Am J Transl Res 2022;14(12):8562-8571
www.ajtr.org /ISSN:1943-8141/AJTR0146659

Original Article

An artificially designed elastin-like recombinant polypeptide improves aging skin

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Received September 23, 2018; Accepted November 13, 2022; Epub December 15, 2022; Published December 30, 2022

Abstract: Background: As a substrate for cell growth, elastin can promote the regeneration and remodeling of the epidermis, which plays an important role in delaying skin aging. However, elastin proteins are more than 700 amino acids long and cannot be absorbed through the skin, which prevents the direct utilization of elastin in the prevention and treatment of aging skin. Methods: We designed an elastin-like recombinant polypeptide (ELR) which could be absorbed through the skin based on the property of hexapeptide VGVAPG. Thirty healthy Chinese Han female participants which met the criteria were enrolled in this study and all of them completed the tests including elasticity, tightness, and wrinkle detection. The participants used this polypeptide for 4 weeks and were tested in three visits: one day before trial started (D0), and 14 and 28 days after the trial (D14 and D28, respectively). Paired t-tests or Wilcoxon signed-rank tests for non-parametric measures were used to determine the difference between D0 and D14, or D0 and D28. Results: The skin elasticity level in the thirty participants was significantly increased after using ELR for 28 days (P=0.024), and the average value of skin firmness (Uf) declined from 3.313 (D0) to 3.292 (D14) and 3.265 (D28), although there was no statistically significant difference between treatment and pre-treatment. Furthermore, the wrinkle count (D14: P<0.001; D28: P<0.001), wrinkles volume (D14: P<0.001; D28: P=0.008), and wrinkles area (D14: P<0.001; D28: P<0.001) of Crow's feet were significantly improved by using ELR for 14 days or 28 days. Conclusion: Continuous use of ELR could significantly improve skin elasticity and reduce wrinkles.

Keywords: Elastin, ELR, elasticity, wrinkles

Introduction

As the largest organ of the human body exposed to the external environment, the skin protects us while being exposed to the effects of external and internal aging factors, causing skin aging [1]. The typical characteristics of aging skin include wrinkles, loss of elasticity, relaxation, and roughness, along with the loss of moisture, the reduction of superficial fat, and pigmentation [2].

Since skin aging is caused by a combination of intrinsic and extrinsic factors, and as a result it can be divided into both intrinsic aging and extrinsic aging [3]. Intrinsic aging is regulated by genetic factors, and the most significant histological change is the decreased proliferation of skin basal layer cells which increases age-like effects, also known as the process of cell senescence [4]. Cell senescence leads to a decreased ability of skin fibroblasts to synthesize collagen and elastin, thereby leading to a

decreased production of the extracellular matrix, with an increased melanin production in melanocytes, resulting in epidermal atrophy, dermal thinning, wrinkle and elastic loss, and ultimately skin aging [5].

The progressive reduction and loss in the density of collagen and elastin in the skin are a sign of both intrinsic and extrinsic skin aging. Elastin is an extracellular matrix protein and endows vertebrate tissues with unique physiological elasticity [6]. It provides elasticity to tissues such as arteries, lungs, skin, and elastic cartilage, and also plays a key role in maintaining healthy cells [7]. As the main component of elastic fibers, elastin is composed of crosslinked convective elastin, which is then crosslinked and combined with microfibers to form elastic fibers, so that the skin has ductility and reversible recoil, enabling it to withstand repeated mechanical deformation pressure and avoid irreversible damage [8]. Although it accounts for only 2% of dermal components, elastin is important in inhibiting the formation of wrinkles and maintaining skin homeostasis, which is indispensable to the young, healthy state, and normal function of skin [9].

