

Article

Targeting the Dual Nature of Facial Aging: A Clinical and Instrumental Study of a Multi-Active Cream on Static and Dynamic Wrinkles

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Abstract

Background: Static (at-rest) and dynamic (expression-linked) wrinkles are complementary hallmarks of facial aging. While static wrinkles are widely studied, the objective quantification of dynamic wrinkles during active facial movement remains a novel and underexplored frontier. Quantifying both phenotypes under real-life product use requires objective, non-invasive endpoints alongside standardized clinical grading. **Aim:** This study aimed to evaluate the clinical and instrumental efficacy of a multi-active topical cream on static and dynamic wrinkles over 8 weeks of twice-a-day use. **Methods:** After a 2-week washout, we conducted a monocentric, open-label study on 62 Chinese women (25–55) who used the topical cream twice daily for 8 weeks (per-protocol $n = 49$; dynamic-wrinkle subset $n = 41$; dermatologist 0–9 grading at T0/Timm/W4/W8). The instrumental endpoints were PRIMOS-CR wrinkle morphometry (forehead, crow's feet) and periocular high-frequency ultrasound (UC22). Dynamic wrinkles were assessed via high-speed smile imaging (max P10; mean P1–P10). Statistics comprised Wilcoxon's tests for dermatologist-graded (ordinal) endpoints and repeated-measures ANOVA with Dunnett's tests for continuous instrumental endpoints ($\alpha = 0.05$). **Results:** Improvements were evident at Timm (peri-orbital elasticity -17.70% , global-face elasticity -15.23% , firmness -19.47% , smoothness -20.16% , radiance -25.75% ; all $p < 0.001$). By Week 8, dermatologist-graded wrinkles generally decreased: crow's feet -26.89% , under-eye -33.74% , glabellar -35.30% , forehead -34.69% (all $p < 0.001$). PRIMOS showed reductions in wrinkle area/length (forehead area -8.69% , length -12.05% ; crow's feet area -8.70% , length -16.03% ; all $p < 0.001$). Ultrasound indicated increased periocular epidermal thickness ($+26.57\%$) and density ($+12.69\%$) (both $p = 0.005$). Dynamic-wrinkle grades improved during smiling (under-eye: max -12.64% , mean -15.74% ; crow's feet: max -15.97% , mean -16.89% ; all $p < 0.001$), with reductions across P1–P10. **Conclusions:** In real-life, with twice-daily use, the multi-active cream demonstrated significant within-subject improvements in both static and dynamic (expression-linked) wrinkles, as supported by dermatologist grading, PRIMOS 3D wrinkle morphometry, and periocular high-frequency ultrasound.



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1. Introduction

Skin aging is a complex and multifactorial biological process that involves both intrinsic and extrinsic mechanisms. One of the most visible manifestations of this process is

wrinkle formation, which is driven by the progressive depletion of dermal extracellular matrix (ECM) components, including collagen, elastin, and glycosaminoglycans (GAGs). These structural macromolecules are essential for maintaining skin firmness, elasticity, and overall biomechanical integrity [1].

Intrinsic aging is primarily governed by genetically programmed cellular senescence, whereas extrinsic aging is predominantly induced by environmental insults such as ultraviolet (UV) radiation, pollution, and oxidative stress, with reactive oxygen species acting as key mediators of UV-induced photodamage [2–4]. Among these, chronic UV exposure is known to trigger the overexpression of matrix metalloproteinases (MMPs), which accelerate ECM degradation and collagen breakdown, contributing to premature wrinkle formation, with MMP-mediated matrix degradation now regarded as a central mechanism of photoaging [5–7].

Wrinkle formation is a salient clinical marker of facial aging. Static wrinkles—visible at rest—stem from cumulative extracellular-matrix degradation and tissue laxity, whereas dynamic (expression-linked) wrinkles appear during muscle contraction. Although historically framed as distinct phenotypes, longitudinal evidence indicates continuity between them: in an eight-year cohort, expression lines deepened and persisted as permanent furrows with age [8]. This progression supports targeting both static and dynamic wrinkles in tandem, pairing structural strategies that counteract matrix loss with approaches that temper expression amplitude, and motivates the concurrent evaluation of both phenotypes in clinical studies.

To address the dual genesis of static and dynamic wrinkles, the tested cream is formulated with a synergistic complex of bioactives, each selected for its compelling biological mechanism. At the core of the formulation is hydroxypropyl tetrahydropyrantriol (Pro-Xylane™). Originally developed through green-chemistry principles from beech wood xylose, this C-xylopyranoside derivative specifically stimulates the biosynthesis of glycosaminoglycans—particularly dermatan sulfate—in keratinocytes, helping to re-anchor the dermal-epidermal junction and restore extracellular matrix (ECM) volume [9]. Complementing this structural support are the matrikines palmitoyl tripeptide-1 (Pal-GHK) and palmitoyl tetrapeptide-7 (Pal-GQPR). Operating as cellular messengers, these peptides stimulate fibroblasts for matrix renewal while concurrently dampening pro-inflammatory signaling cascades (e.g., IL-6), creating an optimal environment for tissue repair; such matrikines exemplify the expanding class of bioactive peptides developed to counter skin senescence [10,11]. Most interestingly, to specifically target the dynamic component of aging, the formula incorporates dipeptide diaminobutyroyl benzylamide diacetate. This advanced biomimetic peptide was inspired by the neuromuscular-blocking properties of Waglerin-1, a compound found in the venom of the Temple Viper snake. By acting as a reversible antagonist at the muscular nicotinic acetylcholine receptors, it safely and temporarily tempers facial muscle contraction amplitude, thereby softening expression-related lines [12]. Furthermore, the base formulation is enriched with supportive dermatological ingredients, such as niacinamide and panthenol, to accelerate barrier recovery and provide immediate optical smoothing.

In this study, we aimed to evaluate the clinical efficacy of a topical cream formulated with these three active compounds to improve both static and dynamic wrinkles. The evaluation combined dermatologist assessments and non-invasive instrumental techniques to provide a comprehensive analysis of the product's anti-aging performance.

2. Materials and Methods

2.1. Study Design and Subjects

This was a monocentric, open-label clinical study evaluating the anti-aging efficacy of a topical cream (FLA# 730695 20) on static and dynamic wrinkles under real-life use—that is, twice-daily, at-home application by participants within a standardized, consumer-like skincare regimen (cleanser and sunscreen), rather than a controlled single-application laboratory exposure. A total of 62 healthy Chinese women aged 25–55 years were enrolled. While this initial chronological age range was broad to encompass both early and mature stages of facial aging, potential age-related physiological variability was strictly controlled by enforcing rigorous clinical severity baseline thresholds for inclusion. After a 2-week washout, the participants applied the product twice daily to their entire face for 8 weeks.

All subjects were regular users of eye care products and reported concerns, including fine lines, wrinkles, dryness, and sagging. Eligibility was confirmed by a dermatologist using standardized photographic atlases: crow's feet (Atlas P38, grades 2–5), under-eye/infraorbital wrinkles (Atlas P44, grades 2–5), inter-ocular wrinkles (Atlas P36, grades 2–4), glabellar lines (Atlas P34, grades 2–4), forehead wrinkles (Atlas P30, grades 2–5), and drooping of the upper-outer eyelid (Atlas P40, grades 1–3). Global assessments of fine lines, wrinkles, radiance, firmness, and smoothness were required to score 4–6 on a 0–9 scale.

