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The Effects of a Peptide Complex Cream for Improving Skin Photoaging

QIAO TANG, WENTING CAO, WENFANG WANG, JICHUN YANG, JICHAO QIAN AND DANQI DENG
Department of Dermatology and Venereology, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, China (Q.T., W.C., W.W., D.D.)
Dermatology Department, Medical Center Hospital of Qionglai, Chengdu, China (Q.T.)
Department of Epidemiology and Biostatistics, School of Population Medicine and Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (J.Y.)
Zhuhai Yasha Biotechnology Co, Ltd., Zhuhai, Guangdong, China (J.Q.)

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Synopsis

Bioactive peptides are different peptides composed of natural amino acids in different compositions and arrangements. They are now widely used in skin care products, but there are few studies on anti-photoaging. This article aims to investigate the efficacy of a peptide complex cream in the treatment of skin photoaging. 80 female subjects were recruited and assigned to 2 groups (40 in each group) based on a randomized, double-blind, placebo-controlled, parallel-group protocol, and were topically treated with either a peptide complex cream or a base cream. Subjective assessment was done by a physician and a non-invasive skin examination was performed at weeks 0, 2, 4, 6, 8 during the treatment and then again 4 weeks after the treatment was complete. The results showed that there was no significant improvement in facial wrinkles and color spots in the peptide complex cream group, but there was significant facial improvement ($P < .05$) in both the Dermoscopy Photoaging Scale (DPAS) scores and with acne. The peptide complex cream can safely and effectively improve some skin photoaging symptoms, but the effect on wrinkles and color spots is not obvious in the short term.

INTRODUCTION

Skin photoaging is a chronic inflammation of the skin caused by long-term exposure to ultraviolet radiation. It is clinically manifested by symptoms such as skin roughness, dryness, increased wrinkles, hyperpigmentation, laxity, and capillary dilation, with a small number of people developing benign or malignant skin tumors.[1] The global anti-aging product market was estimated to have reached US $34.2 billion in 2020 and is expected to reach US $47.8 billion by 2027. Therefore, anti-skin photoaging is a very promising area of research.[2]

*Address all correspondence to Danqi Deng, danqid128@sina.com and Jiehao Qian, 825946043@qq.com

The peptide complex cream used in this study is Yashaer Polypeptide Hydrating Cream (Zhuhai Yasha Biotechnology Co., Ltd., Zhuhai, Guangdong, China). The core ingredients include carnosine, palmitoyl pentapeptide-4, and acetyl hexapeptide-8. All 3 core ingredients are present in the cream at a concentration of 2%. Carnosine is a dipeptide (β-alanyl-L-histidine) that induces skin rejuvenation and anti-aging via telomere shortening inhibition, antioxidant activity, and anti-glycosylation (carbonyl scavenging).[3] Palmitoyl pentapeptide (Lys-Thr-Thr-Lys-Ser, pal-KTTKS) promotes the production of the extracellular matrix (ECM) along with type I and type III collagen.[4] Acetyl hexapeptide-8, also known as Argireline (Ac-Glu-Glu-Met-Gln-Arg-ARG-NH_2), has an anti-wrinkle effect similar to that of botulinum neurotoxin, which relaxes muscles and reduces wrinkle formation.[5] This study utilized a randomized, double-blind, placebo-controlled, parallel-group method to investigate whether the peptide complex cream had the capability to improve facial wrinkles, pigmentation, roughness, and pores in order to understand the tolerance and adverse reactions of the subjects to the peptide complexes.

MATERIALS

Yashaer Polypeptide Hydrating Cream, Yashaer base cream, and Yashaer Icy Spring Isolation Emulsion (Zhuhai Yasha Biotechnology Co., Ltd., Zhuhai, Guangdong, China).

METHODS

SUBJECTS

Subjects were enrolled from March 2021 to September 2021. The study was approved by the ethics committee of the Second Affiliated Hospital of Kunming Medical University, and all enrolled subjects signed the informed consent form. In the treatment group, Yashaer Polypeptide Hydrating Cream and sunscreen (Yashaer Icy Spring Isolation Emulsion) were applied to the face. In the control group, Yashaer base cream and sunscreen (Yashaer Icy Spring Isolation Emulsion) were applied to the face.

