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White paper

Clinical evaluation of Matrikynes®: a novel cosmetic ingredient comprised of matrikine peptides

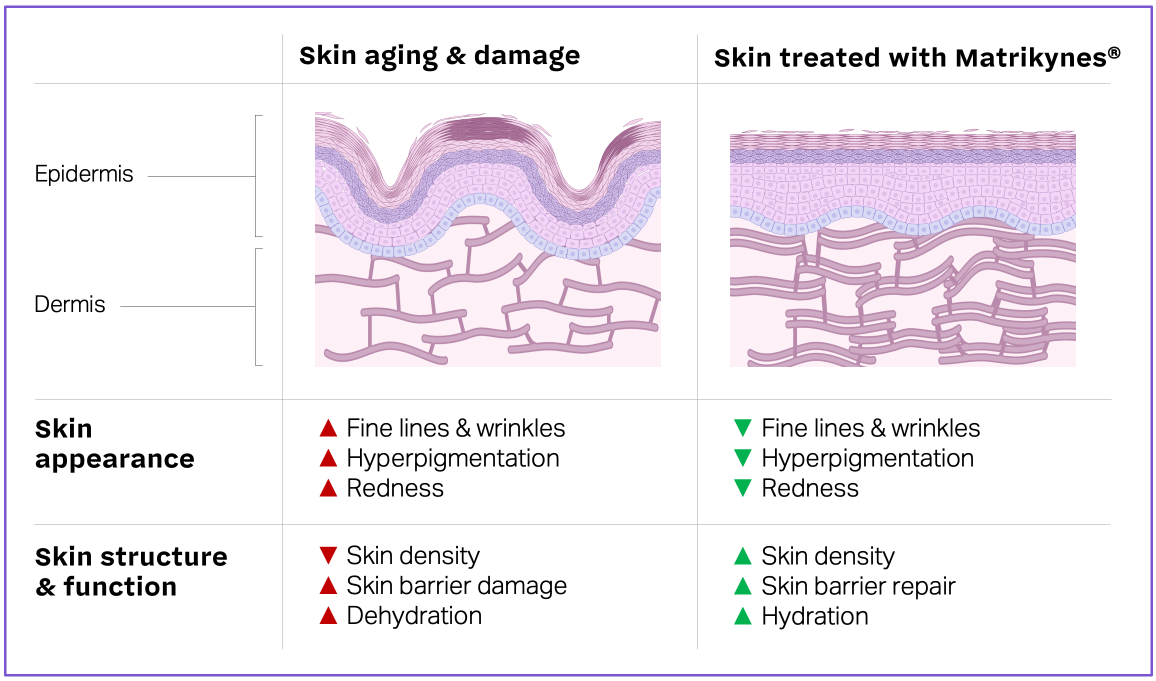
AUTHORS

John D. O'Neill, Alexandra Nichols Chiu, Natalia Kissel, Daniel P. King, Stuart Sklar, Evelyn Aranda, Andrea Nye

CORRESPONDENCE

john@xylyxbio.com

GRAPHICAL ABSTRACT



IN BRIEF

Matrikynes® is a novel multi-functional cosmetic ingredient comprised of a mixture of natural extracellular matrix-derived peptides. Topical application of Matrikynes® showed a robust clinical safety profile and statistically significant improvements in the structure, function, and appearance of damaged and aging skin, including reduction of fine lines and wrinkles.

HIGHLIGHTS

- Human repeated insult patch testing showed no allergic sensitization or irritant reaction to Matrikynes®.
- Within 1 hour after injury, topical Matrikynes® repaired the skin barrier 12% faster and 61% better than control.
- After 8 weeks of application (twice daily), Matrikynes® increased skin density by 15% and decreased global lines and wrinkles by more than 4%.
- Matrikynes® was shown to be a safe and highly effective multi-functional cosmetic ingredient for anti-aging and other topical skin applications.

