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An Innovative Rhythm-Regulating Tetrapeptide Resynchronizes Skin's Circadian Clock for Well-Aging

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Abstract

Objective: The circadian clock is crucial for coordinating key physiological processes and behaviours in living organisms to adapt to daily environmental changes. However, clinical observations indicate that chronodisruption induced by environmental stressors (e.g. UV radiation) and endogenous factors (e.g. chronological aging) is closely correlated with circadian desynchronization in skin. The aim of this study was to investigate the potential of a novel tetrapeptide to attenuate UVB-induced circadian rhythm disruption and alleviate skin photoaging.

Methods: The effects of tetrapeptide-109 on human fibroblast HSF cells in the presence and absence of UVB were evaluated by MTT assays. Furthermore, the levels of collagen types I and III in UVB-exposed HSF cells were examined by ELISA. To assess the effect of tetrapeptide-109 on circadian rhythm, the expression levels of the circadian clock genes CLOCK and BMAL1 were analyzed by RT-PCR and the total level of the clock-controlled PER1 protein was determined by ELISA. Finally, a randomized, double-blind, placebo-controlled clinical trial was conducted in which 30 participants applied a cream containing tetrapeptide-109 topically to their facial skin daily for 9 weeks.

Results: Cell viability assays demonstrated the non-toxicity of tetrapeptide-109 to HSF cells and a remarkable cell protection in UVB-exposed HSF cells in a dose-response manner. Collagen expression assays showed that tetrapeptide-109 increased the cellular content of collagen types I and III under UVB exposure. RT-PCR analysis showed that tetrapeptide-109 significantly upregulated the mRNA levels of *CLOCK* and *BMAL1* in UVB-exposed HSF cells, together with increasing PER1 protein levels. In the clinical trial, topical application of tetrapeptide-109 significantly improved reduced skin elasticity parameters (R2, R7 and Q1) and wrinkle area and length compared to the placebo group at 3, 6 and 9 weeks.

Conclusion: These findings present an investigative validation of the multiple functionality of tetrapeptide-109 in collagen and circadian modulation in human dermal fibroblasts and clinical improvement in skin elasticity and wrinkle formation, paving a promising way for the

development of circadian-informed cosmetics that synergistically address both molecular mechanisms and clinical manifestations of skin well-aging.

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1. Introduction

The circadian clock is a periodic cycle of approximately 24 hours that coordinates key physiological processes and behavior patterns in living organisms to adapt to daily environmental changes, such as the sleep-wake cycle and eating [1]. The rhythmicity is created endogenously and governed by a hierarchical network of central and peripheral pacemakers. At the molecular level, a conserved set of core clock genes that responsible for the circadian oscillation is controlled by a complex system of autoregulatory transcription-translation feedback loops (TTFLs). These genes includes the transcriptional activators circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1), along with their transcriptional repressors period circadian regulator (PER1/2/3) and cryptochrome (CRY1/2) families. Within the positive regulatory arm of this loop, CLOCK and BMAL1 proteins heterodimerize to form a functional transcriptional complex that initiates various clock-controlled genes, including *PER* and *CRY*. Conversely, in the negative regulatory phase, newly synthesized PER and CRY proteins assemble into multimeric complexes that translocate to the nucleus, where they interact with the CLOCK-BMAL1 heterodimer to repress its transcriptional activity, thereby establishing an autoregulatory inhibitory circuit that modulates the rhythmic expression of both core clock components and output genes. Notably, the CLOCK-BMAL1 complex further regulates circadian precision through other coordinated activation of nuclear receptors, such as REV-ERB α/β and ROR α/β, thereby reinforcing the robustness of the core oscillators [2-3].