Extrinsic aging is caused by environmental factors, including solar radiation, air pollution, and cosmetics, which will in turn accelerate intrinsic aging [10]. Studies have shown that reactive oxygen species (ROS) play an important role in skin aging [11]. ROS can activate numerous signaling pathways, resulting in the activation of the transcription of various matrixes metalloproteases (MMP), thereby leading to abnormal matrix degradation and the accumulation of non-functional matrix components [12]. Furthermore, MMP can degrade various protein components in the extracellular matrix, including collagen and elastin, thus accelerating the process of skin aging [13]. “Photoaging”, an exposure to ultraviolet radiation, is the main factor of extrinsic aging, accounting for approximately 80% of facial aging [14]. Ultraviolet radiation can also generate ROS in the skin, causing destructive oxidative stress and mediating inflammatory reactions. It reduces the activity and the renewal of keratinocytes, thus resulting in dry and desquamated skin [15]. Moreover, during photoaging, the number of fibroblasts in the dermis decreases gradually, while the synthesis of collagen and elastin slows down and decomposition accelerates. Hence, the symptoms of “photoaging” are more severe than intrinsic aging. Many biochemical and histological studies on photoaging skin show that the abnormal accumulation of elastic fibers and the pathological changes such as disorganized and damaged collagen fibers in the dermis lead to the formation of skin wrinkles [16].

Although elastin is considered an inert protein, it is strongly resistant to protease degradation with a low turnover rate in healthy tissues and a half-life of more than 70 years, it is vulnerable to many factors, such as disease, solar radiation, free radicals and inflammation [18]. Elastin will be gradually degraded, crosslinked, and broken down under the exposure of harmful factors in the environment. In addition, the production of elastin declines as the body matures. Together, these factors contribute to the loss of structural integrity and elasticity of the skin. Moreover, the reduction of subcutaneous fat causes skin relaxation, which shows the symptom of skin aging [19].

Elastin not only provides mechanical elasticity for the skin but also acts as a substrate for cell growth to promote the regeneration and remodeling of the epidermis, which plays an important role in delaying skin aging [20]. However, elastin protein is usually more than 700 amino acids long and cannot be absorbed through the skin. Hence, currently, several synthetic forms of elastin have been designed, including: VGVAPG, GPGVGAGVP, GLGBGAGVP, PGAIPG, and LREGDPS, among which elastin-derived peptides, the VGVAPG hexapeptide, is known for its chemotactic activity and metalloproteinases upregulation properties. VGVAPG hexapeptide not only has chemotactic activity against monocytes, fibroblasts, and tumor cells [21, 22], but it also activates metalloproteinases [23, 24]. Therefore, VGVAPG oligopeptide has been widely used as a cosmetic and skin care additive [25]. In this study, by bioinformatics analysis and codon optimization, we designed an elastin sequence based on this hexapeptide to investigate the ameliorative effect of this sequence on the human skin.

Material and methods

Design of elastin-like recombinant polypeptide (ELR)

We searched for elastin protein sequences by transcript XP_011514170.1 in the Proteins

database of NCBI, and two elastin types with less than 300 amino acids were removed. MEGA and GeneDoc were used to conduct Multiple Sequence Alignment (MSA) on human elastin. The tertiary structure of transcript XP_011514170.1 was predicated by RoseTTA-Fold. Since the native elastin protein cannot be absorbed by the skin due to the macromolecular property of elastin, we designed one polypeptide sequence of elastin (less than 50 kd) based on hexapeptide VGVAPG, which can be absorbed through the skin with stable expression and high production.

Study participants

This study was conducted by SGS-CSTC Standards Technical Services Co., Ltd. Guangzhou Branch, which is a China national Compulsory Product Certification (CCC) and European Notified Bodies (EU NB) designated certification body. This research was approved by the Biomedical Ethics Committee of Anhui Medical University (20190366) and research protocols were conducted in accordance with the Declaration of Helsinki on human subjects.