Clinical evaluation of Matrikynes®: a novel cosmetic ingredient comprised of matrikine peptides

John D. O'Neill, Alexandra Nichols Chiu, Natalia Kissel, Daniel P. King, Stuart Sklar, Evelyn Aranda, Andrea Nye
Xylyx Bio, Inc., Brooklyn, New York, USA
Correspondence: john@xylyxbio.com

SUMMARY

Matrikynes® is a novel cosmetic ingredient comprised of natural extracellular matrix-derived peptides (matrikines). In human repeated insult patch testing, Matrikynes® caused no allergic sensitization or irritant reactions. After injury to the stratum corneum by a standardized tape-stripping procedure, Matrikynes® significantly accelerated skin barrier repair compared to control within 1 hour. In an 8-week clinical efficacy study in 56 women representing different skin tones, Matrikynes® showed statistically significant improvements in skin hydration, barrier function, skin density, hyperpigmentation, redness, fine lines, and deep wrinkles. Self-assessments by study participants were positive and consistent with clinical evaluations. Altogether, these data indicate that Matrikynes® is a safe and highly effective multi-functional cosmetic ingredient for anti-aging and other topical skin applications.

Keywords: anti-aging, barrier function, barrier repair, collagen, cosmetic, dermis, efficacy, epidermis, extracellular matrix, fine lines, hyperpigmentation, ingredient, matrikines, matrix synthesis, moisturizing, naturally-derived, peptides, regeneration, safety, skin, topical, wrinkles

INTRODUCTION

Aging is a multi-factorial process that affects the structure, function, and appearance of skin. Common signs of aging include reduced barrier function, decreased repair after insult, xerosis (dryness), lentigines (hyperpigmented age spots), laxity, and rhytids (fine lines, coarse wrinkles)[1]. With age, epidermal thickness and dermal density decrease, and the dermal–epidermal junction flattens due to cellular senescence and dysregulation of extracellular matrix (ECM)[2]. Reduced synthesis, increased breakdown, and disorganization of ECM proteins (e.g., collagens, elastin), glycoproteins (e.g., fibronectin, laminins), and proteoglycans (e.g., glycosaminoglycans such as hyaluronic acid) result in loss of skin density, elasticity, hydration, and tensile strength, and lead to formation of wrinkles[3].

A promising class of cosmetic ingredients to treat skin damage and aging is peptides, which are short sequences of less than about 50 amino acids. Peptides can possess potent signaling activity, including the ability to stimulate regenerative processes (e.g., angiogenesis, granulation tissue formation, cellular proliferation, matrix synthesis), first recognized in wound healing applications[4]. As an active ingredient, peptides are appealing due to their (i) safety: low/no sensitization and irritation in repeated insult patch testing (RIPT), (ii) efficacy: high potency at low dosage, (iii) penetrability: low molecular weight (≲ 500 Da) enabling permeation of the stratum corneum, and (iv) compatibility: compatible with a wide variety of delivery systems, carriers, and other ingredients, including alpha hydroxy acids, retinoids, and vitamin C[5]. Single peptides successfully developed for topical applications (e.g., acetyl hexapeptide, copper peptide, palmitoyl pentapeptide) have demonstrated notable but limited anti-aging benefits.

Informed by translational research to promote tissue repair and wound healing in lungs, Matrikynes® was developed as a first-line, multi-functional cosmetic ingredient for topical skin applications. Matrikynes® is comprised of a proprietary mixture of natural extracellular matrix-derived peptides (matrikines), which are fragments of 'parent' ECM macromolecules and function as signal peptides by binding cell surface receptors and activating intracellular pathways[6,7]. Natural extracellular matrices are rich repositories of bioactive factors that regulate tissue repair, and ECM-based technologies have demonstrated significant regenerative abilities in multiple tissues, including bone, heart, liver, and skin[8]. In prior studies, human dermal fibroblasts treated with Matrikynes® *in vitro* showed significantly increased proliferation and synthesis of ECM components, and decreased expression of matrix-degrading proteases and inflammatory cytokines, suggesting Matrikynes® can exert multiple regenerative and anti-aging effects.