The skin serves as a multifunctional barrier that dynamically safeguards the body through various protection, including shielding against mechanical/chemical insults, maintaining structural integrity of subcutaneous tissues, and executing immunovigilance against microbial pathogens [4]. Emerging evidence reveals that cutaneous cells, particularly keratinocytes and fibroblasts, harbor cell-autonomous circadian oscillators that orchestrate tissue homeostasis through temporally gated regulation of cellular processes [5]. Circadian regulation extends to critical biological processes including transepidermal water balance regulation, stratum corneum renewal, dermal microvascular perfusion, and thermoregulatory responses [6]. Notably, antioxidant defenses and DNA repair mechanisms exhibit diurnal peaks during daylight hours, enhancing protection against ultraviolet-induced oxidative stress and environmental xenobiotics. Conversely, nocturnal phase rhythms prioritize tissue repair and regenerative processes, manifested through cellular turnover acceleration, collagen biosynthesis, and microcirculation enhancement [7-8]. Clinical observations indicate that chronodisruption induced by environmental stressors (e.g., UV radiation) and endogenous factors (e.g., chronological aging) is closely correlated with circadian desynchronization in skin. Such dysregulation manifests clinically as barrier dysfunction syndrome, characterized by xerosis, delayed wound re-epithelialization, photodamage accumulation, and hypersensitivity reactions [9-10]. Therefore, active ingredients modulating circadian rhythms in skin would become promising implications for cosmetic or dermatological chronotherapy aimed at re-establishing skin rejuvenation.

This study presents an investigative validation of the multiple functionality of a novel tetrapeptide in collagen and circadian modulation in human dermal fibroblasts and clinical improvement in skin elasticity and wrinkle formation. By elucidating the modulatory effects of tetrapeptide-109 on protein levels of different types of collagen and mRNA levels of molecular

clocks in UVB exposure, we sought to establish underlying links between circadian phase optimization and extracellular matrix (ECM) remodeling, and to speculate how clock-targeted peptide interventions can enhance cutaneous resilience through coordination of collagen and circadian clock. These findings may pave a promising way for the development of circadian-informed cosmetics that synergistically address both molecular mechanisms and clinical manifestations of skin well-aging.

2. Materials and Methods

Material and chemicals

Tetrapeptide-109 was provided by Shenzhen Winkey Technology Co., Ltd (ShenZhen, China). The human skin fibroblast (HSF) cell line was obtained from the cell bank of Chinese Academy of Sciences Institution (Shanghai, China). Phosphate buffer solution (PBS) was purchased from Solaibao Bioscience & Technology Co., Ltd (Shanghai, China). Thiazolyl blue (MTT) was purchased from Shanghai yuanye Bio-Technology Co., Ltd. Human Collagen I/III ELISA Kits and PER1 ELISA kit were purchased from EIAab science Inc (Wuhan, China). The RNA extract, SweScript All-in-One First-Strand cDNA Synthesis SuperMix for qPCR, 2 × SYBR Green qPCR Master Mix (None ROX), and primers were purchased from Wuhan Servicebio Technology Co., Ltd (Wuhan, China).

Cell culture and UVB radiation

HSF Cells were grown in Dulbecco's modified Eagle's medium (DMEM; Gibco, Shanghai, China) containing 10% (v/v) fetal bovine serum (FBS; Yikesai Biotechnology, Suzhou, China) and 1% (v/v) penicillin-streptomycin (Gibco, Shanghai, China) under a humidified atmosphere of 5% CO_2 at 37℃. Prior to UV radiation, cells were washed with PBS and exposed to a radiation dose of 80 mJ/cm^2 of UVB light for 15 min in PBS. After radiation, the cells were washed with PBS and replaced with different concentrations of tetrapeptide-109 for 48h. At the same time, no radiation control cells were treated in the same way, although the wells were covered with aluminium foil to prevent radiation.

Cell viability analysis

HSF cells were seeded in 96-well plates at a density of 5×10^4 cells/well and incubated overnight. Prior to MTT assays, cells were treated in the presence or absence of UVB and cell viability was determined after 48 h treatment with the indicated concentrations of tetrapeptide-109.

ELISA measurement

The protein levels of types I and III collagen and PER1 in fibroblasts were measured using corresponding ELISA kits. Cells were seeded as previously described, followed by UVB radiation (80 mJ/cm^2) for 15 min. Subsequently, the UVB-exposed cells were treated with or without the indicated concentrations of tetrapeptide-109 for 48 h. Then, the cell lysate were collected and analyzed by ELISA kits according to the manufacturer’s instructions.

