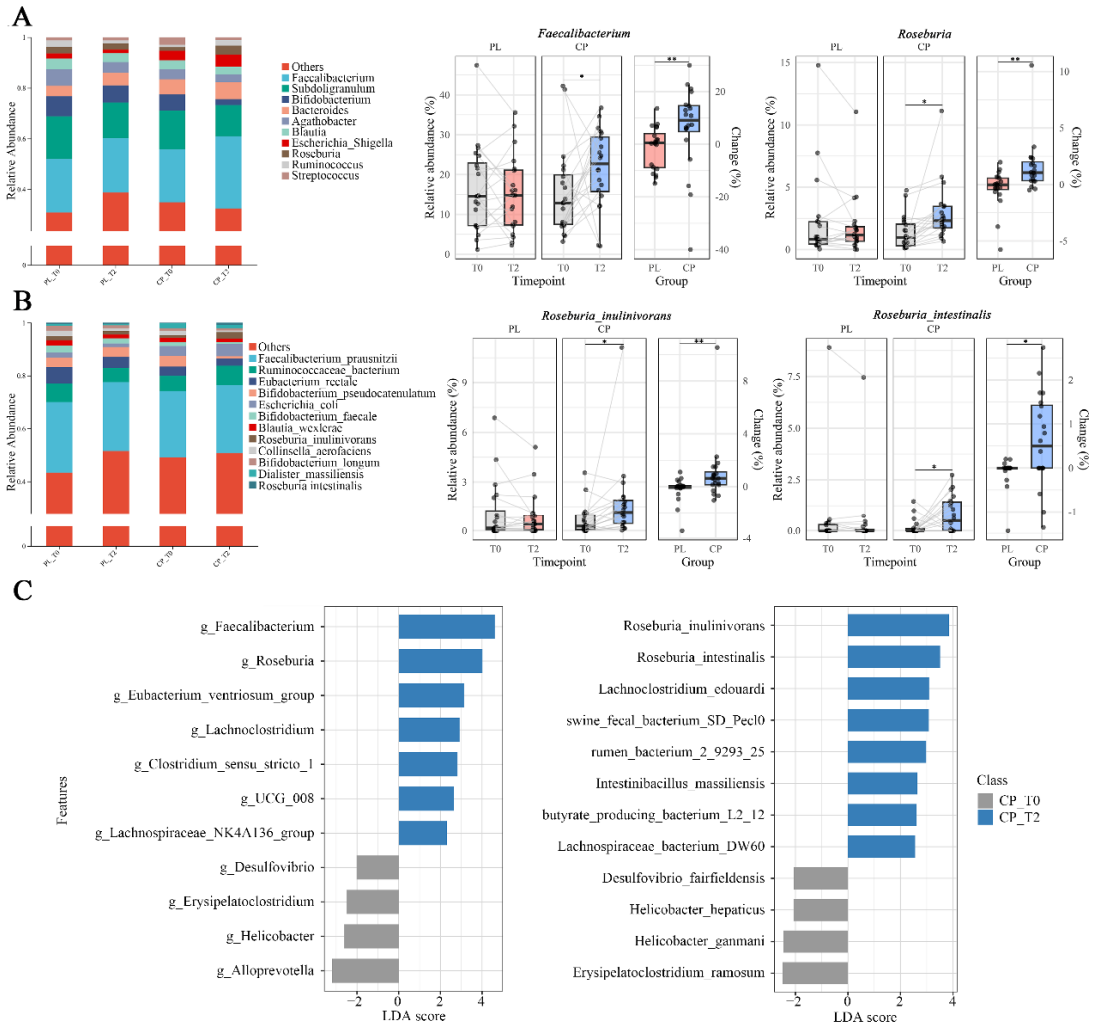


Fig. 6. Changes in skin metabolite profiles. (A, B) Orthogonal partial least squares discriminant analysis (OPLS-DA) score plots and permutation plots comparing facial metabolite profiles in CP and MP groups. Alterations in facial metabolites: (C) Pro-Pro, (D) N-Undecanoylglycine, (E) Leu-Ser, (F) 6-Hydroxymelatonin, (G) Chenodeoxyglycocholic acid, (H) 3-Hydroxykynurenine, (I) Asp-Pro, (J) Neopterin, (K) Methionine sulfoxide, (L) Xanthosine, (M) Aminoadipic acid in different groups detected by metabolomics. (N) Heatmap of Spearman correlation between the skin indices and key skin metabolites. *$P < 0.05$ and **$P < 0.01$. P values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate correction. T0, baseline; T2, week 8; PL, placebo group (n = 20); CP, collagen peptides group (n = 20); MP, mixed peptides group (n = 20). The Wilcoxon signed-rank test was used for within-group comparisons (T0 vs T2), and the Kruskal–Wallis test was used for between-group comparisons.