Participants were recruited at a single clinical site in Shanghai, China, through public advertisements and the site's volunteer registry. Interested women were provided with study information and invited to an on-site screening visit, where written informed consent was obtained. A board-certified dermatologist confirmed eligibility against predefined inclusion/exclusion criteria using the above photonic atlases. Enrollment proceeded consecutively until the planned sample size was reached.

Exclusion criteria included pregnancy or breastfeeding; legal incapacity; residence in care institutions; acute or chronic skin diseases in test areas; systemic illness; immune compromise; known allergies to cosmetic ingredients; excessive UV exposure; regular aquatic sports or sauna use; cardiovascular history; skin cancer; or recent use of antihistamines, corticosteroids, NSAIDs, or immunosuppressants.

Clinical assessments were conducted at baseline (T0), 1 min post-application (Timm), Week 4 (T4wk), and Week 8 (T8wk), covering the elasticity of the eye area and global face, firmness, plumpness, smoothness, radiance, and severity of key wrinkles. Instrumental evaluations were conducted using VISIA-CR (standardized photos), PRIMOS-CR (3D wrinkle imaging), and UC22 ultrasound (epidermal thickness and density near the eye area). High-speed camera imaging (Canfield Scientific, Parsippany, NJ, USA; Cortex Technology, Hadsund, Denmark; Panasonic, Osaka, Japan) was used to capture dynamic-wrinkle patterns during smiling expressions. The protocol was approved by the Shanghai China Norm Ethics Committee (Approval No. FSEC 2022-71-01) and conducted in accordance with the Declaration of Helsinki; all participants provided written informed consent.

2.2. Intervention Protocol

Subjects were instructed to apply the tested cream (FLA# 730695 20)—which was formulated and provided by L'Oréal Research & Innovation (Shanghai, China)—twice daily, morning and evening, after facial cleansing, using gentle tapping motions around the eye contour and extending to the entire face. The product was formulated with a complex of active ingredients, including Pro-Xylane™ (21%), dipeptide diaminobutyryl benzylamide diacetate (4%), a peptide complex of palmitoyl tripeptide-1 and palmitoyl tetrapeptide-7 (3%), as well as niacinamide, rhamnose, panthenol, carnosine, sialic acid, caffeine, and escin. Before intervention, all subjects underwent a 2-week washout period

(from T-2wk to T0) during which they discontinued any anti-aging products and followed a standardized skincare regimen: cleanser (FLA# 730457 36), moisturizer (FLA# 609801 04D), and sunscreen (FLA# 885218 3) in the morning, and cleanser plus moisturizer in the evening. During the 8-week application phase (T0–T8wk), participants used the same cleanser and sunscreen alongside the test product while maintaining their usual skincare routine. Compliance with the application protocol was reviewed at each scheduled visit. Unless otherwise specified, ingredient percentages refer to *w/w* concentrations of the commercial raw materials as supplied (raw-material loadings).

2.3. Clinical and Instrumental Assessments

Dermatological assessments were performed live (in-person) at baseline and various follow-up time points (baseline (T0), 1 min post-application (Timm), Week 4 (T4wk), and Week 8 (T8wk)), depending on the parameter. To ensure high intra-rater reliability, each subject was consistently evaluated by the same board-certified, pre-trained dermatologist without access to previous grading results. The severity of parameters was graded using a 10-point clinical scale (0–9), where 0 represents the complete absence of the feature and 9 represents the maximum severe manifestation. This scale was mapped to visual reference anchors from the validated Skin Aging Atlas (Volume 2, Asian Type) and Griffiths criteria. Parameters graded included skin elasticity (eye area and global face), firmness, plumpness, smoothness, and radiance, along with wrinkle severity at multiple facial sites, including crow's feet, under-eye, glabellar area, forehead, and inter-ocular regions. The global appearance of fine lines and wrinkles, dark eye circles (vascular vs. pigmentary), and the intensity of pigmentation and vascular involvement around the eyes were also evaluated using relevant atlases.

Instrumental measurements were conducted under standardized conditions (temperature 20 ± 2 °C, relative humidity $50 \pm 5\%$). Standardized photographs were captured using VISIA-CR and IMAGE LAB systems at frontal and lateral views. 3D wrinkle morphology was quantified using the PRIMOS-CR system (Canfield Scientific, Parsippany, NJ, USA), utilizing digital stripe projection technology to calculate parameters including wrinkle area (mm²) and total wrinkle length (mm). Epidermal thickness and density in the periocular region were assessed using the UltraSkin UC22 high-frequency ultrasound system (DermaScan, Cortex Technology, Hadsund, Denmark) equipped with a 22 MHz probe, which offers sufficient resolution to visualize the epidermal-dermal junction; high-frequency ultrasound is an established, non-invasive method for assessing skin aging [13]. All imaging procedures were performed by trained technicians under controlled lighting and positioning conditions. To mitigate evaluator bias, instrumental data extraction and quantification were performed using automated software algorithms by technicians who were blinded to the subjects' evaluation time points.

In parallel, dynamic-wrinkle evaluation was conducted by capturing facial expressions using a high-speed camera system (Panasonic DC-GH5, Osaka, Japan) under standardized settings. Subjects were instructed to fully smile while 180 sequential images were captured per direction (front and 45° right). From this sequence, frames per time point (T0, Week 4, and Week 8) spanning neutral to maximal expression were selected. Dermatologist grading used a 0–9 photonumeric scale based on the Skin Aging Atlas (Asian type) and Griffiths' photodamage criteria, with standardized photographic references for each sign [14]. Two endpoints were derived for each subject: the maximal expression score (P10) and the average expression score (mean of P1–P10).

2.4. Statistical Analysis

All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). This study was designed as an exploratory investigation to evaluate the broad efficacy profile of the test product. Therefore, the dermatologist-based clinical grading of wrinkles was considered the primary endpoint, with instrumental measurements serving as secondary, supportive endpoints. All *p*-values are reported as descriptive indicators of efficacy and were not adjusted for multiplicity. For descriptive analysis, the number of observed values, mean, standard error, median, interquartile range, minimum, and maximum were reported for each evaluation parameter. All data analyses were based on the per-protocol population. Consistent with the ordinal nature of the clinical grading scales (0–9), changes from baseline to Weeks 4 and 8 were analyzed using the non-parametric Wilcoxon signed-rank test, which was applied to all dermatologist-graded static and dynamic (expression-linked) endpoints. Continuous instrumental endpoints (PRIMOS-CR wrinkle morphometry and UC22 ultrasound) were analyzed using repeated-measures ANOVA followed by Dunnett's post hoc tests versus baseline (T0). For the ordinal grading endpoints, medians and interquartile ranges are additionally reported, and the mean $\pm$ standard error shown in the figures serves as a descriptive indicator to aid visual comparison across time points. A two-sided *p*-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Participant Characteristics

A total of 62 Chinese female subjects were enrolled in the study. During the 8-week period, 13 participants were excluded from the per-protocol (PP) analysis. These exclusions were due to voluntary withdrawal or protocol deviations ($n = 13$), none of which were related to adverse events. Consequently, 49 participants completed the full clinical evaluation and constituted the main efficacy analysis set.