RNA quantification

To achieve the synchronization, the HSF cells were treated with 100 nM dexamethasone (DXM) for 30 min. The cell were then washed with PBS and exposed to UVB radiation (80 mJ/cm^2) for 15 min. After radiation, the cells were treated with or without tetrapeptide-109 at 50 ppm at the indicated intervals over 24 h. After harvesting the cells, mRNAs were isolated using RNA extraction reagent and converted to cDNA using SYBR Green-based real-time quantitative PCR. GAPDH was used as a reference gene. The primers used in RT-qPCR

were as follows: *GAPDH*, 5'-CCTCGTCCCGTAGACAAAATG-3' and 5'-TGAGGTCAATGAAGGGGTCGT-3'; *CLOCK*, 5'-AGAAGTTAGGGCTGAAAGACGG-3' and 5'-ATGCTGTCTGGGAGGAGTGCTA-3'; *BMAL1*, 5'-GGGGAAATACGGGTGAAATCTA-3' and 5'-CTGAACCATCGACTTCGTAGCG-3'.

Human clinical study

A randomized, double-blind, placebo-controlled clinical trial was conducted in accordance with the 1964 Helsinki Declaration and subsequent amendments. A total of 30 eligible Chinese women, aged 40 to 50 years, were randomly and equally divided into 2 groups. A placebo control group (no tetrapeptide-109) and an experimental group (50 ppm tetrapeptide-109) were set up for blinded experiments. After cleansing in the morning and evening, 1 mL of the given sample was applied to both sides of the face and eye area and then massaged until completely absorbed. At the scheduled return visits at baseline (D0), D21, D42 and D63, facial images of each participant were taken using the Cutometer®MPA580, while the wrinkle length and area were measured using the PRIMOS-CR. The skin elasticity tester MPA580 was used to test the skin parameters R2, R7, and Q1. Each participant was questioned about any symptoms such as itching, tingling and burning sensation of the facial skin during the use of the test product, accompanied with a documentation of adverse reaction records, including erythema, edema and rash.

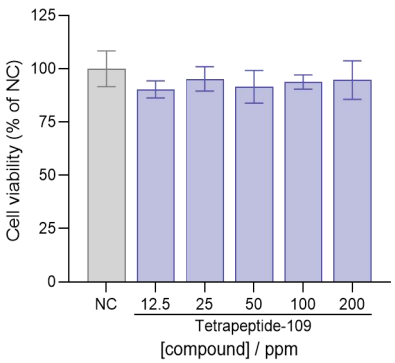
Statistical analysis

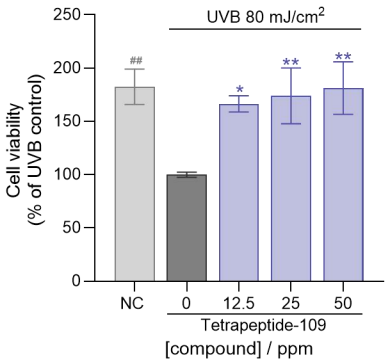
Data are expressed as the mean±SD (standard deviation) of triplicate determinations. Statistical significance was analyzed by one-way analysis of variance (ANOVA) and Student's test with GraphPad Prism software (GraphPad, San Diego, CA, USA). $P<0.05$ was considered statistically significant.

3. Results

Photo-protection of tetrapeptide-109 in human fibroblasts

We first evaluated the toxic effects of tetrapeptide-109 against HSF cells in the absence or presence of UVB by MTT assays. Treatment with different concentrations of tetrapeptide-109 for 48 h showed no toxicity to HSF cells without UVB exposure (Figure 1a). To investigate the efficacy of tetrapeptide-109 to protect HSF cells against UVB, a reported mean lethal irradiance of 80 mJ/cm^2 for UVB was selected as the subsequent dosage. Exposure to UVB for 15 min resulted in a significant reduction in HSF cell viability. However, a dose-dependent increase in viability was observed when UVB-exposed cells were treated with the indicated concentrations of tetrapeptide-109 for 48h (Figure 1b). These results suggest that tetrapeptide-109 may exert a protective effect against UVB-induced cell growth inhibition without toxicity to human fibroblasts.