3.9 Effect of CP supplementation on fecal microbiota

Given that no significant differences in skin-related outcomes were observed between the CP and MP groups, and given the simpler composition of the CP supplement, 16S rRNA sequencing of fecal microbiota was conducted only for participants in the PL and CP groups. No significant changes in α- or β-diversity were observed in either group following supplementation (Fig. S5).

At the genus level, the relative abundances of *Faecalibacterium* and *Roseburia* were significantly increased in the CP group after supplementation ($P < 0.05$), and both were significantly higher compared to the PL group ($P < 0.01$, Fig. 7A). At the species level, *Roseburia inulinivorans* and *Roseburia intestinalis* were significantly enriched in the CP group, with corresponding differences relative to the PL group ($P < 0.05$, Fig. 7B). LEfSe analysis further identified significant enrichments of *Lachnoclostridium* and *Lachnoclostridium edouardi* in the CP group ($P < 0.05$, LDA score > 2, Fig. 7C). Conversely, the genera *Alloprevotella* and *Helicobacter* were significantly depleted following supplementation. Notably, the GMWI was significantly elevated in the CP group after supplementation (+0.67 units), whereas the PL group exhibited a decrease (−0.24 units), resulting in a significant difference between the two groups ($P < 0.05$, Fig. 7D). Functional predictions analysis revealed 16 microbial pathways that were significantly altered in the CP group ($P < 0.05$, Fig. 7E), including increases in glycine, serine and threonine metabolism, histidine metabolism, arginine and proline metabolism, and tryptophan metabolism.