The objective of this study was to evaluate the clinical safety and efficacy of Matrikynes® as a multi-functional cosmetic ingredient for anti-aging and other topical skin applications. Accordingly, sensitization, irritation, skin barrier repair, skin hydration, barrier function, skin density, hyperpigmentation, and fine lines and wrinkles were assessed by standard dermatological methods. Self-assessments by the study participants were also evaluated.

METHODS

Research standard. All studies were conducted in accordance with the International Conference of Harmonization Tripartite Guideline on Good Clinical Practice and applicable U.S. FDA regulations and guidelines[9].

Safety study design. Study participants (n = 106; 60 females, 46 males) age 21 – 71 years (mean: 55.8 ± 10.7 years), free of systemic and dermatologic disorders, and representing different skin types (Asian, 5%; Black, 69%; White, 26%), completed a medical screening procedure and signed an informed consent form. The 6-week study consisted of three sequential phases: (1) Induction: 9 serial applications of Matrikynes®, week 1 – 3; (2) Rest: 0 applications of Matrikynes®, week 4 – 5; (3) Challenge: 1 application of Matrikynes®, week 6. Application sites were evaluated by a board-certified dermatologist. All testing and data collection were performed at the clinical site by a third-party contract research organization.

Repeated insult patch test. Matrikynes® (2.5%) was applied to a 2 cm^2 pad (Webril) attached to a non-porous, plastic film adhesive bandage (3M) and secured with hypoallergenic tape (Micropore) to the infrascapular area of the back, as previously described[10,11].

Cumulative irritation test. After patch removal, irritation potential of Matrikynes® (2.5%) was evaluated as previously described[12]. Sodium lauryl sulfate (0.2%, aqueous), a surfactant

frequently used to induce experimental irritant contact dermatitis, was applied as a positive control. Any sign of irritant contact dermatitis (e.g., erythema, edema, papules, papulovesicular lesions) was graded and recorded.

Efficacy study design. Matrikynes® efficacy was evaluated in a single-blind within-patient before-and-after study. Study participants (n = 56 females) age 36 – 64 years (mean: 52.5 ± 8.3 years) and representing Asian (29%), Black (30%), and White (41%) skin types spanning the Fitzpatrick scale signed an informed consent form, photography release form, and medical history form. Five days prior to initiation of the study, participants discontinued use of all facial skincare products except for the provided soap (Gentle Skin Cleanser, Cetaphil) and sunscreen (Ultra Sheer Dry-Touch Sunscreen SPF 30, Neutrogena), and did not use any other facial skincare products for the duration of the study. Participants applied a quarter size (1.5 g) of neutral inactive carrier cream containing Matrikynes® (0.2%) twice daily (morning, evening) to a clean, dry face for 8 weeks. Participants were evaluated at week 0 (baseline), week 4, and week 8 using standard clinical bioinstrumentation and validated quantitative measurement techniques. All measurements were performed in triplicate at pre-determined, designated sites in the left and right periocular regions of the face (unless otherwise specified). All testing and data collection were performed at the clinical site by a third-party contract research organization.

Skin barrier repair. A standardized tape-stripping procedure[13] was performed on the volar forearm to damage the stratum corneum and disrupt the skin barrier. An evaporimeter (DermaLab TEWL Probe, Cortex Technology) was used to measure trans-epidermal water loss (TEWL), an indicator of skin barrier integrity, at pre-determined, designated treated and untreated (control) sites on the volar forearm, as previously described[14].

Skin hydration. A corneometer (CM 825, Courage + Khazaka Electronic) was used to measure skin electrical conductance, which directly correlates to skin water content, as previously described[14].

Skin barrier function. An evaporimeter (DermaLab TEWL Probe, Cortex Technology) was used to measure trans-epidermal water loss (TEWL), as previously described[15].

Skin density. An ultrasound scanner with rotating single element transducer (DermaLab Combo Ultrasound Probe, Cortex Technology) was used to measure physical parameters of the skin. Focused ultrasound images were captured at a frequency of 20 MHz, and echogenicity (average ultrasound echo intensity) across the dermis was calculated, as previously described[16].