For the dynamic wrinkle evaluation, a subset of the PP population was analyzed. Of the 49 completers, 8 subjects were excluded solely for technical reasons, as they were unable to reproduce a consistent smile amplitude across all time points, which is a prerequisite for valid longitudinal comparison. Thus, the final dataset for dynamic wrinkle analysis comprised 41 subjects.

To ensure the validity of the per-protocol approach, we compared baseline characteristics between the total enrolled population ($n = 62$) and the final PP population ($n = 49$). No significant differences were found in mean age or baseline wrinkle severity scores ($p > 0.05$), indicating minimal risk of attrition bias. The per-protocol participants were aged between 32 and 50 years (mean age: 44.63 ± 4.44 years). The cohort included various skin types (42.6% dry, 16.3% normal, 4.1% oily, 36.7% combination). To ensure a representative distribution of moderate aging signs, the baseline inclusion criteria strictly required specific severity grades: global appearance of wrinkles (grade 4–6), crow's feet and under-eye wrinkles (grade ≤ 5), and glabellar/inter-ocular wrinkles (grade 2–4). All enrolled participants presented visible signs of aging in the eye contour or facial regions, with mean baseline scores reflecting moderate skin elasticity, firmness, radiance, and multiple types of wrinkles, as determined by trained dermatologists using validated visual grading scales and Skin Aging Atlas references.

3.2. Clinical and Instrumental Treatment Efficacy

Lower dermatologist grades indicate improvement; thus, decreases from baseline reflect clinical benefit. At the early time point of Timm (after short-term use), clinical assessments already revealed significant improvements in multiple skin quality param-

ters (Figure 1). Compared with baseline (T0), periorbital elasticity decreased (improved) from 4.27 ± 0.09 to 3.51 ± 0.08 (-17.70% , $p < 0.001$), and elasticity on the global face improved from 4.02 ± 0.07 to 3.41 ± 0.10 (-15.23% , $p < 0.001$). Skin firmness on the global face significantly improved from 4.61 ± 0.07 to 3.71 ± 0.09 (-19.47% , $p < 0.001$), and skin plumpness showed a similar trend, with a score reduction from 4.55 ± 0.07 to 3.82 ± 0.09 (-16.14% , $p < 0.001$). In addition to structural attributes, surface-related features also responded rapidly to the treatment. Skin smoothness improved from 5.06 ± 0.07 to 4.04 ± 0.07 (-20.16% , $p < 0.001$), and radiance from 4.76 ± 0.09 to 3.53 ± 0.09 (-25.75% , $p < 0.001$). These short-term improvements suggest an early onset of efficacy in both mechanical and visual parameters of skin aging.

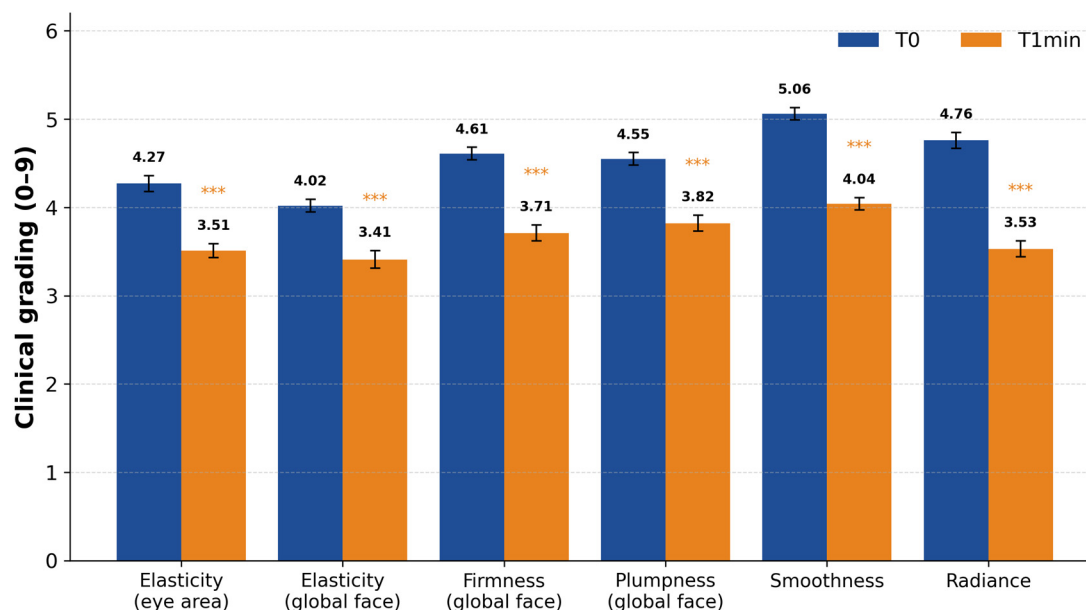


Figure 1. Clinical scoring of skin qualities at baseline (T0) and short-term follow-up (T1min). Dermatologist visual assessments revealed significant improvements in elasticity (eye and face), firmness, plumpness, smoothness, and radiance. Data are presented as mean $\pm$ SE; *** $p < 0.001$ vs. T0.

At later time points (T4wk and T8wk), clinical assessments confirmed progressive and significant improvements in all skin quality parameters (Figure 2). Compared with baseline, periorbital elasticity improved from 4.27 ± 0.09 to 3.52 ± 0.09 (-17.46% , $p < 0.001$) and 3.02 ± 0.07 (-29.19% , $p < 0.001$) at Weeks 4 and 8, respectively. Similarly, global face elasticity improved from 4.02 ± 0.07 to 3.49 ± 0.09 (-13.20% , $p < 0.001$) and 3.03 ± 0.07 (-24.62% , $p < 0.001$) at Weeks 4 and 8, respectively. Skin firmness on the global face decreased from 4.61 ± 0.07 to 4.03 ± 0.07 (-12.61%) and 3.64 ± 0.07 (-21.02%) at Weeks 4 and 8, respectively (both $p < 0.001$). Skin plumpness improved from 4.55 ± 0.07 to 4.09 ± 0.08 (-10.09%) and 3.71 ± 0.07 (-18.39%) at the corresponding time points. Surface attributes also showed continued improvement: skin smoothness improved from 5.06 ± 0.07 to 4.30 ± 0.10 (-15.12%) and 3.86 ± 0.08 (-23.79%), and radiance from 4.76 ± 0.09 to 4.12 ± 0.08 (-13.30%) and 3.83 ± 0.08 (-19.53%) at Weeks 4 and 8, respectively (all $p < 0.001$). These data indicate that the tested cream demonstrated not only rapid onset but also cumulative efficacy in improving key clinical markers of facial skin aging.