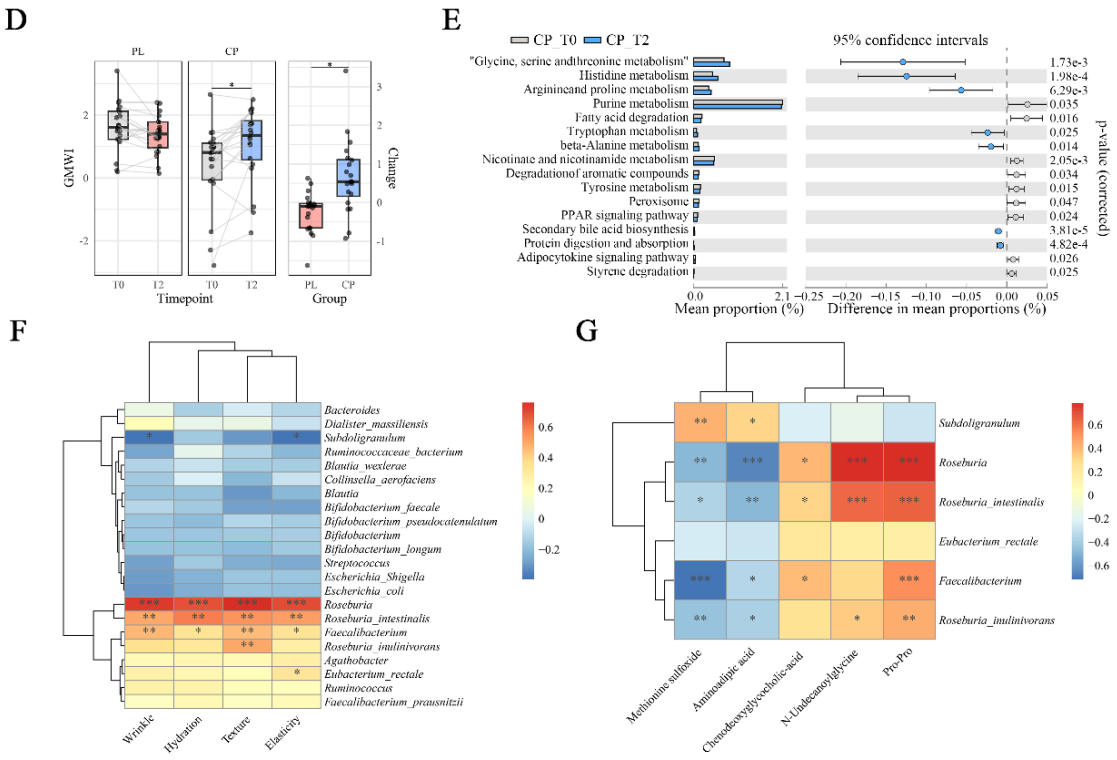


Fig. 7. Changes in gut microbiota composition and function. (A) Relative abundance of bacterial taxa at the genus level and significantly different genera. (B) Relative abundance of bacterial taxa at the species level and significantly different species. (C) Differentially abundant genera and species identified by linear discriminant analysis (LDA) effect size. (D) Gut Microbiome Wellness Index (GMWI). (E) Predicted differences in microbial function. (F) Heatmap of Spearman correlation between the skin indices and key gut microbiota. (G) Heatmap of Spearman correlation between the key gut microbiota and skin metabolites. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$. T0, baseline; T2, week 8; PL, placebo group (n = 20); CP, collagen peptides group (n = 20). The Wilcoxon signed-rank test was used for within-group comparisons (T0 vs T2), and the Kruskal–Wallis test was used for between-group comparisons.

Correlation analyses showed that *Roseburia* and *Faecalibacterium* were positively associated with improvements in skin parameters (Fig. 7F). Specifically, *R. intestinalis* was positively associated with improvements in facial wrinkle ($r = 0.502$), texture ($r = 0.544$), hydration ($r = 0.586$), and elasticity ($r = 0.517$). Furthermore, *R. intestinalis* was also positively associated with the skin metabolites N-Undecanoylglycine ($r = 0.629$) and Pro-Pro ($r = 0.646$, Fig. 7G).

Collectively, collagen peptide supplementation promoted enrichment of beneficial butyrate-producing bacteria and enhanced amino acid–related metabolic pathways. The strong associations between *R. intestinalis* and skin metabolites support a potential mechanism mediated by the gut–skin axis for skin improvement.

3.10 Skin response differences according to intestinal R. intestinalis dynamics

Given the potential role of intestinal *R. intestinalis* in mediating skin improvement, a subgroup analysis was conducted to assess whether variations in skin enhancement were associated with differential changes in its abundance. Participants in the CP group were stratified based on the degree of improvement in skin parameters. According to linear regression analysis, individuals in the top 50% for improvements in skin hydration, elasticity, wrinkle, and texture exhibited 38.33-, 9.00-, 11.33-, and 8.17-fold greater increases, respectively, in the abundance of *R. intestinalis* compared to those in the bottom 50%, with significant group interaction effects observed ($P < 0.05$, Fig. 8).

These results indicate that individuals exhibiting greater skin improvement tended to experience a more pronounced enrichment of *R. intestinalis* after supplementation, suggesting that this species may play a pivotal role in mediating the skin-beneficial effects of collagen peptides through the gut–skin axis.