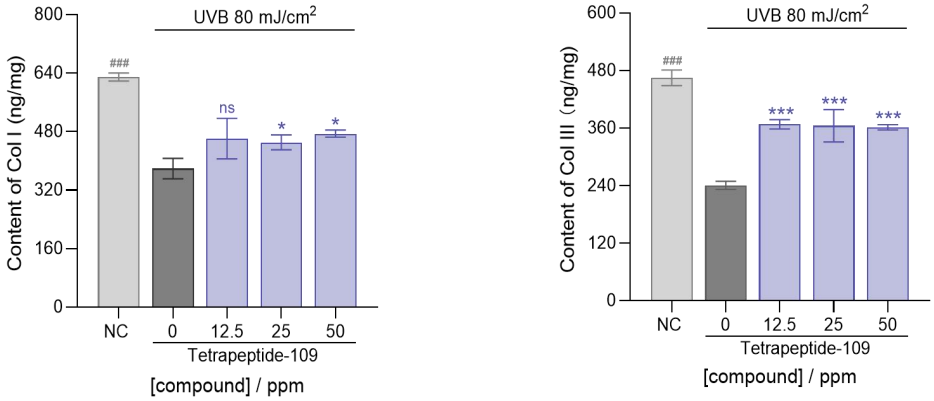


(**a**) (**b**)

Figure 1. Effects of tetrapeptide-109 on the viability of HSF cells exposed with or without UVB as measured by MTT assays. (a) HSF cells were seeded in a 96-well plate and incubated with the indicated concentrations of tetrapeptide-109 for 48 h; (b) HSF cells were seeded in a 96-well plate and exposed to 80 mJ/cm^2 UVB radiation for 15 min prior to the addition of indicated concentrations of tetrapeptide-109. Cell viability of tetrapeptide-109 in the presence or absence of UVB exposure was determined by MTT assays. Significance: *P<0.05, $^{\#\#}$, **P<0.01. $^{\#}$UVB control group (0 ppm of tetrapeptide-109) vs negative control (NC) group, *UVB control group (0 ppm of tetrapeptide-109) vs treatment group.

Collagen stimulation of tetrapeptide-109 in human fibroblasts

To assess the potential effect of tetrapeptide-109 on collagen expression, a UVB-exposed HSF cell model was used to quantify the total content of collagen types I and III. Notably, a significant decrease in the total content of collagen types I and III were found when the cells were stimulated with UVB radiation at 80 mJ/cm^2. Treatment with tetrapeptide-109 for 48 h significantly reversed the UVB-induced inhibition of collagen type I and III protein levels in HSF cells (Figure 2). These results suggest that tetrapeptide-109 may have greater potential to promote the expression of collagen types I and III in human fibroblasts against UVB stimulation.



(**a**) (**b**)

Figure 2. Effects of tetrapeptide-109 on the content of collagen types I and III in UVB-exposed HSF cells. HSF cells seeded in 6-well plates were stimulated with UVB radiation at 80 mJ/cm^2 for 15 min. Cells were then incubated with tetrapeptide-109 at 12.5 to 50 ppm for 48 h. The total content of different types of collagen was collected and measured by (a) type I and (b) type III collagen ELISA kits. Significance: *P<0.01, $^{\#\#\#}$, ***P<0.001. $^{\#}$UVB control group vs negative control (NC) group, *UVB control group (0 ppm of tetrapeptide-109) vs treatment group.

Circadian rhythm modulation of tetrapeptide-109 in human fibroblasts

Considering that collagen is controlled by the circadian clock, the core of the molecular clockwork are the genes *CLOCK* and *BAML1*, as well as the genes *CRY1/2* and *PER1/2*. To evaluate the impacts of tetrapeptide-109 on the molecular clockwork, UVB-exposed HSF cells synchronized with DXM were treated with or without 50 ppm tetrapeptide-109. To measure the transcriptional levels of core clock components, cells were harvested at every 4 h-interval over a 24-hour time course. The oscillatory amplitude of *CLOCK* and *BAML1* mRNA expression levels were both significantly lower in the UVB-exposed cells (Figure 3a and b). After treatment with tetrapeptide-109, the levels of the CLOCK and BMAL1 genes in the

positive arm of the oscillator were significantly increased and restored to a similar oscillatory amplitude as in the NC group. In addition, PER1, a component of the negative arm of the oscillator, plays a critical role in the cell cycle in modulating epidermal regeneration, dermal organization and collagen deposition. Our results showed comparable protein abundances in the presence of different concentrations of tetrapeptide-109 for 48 h in the UVB-exposed HSF cells (Figure 3c), which were consistent with the result of content of collagen types I and III. These results suggest that tetrapeptide-109 could remodel the approximate 24 h rhythms in mRNA levels in the positive arm (*CLOCK* and *BMAL1*) against UVB stimulation and enhance PER1 protein levels to partially protect the loss of collagen types I and III.

