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ORIGINAL ARTICLE

Clinical evidence of the efficacy and safety of a new multi-peptide anti-aging topical eye serum

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Abstract

Background: Skin aging is a complex multifactorial progressive process. With age, intrinsic and extrinsic factors cause the loss of skin elasticity, with the formation of wrinkles, resulting in skin sagging through various pathways. A combination of multiple bioactive peptides could be used as a treatment for skin wrinkles and sagging.

Objectives: This study aimed to evaluate the cosmetic efficacy of a multi-peptide eye serum as a daily skin-care product for improving the periocular skin of women within the ages of 20–45 years.

Methods: The stratum corneum skin hydration and skin elasticity were assessed using a Corneometer CM825 and Skin Elastometer MPA580, respectively. The PRIMOS CR technique based on digital strip projection technology was used for skin image and wrinkle analysis around the "crow's feet" area. Self-assessment questionnaires were filled on Day 14 and 28 of product use.

Results: This study included 32 subjects with an average age of 28.5 years. On Day 28, there was a significant decrease in the number, depth, and volume of wrinkles. Skin hydration, elasticity, and firmness increased continuously during the study period, consistent with typical anti-aging claims. A majority of the participants (75.00%) expressed overall satisfaction with their skin appearance after using the product. Most participants noted a visible skin improvement, with an increase in skin elasticity and smoothness, and confirmed the extensibility, applicability, and temperance of the product. No adverse reactions related to product use were observed.

Conclusions: The multi-peptide eye serum uses a multi-targeted mechanism against skin aging to improve the skin appearance, making it an ideal choice for daily skincare.

KEYWORDS
anti-aging, peptides, skincare, wrinkles

1 | INTRODUCTION

Skin is the most voluminous organ of the human body and its aging begins from birth.[1] Skin aging, a complex and multifactorial biological process, involves numerous biochemical and physical interactions.[1,2] Analyzing data available on model organisms and humans, the intrinsic (e.g., time, genetic factors, and hormones)[3] and extrinsic (e.g., UV exposure, pollution, smoking, and poor diet)[4,5] factors contributing to the aging process have been identified. The intrinsic causes of skin aging can be divided into six broad categories: cellular senescence (the Hayflick limit), telomere shortening, point mutations of extranuclear mitochondrial DNA, chromosomal abnormalities and gene mutations, oxidative stress, and hormone deficiency.[6,7] Extrinsic skin aging is lifestyle dependent and results from exposure to aging-promoting environmental factors, particularly UV radiation.[8] UVA (320–400 nm), a mutagen responsible for significant skin damage and aging, mainly induces the production of reactive oxygen species (ROS); this causes DNA damage, leading to cellular senescence and a reduction in the total collagen content of skin.[8,9] Extrinsic aging is laid on intrinsic aging, and depends on the intensity, duration, and chronicity of UV exposure.[4,9] During aging, various skin-cell types undergo senescence to develop a specific senescent phenotype. Dry skin is caused by a thickened and stiffened stratum corneum, along with increased cellular cohesion, due to the reduced secretion of sebocytes and a low sebaceous lipid content. Senescent fibroblasts, a reduction in the numbers of melanocytes, mast cells, and Langerhans cells, and the reduced proliferation of basal keratinocytes can lead to a thinning of the epidermis. Collagen and elastin, two major constituents of the extracellular matrix (ECM) of the dermis, impart strength and resilience to the skin. Fibroblast senescence contributes to ECM degradation by secreting a senescence-associated secretory phenotype (SASP) that activates matrix metalloproteinases (MMPs); this causes a loss of skin stiffness and resilience, clinically observed as wrinkling and sagging.[10–15]

Facial aging, especially wrinkling and sagging, are the principal indications of aging skin.[2] In recent times, the impact of aging on the function and appearance of skin has received immense attention. Not only does smooth and elastic skin protect the body from moisture loss and microorganism infection, it positively influences the social behavior of humans. An in-depth understanding of aging-process mechanisms is necessary to facilitate the development of products that effectively decrease the visible indications of senescence (a significant commercial challenge for cosmetic laboratories).