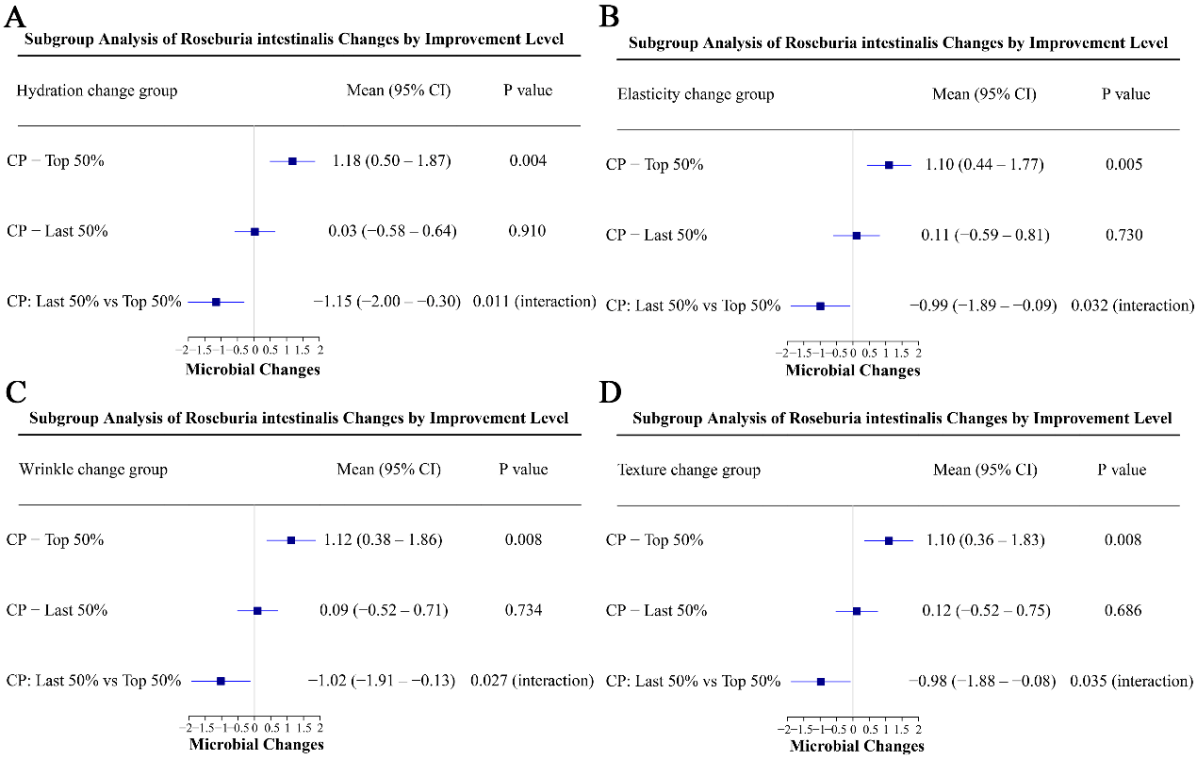


Fig. 8. Subgroup analysis of the association between the degree of skin improvement and changes in gut *Roseburia intestinalis* abundance. (A) Hydration; (B) Elasticity; (C) Wrinkle; (D) Texture. Data are presented as mean values with 95% confidence intervals (CI) and were analyzed using a linear regression model. CP, collagen peptides group (n = 20).

4. Discussion

This study demonstrates that oral supplementation with CP or MP significantly improved skin condition in healthy women aged 30–55 years. Compared with placebo, both interventions led to significant improvements in wrinkles, texture, hydration, and elasticity, with more pronounced effects observed in participants aged over 40 years. Both CP and MP modulated the skin microbiota, increasing the abundance of *Cutibacterium* and *Lactobacillus*, and reshaped the skin metabolomic profile, with higher levels of Pro-Pro and N-undecanoylglycine and lower levels of aminoadipic acid. CP supplementation further enriched the abundance of gut *Roseburia* and *Faecalibacterium*, promoted amino acid metabolism, and increased the GMWI (+0.67 units). Notably, greater skin improvements were associated with increased *R. intestinalis*, suggesting a gut–skin interaction may underlie these benefits.

The beneficial effects of collagen and elastin peptides on skin health have been widely reported. Previous clinical trials have shown that oral supplementation with collagen peptides at doses ranging from 1.65 to 5 g/day for 6–12 weeks improves skin hydration, elasticity, and wrinkles[21,26,27], while elastin peptide intake has been associated with reduced fine lines and enhanced skin moisture[11]. In the present study, daily supplementation with 2 g of tilapia-derived collagen peptides or 2 g of collagen peptides combined with 0.09 g of elastin peptides for 8 weeks similarly improved wrinkles, texture, hydration, and elasticity, with no

significant differences between the two peptide groups. This lack of additional benefit may be attributable to the relatively low proportion of elastin peptides in the mixed formulation, highlighting the need for future studies with higher elastin peptide doses. Subgroup analysis further indicated that participants aged over 40 years benefited more in terms of wrinkle reduction and elasticity, consistent with evidence that older individuals, particularly postmenopausal women, respond more strongly to collagen supplementation due to age-related declines in dermal matrix integrity[22].