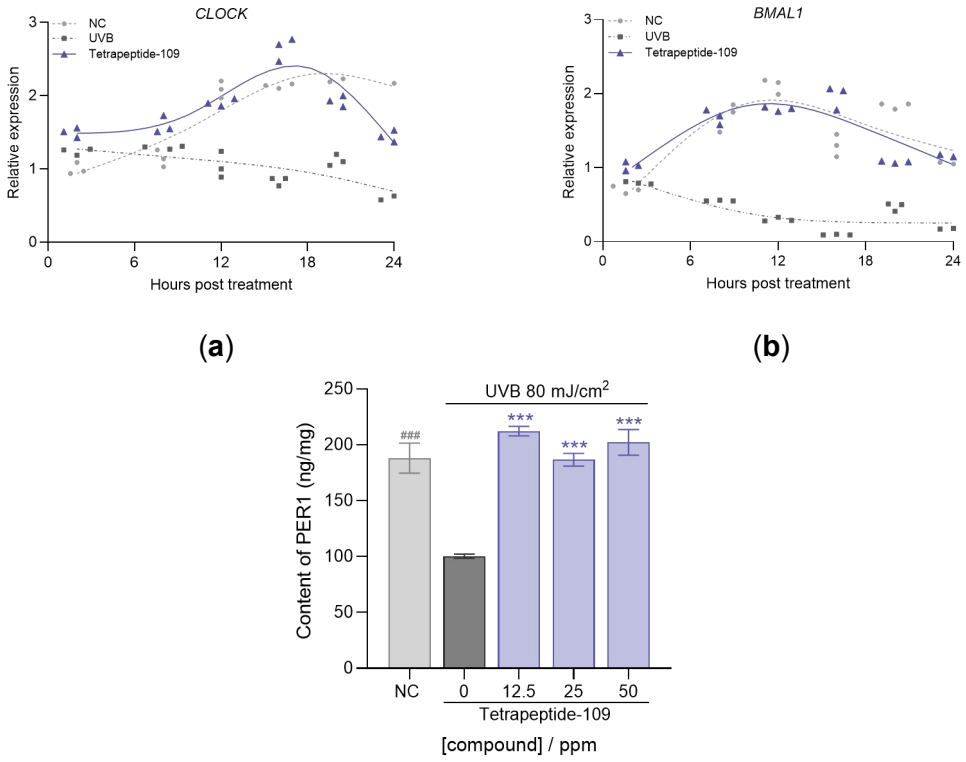


Figure 3. Effects of tetrapeptide-109 on molecular levels of circadian clock in UVB-exposed HSF cells. Relative (a) *CLOCK* and (b) *BMAL1* mRNA levels over the time course of 24 h were determined by RT-PCR; (c) Expression of PER1 protein levels after 48 h-treatment of tetrapeptide-109 was determined by ELISA. Significance: ###, ***P<0.001. #UVB control group vs negative control (NC) group, *UVB control group (0 ppm of tetrapeptide-109) vs treatment group.

Skin elasticity improvement of tetrapeptide-109 in humans

To further evaluate the potential anti-aging efficacy of tetrapeptide-109, a 63-day clinical study was conducted on 30 participants to assess their skin elasticity and firmness. The skin parameters R for the elasticity and Q for the firmness after the topical application of tetrapeptide-109 were determined by means of the Cutometer® MPA580. Compared to the placebo group, topical application of tetrapeptide-109 at the concentration of 50 ppm for 21, 42 and 63 days found significant improvements in skin elasticity (Figure 4a, c and e). The statistical analysis revealed that ΔR2 (P<0.001), ΔR7 (P<0.001) and ΔQ1 (P<0.001) values of tetrapeptide-109 exhibited a significantly difference at day 21, 42 and 63 between placebo group (Figure 4b, d and f). More specifically, participants treated with tetrapeptide-109

showed a 28.28% increase in R2, a 30.52% increase in R7 and a 29.47% increase in Q1 after a 63-day topical treatment. These effects on skin elasticity and firmness may be attributed to the enhancement of collagen types I and III and the modulation of circadian rhythms after topical application of tetrapeptide-109.