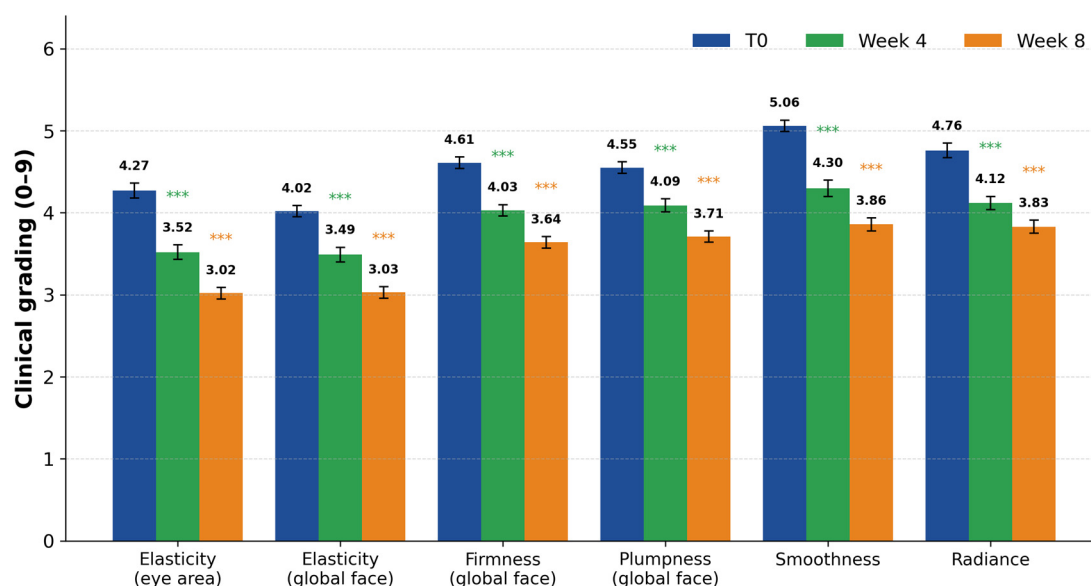


Figure 2. Clinical assessment of skin qualities at baseline (T0), Week 4 (T4wk), and Week 8 (T8wk). All parameters—including elasticity (eye and face), firmness, plumpness, smoothness, and radiance—showed significant improvements. Data are presented as mean $\pm$ SE; *** $p < 0.001$ vs. T0.

Facial aging parameters, including both static and expression-linked wrinkles, showed robust improvement over time (Figure 3). Compared with baseline, significant reductions were observed at Week 4 and sustained through Week 8. At Week 8, crow's feet and under-eye wrinkles decreased from 2.98 ± 0.11 to 2.18 ± 0.11 (-26.89% , $p < 0.001$) and from 3.38 ± 0.14 to 2.24 ± 0.14 (-33.74% , $p < 0.001$), respectively. Inter-ocular and glabellar wrinkles decreased from 2.50 ± 0.08 to 1.70 ± 0.11 (-32.14% , $p < 0.001$) and from 2.49 ± 0.10 to 1.61 ± 0.12 (-35.30% , $p < 0.001$), respectively. Forehead fine lines and wrinkles improved from 1.70 ± 0.08 to 1.10 ± 0.06 (-35.10% , $p < 0.001$), and from 2.51 ± 0.10 to 1.64 ± 0.12 (-34.69% , $p < 0.001$), respectively. In parallel, improvements were observed in the global appearance of fine lines (4.59 ± 0.08 to 3.24 ± 0.10 ; -29.33% , $p < 0.001$) and wrinkles (4.96 ± 0.09 to 4.02 ± 0.10 ; -18.93% , $p < 0.001$). The product also reduced signs of fatigue and skin sagging, with dark eye circle scores decreasing from 2.49 ± 0.14 to 2.09 ± 0.12 (-16.07% , $p < 0.001$) and drooping of the upper outer eyelid from 2.60 ± 0.04 to 2.03 ± 0.06 (-21.94% , $p < 0.001$). These findings confirm the efficacy of the tested cream in both dynamic and structural signs of aging across multiple facial zones.

Instrumental measurements confirmed the long-term clinical findings, providing quantitative evidence of dermal structural improvements (Figure 4). After 8 weeks of use, epidermal thickness around the eyes increased significantly from $49.31 \pm 4.55 \mu\text{m}$ to $62.41 \pm 3.91 \mu\text{m}$ ($+26.57\%$, $p = 0.005$), while epidermal density rose from $25.89 \pm 0.80\%$ to $29.17 \pm 1.12\%$ ($+12.69\%$, $p = 0.005$). Simultaneously, improvements in wrinkle morphology were observed via PRIMOS 3D analysis. The forehead wrinkle area and total wrinkle length decreased from $112.18 \pm 3.66 \text{ mm}^2$ to $102.43 \pm 3.44 \text{ mm}^2$ (-8.69% , $p < 0.001$) and from $254.37 \pm 8.58 \text{ mm}$ to $223.71 \pm 7.99 \text{ mm}$ (-12.05% , $p < 0.001$), respectively. The crow's feet area also declined significantly from $61.22 \pm 0.76 \text{ mm}^2$ to $55.89 \pm 0.79 \text{ mm}^2$ (-8.70% , $p < 0.001$), and total wrinkle length from $122.00 \pm 3.14 \text{ mm}$ to $102.44 \pm 2.05 \text{ mm}$ (-16.03% , $p < 0.001$). These instrumental outcomes reinforce the efficacy of the tested cream in improving both superficial skin properties and deeper wrinkle architecture.

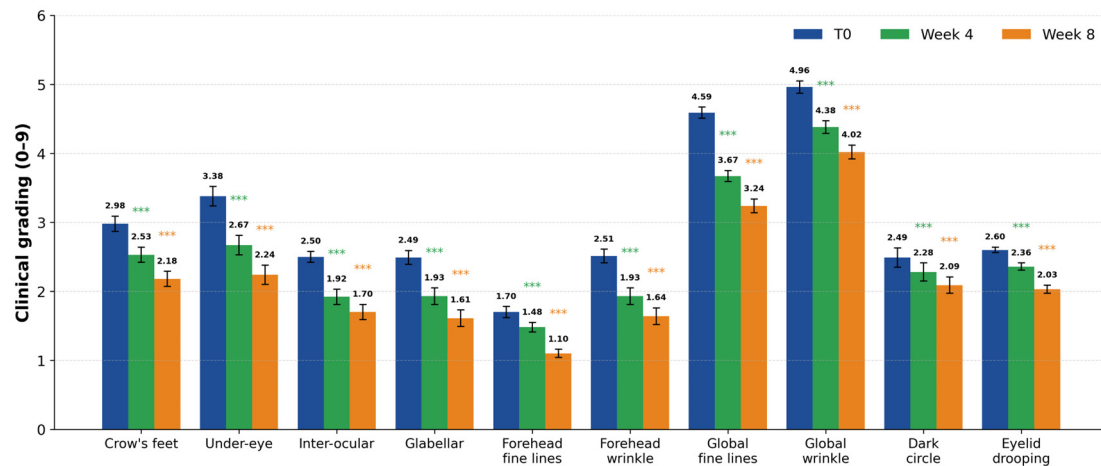


Figure 3. Clinical assessment of aging-related facial features at T0, T4wk, and T8wk. Significant improvements were observed in expression-related wrinkles (e.g., crow's feet, glabellar lines, forehead lines), static wrinkles (e.g., under-eye, inter-ocular), and secondary signs of aging (e.g., dark eye circle, upper eyelid drooping). Data are presented as mean $\pm$ SE; *** $p < 0.001$ vs. T0.