Acetyl hexapeptide-8, with the sequence Acetyl-Glu-Glu-Met-Gln-Arg-Arg-NH_2, is also called botulinum-like neurotoxin Type A. It competitively inhibits six amino acids of the N-terminal domain of the synaptosomal-associated protein 25 (SNAP25); this adversely affects the assembly of the SNARE ternary complex and release of Ca^{2+}-dependent acetylcholine at nerve endings.[16,17] Consequently, muscles fail to receive contraction signals from the vesicular fusion (known as SNARE) complex during neurotransmission; this relaxes the muscles and smooths out wrinkles.[18]

Palmitoyl tetrapeptide-7 (Sequence: Pal-Gly-Gln-Pro-Arg or Pal-GQPR) is a fragment of immunoglobulin G that reduces interleukin-6 (IL-6) secretion in keratinocytes and inhibits the UVB radiation-exposure inflammatory response of skin.[19,20] IL-6 has been used as a marker for cellular senescence in senescent dermal fibroblasts.[3]

Palmitoyl tripeptide-1 (Sequence: Pal-Gly-His-Lys), a signal peptide that increases the activity of stromal cells, can stimulate the synthesis of stromal proteins, especially collagen. It promotes the production of elastin, hyaluronic acid, glycosaminoglycan, and fibronectin.[21,22]

Valine-tryptophan (VW), also known as dipeptide-2 (or Dipeptide VW), has been identified as an effective angiotensin-converting enzyme (ACE) inhibitor. Peptide VW reduces the contraction of capillary walls by preventing the conversion of angiotensin I to angiotensin II by ACE and inhibiting bradykinin breakdown.[23] Additionally, as it reduces eye edema and eye bags, it is used for eye care (in vitro).

As facial aging is a consequence of multi-dimensional factors, anti-aging products should be rigorously designed to eliminate potential therapeutic targets, to effectively and non-invasively retard and prevent senescence. In this study, the anti-wrinkle performance of a combination of multiple peptides, namely, acetyl hexapeptide-8, palmitoyl tetrapeptide-7, palmitoyl tripeptide-1, and dipeptide-2, was analyzed. In this clinical trial, the peptide mixture was used twice daily for 28 days by women with fine wrinkles and crow's feet at the outer corners of their eyes and/or visible signs of natural and photo aging on their face, for an efficacy analysis (including an estimation of the wrinkle parameters, hydration, skin elasticity, and firmness).

2 | MATERIALS AND METHODS

2.1 | Study design

A 28-day experiment was designed to evaluate the specific cosmetic efficacy of the product in 32 healthy women with naturally aged skin. The test product was applied from the first day until the 28th day. Subjects were advised to apply approximately 0.5 mL (half of a reclosable ampoule filled to 1 mL) of test product on the eye-area twice a day (in the morning and evening). After cleansing the face with water, the skin biophysical parameters of the subjects were measured at the baseline (the day before the first day), on Day 14, and on Day 28 of product use by the attending researcher. The trial was performed in accordance with the ethical guidelines detailed in the Declaration of Helsinki and it complied with other national and international regulations and guidelines involving human subjects.

2.2 | Participants

All participants for in-vivo testing were recruited by the Centre Testing International Co., Ltd. (Hangzhou, China). A total of 34 healthy Asian females, aged between 20 and 45 years, were enrolled in this study according to the inclusion and exclusion criteria. Two subjects withdrew from the study for personal reasons and 32 subjects completed the study. The inclusion criteria were

as follows: 20 years and older, with wrinkles, fine wrinkles, and crow's feet at the outer corners of the eye, and/or visible signs of facial natural and photo aging; and ability to communicate with the attending researchers to comprehend and follow the requirements of this clinical-dermatological application study. The exclusion criteria were as follows: acute or chronic skin diseases or dermatological disorders; serious internal or chronic diseases; consumption of drugs that may interfere with skin reactions (e.g., glucocorticoids, topical immune modulators, and antiallergics); tattoos on or near the test area; laser treatments, botulinum toxin injections, and filler injections on the test area within 6 months; known neoplastic diseases; pregnancy and breastfeeding; oral and/or topical cosmetic products that may affect test results within 2 weeks; cognitively impaired and/or unable to give informed consent; or any other condition which, in the investigator's opinion, may adversely affect the individual's ability to complete the study, or pose a significant risk to the individual.