Skin hyperpigmentation and redness. A clinical facial imaging system (VISIA-CR, Canfield) was used to capture standardized clinical photographs of the face (frontal, lateral) with Standard 1 modality, and skin hyperpigmentation and redness were evaluated, as previously described[17,18]. Standard guidelines were used for clinical photographs in accordance with regulations of consumer protection agencies (FDA, FTC) and other regulatory authorities[9]. No images were altered.

Fine lines and wrinkles. A clinical facial imaging system (VISIA-CR, Canfield) was used to capture clinical photographs of the face, as described above. Clinical photographs were analyzed using image analysis software (VAESTRO Image Analysis Toolkit, Canfield) to quantify changes in global fine lines and wrinkles across the whole face, as previously described[19]. No images were altered.

Self-assessments. A self-assessment survey was completed by study participants at week 4 and week 8.

TABLE 1 | MATRIKYNES® SAFETY TESTING

Sensitization		
Maximum elicited response	Subjects	%
[–] No visible reaction	105	99.1
[?] Minimal or doubtful erythema	0	0.0
[+] Definite erythema	1	0.9
Irritation		
Maximum elicited response	Subjects	%
[–] No visible reaction	106	100.0

Statistical analyses. A *Z*-test or Student's *t*-test was performed between pre- and post-treatment, and $p \leq 0.05$ was considered statistically significant.

RESULTS

Sensitization. Sensitization reactions are characterized by allergic contact dermatitis, and typically begin with an immunological type IV or delayed hypersensitivity response in the dermis, resulting in erythema, edema, and vesiculation[20]. Of 106 participants who completed the occlusive Repeated Insult Patch Test (RIPT), 105 participants (99.1%) had no visible reaction, and 1 subject (0.9%) had definite erythema (Table 1).

Irritation. Irritant contact dermatitis is a localized, superficial, exudative inflammatory response of the skin due to externally applied material[21]. Of 106 participants who completed the Cumulative Irritation Test, 106 participants (100.0%) had no visible reaction (Table 1). No adverse events were reported.

Skin barrier repair	**1 hour**
Improvement (from 0 hour post-injury)	+ 72.1%
Differential repair (ΔMatrikynes® – ΔControl)	+ 60.5%

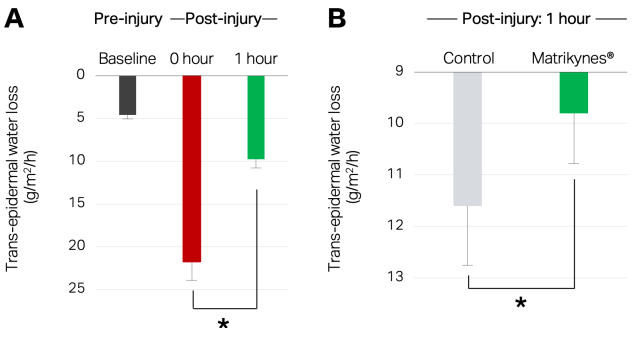


Figure 1. Skin barrier repair. (**A**) After injury, Matrikynes® significantly reduced trans-epidermal water loss toward baseline within 1 hour. (**B**) At 1 hour post-injury, Matrikynes® significantly reduced trans-epidermal water loss compared to untreated control. n = 56, * $p < 0.05$.

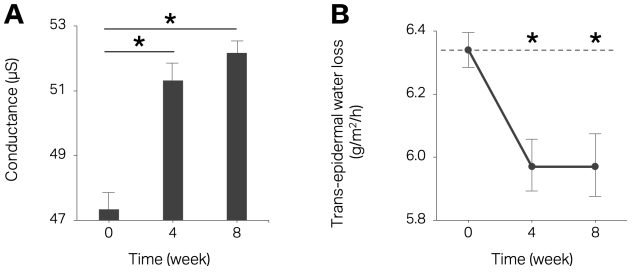


Figure 2. Skin hydration and barrier repair. Matrikynes® significantly improved (**A**) skin hydration and (**B**) skin barrier function over 8 weeks. n = 56, * $p \leq 0.05$.