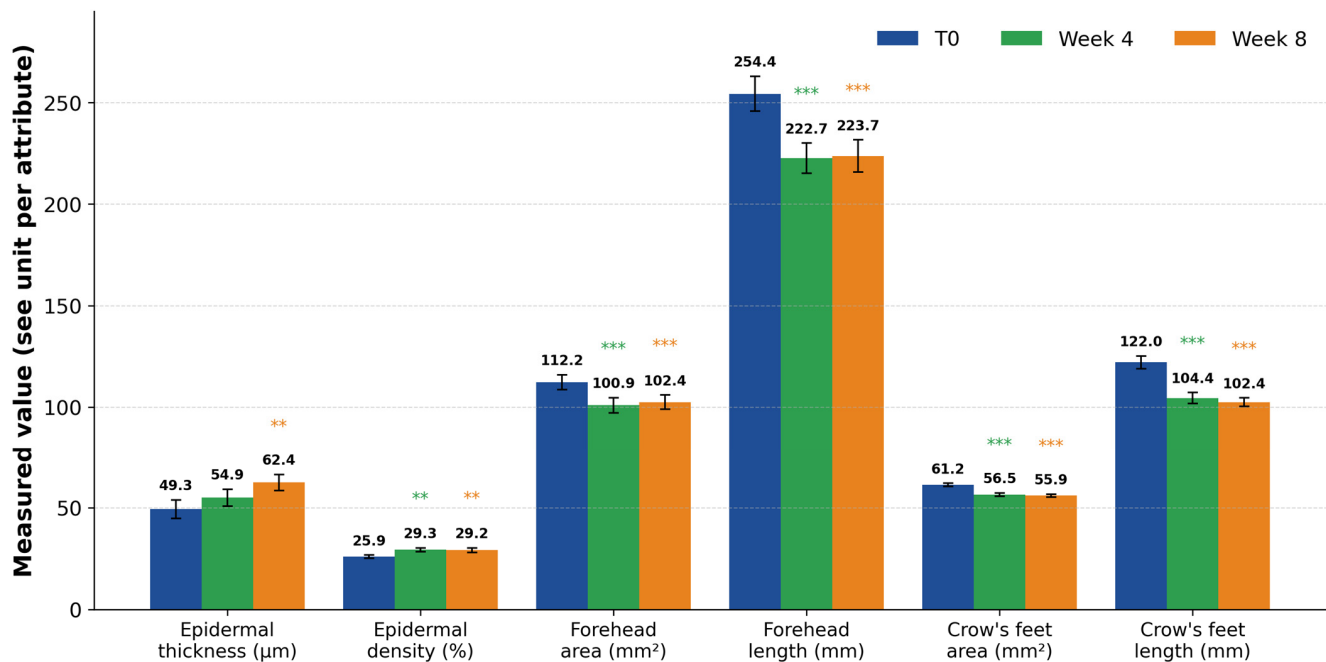


Figure 4. Instrumental evaluation of epidermal structure and wrinkle morphometry at T0, T4wk, and T8wk. Epidermal parameters were measured using UC22; wrinkle area and length were similarly assessed for the forehead and crow's feet using PRIMOS 3D. Data are presented as mean $\pm$ SE; *** $p < 0.001$, ** $p < 0.01$ vs. T0.

In addition to static-wrinkle assessments, dynamic-wrinkle analysis under smile expression further confirmed the anti-aging benefits of the tested cream (Figure 5). Compared with baseline, significant reductions were observed in both maximum and mean expression grades. For under-eye wrinkles, the maximum and mean expression scores decreased from 4.17 ± 0.14 to 3.64 ± 0.15 (-12.64% , $p < 0.001$) and from 3.70 ± 0.12 to 3.12 ± 0.14 (-15.74% , $p < 0.001$), respectively. Similarly, crow's feet wrinkles showed notable improvement, with the maximum and mean scores reduced from 4.09 ± 0.14 to 3.44 ± 0.14 (-15.97% , $p < 0.001$) and from 3.57 ± 0.12 to 2.96 ± 0.13 (-16.89% , $p < 0.001$), respectively. These findings suggest that the tested cream effectively softens dynamic wrinkles triggered by facial muscle activity, potentially preventing their evolution into permanent static lines.

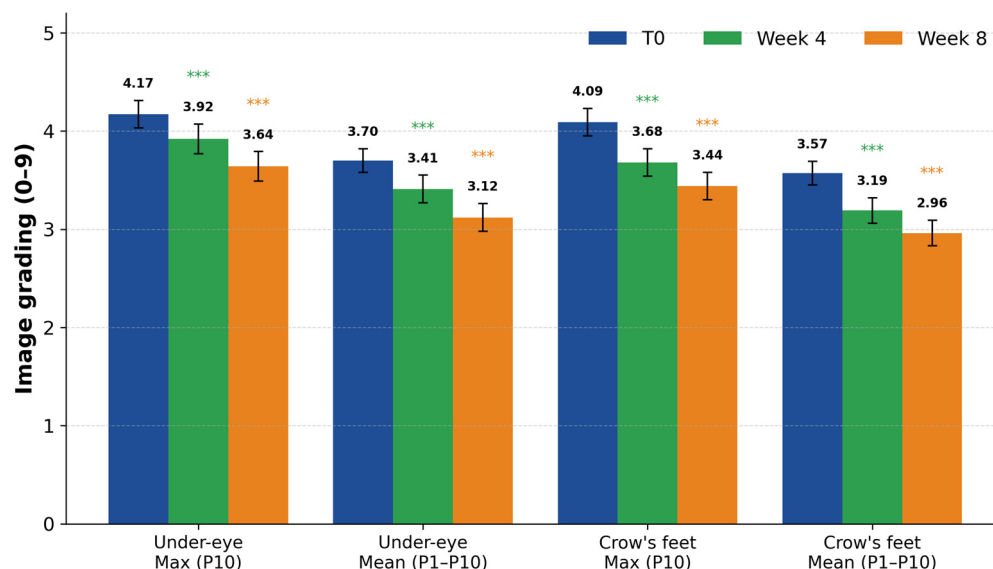


Figure 5. Clinical grading of dynamic wrinkles during smile expression at T0, T4wk, and T8wk. Parameters include maximum and mean wrinkle grades for under-eye and crow's feet wrinkles. Data are presented as mean $\pm$ SE; *** $p < 0.001$ vs. T0.