2.3 | Formulation of the test product

The product was provided by UNILIPO Company and commercially available as a multi-peptide eye serum containing 10% Argireline® (acetyl hexapeptide-8), 4% Matrixyl® 3000 (palmitoyl tetrapeptide-7, palmitoyl tripeptide-1), and 2% Eyeliss™ (dipeptide-2, palmitoyl tetrapeptide-7, hesperidin methyl chalcone) as effective ingredients. According to the International Nomenclature of Cosmetic Ingredients, the ingredients of the test product were 1,3-butanediol, acetyl hexapeptide-8, hesperidin methyl chalcone, steareth-20, dipeptide-2, palmitoyl tetrapeptide-7, polysorbate-20, palmitoyl tripeptide-1, trehalose, caffeine, soluble collagen, L-carnosine, allantoin, carbomer, xanthan gum, avena sativa (oat) kernel extract, D-panthenol, idebenone, soy lecithin, triethanolamine, ceramide [NS], portulaca oleracea L. extract, propylene glycol, phenoxyethanol, 1,2-pentanediol, and *p*-hydroxyacetophenone.

2.4 | Skin assessment methods

The measurements were conducted under air conditioning (temperature, 21 ± 1°C; relative humidity, 50 ± 10%) after an acclimatization period of at least 30 min. The in-vivo skin biophysical parameters were evaluated using various biophysical techniques. The skin hydration of the stratum corneum (to a depth of 10–20 μm) was detected by capacitance measurements using a Corneometer CM825 (Courage & Khazaka Electronic GmbH). The capacitance of the conductor track changes with skin-surface hydration, which changes the dielectric constant of the precision capacitor; with increasing hydration, the permittivity of the skin increases, increasing the measurement results, which are indicated in relative units (Arbitrary Units = AU, min. = 0, max. = 130; uncertainty ± 3%). In this test, hydration was analyzed at the intersection of a vertical line from the eye with a horizontal line from the cheekbone.

Skin elasticity was determined using a Cutometer MPA580 (Courage & Khazaka Electronic GmbH) at the lateral horn of both eyes, the so-called "crow's feet" area. The measuring principle of the cutometer is based on the suction method, where negative pressure created in the device draws skin into the aperture of the probe, and releases it later (after a definite period of time). The penetration depth inside the probe was determined using a non-contact optical measuring system. The resistance of the skin to negative pressure (firmness) and its ability to recover (elasticity) in real time were analyzed by curves (penetration depth in mm/time). From these curves, a variety of parameters could be calculated, based on the elastic and viscoelastic properties of the skin, and skin aging. Among them, R-parameters represent the skin visico-elastic properties and R2 is related with the overall elasticity (ability of recovery), increasing with higher elasticity.[24] F-parameters represent the correlations between skin fatigue and firmness and F3/F4 is related with the firmness of the skin (resistance to the suction), increasing with higher firmness.

Wrinkle analysis around the "crow's feet" area and skin image acquisition were conducted using a PRIMOS CR (Canfield Scientific GmbH) based on the digital strip projection technique. A typical surface area roughness parameter Sa, calculated by an image analysis of gray levels, describes only the fine lines and/or microstructures of the skin wrinkles.[25,26] This analysis system assesses the number, length, and volume of visible wrinkles (in the area that lies in the middle of a horizontal line from the eye corner to the hair border) and provides a score, with a lower score indicating fewer wrinkles.