This study was a placebo-controlled superiority clinical trial and the improvement rate of facial wrinkles in the subjects was the primary endpoint of the study. Based on a review of literature and clinical experience, the improvement rate of facial wrinkles was 10% in the control group and 40% in the treatment group. Using a one-sided test with a significance level of $\alpha = 0.05$ and a power of 90%, the total sample size for the two groups was calculated to be $N = 64$. Considering a potential 20% dropout rate, a sample size of $N1 = 64/0.8 = 80$ was required. Thus, at least 40 subjects were required in each group for a 1:1 assignment. The inclusion criteria for subjects were: (1) participates in the study voluntarily, is able to provide written informed consent, and is able to voluntarily accept and comply with the trial treatment, follow-up, and assessment requirements; (2) meets the diagnostic criteria for photoaging with a Glogau grade of II–III; (3) female, aged from 45–55 years; (4) indoor workers with no history of prolonged exposure to the sun within the last month (e.g., traveling, visiting the beach, hiking snowy mountains, etc.). The exclusion criteria for subjects were: (1) received relevant cosmetic treatments (e.g., laser, radiofrequency, photons, botulinum toxin injection, hyaluronic acid injection, chemical peeling, etc.) within the last month; (2) use of oral or topical use of relevant medications (e.g., tretinoin, steroids, etc.) that can affect test results within the last month; (3) pregnant or breastfeeding females;

(4) patients with psychiatric disorders; (5) alcohol or drug abuse; (6) patients with systemic diseases or severe skin conditions; (7) and history of photosensitivity or keloid disease.

RANDOMIZATION AND BLINDING

The statistician, who was independent of this clinical trial, generated a random sequence of 80 random numbers using a seed in R3.5 and generated a random assignment table. Double-blinding was set up by a nurse independent of this study, who pre-labeled identical looking, unmarked Yashaer Polypeptide Creams and Yashaer Base Creams with numbers according to the randomly generated assignment table. The blind code envelope was also prepared by the nurse. Unless the blind code was opened urgently (the blind breaking rate must be less than 20%), the blind code envelope would not be opened before the end of the test. Neither the statistician nor the nurse was involved in this clinical trial, and no one involved in the study had access to the randomized data until the study was completed and the database was locked.

EXPERIMENT PROCEDURES AND EVALUATION METHODS

After facial cleansing, the subjects evenly applied Yashaer Polypeptide Hydrating Cream or Yashaer Base Cream (without active ingredients) to the face, once in the morning and once in the evening. Both groups of subjects evenly applied sunscreen (Yashaer Icy Spring Isolation Emulsion) to the face, once in the morning and once after noon. For each application, a dosage of 1 fingertip unit (.5g) was taken, dabbed on the face, and spread carefully and evenly with the finger. The treatment period lasted 8 weeks and the followup period lasted 4 weeks.

Subjective physician evaluation and non-invasive skin examination were performed at week 0 (pretreatment), at treatment weeks 2, 4, 6 and 8, and then 4 weeks after treatment was complete. For the subjective physician evaluation, Chung's standardized wrinkle[6] (grade 0-7) was used to rate subjects for wrinkles. For the noninvasive skin examination, the dermoscopy Photoaging Scale (DPAS) was measured by dermoscopy (DERMOSCOPY-II, Beijing Dermat Speedy Recovery T&D Co., Ltd., Beijing, China) and the total score of DPAS[7] was calculated. Next, six indicators (panoramic (RGB) spots, RGB pores, RGB roughness, RGB wrinkles, ultraviolet (UV) acne, and UV pigmentation) of the frontal, left, and right views of the subjects' faces were measured by a computerized magic mirror skin analyzer-1200 (FS-1200, CBS Taiwan Medical Skin Analysis, Taiwan, China). The indicators of frontal, left, and right views were then averaged.

STATISTICAL ANALYSIS

Statistical analysis was performed (IBM SPSS Statistics 26.0, IBM, Armonk, New York, USA). The Mann-Whitney U test was used for baseline analysis to compare the balance of the basic data between the two groups. Mean $\pm$ standard deviation or median (interquartile range) were used for continuous variables, and rank mean was used for grade data. For the comparisons of continuous variables in the efficacy analysis between the test group and the control group, the independent t-test was used for data with a normal distribution and

Table I
Baseline Characteristics of Subjects in Test and Control Groups

Group	Age (y)	Outdoor Sun Exposure Duration (min/day)	Glogau Photoaging Classification Standard Grade I–IV (rank mean)	dropout rate (n,%)
Test group (n = 40)	48.00 (3.75)	40.00 (18.75)	40.50	4(10.0%)
Control Group (n = 40)	49.50 (4.75)	45.00 (23.75)	40.50	1(2.5%)
Z	–1.800	–1.410	0.000	
P	0.072	0.159	1.000	

Note: Nonnormal measurement data are described using the median (interquartile range); grade data are described using the rank mean.

the Mann-Whitney U test was used for data with a non-normal distribution. The Mann-Whitney U test was used for the comparisons between both groups of grade data.