To further characterize dynamic-wrinkle evolution, a detailed temporal grading analysis was conducted on under-eye wrinkles across ten expression points (P1 to P10). As shown in Figure 6, significant decreases in image grading were observed at all points after applying the tested cream. For instance, the grade at maximal expression (P10) dropped from 4.17 ± 0.14 at baseline to 3.64 ± 0.15 at Week 8 (-12.64% , $p < 0.001$), while early and mid-expression phases also exhibited improvements (e.g., P3: 3.43 ± 0.12 to 2.80 ± 0.14 , -18.43% , $p < 0.001$). These findings demonstrate that the tested cream not only reduced final expression depth but also mitigated wrinkle formation throughout the entire muscle contraction process. These improvements were also visually confirmed by representative expression images shown in Figure 7.

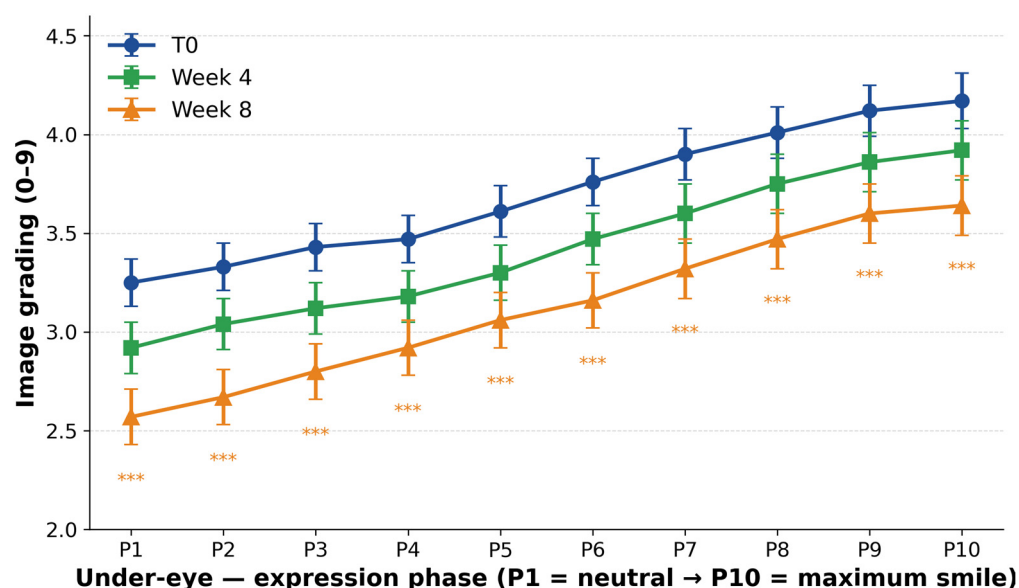


Figure 6. Dynamic-wrinkle evolution of under-eye wrinkles during smile expression at T0, T4wk, and T8wk. Clinical grading was recorded across ten sequential expression stages (P1–P10), from no expression to maximum expression. Data are presented as mean $\pm$ SE; *** $p < 0.001$ vs. T0.

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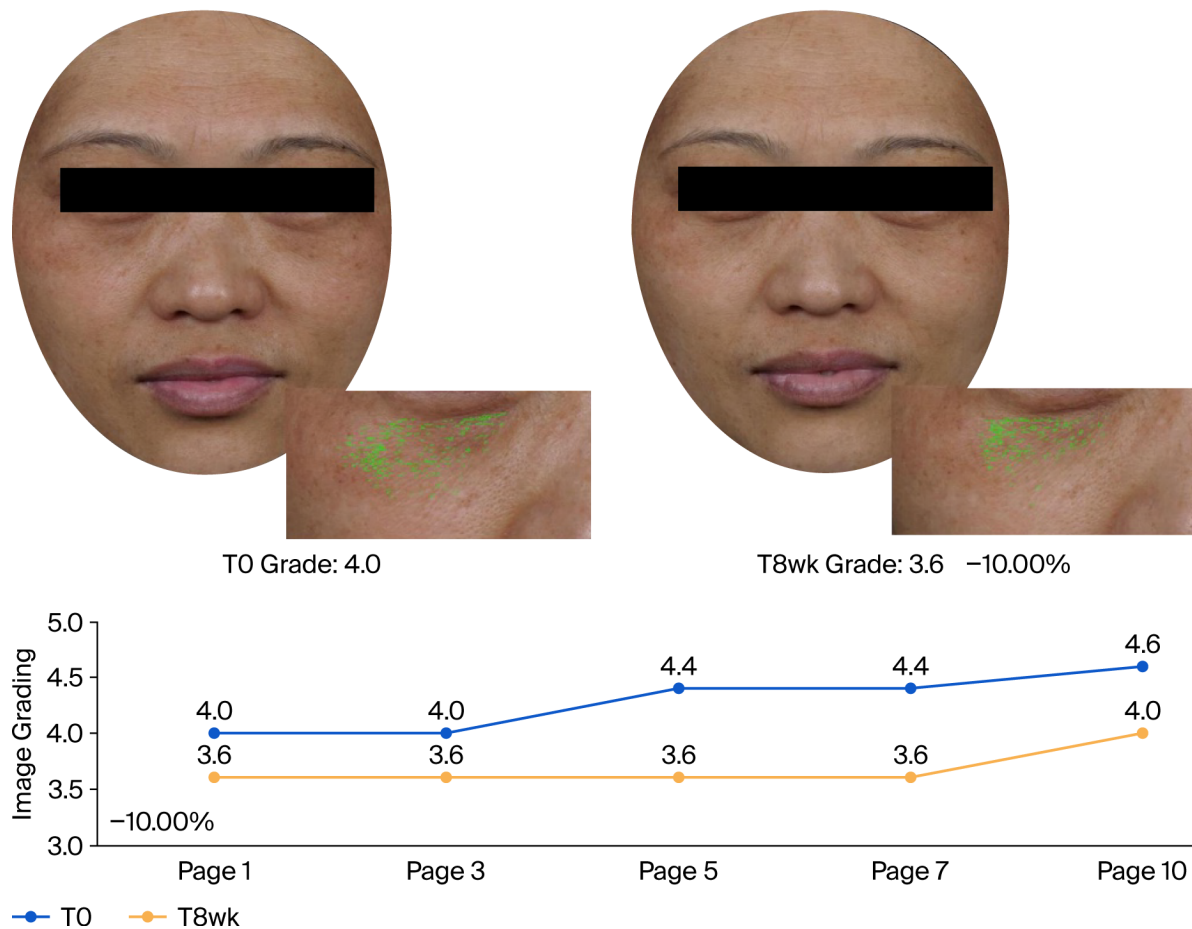


Figure 7. Representative facial images showing the improvement in under-eye wrinkles during smile expression. Images from T0 and T8wk demonstrate visible wrinkle reduction across all expression phases (P1–P10).

Similarly, dynamic-wrinkle grading of crow's feet wrinkles during a smile also showed consistent improvements after applying the tested cream (Figure 8). Scores across all ten expression points (P1–P10) significantly decreased at both Weeks 4 and 8. For example, the grade at maximal expression (P10) decreased from 4.09 ± 0.14 at baseline to 3.44 ± 0.14 at Week 8 (-15.97% , $p < 0.001$), and at early expression (P3), the value dropped from 3.24 ± 0.12 to 2.62 ± 0.12 (-19.25% , $p < 0.001$). These results further support the efficacy of the tested cream in attenuating dynamic wrinkles throughout the full facial movement range. Corresponding expression-phase photographs are provided in Figure 9 to illustrate the visible wrinkle improvement.