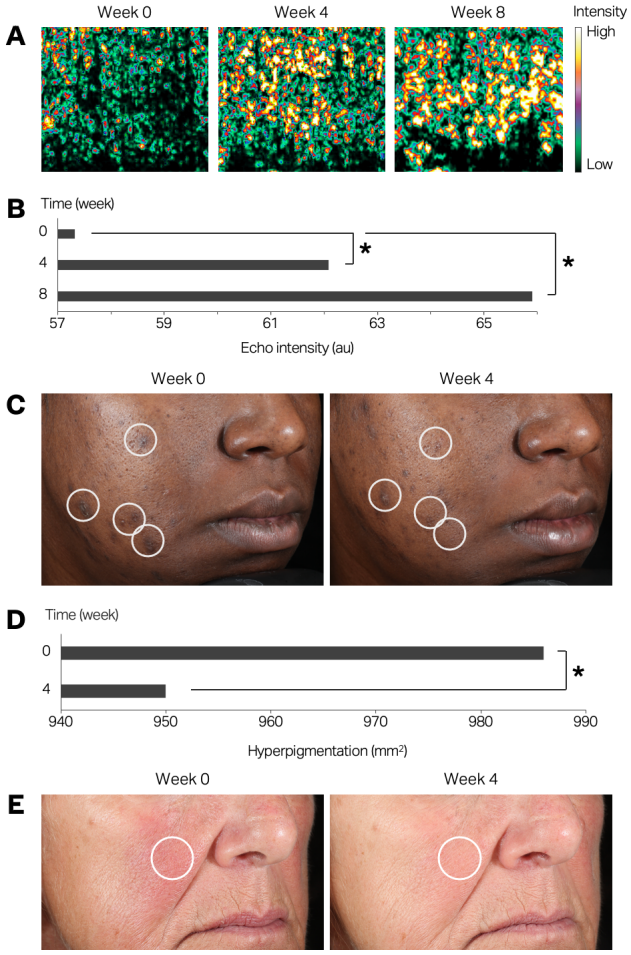


Figure 3. Skin density, hyperpigmentation, and redness. (**A**) Representative ultrasound echo images of the dermis. Color denotes echo intensity, which correlates to skin (dermis) density. Darker colors (black, green) indicate low skin density, lighter colors (yellow, white) indicate high skin density. (**B**) Quantification of ultrasound echo intensity in the dermis. n = 56, * $p \leq 0.05$. (**C**) Representative VISIA-CR photographs of Black female, age 38 years. Circle outlines area of hyperpigmentation. No photograph was altered, edited, or retouched. (**D**) Quantification of area with hyperpigmentation. n = 19, * $p \leq 0.05$. (**E**) Representative VISIA-CR photographs of White female, age 62 years. Circle outlines area of significant reduction in redness. No photograph was altered, edited, or retouched.