Additionally, the volunteers were asked to complete a satisfaction questionnaire regarding the anti-aging effects of the product at Day 14 and 28 of product use. For each subject, answers were recorded on a 5-point grading scale (1 = definitely not, 2 = probably not, 3 = neutrally, 4 = probably, 5 = definitely) and results were expressed as percentage of subjects in satisfaction. The satisfaction rating was calculated using the following formula: (subjects of scoring >3)/(total subjects). At all visits, the participants were questioned about concomitant therapies and adverse events.

2.5 | Statistical analysis

Statistical analysis was performed by SPSS v26 (IBM). The Shapiro–Wilk test was used to determine the normality of the data distribution. After testing for a normal distribution, a Paired Sample *T* test was performed. A *p*-value (probability of error) of 0.05 was regarded as statistically significant.

3 | RESULTS

3.1 | Skin biophysics analysis

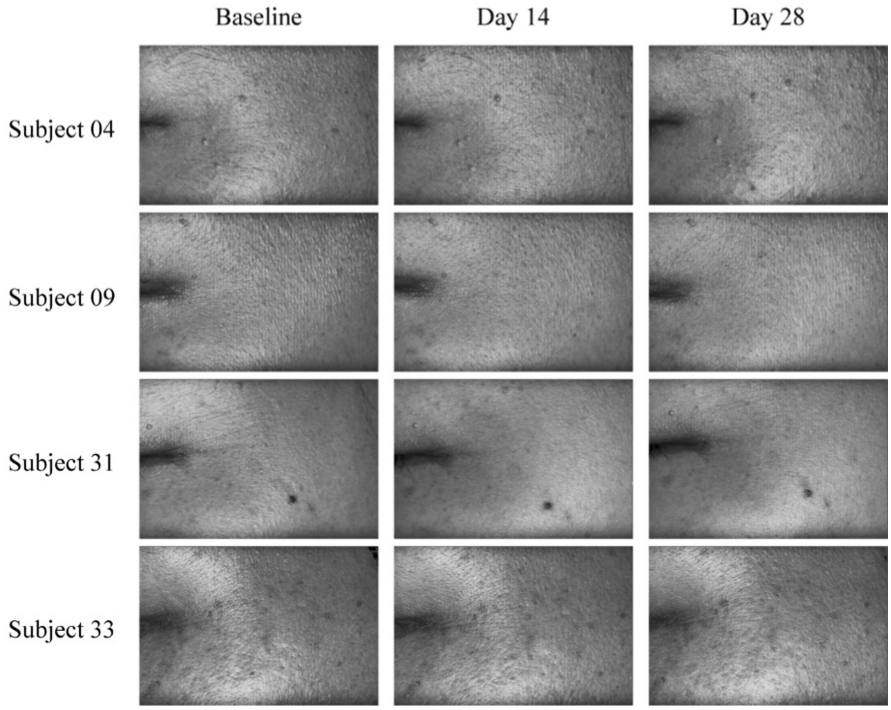
A total of 34 subjects were enrolled; 32 subjects with a mean age of 28.2 years ±6.9 years (within a range of 20–45 years) completed the study. The test eye serum was applied twice daily onto the

TABLE 1 Changes in the skin parameters.

Parameters	Baseline	Day 14	Day 28	Δ1	Δ2	p1	p2
Wrinkle number	732.28 ± 199.37	499.40 ± 136.80	488.50 ± 129.58	−31.80%	−33.29%	<0.001	<0.001
Wrinkle length (μm)	346.84 ± 64.72	285.81 ± 52.75	284.19 ± 51.82	−17.60%	−18.06%	<0.001	<0.001
Wrinkle volume (mm^3)	4.92 ± 1.41	4.38 ± 1.36	4.30 ± 1.26	−11.03%	−12.69%	<0.001	<0.001
Sa Value	18.74 ± 4.40	17.57 ± 4.41	17.32 ± 4.15	−6.23%	−7.59%	0.017	0.009
Hydration	48.30 ± 13.41	49.72 ± 10.08	50.39 ± 12.85	2.94%	4.34%	0.229	0.149
R2 ratio	0.79 ± 0.08	0.79 ± 0.10	0.80 ± 0.10	0.06%	1.23%	0.972	0.553
F3/F4 ratio	0.74 ± 0.08	0.74 ± 0.11	0.78 ± 0.10	−1.13%	1.83%	0.559	0.370