3.3. Safety and Tolerability

The multi-active cream was excellently tolerated throughout the 8-week study. No adverse events were reported, and no cutaneous reactions (e.g., erythema, edema, scaling, or pruritus) were observed in any subject during the entire study period. Because the product was applied to the periocular area, subjects were specifically monitored for ocular and periocular tolerability at every scheduled visit: the attending dermatologist assessed for signs of ocular irritation, stinging, watering, or conjunctival redness, and participants were queried regarding any periocular discomfort. No ocular or periocular adverse effects were recorded, and no subject discontinued the study because of intolerance, indicating a favorable safety and tolerability profile for twice-daily use in the eye-contour area.

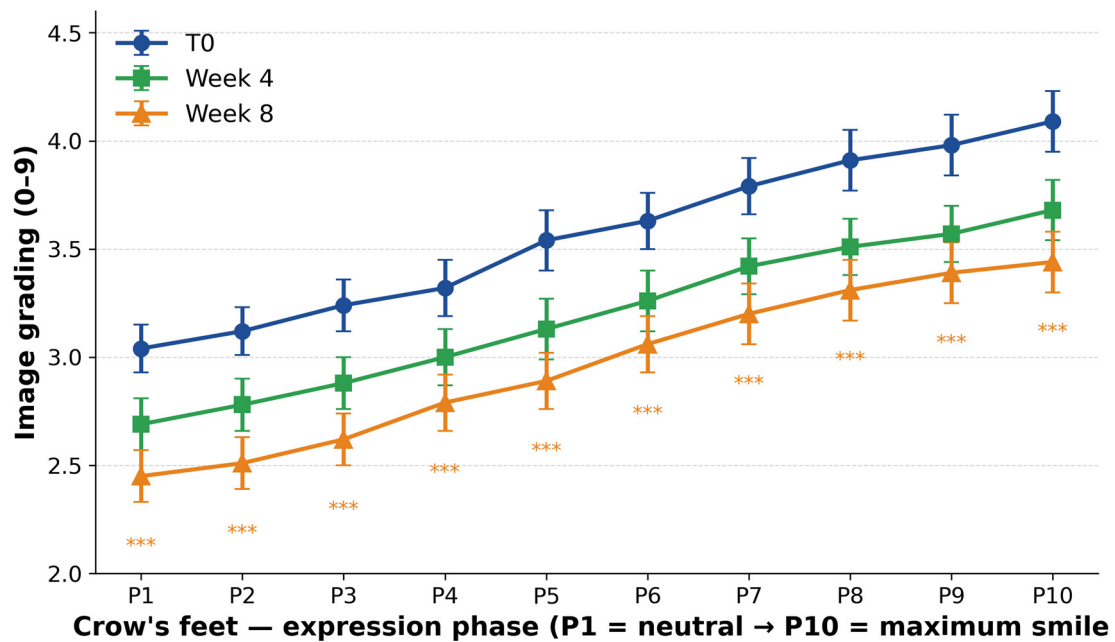


Figure 8. Dynamic-wrinkle grading of crow's feet wrinkles under smile expression at T0, T4wk, and T8wk. Clinical scores were assessed across ten sequential expression stages (P1–P10). Data are presented as mean $\pm$ SE; *** $p < 0.001$ vs. T0.

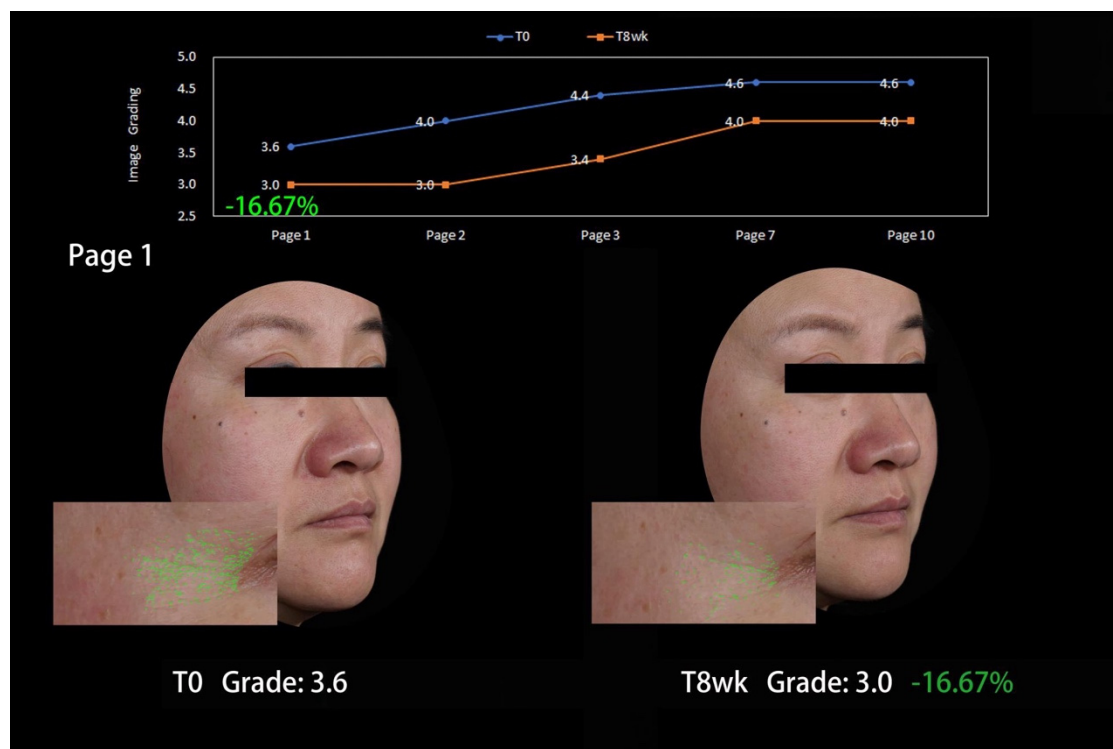


Figure 9. Representative images of crow's feet wrinkle evolution under smile expression. Sequential photos from T0 and T8wk reveal visible improvements in wrinkle appearance from no expression to maximum expression (P1–P10).

4. Discussion

This study provides an integrated clinical readout showing that twice-daily use of the cream produced both immediate and cumulative benefits across signs of facial aging. At the immediate time point (Timm), significant improvements were observed in skin

smoothness, radiance, and plumpness. These rapid-onset effects are likely attributable to the film-forming properties of the formulation and the immediate hydration provided by humectants such as panthenol, rather than structural biological remodeling. However, by Weeks 4 and 8, the sustained and progressive reduction in wrinkle scores—verified by PRIMOS morphometry and ultrasound—suggests a transition from superficial cosmetic benefits to changes compatible with deeper structural effects. By Week 8, wrinkle scores declined broadly across anatomic sites—crow’s feet (−26.9%), under-eye (−33.7%), glabellar (−35.3%), and forehead wrinkles (−34.7%)—with parallel improvements in overall fine lines and global wrinkle appearance. Instrumental outcomes corroborated these changes, with PRIMOS-derived reductions in wrinkle area and total length and ultrasound-detected increases in periocular epidermal thickness and density, a pattern suggestive of a structural contribution to the clinical effects. Beyond static features, dynamic-wrinkle burden lessened: both maximal and mean grades during smiling decreased for the under-eye (−12.6% and −15.7%) and crow’s feet (−16.0% and −16.9%), and reductions were observed throughout the full expression trajectory (P1–P10). Given evidence that expression lines can progress into persistent wrinkles over time, dynamic-wrinkle attenuation is clinically salient in its own right [8].