The skin microbiota plays a critical role in skin aging by regulating immune responses, maintaining barrier integrity, modulating inflammation, and preventing colonization by pathogens microorganisms[16]. Previous studies have shown that *Cutibacterium* and *Lactobacillus* are predominant taxa in healthy young skin, whereas their relative abundances decline with age, reflecting microbial shifts associated with skin dryness and reduced structural integrity[28–30]. Among these taxa, *Cutibacterium acnes* is a key commensal bacterium inhabiting sebaceous regions. It contributes to maintaining an acidic skin surface, suppressing pathogenic colonization, and regulating local immune homeostasis. A reduced abundance of *C. acnes* has been linked to aged skin, whereas its restoration is regarded as a hallmark of balanced and youthful skin microbiota[31–33]. Similarly, *Lactobacillus crispatus* is recognized as a beneficial bacterium that produces lactic acid and antimicrobial peptides, thereby sustaining an acidic environment and reducing inflammatory responses[34,35]. Emerging evidence further indicates that its metabolites and extracellular vesicles can promote epidermal barrier repair and stimulate collagen synthesis, supporting a rejuvenated skin phenotype[36]. In the present study, CP supplementation significantly increased the relative abundances of *Cutibacterium* and *Lactobacillus* at the genus level, particularly *C. acnes* and *L. crispatus* at the species level, suggesting a shift toward a more youthful and balanced microbiota.

Skin metabolites also play a crucial role in maintaining skin health. Emerging evidence has highlighted the dynamic interplay between skin metabolites and cutaneous cells, linking metabolic alterations to skin aging, inflammation, and impaired barrier function[37]. In this study, levels of N-undecanoylglycine, an N-acyl amino acid and a reported gut microbial metabolite, were significantly elevated following both CP and MP supplementation. This metabolite has been reported to modulate immune responses and protect against pathogenic infections[38]. Its positive correlation with *Roseburia* suggests that it may be associated with microbial metabolic activity, raising the possibility that gut-derived metabolites may translocate to the skin and exert antimicrobial effects. Pro-Pro, a major dipeptide derived from collagen hydrolysates due to high proline content[39], increased significantly after supplementation, implying efficient systemic absorption and potential delivery to the skin. Its positive associations with beneficial gut genera such as *Roseburia* and *Faecalibacterium* suggest possible prebiotic-like properties. In contrast, aminoadipic acid, a lysine-derived oxidative metabolite linked to reactive oxygen species production[40], was significantly reduced following peptide supplementation, suggesting that collagen peptides may help attenuate oxidative stress and improve skin homeostasis.

The gut–skin axis, which describes the bidirectional interaction between the gut microbiota and skin health, has attracted increasing scientific interest. Disruptions in gut barrier function and microbial balance can influence systemic immunity and skin homeostasis[41]. *Roseburia* and *Faecalibacterium* are key short-chain fatty acid-producing genera known for their anti-inflammatory properties and support of gut barrier integrity[42,43]. These taxa may promote intestinal TGF-β production, indirectly enhancing collagen synthesis[7]. In the present study, these two genera were significantly enriched following CP supplementation. Notably, *R. intestinalis* has been shown to upregulate TLR5 expression, suppress inflammatory cytokine release, and alleviate symptoms in inflammatory bowel disease[44]. Together with correlation analysis, these findings suggest that *R. intestinalis* may contribute to improvements in skin parameters through its anti-inflammatory and barrier-supporting activities. Subgroup analysis further revealed that volunteers exhibiting greater improvements in skin metrics showed more pronounced increases in *R. intestinalis* abundance. Additionally, the GMWI[45], an integrative indicator of gut microbial health, was significantly elevated in the CP group, suggesting a shift toward a balanced, anti-inflammatory, and metabolically favorable gut ecosystem. Functional prediction analysis also revealed enhanced amino acid metabolism in the gut microbiota of participants, aligning with the CP intervention and the observed increase in collagen-derived peptides in skin metabolite profiles. These findings collectively support the hypothesis that collagen peptide supplementation promotes skin health by modulating gut microbiota and reinforcing the gut–skin axis. Based on the overall findings of this study, the potential mechanisms by which collagen peptides improve skin aging are illustrated in Fig. 9. Although α- and β-diversity of the skin and gut microbiota did not change significantly, this is reasonable given that participants were healthy adults and the intervention (2 g/day collagen peptides) is unlikely to induce large-scale alterations in microbial community structure. Importantly, the selective shifts in key genera still reflect functional activity and likely contribute to the observed dermatological improvements.