Participants included in the study met the following inclusion criteria:

1. Healthy women aged 30-55 years.

2. Self-assessed as slacked facial skin and losing elasticity and firmness.

3. Had visible Canthus wrinkle.

4. No obvious skin lesions, scars, or hair in the test area.

5. Can cooperate well with the experimenter.

Participants were excluded from this study if the participants:

1. Can't read or understand the contents of study, or do not voluntarily sign the informed consent form.

2. Unwilling to comply with required tests.

3. Have participated in other clinical trials during the past 30 days.

4. Used other skin care products during the test.

5. Pregnant or breastfeeding or planning for pregnancy during the test.

6. Had infectious skin disease or atopic dermatitis.

7. Had nevus, telangiectasia, and other skin abnormalities on the test area.

8. Had received skin peeling, skin treatment, or immunosuppressive therapy within 3 months.

9. Have received systemic steroid therapy or phototherapy within 1 month.

10. Had used external medicine or special efficacy cosmetics (such as skin Whitening and repairment) in the test area or exposed to hot sun or ultraviolet rays within 1 week.

11. Had lesions in the test area that made evaluation difficult.

12. Had experienced severe reaction or allergy to cosmetics, drugs, or natural light.

A total of 42 participants were recruited, and 33 participants (aged 30-55 years) were eligible and included in this study.

Study design and intervention

Freeze-dried ELR powder was dissolved in solvent at the concentration of 0.1 mg/ml. Then, the participants were advised to gently apply proper amount of completely dissolved essence on one side of cleaned cheek or outer corner of one eye every morning and evening for 28 days. The study was conducted over 4 weeks and consisted of three visits: before application (day 0, D0), 14 days after application (D14), and 28 days after application (D28).

Facial grading and analysis

All the measurements were conducted under constant temperature (21±1°C) and relative humidity of 50±5%. Before the measurements, all participants cleaned their face with cleansing products, and the face was dried with face towel. The participants had 30 minutes' acclimatization in the measuring room.

A constant vacuum of 450 mbar was applied to the skin for 2 seconds, followed by a relaxation

time of 2 seconds. Then, the overall skin firmness (Uf) and skin elasticity (R2) on one side of the cheek (randomly) was measured using Cutometer MPA580® (Courage + Khazaka Electronic GmbH). The R2 was calculated by the formula: R2=Ua/Uf, R7=Ur/Uf; Ua is the skin recovery value from when negative pressure is removed to when negative pressure is added to the skin surface during the next successive test. Uf is total skin deformation.

The primary efficacy endpoint of periorbital wrinkles was measured using a three-dimensional skin measurement device PRIMOS® (Canfield Scientific Inc., Fairfield, NJ, USA) by analyzing wrinkle parameters to obtain the average depth of wrinkles (μm), a total number of wrinkles, total wrinkle area (mm^2), and surface roughness Ra (μm).

Statistical analysis

The difference of mean change between the treatments (D14 and D28) and pre-treatment (D0) was analyzed by GraphPad Prism 9. Difference among participant were analyzed by the paired t-test. Otherwise, the Wilcoxon rank sum test were used. *P* values less than 0.05 were considered statistically significant.

Results

Multiple sequence alignment and 3D structure prediction

The Multiple Sequence Alignment of elastin proteins indicated that the regions containing VGVAPG motif were highly conserved among different isoforms of elastin (**Figure 1**). 3D structure prediction demonstrated two regions, each of which contained 3 VGVAPG repeats, and a tag peptide VGLAPG (**Figure 2**). This sequence domain has been revealed to be able to combine with elastin-derived peptides (EDP) at the surface of the cells to stimulate the length and quantity of the dendrites of melanocyte precursors (NCCmelan5 cells) [26]. Hence, it is less likely for ELR to cause rejection when applied to the skin surface, which makes it more suitable to be used as an ingredient of cosmeceuticals.

Design of ELR polypeptide

The nucleotide sequence of native elastin optimized by yeast codons includes Not I site, Xba I site, start codon, stop codon, and 6 × His tag sequence. Among them, the nucleotide sequence of the Not I digestion site is GCGGCCGC. The nucleotide sequence of the Xba I digestion site is TCTAGA. The nucleotide sequence of the starting codon is ATG. The nucleotide sequence of the stop codon is TAA. 6 × His tag sequence is CATCACCATCACCATCAC. The nucleotide sequence of long-acting ELR was obtained by carrying out yeast codon optimization on the original sequence of native elastin, which contains 10 key six-amino acid repeat VGVAPG sequences.