The structural changes detected by high-frequency ultrasound in this study—namely increased periocular epidermal thickness (+26.6%) and density (+12.7%)—are consistent with the known biology of the C-xylopyranoside Pro-Xylane, which enhances glycosaminoglycan biosynthesis (with a marked effect on dermatan sulfate) and supports extracellular-matrix and dermal–epidermal junction remodeling in human skin [9]. However, it is important to note that ultrasound parameters, particularly epidermal thickness, can also be modulated by tissue hydration status. Given the significant immediate improvements in skin plumpness observed in this study, it is plausible that the ultrasound findings reflect a combination of GAG-mediated structural support and enhanced water retention within the epidermis. Concordantly, an evaluator-blinded, randomized multicenter trial in postmenopausal women using a Pro-Xylane-containing regimen reported clinically visible improvements across aging signs, providing human-level evidence that aligns with the structural readouts observed here [15]. Taken together with earlier mechanistic work in keratinocytes, these data plausibly bridge GAG-centric matrix support to the ultrasound-based increases in periocular tissue metrics seen after eight weeks of use in our cohort [9].

The peptide blend of palmitoyl tripeptide-1 (Pal-GHK) and palmitoyl tetrapeptide-7 (Pal-GQPR) provides a signaling-driven route to matrix renewal that closely aligns with the reductions in wrinkle area and total length observed by PRIMOS in this study. As matricines, these sequences act as extracellular-matrix-derived cues that upregulate collagen and other matrix components; notably, Pal-GQPR also dampens pro-inflammatory mediators such as interleukin-6, a pathway increasingly implicated in aging phenotypes [10,16]. Complementing these mechanistic data, *in vivo* imaging has documented structural improvements at the dermal–epidermal interface after treatment with the Pal-GHK/Pal-GQPR combination: reflectance confocal microscopy and MALDI mass-spectrometric imaging showed enhanced extracellular-matrix features relative to placebo, a pattern that aligns with the topographic smoothing captured by PRIMOS here [17].

In this study, the attenuation of expression-linked wrinkles observed across the entire smile trajectory is compatible with the intended action of dipeptide diaminobutyroyl benzylamide diacetate, a Waglerin-1-mimetic peptide that reversibly antagonizes muscle nicotinic acetylcholine receptors (mnAChRs) to temper neuromuscular drive. *In vitro* and formulation reports describe this peptide class as mnAChR antagonists, based on the pharmacology of Waglerin-1, which selectively blocks the ϵ -subunit-containing muscle nAChR, thereby transiently reducing contraction amplitude [18]. Consistent with the broader evidence

base for non-invasive “Botox-like” peptides, clinical validations remain fewer, and effects are expected to be milder and reversible, but measurable reductions in expression lines have been documented in short-term studies, including peptides engineered to antagonize the muscle nicotinic acetylcholine receptor while concurrently inhibiting MMP-1, thereby addressing dynamic and static wrinkles in tandem [19,20]. Against this backdrop, our concurrent decreases in maximal and mean dynamic-wrinkle grades for both the under-eye and crow’s feet—and their stepwise reduction across P1–P10—support a functional modulation of expression amplitude that complements the structural improvements captured with PRIMOS-CR and ultrasound in the same cohort.

The supporting active compounds in the cream likely amplified the core effects through complementary pathways aligned with the observed clinical signals. Niacinamide improves barrier function and modulates inflammation and melanosome transfer, corresponding with the early gains in smoothness and radiance [21]. Panthenol (dexpantenol) promotes rapid barrier recovery and hydration, translating into perceptible surface evenness at short time scales [22]. Rhamnose has been reported to benefit the papillary dermis and the dermal–epidermal junction—features consistent with the PRIMOS-captured topographic smoothing after repeated use [23]. Carnosine provides antiglycation and antioxidative support relevant to texture and tone, offering a biochemical rationale for parallel improvements in surface quality [24]. For pigmentary outcomes, N-acetylneuraminic acid (sialic acid) modulates melanogenesis (e.g., tyrosinase downregulation and autophagy), which may contribute to the radiance improvement observed [25]. Finally, periocular changes—dark circles and upper-outer eyelid droop—are plausibly supported by caffeine and escin. Caffeine-containing eye creams show reductions in periocular hyperpigmentation, and escin exhibits venotonic and anti-edematous actions with supportive clinical evidence; together, these mechanisms are consistent with decreased dark circle scores and eyelid droop in our cohort [26,27].

Limitations: Several limitations must be considered when interpreting these findings. A fundamental limitation is the open-label, single-arm design without a vehicle or placebo control. Consequently, the observed improvements represent within-subject changes under use conditions, and we cannot definitively distinguish the specific pharmacological effects of the active ingredients from confounding factors such as improved hydration from the base formula, the mechanical effect of massage during application, regression to the mean, or the placebo effect. Additionally, the study was monocentric and restricted to Chinese women aged 25–55 years, which may limit the generalizability of the results to other demographics. Additionally, reporting active ingredient concentrations based on raw-material loadings, due to proprietary constraints, limits the exact reproducibility of the formulation by independent researchers. Furthermore, specific lifestyle confounders (such as cumulative UV exposure and smoking history) and exact Fitzpatrick phototype distributions were not explicitly recorded, although the study population implicitly represents typical Asian phototypes (III–IV). This study was designed as an exploratory, real-life evaluation; therefore, future work should adopt assessor-blinded, randomized, vehicle-controlled designs to rigorously confirm the specific biological efficacy of the active complex [28].

Twice-daily use of the multi-active cream produced immediate (Timm) and progressive (Weeks 4–8) improvements in both static and expression-linked wrinkles. Concordant gains across dermatologist grading, PRIMOS 3D wrinkle morphometry, and periocular high-frequency ultrasound demonstrate a robust, multi-modal efficacy signal under real-life use conditions.

In conclusion, the twice-daily application of the multi-active cream over eight weeks demonstrated significant within-subject improvements in both static and dynamic facial aging phenotypes. Clinically, static wrinkle severity was reduced by up to 35.30% (glabellar

lines), while dynamic wrinkle amplitude during maximum smile expression decreased by up to 15.97% (crow's feet). These clinical gradings were quantitatively supported by instrumental reductions in 3D wrinkle morphometry and significant increases in periocular epidermal thickness (+26.57%) and density (+12.69%). Furthermore, the product was excellently tolerated with no reported adverse events. Given the limitations of the current open-label design, future research should adopt randomized, vehicle-controlled, and assessor-blinded methodologies to further isolate the specific pharmacological efficacy of the active complex and validate these findings across broader demographic populations.

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