Despite these promising findings, several limitations should be acknowledged. First, the relatively small sample size may limit statistical power and generalizability, and larger trials are needed to confirm efficacy. Second, the study included only healthy women, so results may not extend to men or individuals with different baseline skin conditions. Third, the 8-week intervention allowed observation of short-term effects, but the long-term durability of benefits remains unknown. In addition, although participants were instructed to maintain their habitual diet and lifestyle throughout the study, detailed dietary intake was not formally recorded, and unmeasured dietary variations may have influenced gut microbiota composition. Finally, although the multi-omics analyses revealed associations among skin parameters, microbiota, and metabolites, definitive causal relationships cannot be established in this study, and further mechanistic investigations are needed to elucidate the underlying pathways.

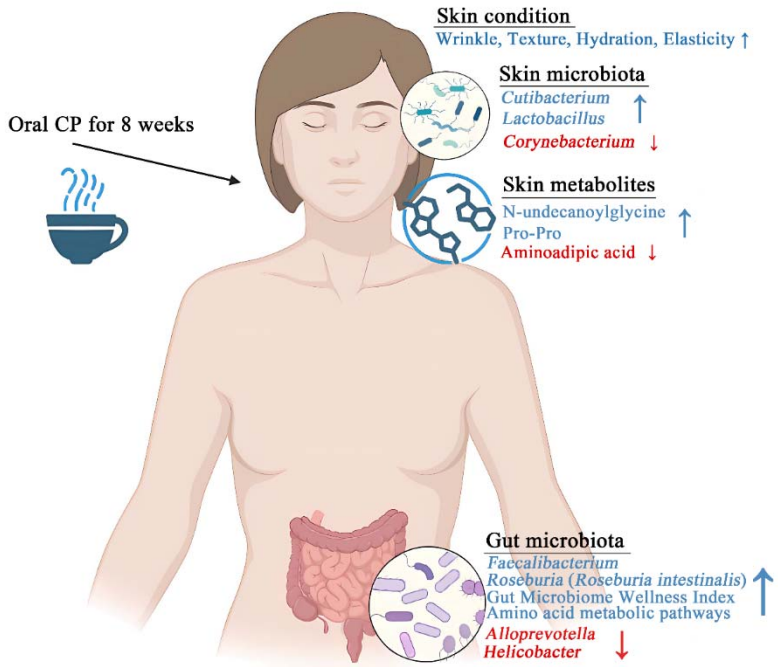


Fig. 9. Potential mechanisms of collagen peptides in improving skin aging. Upward arrows (↑) indicate increases; downward arrows (↓) indicate decreases. CP, collagen peptides.

5. Conclusion

This study demonstrates that oral supplementation with collagen peptides, with or without elastin peptides, effectively improves clinical skin parameters in healthy adult females. Under the present formulation and intervention duration, the addition of elastin peptides did not confer additional benefits compared with collagen peptides alone. The observed skin improvements were accompanied by coordinated alterations in the skin microbiota and metabolomic profiles, indicative of a shift toward a more favorable cutaneous microenvironment. Notably, collagen peptide supplementation alone further improved gut microbial composition and metabolic function, as reflected by an increase in the GMWI of 0.67 units. Collectively, these findings support the concept that dietary collagen peptides promote skin health through integrated modulation of skin and gut microbial ecosystems and their metabolic activities, highlighting the gut–skin axis as a key pathway underlying the skin-beneficial effects of collagen peptide supplementation.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Data availability

Raw sequencing data have been deposited in the NCBI Sequence Read Archive under the following BioProject accession numbers: PRJNA1348445 for the skin microbiome and PRJNA1268169 for the gut

microbiome. Other dataset supporting the current study are available from the corresponding author upon request.

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