The designed polypeptide sequence is VAPG-VGVAPGVGVAPGVGSVAPGVGVAPGVGVAPGV-GSVAPGVGVAPGVGVAPGVGSVAPGVGVAPG-VGVAPGVGSVAPGVGVAPGVGVAPGVGS, which is governed by the repeat motif VGVAPG. To obtain this ELR, Shanghai Anyi Beauty Skin Research Institute designed the key six-amino acid repeats, and the Wuhu Interfill Biological Products Industry Research Institute Co., Ltd. completed the heterologous expression of the repeats in *Saccharomyces cerevisiae*.

Mean change of skin parameters

All the 30 participants completed the 28-day trial. Throughout the 28-day observation period, no manifested skin irritation was observed. The primary outcomes of the study were presented in **Table 1**.

After using ELR for 14 days, the skin elasticity level was increased compared to the baseline, and it was significantly increased at day 28 (P=0.884 at day 14 and P=0.024 at day 28) (**Figure 3**). In contrast, the firmness level of skin (Uf) was declined from 3.313 (day 0) to 3.292 (day 14) and 3.265 (day 28), but there was no statistically significant difference between pre-treatment and treatment (**Figure 4**).

Furthermore, the topical application of ELR significantly relieved the symptoms of wrinkle in wrinkle count, wrinkle volume, and wrinkle area. As shown in **Figures 5**, **6** and **Table 1**, ELR significantly reduced the wrinkle count and the wrinkle volume at both the 14- and the 28-day time points when compared to the baseline. The wrinkle area was not only significantly reduced after treatment compared to the baseline (**Figure 7**), it was also significantly