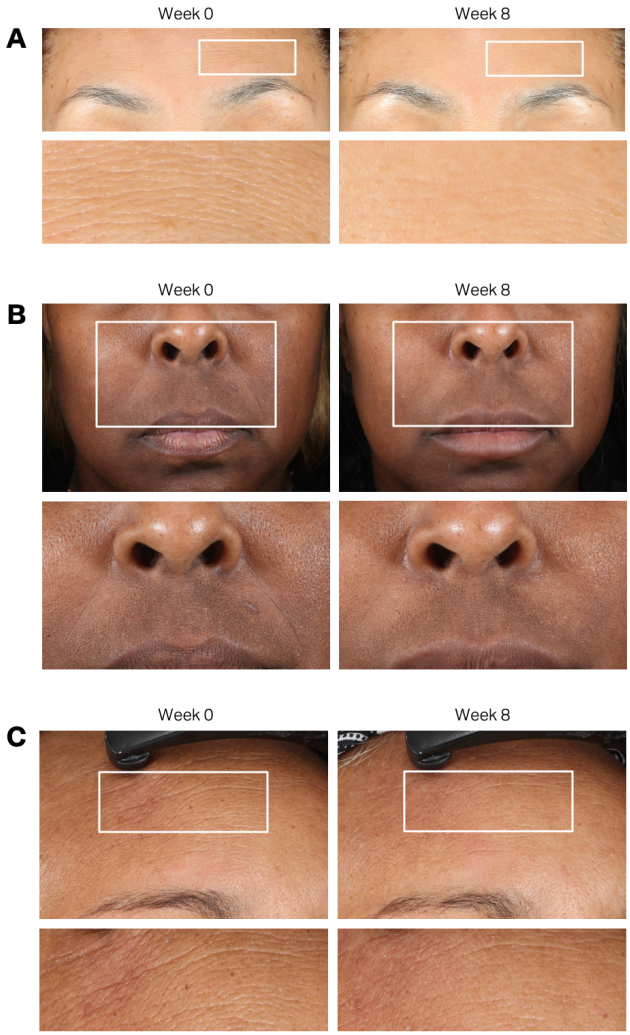


Figure 4. Fine lines and wrinkles. Representative VISIA-CR photographs: (**A**) Reduction of forehead lines, Asian female, age 59 years. (**B**) Reduction of nasolabial lines, Black female, age 49 years. (**C**) Reduction of forehead lines, Black female, age 54 years. Box outlines magnified region of interest. No photograph was altered, edited, or retouched.

Skin barrier repair. To assess whether Matrikynes® can have an acute therapeutic effect, skin barrier repair was evaluated 1 hour after injury to the stratum corneum by a standardized tape-stripping procedure. Matrikynes® improved the skin barrier by significantly reducing trans-epidermal water loss ($p < 0.001$), restoring 72.1% of baseline barrier function within 1 hour (Fig. 1A). Compared to untreated control, Matrikynes® repaired the skin barrier 12.4% faster and 60.5% better ($p = 0.009$) at 1 hour post-injury (Fig. 1B). Thus, rapid onset of action for Matrikynes® was confirmed by statistically significant restoration of skin barrier function within 1 hour of injury, a remarkable reparative effect.

Skin hydration and barrier function. Matrikynes® significantly increased skin conductance, which directly correlates to skin water content, by 8.4% after 4 weeks, and by 10.2% after 8 weeks, representing continued significant improvement ($p \leq 0.05$) in skin hydration across the duration of the study (Fig. 2A). Matrikynes® also significantly reduced trans-epidermal water loss (TEWL) by 5.8% after 4 weeks, and by 5.9% after 8 weeks, demonstrating sustained statistically significant improvement ($p \leq 0.05$) in skin barrier function (Fig. 2B). These results indicate that Matrikynes® can support fundamental aspects of skin health, as the ability to retain water is essential for healthy skin, and strengthening barrier function increases protection against pathogens, oxidative stress, mechanical injury, dehydration, and chemical insult[22].

Skin density. Ultrasound echography revealed that Matrikynes® significantly increased ultrasound echo intensity, a non-invasive visualization of the density of the dermis, over 8 weeks (Fig. 3A). Notably, the primary phenotypic effect of aging in skin is decreased dermal density due to physiochemical changes in the quantity and organization of skin ECM proteins. After treatment with Matrikynes®, ultrasound images showed higher dermal echogenicity (increased dermal density) and fewer irregularities across the dermis, which is consistent with stereotypical echo signatures of young skin[23]. Thus, increasing dermal density is a significant and direct anti-aging effect of Matrikynes®. As increased expression of ECM proteins including collagen type I was previously observed in human dermal fibroblasts treated with Matrikynes® *in vitro*, the increased dermal density may reflect increased expression of dermal collagens, which is also associated with improved skin integrity and firmer smoother texture character-

