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ORIGINAL CONTRIBUTION

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Global periorbital skin rejuvenation by a topical eye cream containing low molecular weight heparan sulfate (LMW-HS) and a blend of naturally derived extracts

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Summary

Background: Maintaining a youthful appearance is a priority for many people. Global eye rejuvenation is sought more frequently and at a younger age than other treatments. Major concerns around the eye area are periorbital hyperpigmentation, puffiness, and lines and wrinkles. Glycosaminoglycans (GAGs) are complex carbohydrates that modulate skin health, repair and renew skin's appearance. Heparan sulfate (HS) is the most biologically active GAG, although it is too large and polar to penetrate the skin. Low Molecular Weight Heparan Sulfate (LMW-HS) is a smaller version of HS designed for skin penetration while preserving its activity. In this study, we investigated the effects of a topical eye cream containing LMW-HS and a blend of naturally derived extracts to address global periorbital rejuvenation.

Method: A single-center, open-label study including female and male subjects (n = 15) was conducted to evaluate the efficacy and tolerability of an eye cream containing LMW-HS and a blend of naturally derived extracts applied twice daily for 12 weeks.

Results: Improvements in the appearance of periorbital hyperpigmentation and fine and coarse wrinkles were observed as early as week 2 with continuous improvement up to 12 weeks. Decrease in puffiness (73%) and dark circles (93%) were reported by subjects. The test product was highly rated by subjects on performance and attributes and was well tolerated by all the subjects in this study.

Conclusion: Results demonstrated that an eye cream containing LMW-HS and a blend of naturally derived extracts achieved global skin rejuvenation by improving appearance of periorbital hyperpigmentation, puffiness, and fine and coarse wrinkles.

KEYWORDS
anti-aging, dark circles, hydration, puffiness, wrinkles

1 | INTRODUCTION

Glycosaminoglycans (GAGs) are large, linear, negatively charged, and the most abundant heteropolysaccharides in the body. Among the four classes of GAGs known today, namely: chondroitin sulfate (CS)/dermatan sulfate (DS), heparin/heparan sulfate (HS), keratin sulfate (KS), and hyaluronic acid (HA), only HA is non-sulfated nor forms part of proteoglycans. Sulfated GAGs (SuGAGs) are present on all animal cell surfaces or as components of the extracellular matrix (ECM). The SuGAG sugar backbone is sulfated in various positions, creating a great variety of potential interactions with partner proteins.[1] Biologically active SuGAGs regulate numerous skin functions such

as tissue development, remodeling, and healing. More specifically, heparan sulfate (HS), a vital component of all animal cells,[2,3] interacts with a plethora of partner molecules, including growth factors (GFs), chemokines-cytokines, ECM components, enzymes, morphogens, and pathogen-derived molecules.[4] HS facilitates self-assembly and structural integrity of ECM components and can hold millions of distinct structural modifications, which explains why it has been called *"the most information-dense biopolymer in nature."*[5] HS has a large variety of regulatory functions that give it great potential as a cosmetic ingredient to restore aged-skin homeostasis and health. Unfortunately, naturally occurring HS has limited skin penetration due to its large molecular size and high polar charge. Low Molecular Weight Heparan Sulfate (LMW-HS) is a pharma-grade cosmetic ingredient that was developed to overcome skin penetration limitations while preserving its activity.[4] LMW-HS is a modified form of endogenous HS in which size (6-12 kDa), shape, and charge were optimized. Previously, Gallo et al[4] showed that an LMW-HS-containing facial cream triggered improvements in skin hydration, barrier function, firmness, and elasticity. Thus, the aim of this study was to evaluate the efficacy and tolerability of an eye cream containing LMW-HS and a blend of naturally derived extracts to accomplish global periorbital rejuvenation.