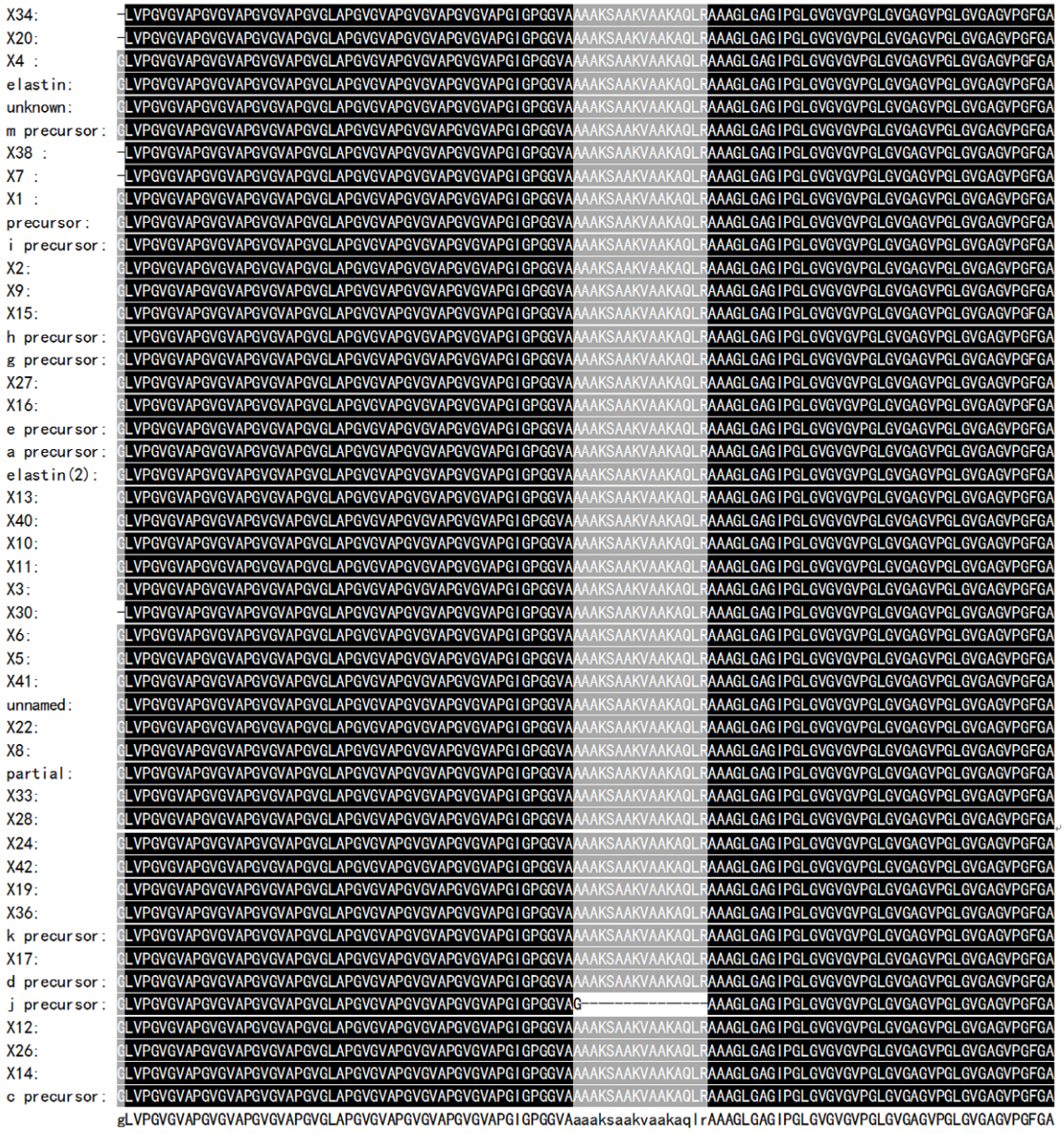

Figure 1. Multiple Sequence Alignment (MSA) in elastin-like recombinant polypeptide (ELR).

Table 1. The skin parameters examined

Variable	Baseline	D14	D28	*P*-value1	*P*-value2
Skin Elasticity Value R2	53.883±6.552	54.023±6.144	56.867±4.473	0.884	0.024
Skin Firmness Value Uf	3.313±0.491	3.292±0.624	3.265±0.599	0.843	0.630
Wrinkles Count (Crow's feet wrinkles)	102±28	79±22	78±22	<0.001*	<0.001*
Wrinkles Volume (Crow's feet wrinkles)	2.53±0.57	2.34±0.56	2.33±0.57	<0.001*	0.008*
Wrinkles Area (Cross feet wrinkles)	46.10±2.50	42.84±2.75	41.93±2.84	<0.001**	<0.001**

Abbreviations: P1, *P*-value at D14 (compared to D0); P2, *P*-value at D28 (compared to D0); *P* value <0.05 was considered statistically significant. *Represents the difference between two groups by using paired T-test method. **Represents the difference between two groups by using the Willcoxon test method.

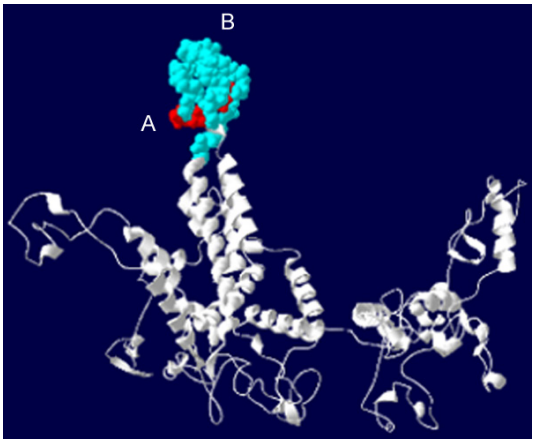

Figure 2. Tertiary structure of elastin. A. Tag peptide: VGLAPG (red); B. Two typical sequences, each contained 3 repeated typical VGVAPG sequences (blue).