Note: Date at baseline, Day 14 and Day 28 were indicated as mean ± SD; SD, standard deviation; Δ1, percentage changes on Day 14 (vs. baseline); Δ1, percentage changes on Day 28 (vs. baseline); *P*1, *p*-value on Day 14 (vs. baseline) with the Paired Sample *T* test; *P*2, *p*-value day on Day 28 (vs. baseline) with the Paired Sample *T* test; Sa value, skin roughness; R2 ratio, skin elasticity; F3/F4 ratio, skin firmness.

FIGURE 1 Representative images of the skin-surface changes of the subjects.



periorbital region for 28 days by 32 subjects. As shown in Table 1, the physiological parameters were assessed on Day 14 and 28. All parameters related to wrinkle characterization indicated a statistically significant decrease in the number, depth, and volume of skin deformations ($p < 0.0001$ for each). In particular, the number of wrinkles decreased by 31.80% and 33.29% on Day 14 and 28, respectively. This was verified by a PRIMOS CR image analysis. As shown in Figure 1, wrinkling decreased significantly by Day 14 compared to the baseline, and this reduction was maintained till Day 28. The mean wrinkle-length was 346.84 (±64.72) μm at the baseline and 284.19 (±51.82) μm on Day 28 (a 18.06% reduction vs. baseline), whereas the wrinkle volume was 4.92 (±1.41) mm^3 at the baseline and 4.30 (±1.26) mm^3 on Day 28 (a reduction of 12.69% vs. baseline) (Table 1). The mean decrease in Sa values were 6.23% ($p = 0.017$) after 14 days and 7.59% ($p = 0.009$) after 28 days of treatment; thus, the eye serum showed a significant firming effect.

No significant changes in skin hydration or elasticity (at a definite point around the eye) were observed after 28 days of product use. However, the participants experienced a 4.34% ($p = 0.149$) improvement in hydration below the eye at the end of the experiment. Simultaneously, the R2 and F3/F4 ratios around the corner of the eye increased by 1.23% ($p = 0.553$) and 1.83% ($p = 0.370$), respectively, after 28 days of product use. Overall, the data indicated a definite improvement in skin firmness, with a high anti-wrinkle effect, on Day 28.

3.2 | Subjective evaluation

Figure 2 shows the results of a questionnaire on the efficacy and cosmetic qualities of the multi-peptide eye serum. Subject satisfaction with the test products remained high, with 87.50% and 75.00%

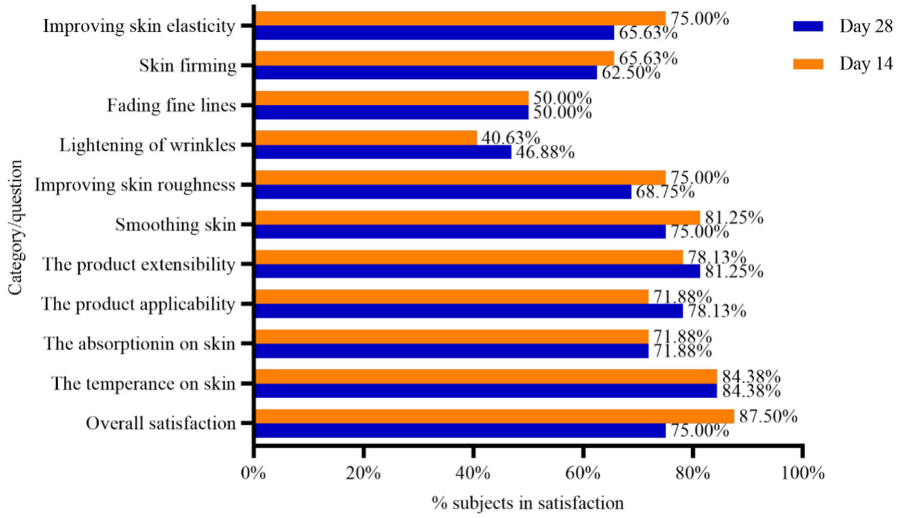


FIGURE 2 Subject questionnaire results for Day 14 and Day 28.