2 | MATERIALS AND METHODS

All activities performed within the scope of this study complied with recognized Good Clinical Practice guidelines and applicable regulatory requirements. Subjects were recruited using an IRB-approved advertisement method. Subjects completed an Informed Consent Form (ICF) in conformance with 21 CFR Part 50: "Protection of Human Subjects," which was signed on the day of enrollment.

2.1 | Subjects

Single-center (SENTÉ Aesthetic Clinic, Carlsbad CA), open-label study. Inclusion criteria: female and male subjects (n = 15), ages 35-65, Fitzpatrick skin types II-IV. Subject ethnicities included Caucasian, East Indian, and Hispanic. Subjects presented with at least one of the following MODERATE to SEVERE skin conditions: fine lines and wrinkles, coarse wrinkles, under-eye puffiness, and/or under-eye dark circles. Exclusion criteria: subjects who reported they were pregnant, planning a pregnancy, or nursing; individuals with active (flaring) skin diseases, such as atopic dermatitis or eczema, on the skin around the eyes; individuals who had plastic surgery or ablative laser resurfacing within 1 year preceding the study; individuals who had any cosmetic procedure, such as non-ablative laser resurfacing, neurotoxins, or dermal fillers within the last 6 months prior to enrollment; individuals who received superficial resurfacing treatment (chemical peel, microdermabrasion, microneedling, etc) within the 6 weeks before enrollment; individuals with eyelash extensions.

2.2 | Test materials

All the test materials in this study were provided by SENTÉ INC (Carlsbad, CA, USA). The test product was a cosmetic cream formulated with LMW-HS and a proprietary blend of naturally derived extracts: *Tephrosia purpurea* seed extract (1%-4%), *E Crustaceum plankton* extract (1%-4%), *Hieracium pilosella* (1%-3%), and *Bellis perennis* flower (1%-3%) extracts. Subjects were instructed to apply the test product around the eye area twice daily (morning and evening) after cleansing their facial skin with the provided generic cleanser. The study duration was 12 weeks (August 2017-January 2018), and subjects were evaluated at baseline and weeks 2, 4, 8, and 12.

2.3 | Evaluation

Subjects were evaluated at baseline and weeks 2, 4, 8, and 12. All assessments were performed after subjects washed their skin with a generic cleanser. Investigator efficacy and tolerability were evaluated at each visit by the same well-trained personnel. Skin conditions around the eyes (fine lines and wrinkles, coarse wrinkles, under-eye puffiness, dark circles, and overall skin damage) were evaluated using a ten-point scale (0 = none, 1-3 = mild, 4-6 = moderate, and 7-9 = severe). Global improvement was evaluated by the investigator using a five-point scale: 0 = worse, 1 = no improvement, 2 = mild improvement (25% overall improvement), 3 = moderate improvement (50% overall improvement), and 4 = marked improvement (75% overall improvement). Skin tolerability (under-eye skin dryness and erythema) was evaluated using a ten-point scale (0 = none, 1-3 = mild, 4-6 = moderate, and 7-9 = severe).

2.4 | Standardized clinical photography

Digital photographs were obtained at baseline and weeks 2, 4, 8, and 12 using VISIA CR Imaging System, Canfield Scientific.

2.5 | Subject self-assessment

Subjects completed a self-assessment questionnaire at weeks 2, 4, 8, and 12.

3 | RESULTS

Under-eye pigmentation results from a combination of different colors/pigments and therefore, is developed through different mechanisms. The contribution of each of these colors/pigments (ie, red/pink, blue/gray, and brown) to the appearance of under-eye pigmentation varies among individuals. We investigated the efficacy of the test product to address periorbital hyperpigmentation in subjects with moderate to severe photodamage. Improvements in periorbital erythema were observed as early as 2 weeks in subjects using the test product twice daily (Figure 1A,B). Further improvements (long-term improvements) of periorbital erythema were