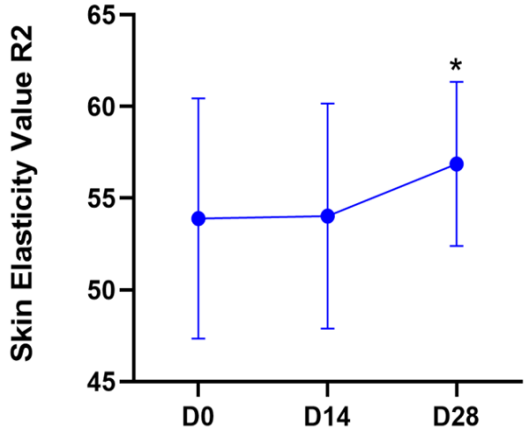

Figure 3. Changes in the Skin Elasticity Value R2 compared to D0 were assessed at D14 and D28. *Represent P ≤ 0.05. **Represent P ≤ 0.01. ***Represent P ≤ 0.001.

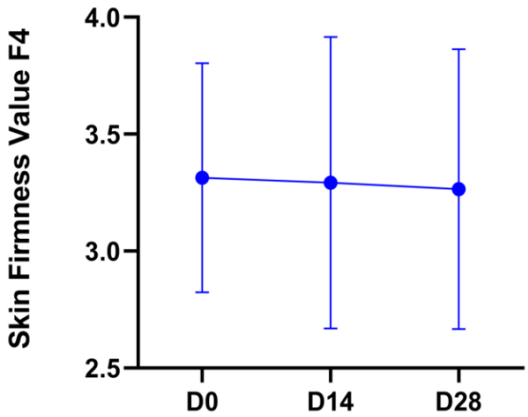

Figure 4. Changes in the Skin Firmness Value F4 compared to D0 were assessed at D14 and D28. *Represent P ≤ 0.05. **Represent P ≤ 0.01. ***Represent P ≤ 0.001.

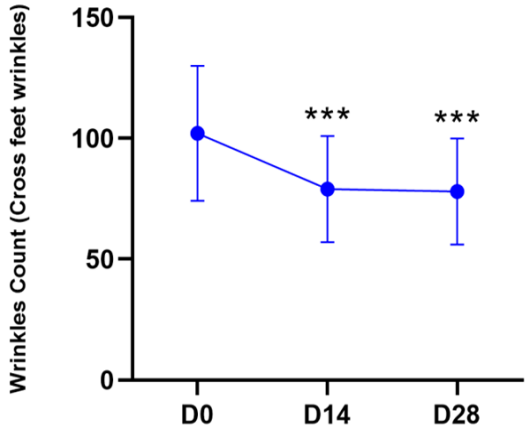

Figure 5. Changes in the Wrinkles Count (Cross feet wrinkles) compared to D0 were assessed at D14 and D28. *Represent P ≤ 0.05. **Represent P ≤ 0.01. ***Represent P ≤ 0.001.

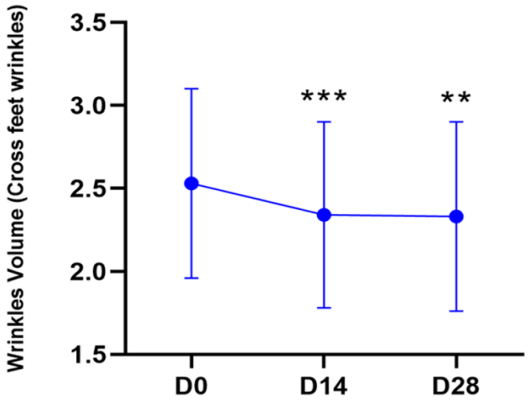

Figure 6. Changes in the Wrinkles Volume (Cross feet wrinkles) compared to D0 were assessed at D14 and D28. *Represent P ≤ 0.05. **Represent P ≤ 0.01. ***Represent P ≤ 0.001.