RESULTS

GENERAL INFORMATION AND ANALYSIS

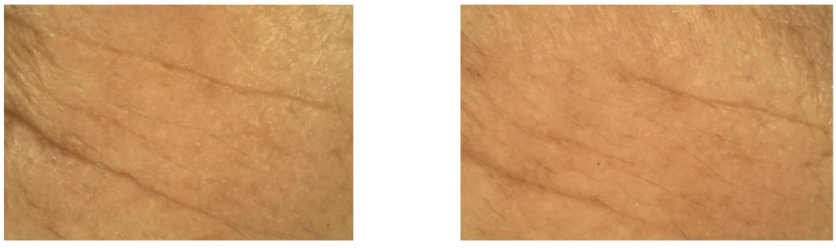
Data were collected from a total of 80 female subjects aged between 45–55 years. The total dropout rate was 6.25%, with a marginally higher rate in the treatment group than in the control group (10.0% vs. 2.5%, Table 1). For the 5 subjects who were lost to follow-up, missing values in efficacy data were imputed with outcomes from the last visit.

BASELINE ANALYSIS

Before treatment (day 0), the basic data on the subjects were compared between the treatment and control groups, including age, outdoor sun exposure duration, and the degree of skin photoaging (Glogau photoaging classification standard (grade I-IV)). There were no statistically significant differences found between the two groups for all three indicators ($P > .05$, Table 1), indicating that efficacy analysis could be properly carried out.

EFFICACY ANALYSIS

Between-group comparisons of the Chung's standardized wrinkle scale and RGB wrinkle showed no statistically significant differences between the two groups at all follow-up points ($P > .05$). Decrease in the length and depth of coarse wrinkles and decline in the number of fine wrinkles were noticed in some subjects of the peptide complex cream treatment group (Figure 1). Between-group comparison of DPAS identified a statistically significant difference between the treatment and control groups at treatment week 8 ($P = .047$), suggesting that the treatment group was superior to the control group (Figure 2). In addition, reduction in hyperpigmentation was noticed in some subjects of the peptide complex cream treatment group (Figure 3). At all follow-up points, there were no significant differences between the treatment group and the control group in RGB spots, RGB pores, RGB roughness, or UV pigmentation ($P > .05$). Statistically significant differences were observed in UV acne between the treatment and control groups at treatment weeks 2 ($P = .046$) and 4 ($P = .027$).



(a) Week 0 (c) Week 8

Figure 1. Peptide complex cream group. At weeks 8, coarse wrinkles were shorter in length and shallower in depth and the number of fine wrinkles were decreased compared to week 0.

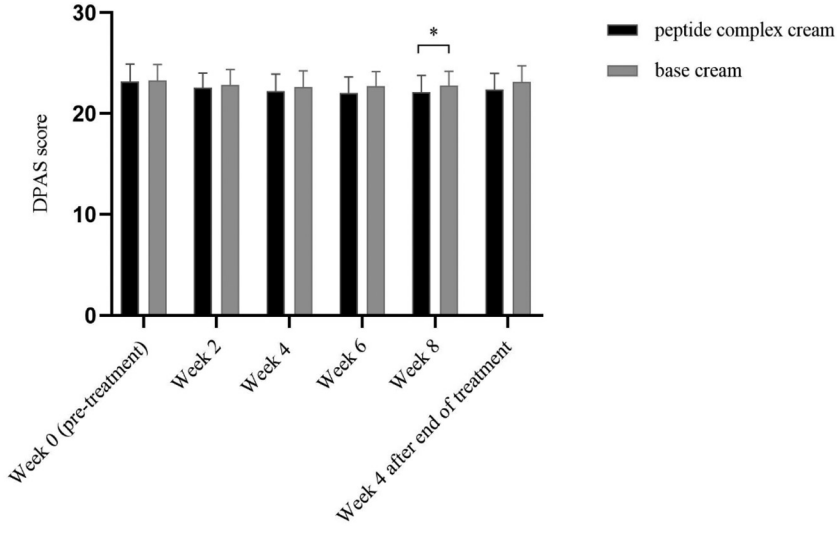
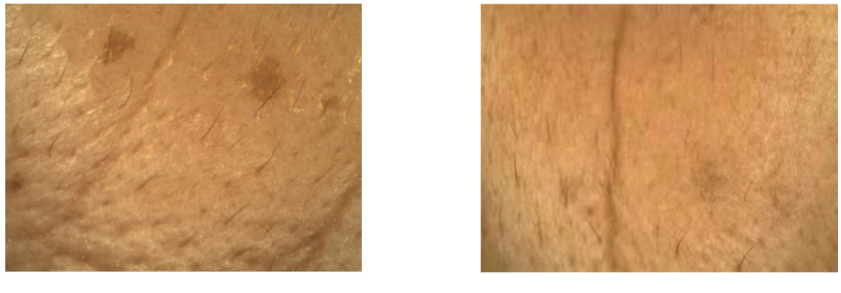