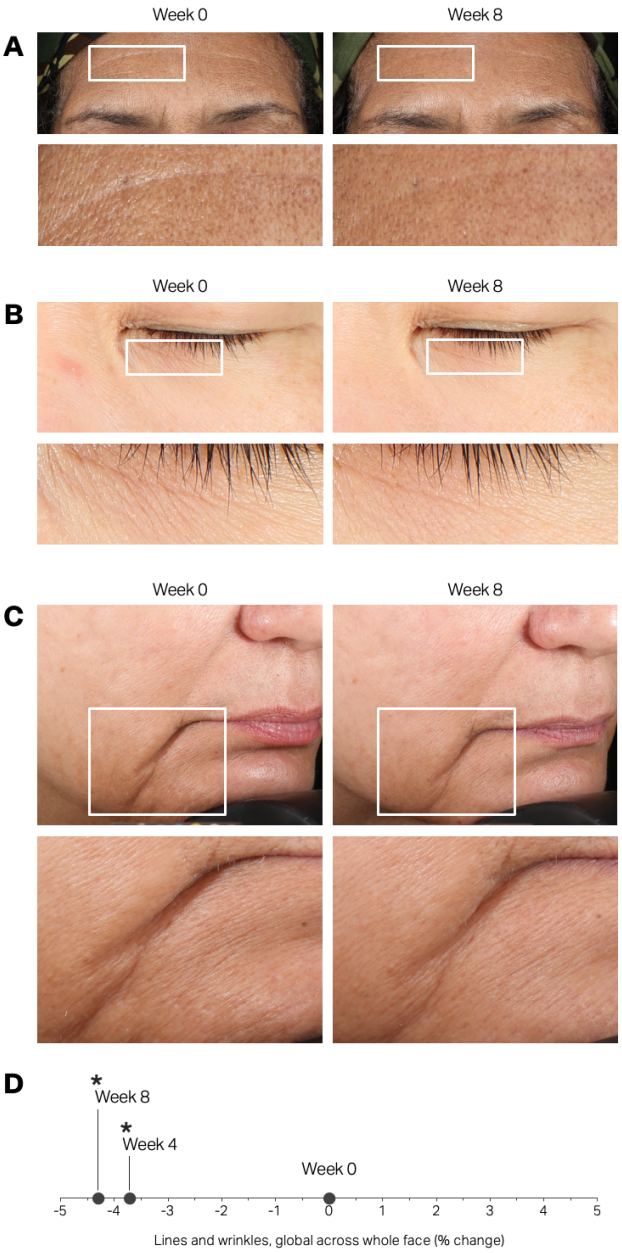


Figure 5. Fine lines and wrinkles. Representative VISIA-CR photographs. (**A**) Reduction of forehead wrinkle, Black female, age 62 years. (**B**) Reduction of under-eye wrinkles, Asian female, 40 years. (**C**) Reduction of oral commissure line (marionette line), White female, age 62 years. Box outlines magnified region of interest. No photograph was altered, edited, or retouched. (**D**) Quantification of global fine lines and wrinkles. n = 56, * $p < 0.05$.

istic of young healthy skin. Quantitative analysis of ultrasound images showed that Matrikynes® increased skin density by 8.3% after 4 weeks ($p = 0.010$), and by 15.0% after 8 weeks ($p \leq 0.001$), a striking anti-aging effect (Fig. 3B). In a previous study[24], the efficacy of palmitoyl pentapeptide-4 (tradename: Matrixyl®), one of the best-known and most widely used cosmetic ingredients for anti-aging, was evaluated in 16 participants. Ultrasound echography showed that palmitoyl pentapeptide-4 (0.0003%) increased skin density by about 9% after 16 weeks; however, effects were only observed after 8 weeks. Remarkably, Matrikynes® showed statistically significant increase in skin density after only 4 weeks, suggesting that Matrikynes® can achieve results significantly faster than Matrixyl®. Furthermore, over the course of 8 weeks, Matrixyl® showed an average improvement in skin density

TABLE 2 | MATRIKYNES® EFFICACY	Week 4	Week 8
Skin hydration		
Improvement (mean, % from baseline)	▲8.4%	▲10.2%
Subjects significantly improved (%)	84%	89%
Skin barrier function		
Improvement (mean, % from baseline)	▲5.8%	▲5.9%
Subjects significantly improved (%)	70%	65%
Skin density		
Improvement (mean, % from baseline)	▲8.3%	▲15.0%
Subjects significantly improved (%)	67%	71%
Skin hyperpigmentation		
Improvement (mean, % from baseline)	▼3.6%	–
Subjects significantly improved (%)	74%	–
Fine lines & wrinkles		
Improvement (mean, % from baseline)	▼3.7%	▼4.3%
Subjects significantly improved (%)	65%	68%

of +0.56% per week, whereas Matrikynes® showed an average improvement in skin density of +1.88% per week. Based on these results, the improvement in skin density achieved by Matrikynes® was not only significantly faster but also superior to that of to Matrixyl® by a factor of approximately 3.36, or 336%.