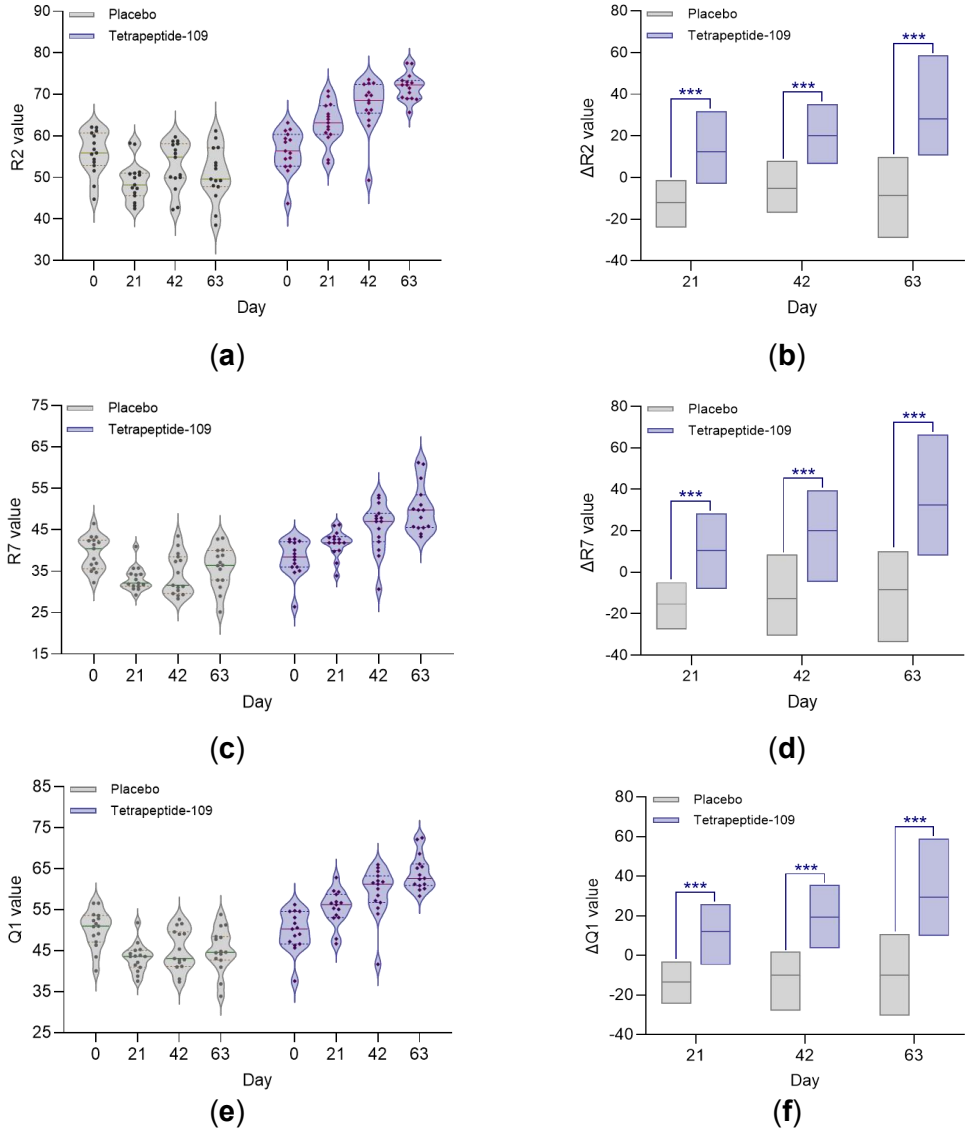


Figure 4. Effects of tetrapeptide-109 on skin elasticity in a 63-day clinical study. The value and changes of (a, b) R2, (c, d) R7, and (e, f) Q1 parameters for placebo and tetrapeptide-109 groups. Significance: ***P<0.001. *Placebo group vs treatment group.