Figure 2. Changes in DPAS parameters in subjects in the peptide complex cream group and the base cream group. Data expressed as mean ± SD; * indicates the *P*-value between the test and control groups, and * indicates $P < .05$.



(a) Week 0 (c) Week 8

Figure 3. Peptide complex cream group. Hyperpigmentation was reduced at week 8 compared to week 0.

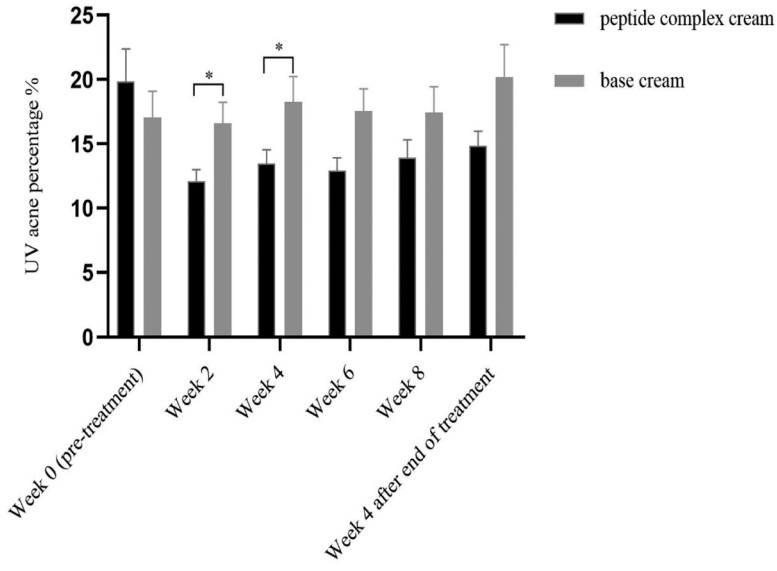


Figure 4. Changes in UV acne parameters in subjects in the peptide complex cream group and the base cream group. Data expressed as mean ± SEM; * indicates the *p*-value between the treatment and control groups, and * indicates $P < .05$.

The improvement in UV acne was significantly more pronounced in the treatment group than in the control group (Figure 4).

ADVERSE REACTIONS

Among the 80 subjects, 2 subjects in the treatment group developed mild erythema, minor scaling, and mild pruritus in the second week of treatment, which were all tolerable. All symptoms were cured spontaneously after 1 week. No adverse reactions such as persistent erythema, blistering, profuse scaling, or severe pruritus were observed.

DISCUSSION

In this study, there was no significant improvement in facial wrinkles and color spots, but the dermoscopic observations revealed reduction in the number of fine wrinkles, improvement in the depth and length of coarse wrinkles, and lighter color spots in some subjects in the peptide complex cream group. In this study, DPAS scores of the peptide complex cream group were significantly decreased at week 8, indicating that the peptide complex cream was capable of significantly improving the signs of photoaging in the subjects. Although improvements in facial hyperpigmentation and wrinkles were observed through skin microscopy, the calculated DPAS scores showed only slight differences. These differences may be attributed to the fact that DPAS scores are based on the quantity of hyperpigmentation and wrinkles without considering changes in the color of hyperpigmentation or the depth of wrinkles. Therefore, even if the color of hyperpigmentation lightens and the depth of wrinkles diminishes, the DPAS scores remain unchanged due to the unchanged quantity

of hyperpigmentation and wrinkles. This difference explains the minor disparities observed in the statistical results of hyperpigmentation and wrinkles in our study. Results from the FS-1200 measurement showed significant improvement in UV acne in the peptide complex cream group at weeks 2 and 4. These results show that although the peptide complex cream cannot significantly improve facial spots and wrinkles in a short time, it can reduce the score of DPAS and comprehensively improve facial photoaging symptoms. Additionally, the subjective rating of wrinkles has a wide range, making it suitable for preliminary screening but not for evaluating subtle changes. Therefore, the results of subjective wrinkle rating were also not significant. Future research should consider selecting more appropriate tools for assessing wrinkles and pigmentation deposition. The results of this study would have been more accurate if the left and right sides of the face were used as the treatment and control, respectively, but since the subjects found this protocol hard to accept, it was not implemented in the end.