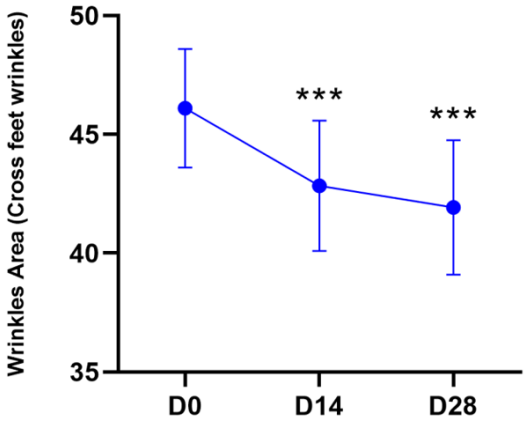

Figure 7. Changes in the Wrinkles Area (Cross feet wrinkles) compared to D0 were assessed at D14 and D28. *Represent P ≤ 0.05. **Represent P ≤ 0.01. ***Represent P ≤ 0.001.

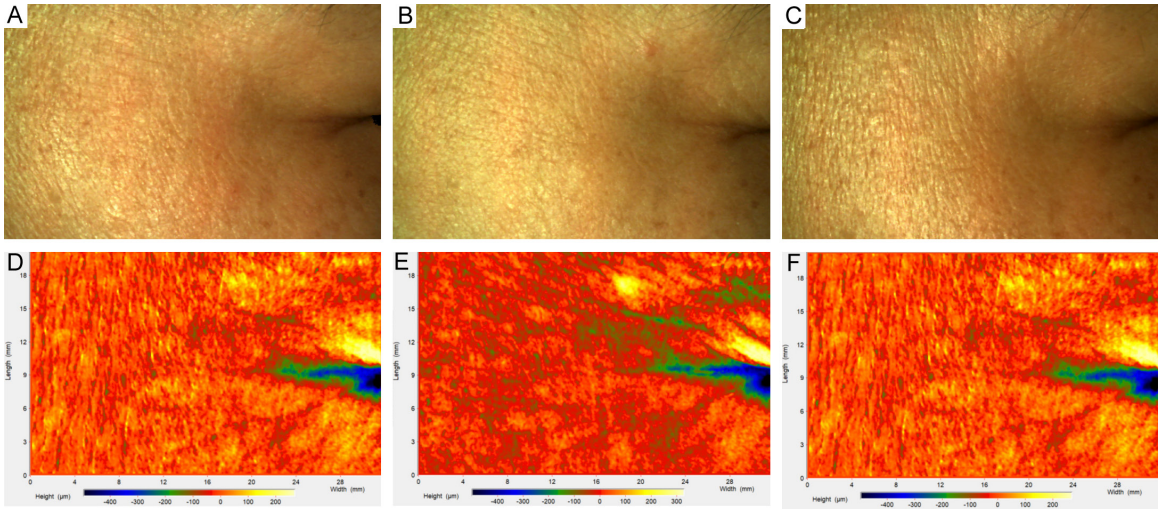

Figure 8. Images of periorbital wrinkles. A-C. Photos of periorbital wrinkles were taken by regular camera in days 0, 14 and 28; D-F. Three-dimensional skin measurement for periorbital wrinkles which were taken by the Phaseshift Rapid In Vivo Measurement of the Skin (PRIMOS) in days 0, 14 and 28.

decreased in the 28-day time point compared the 14-day time point, suggesting the continuous effects of ELR on skin condition (**Table 1**).

Periorbital wrinkles

Moreover, photos of periorbital wrinkles were taken, and three-dimensional skin measurement were performed for all 30 participants. Representative results from one participant were shown in **Figure 8**, demonstrating that wrinkles around the eyes were relieved after the application of ELR for 14 days and 28 days.

Discussion

In this study, we found that twice-daily application of ELR-containing essence for 28 days could significantly improve skin elasticity and reduce wrinkles.