Winkle improvement of tetrapeptide-109 in humans

In addition, the effectiveness of tetrapeptide-109 on the length and area of crow's feet wrinkles was evaluated in 30 participants using the PRIMOS-CR. The results showed that while no significant reduction in wrinkles was observed in placebo group, the visual grade in terms of wrinkle length and area improved significantly from D0 to D63 in tetrapeptide-109 group (Figure 5a). Strikingly, treatment with tetrapeptide-109 showed an improvement of 16.44% in wrinkle length (P<0.01) and 13.04% in wrinkle area (P<0.05) over the course of the study compared to placebo group. These results suggest that tetrapeptide-109 may help reduce wrinkle appearance by restoring collagen levels and skin elasticity, including dynamic and static wrinkles and deep lines, making skin appear firmer and smoother.

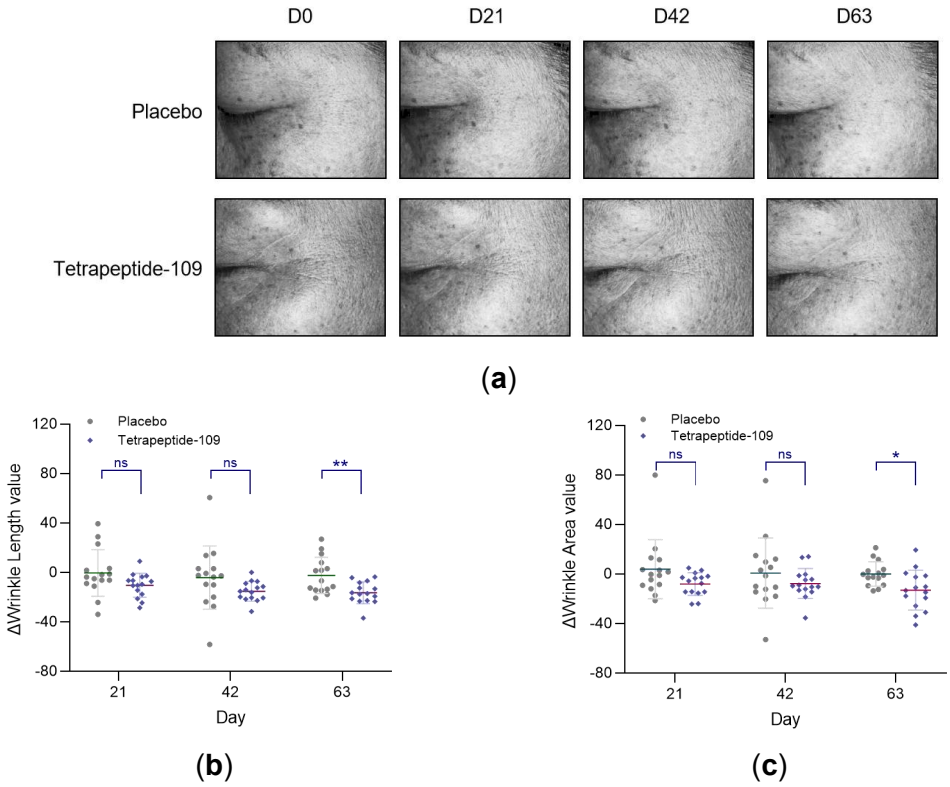


Figure 5. Effects of tetrapeptide-109 on winkle length and area in a 63-day clinical study. (a) Skin images of changes in wrinkles in placebo group and tetrapeptide-109 group; (b) The changes of winkle length values were measured at D0, D21, D42, and D63; (c) The changes of winkle area values were measured at D0, D21, D42, and D63. Significance: *P<0.05, **P<0.01. *Placebo group vs treatment group.

4. Discussion

In this work, tetrapeptide-109 was found to have significant effects on cellular photoprotection, collagen stimulation, and circadian molecular rhythmicity in fibroblasts, as well as on skin elasticity, firmness and wrinkle reduction in humans.

Cell viability assays revealed that tetrapeptide-109 was non-toxic to human fibroblast HSF cells, even at the maximum concentration of 200 ppm. Under the UVB exposure, tetrapeptide-109 showed remarkable cell protection in a dose response fashion. These findings highlight the potential application of tetrapeptide-109 for anti-photoaging.

Collagen expression assays showed that tetrapeptide-109 was able to boost the cellular content of collagen types I and III in the presence of UVB radiation, suggesting underlining effects in preventing and inhibiting collagen collapse in the extracellular matrix (ECM).