of the subjects reporting overall satisfaction with the appearance of their skin on Day 14 and 28, respectively. Additionally, subjects indicated that their skin looked more elastic (75.00%), firm (65.63%), and smooth (81.25%), with fewer fine lines (50.00%) and lesser roughness (75.00%), after 14 days of product use. A slight decrease in the satisfaction (of these indicators) occurred on Day 28, except for the desalination of fine lines, which remained consistent. After 28 days of product use, subjects reported an average increase in the reduction of wrinkles (40.63% on Day 14 and 46.88% on Day 28), with an increase in the satisfaction with the product extensibility (78.13% on Day 14 and 81.25% on Day 28) and applicability (71.88% on Day 14 and 78.13% on Day 28). Furthermore, the satisfaction levels of the absorption and temperature of the test product were 71.88% and 84.38%, respectively, on both Day 14 and 28.

Additionally, no adverse skin reactions (from a clinical dermatological viewpoint) were observed in the test areas, such as burning, itching, redness, and papule formation. Thus, the product did not exhibit a high potential for irritation and sensitization.

4 | DISCUSSION

The cumulative consequence of intrinsic and extrinsic factors on skin aging results in a loss of elasticity and firmness and an increase in skin fine lines, wrinkling, and sagging. The objective of this study was to evaluate the cosmetic efficacy of a multi-peptide eye serum as a daily-use skincare product for aged skin around the eye area in women, 20–45 years of age, with visible signs of natural and photo aging on their face. Data recorded after 14 days of product use indicated a measurable reduction in the lines, depth, and volume of wrinkles compared to the baseline. Additionally, a significant increase in skin firmness was observed; the Sa value around the canthus increased from 18.74 to 17.32. Collectively, an analysis of the clinically graded efficacy parameters indicated an improvement in the overall skin appearance on product use, which was further substantiated by clinical photography. Moreover, the participants reported high improvements in their overall skin-wrinkle score and firmness; thus, considering the self-perceived skin appearance, serum supplementation had a significant anti-wrinkle effect.

The skin aging results described in this study are consistent with those reported in previous studies examining polypeptide supplementation. In-vivo tests analyzing the supplementation of SpecKare EyeS100 indicate considerable reductions in the wrinkle area ratio after 14 days (by 32.48%) and 28 days (by 43.56%).[27] Similar improvements in facial wrinkles have been reported for Matrixyl-3000. Studies with 24 men conducting a half-face daily application for 2 months indicate that a 4% formulation of a combinations of peptides reduces the main-wrinkle mean depth and volume by 10.2% and 17.1%, respectively.[28] As this study analyzes improved ingredients for facial wrinkles, it cannot be directly compared to the present study. The high wrinkle score observed in the current study could be attributed to the synergistic effects of the multi-peptides used. According to Flagler et al.,[29] the incorporation of two peptides (Pal-KT + RGS) or four peptides (Pal-KTTKS + Ac-PPYL + Pal-KT + RGS) synergistically primes the regenerative capacity of skin cells, initiating a key NRF2/CCL2/EGF signaling axis involved in orchestrating tissue repair.

The active ingredients of the serum used in this study are signal peptides, neurotransmitter-inhibiting peptides, enzyme inhibitor peptides, and other functional peptides. The anti-wrinkle effects of this serum can be attributed to multiple different mechanisms. Palmitoyl tetrapeptide-7 increases skin firmness, smoothness, and elasticity by reducing the IL-6 and dipeptide-2 levels; additionally, it reduces eye edema by regulating blood microcirculation. Thus, it improved skin firmness and reduced the appearance of fine lines and wrinkles in this study. However, no significant skin-hydration improvement was observed here, possibly due to insufficient moisturizing factors in the product that inadequately protected the skin surface from moisture loss.