Skin hyperpigmentation. Matrikynes® significantly reduced the total area of hyperpigmentation after 4 weeks ($p \leq 0.05$) in over 70% of participants with focal hyperpigmentation (Fig. 3C,D). Notably, in some participants, Matrikynes® did not prevent development of new post-inflammatory hyperpigmentation, suggesting that Matrikynes® normalizes pigmentation through a more reparative than preventative mode of action. Thus, Matrikynes® may offer a gentler treatment option for hyperpigmentation than harsh chemical peels or irritating retinoids such as retinol and retinoic acid (tretinoin).

Skin redness. Skin redness in the absence of underlying disease, friction, blushing, or exercise is typically indicative of inflammation. After 8 weeks of treatment with Matrikynes®, appearance of redness was reduced (Fig. 3E), which is notably consistent with prior studies that showed statistically significant reduction of inflammatory cytokine interleukin 1 beta (IL-1β) secreted by human dermal fibroblasts that were treated with Matrikynes® *in vitro*. As inflammation is not only associated with eczema (atopic dermatitis) and rosacea but also aging (inflammaging), and IL-1β is a pro-inflammatory biomarker of inflammaging correlated with cellular senescence (dermal fibroblasts, keratinocytes)[25], these results suggest Matrikynes® may be effective at reducing redness by modulating local expression of inflammatory factors.

Fine lines and wrinkles. Changes in fine lines and wrinkles were quantified globally across the whole face using clinical facial imaging and advanced image analysis software. Matrikynes® significantly decreased global fine lines and wrinkles across the whole face by 3.7% after 4 weeks, and by 4.3% after 8 weeks, representing continued significant reduction ($p \leq 0.05$) of lines and wrinkles across the duration of the study (Fig. 4,5). Improvements in skin appearance (reduced lines and wrinkles across the whole face) correlated with concomitant improvements in underlying skin structure (increased dermal density) and function (increased barrier, hydration), representing multiple complementary benefits

of Matrikynes® across the epidermis and dermis. Although a variety of topical agents are available to treat lines and wrinkles, few have demonstrated statistically significant reduction of lines and wrinkles in a clinical study. A systematic review and meta-analysis of 27 randomized controlled trials reported that retinoids were effective in reducing wrinkle severity scores compared to placebo[26]. However, use of retinoids frequently causes skin irritation and photosensitivity, may require guidance from a healthcare provider, and takes months to obtain statistically significant results (vs. 4 weeks for Matrikynes®). In a randomized, double-blind, placebo-controlled study, topical treatment with a mixture of peptides and antioxidants significantly reduced wrinkle depth after 8 weeks[27]. Future studies will investigate the efficacy of Matrikynes® over longer durations of treatment and in combination with other active ingredients, an approach that could significantly enhance wrinkle reduction and other cosmetic benefits.

Self-assessments. Study participants agreed that Matrikynes® improved the texture and look of their skin, and that their skin looked smoother, firmer, healthier, and had more elasticity. They also agreed that they saw reduced lines and wrinkles after 4 weeks and 8 weeks ($p \leq 0.05$), consistent with objective clinical evaluations.

CONCLUSIONS

Matrikynes® is a safe and highly effective multi-functional cosmetic ingredient for topical skin applications (**Table 1, 2**). In addition to use as a standalone topical agent, this clinically-proven anti-aging ingredient may offer a non-invasive alternative or practical adjunct to dermabrasion, injectable fillers, laser resurfacing, or microneedling treatments. Beyond aesthetic benefits, treatment with effective anti-aging agents like Matrikynes® can not only support psychological and social well-being but also help reduce aging-associated risks such as increased susceptibility to infection, chronic wounds, dermatitis, and malignancies such as melanoma for aging populations around the world.

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