Many studies have demonstrated that the circadian clock system, through key regulators such as CLOCK and BMAL1, is crucial in the control of oxidative stress and skin aging. Gene expression analysis elucidated how tetrapeptide-109 modulates the circadian clock in fibroblasts, leading to a resetting of the UVB-induced circadian rhythm. Treatment with tetrapeptide-109 increased the *CLOCK* and *BAML1* mRNA levels in fibroblasts. These changes suggest that tetrapeptide-109 could reprogam the expression of core clock genes in the positive arm of the oscillator, potentially enhancing the robustness of the circadian clock. Besides, tetrapeptide-109 increased the cellular PER1 protein levels, indicating a significant regulation of the negative arm of the oscillator, thus potentially modulating the interlocked TTFL of circadian rhythms. In fibroblasts, PER protein can activate the cell cycle in

circadian-dependent manner *via* several proteins, including a cAMP-specific phosphodiesterease, PDE4D [11]. cAMP has been defined as an integral component of the circadian pacemaker in the suprachiasmatic nucleus (SCN), and its dynamic changes could alter circadian parameters in the SCN, peripheral tissues, and cultured fibroblasts [12]. Furthermore, loss of PER has shown defects in the wound healing process by reducing epidermal regeneration, dermal organization, and collagen deposition [13]. Recent reports showed that knockdown of PER increased the expression of matrix metalloproteinase-1 (MMP-1) via cAMP signaling pathway in HaCaT keratinocytes, suggesting that repression of MMP-1 by PER may be one of the protective mechanisms against UV [14]. As is well known, MMPs are stimulated by UVB radiation and are responsible for degradation of ECM components such as collagen, thereby impairing the structural integrity of the dermis and leadind to skin remodeling. Our results showed that tetrapeptide-109 could maintain the positive arm of circadian oscillator against UVB radiation at the molecular level, potentially activating their transcription and affecting some circadian peacemaker, leading to the expression of PER1 protein and partially to induce collagen types I and III in cellular. These findings provide a fundamental basis for a possible link between circadian modulation and changes in skin collagen against UVB radiation of tetrapeptide-109. Many human skin properties oscillate in a circadian manner including cellular proliferation rate, hydration and transepidermal water loss (TEWL), sebum production, and facial rhytides. As the core clock component can regulate approximately 2-10% of total genome in any tissue, disruption of core circadian clock genes affects the gene expression and cellular processes important for skin function. Our further evaluation in humans showed that tetrapeptide-109 was effectively improved skin parameters R and Q scores and wrinkle length and area after a 63 days of treatment, suggesting that tetrapeptide-109 has positive effects on skin elasticity and firmness, as well as wrinkle formation. These clinical findings are at least partially aligned with the established role of circadian rhythms in regulating skin physiological processes.

In the future, deeper and more insightful molecular mechanisms of tetrapeptide-109 will be performed to illustrate the link between collagen simulation and circadian rhythm in fibroblasts. Using 3D skin models, we aim to better understand how tetrapeptide-109 modulates skin-related processes including circadian regulation, barrier function and cellular repair. This will also allow us to explore their potential therapeutic effects on different skin conditions, helping to develop more targeted and effective cosmetic and dermatological treatments.

5. Conclusion

In short, a novel tetrapeptide has been identified that acts on core clock components to attenuate UVB-induced circadian rhythm disruption and alleviate skin photoaging. Tetrapeptide-109 protects human fibroblasts from UVB-induced damage and prevents UVB-induced inhibition of collagen types I and III. In addition, tetrapeptide-109 has been shown to modulate UVB-induced circadian dysregulation by reversing *CLOCK* and *BMAL1* mRNA amplitude decline over 24 h and increasing PER1 protein levels for 48 h. Topical application of tetrapeptide-109 can effectively increase skin elasticity and firmness and reduce wrinkle length and area without side effects. In light of the aforementioned findings, tetrapeptide-109 is hypothesized to function as a potentially photoprotective ingredient, capable of promoting human skin in well-aging by resetting the circadian rhythm within skin cells, thereby resulting in a restoration of collagen, an improvement in skin elasticity and firmness, and a reduction in wrinkle appearance.

Acknowledgments

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Conflict of Interest Statement

The authors declare no conflict of interest.

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