According to literature reports, the core components (three polypeptides) of the peptide complex cream have the effect of improving wrinkles and color spots. Applying carnosine-containing creams to the face could alleviate skin dryness and make skin firmer and more supple.[8-10] Palmitoyl pentapeptide-4, a derivative of KTTKS, can achieve the antiaging effects of wrinkle reduction and skin texture improvement by stimulating production of the extracellular matrix and type I and type III collagen.[4,11] Acetyl hexapeptide-8, also known as argireline, can reduce the repetitive contraction of the muscles of facial expression by competitive inhibition, thus attaining anti-wrinkle effects by reducing hyperkinetic facial lines.[4,12] A multicenter, placebo-controlled, randomized clinical study showed an overall anti-wrinkle efficiency of 48.9% and a significant decrease in wrinkle depth in the argireline group.[13] To minimize the risk of allergies, irritations, and other side effects, the peptide complex cream used three types of peptides at a lower concentration of 2% each. However, previous studies have shown that using a concentration of 10% for peptides or acetyl hexapeptide yields more significant results.[8,9,13] This may also be one of the reasons why we did not observe significant results in wrinkle and pigmentation improvement.

In this study, among the various indicators in FS-1200, the UV acne index was particularly significant. It demonstrated that the peptide complex cream exhibited significant improvement in acne starting from the second week. There appears to be no current literature on acne improvement by peptide complex creams, but one study has explored the effect of acetyl hexapeptide-8 on certain skin diseases by applying a gel cream containing 10% acetyl hexapeptide-8 to scarred or aging skin areas to treat skin conditions.[14] The study found that the gel cream may improve the appearance of certain skin disorders. Acetyl hexapeptide-8 may help improve skin scarring, hidradenitis, and other conditions. Since acne is associated with excessive oil secretion from the sebaceous glands, acetyl hexapeptide-8 may alleviate facial acne by dampening local sympathetic excitation or reducing local muscle contraction, thus diminishing oil secretion. Although acetyl hexapeptide-8 may play a role in improving UV acne, this speculation requires larger and more in-depth studies in the future. Furthermore, the higher prevalence of acne in the age group of 45-55 years (typically less prone to acne) could be attributed to factors such as excessive sebum production and enlarged pores among these participants. It is possible that they had previously used skincare products inappropriately or lacked proper sun protection. However, after discontinuing their previous skincare products and using our product along with appropriate sunscreen, improvements in acne were observed.

This study investigated the reasons for the loss of follow-up, which were all due to busy work schedules. The dropout rate was higher in the treatment group compared with the control group, which may also lead to the deviation of the results in the treatment group. In addition, during this study, only 2 subjects experienced symptoms of dryness, mild erythema, and mild scaling at week 2, which were resolved spontaneously after one week, possibly due to seasonal changes in windiness and decreased humidity. Therefore, it was found that the peptide complex cream was safe to use and tolerable for subjects.

CONCLUSIONS

The current study demonstrated that the peptide complex cream containing carnosine, palmitoyl pentapeptide-4, and acetyl hexapeptide-8 can improve partial photoaging symptoms of the face, and it is a safe and tolerable treatment for skin photoaging. This study revealed for the first time the unique efficacy of the peptide complex cream in improving acne, which may be more extensively investigated in future studies. The effect of the peptide complex cream on wrinkles and color spots needs to be further studied by increasing the research time and sample size.

AUTHOR CONTRIBUTIONS

Qiao Tang and Wenting Cao contributed equally to this article and are co-first authors. This study was planned and designed by Danqi Deng, Jiehao Qian, Wenfang Wang and Wenting Cao. Jichun Yang contributed to study design. Qiao Tang contributed to data collection and data analysis. Qiao Tang and Jiehao Qian drafted this paper. All authors critically revised this paper and approved the final version to be published. The order of the co-first authors was determined based on the extent and duration of the work each contributed to the project.

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ETHICAL STATEMENTS

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (S-PJ-2020-147) and registered on the Chinese Clinical Trial Registry (ChiCTR2100042842).

PATIENT CONSENT FOR PUBLICATION STATEMENT

All enrolled subjects signed the informed consent form.

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