Elastin is a protein that is essential for the elasticity of ECM [27]. Studies have shown that the exogenous supplement of elastin and the support of elastic fiber network structure will significantly improve the elasticity and appearance of damaged skin and reduce the appearance of skin scars and wrinkles [28]. Elastin hydrolysate has been widely used as an ideal material for wound dressings [10], which has been proven to enhance keratinocyte/fibroblast proliferation [29, 30]. Elastin hydrolysate has a similar function when it is used in cosmetics, as Eri Shiratsuchi and colleagues have found that fish-derived elastin hydrolysate could enhance the proliferation of human skin fibroblasts and elastin synthesis in human skin fibroblasts [31]. VGVAPG, the core fragment of elastin, is now an ingredient in a wide range of cosmeceuticals [25]. D. Rossetti and colleagues have shown that retinol-induced elastin gene expression and elastin fiber formation in cultured human dermal fibroblasts and the increase of endogenous elastin can improve the elasticity of skin explants [32].

Exogenous elastin peptides have been demonstrated to interact with cells through elastin receptor complex (ERC) and Integrin $a_v\beta_3$. As the first step in signal transduction, the elastin binding protein (EBP) of ERC identifies XGXXPG sequences, particularly the abundant, hydrophobic hexapeptide VGVAPG in elastin [21, 33, 34] which induces elastogenesis in human dermal fibroblasts via the activation of Insulin-like growth factor 1 (IGF-1) receptors [35]. Meanwhile, integrin $a_v\beta_3$, the cell-surface receptors of integrin, can bind to the unique RKRK sequence in the C-terminus of tropoelastin and stimulate intracellular signaling pathways through focal adhesion kinase (FAK) [36, 37].

Elastin peptides contribute to fibroblast migration, proliferation, and protease production [38-40], smooth muscle proliferation [38], chemotaxis keratinocyte proliferation [38], and keratinocyte migration [41]. Through the prolif-

eration of skin fibroblasts and smooth muscle cells, ELR promotes the production of endogenous elastin. Since elastin plays an important role in inhibiting the formation of wrinkles, we speculated this could be a potential mechanism for the improvement of skin elasticity and the reduction of skin wrinkles. Moreover, the decreased activity and renewal of keratinocytes causes dry and desquamated skin since keratinocyte proliferation may improve the skin moisture level. Together, we proposed that the ELR we tested could possibly improve the skin barrier.

Other forms of ELRs have been reported, including the hexapeptide sequence of Val-Gly-Val-Ala-Pro-Gly (VGVAPG), Gly-Phe-Gly-Val-Gly-Ala-Gly-Val-Pro (GPGVGAGVP) and Gly-Leu-Gly-Val-Gly-Ala-Gly-Val-Pro (GLGBGAGVP) nine-peptide sequence [42], PGAIPG hexapeptide sequence [43], LREG-DPS octapeptide sequence [44], α-elastin, and β-elastin. Kappa elastin was found in 1950s and was gradually widely used in the field of skin beauty. Skin care products containing κ-elastin are effective in increasing skin hydration and protective to skin erythema reactions caused by UV radiation [45].

In summary, ELR showed powerful ability to improve skin elasticity and reduce wrinkles. Nevertheless, although the skin firmness (Uf) is declined after using ELR for 14 and 28 days, there was no significant difference compared with pre-treatment, which may be caused by small sample size or short ELR treatment time. Thus, more participants and longer testing time are needed in further study.

Acknowledgements

The authors would like to extend deep gratitude to Wuhu Interferon Bio-products Industry Research Institute Co., Ltd. for their assistance in protein preparation. This study was supported by Basic Public Welfare Research Project of Zhejiang Province (LY19C010006), and Research Programs of Zhejiang Provincial Medicine and Health Science and Technology Plan Project (2020KY1068). The central government guides local science and technology development fund projects (Grant No. 216Z2404G). Wuhu City Invention Patent Technology Achievement Industrialization Plan Project (Grant No. 202021). As well as the fund for College Students' Innovative Entrepreneurial Training Plan Program [grant number S202110366010].

Disclosure of conflict of interest

None.

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