Previously published studies[30–32] have primarily focused on the combination of peptides with antioxidants for the topical treatment of aging (with enhanced performance compared to antioxidants alone). Besides, the anti-wrinkle effect of plant extracts has recently attracted extremely interest.[33–35] Most aim to slow skin

aging by repairing the disruption and fragmentation of the ECM and preventing the loss of collagen and elastin. Although a consensus can be reached on some points of view published, skin aging is a complex and multifactorial biological process, and it is insufficient to consider only two aspects during analysis. Nguyen et al. showed that a peptide-based treatment serum was effective in improving expression lines, wrinkles, and skin health in female subjects aged 35–60 years with mild-to-moderate fine lines and wrinkles after 12 weeks of application.[36] Although botanical extracts, neuromodulating peptide and reparative peptides in the serum have statistical significance in reducing the appearance of eye lines and eye wrinkles, they only have effects in terms of inducing muscle relaxation and collagen production. In our study, acetyl hexapeptide-8, a typical neuropeptide widely applied topically on the skin, helped to inhibit muscle contraction, further attenuating facial expression. as messenger molecules, palmitoyl tetrapeptide-7 and palmitoyl tripeptide-1 act synergistically to activate certain genes involved in the process of ECM renewal and cell proliferation. In addition, dipeptide-2 inhibited ACE and increased lymphatic circulation, contributing to treat of puffy eyes. Together, as a serum compounded entirely with peptides, this new topical eye serum supported the improvement of the skin aging appearance by reducing skin fatigue, promoting collagen production, and improving blood microcirculation from both intrinsic and extrinsic skin-aging factors. Therefore, this study is more relevant than previously published studies. Additionally, for serum application, it is vital to consider multiple evaluation indicators to observe changes in the skin improvement process accurately.

Independently, positive responses to the product-evaluation questionnaire administered at the end of the study confirmed consumer acceptance.

5 | CONCLUSIONS

In general, in this study, wrinkle characterization indicated a statistically significant decrease in the number, depth, and volume of skin deformations from the baseline on product use. Variations in skin hydration, elasticity, and firmness were reported in the evaluation instrument. There is a large discrepancy between objective and subjective assessments for fine lines and wrinkles. While statistical significance is achieved in objective assessments of lines and wrinkles, the magnitude of change may not be sufficient as subjects did not rate these very high in satisfaction. Moreover, no adverse events related to the test products were reported. A questionnaire survey of participants who used the multi-peptide eye serum for 28 days indicated that their skin (around the eyes) looked smoother and more elastic. Furthermore, the subjects reported high levels of satisfaction with the cosmetic qualities. Additionally, unlike previously reported studies on anti-aging ingredients, this study provides a multiple-dimensional targeted treatment for senescence. Overall, the results of this study support the application of anti-aging peptide eye serums to improve the skin of the periorbital region (with aging due to intrinsic and extrinsic factors). This study provides critical insights that could facilitate the development of effective anti-aging products based on the mechanisms of aging and skin structure. However, larger multicenter controlled trials, other trials including middle-aged and men, and longitudinal studies are required to elucidate and validate the conclusions drawn from this study.

AUTHOR CONTRIBUTIONS

Haowei Chen and Fang Wang performed the research. Fang Wang, Huabing Zhao, Xihong He, Fengzhu Li and Qingying Shi designed the research study. Haowei Chen and Fang Wang and Dongxiao Chen contributed essential reagents or tools. Haowei Chen, Huabing Zhao, Fengzhu Li, Bingjie Zhang and Qingying Shi analyzed the data. Fengzhu Li wrote the original draft. Huabing Zhao and Qingying Shi reviewed and edited the draft. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the ethic committee of Tianjin University of Science & Technology. Subjects were consented by an informed consent process that was reviewed by Tianjin University of Science & Technology. The study was performed in accordance with the ethical guidelines detailed in the Declaration of Helsinki and it complied with other national and international regulations and guidelines involving human subjects.

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