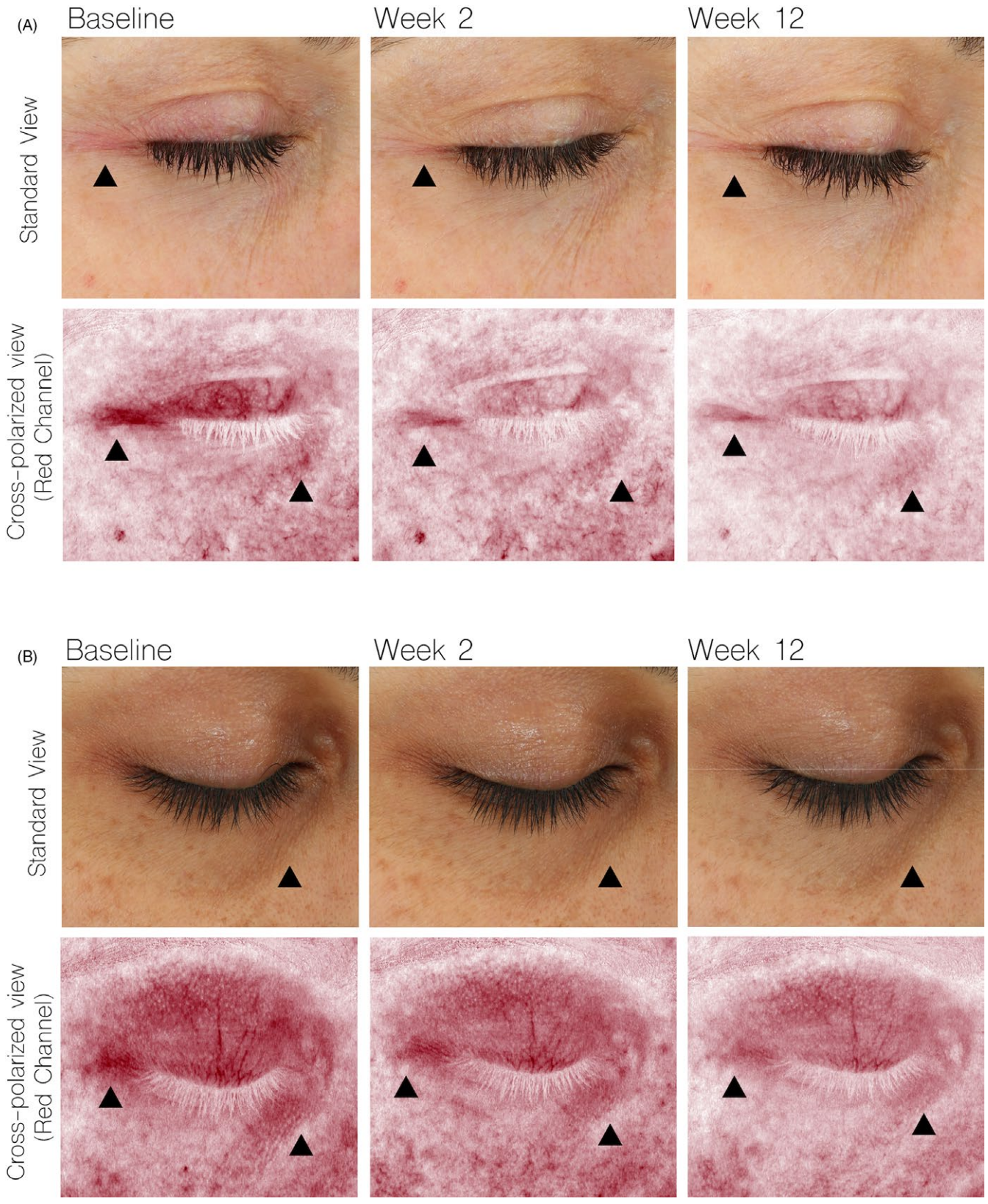

FIGURE 1 Short and long-term improvements in periorbital erythema. Subjects used an eye cream containing LMW-HS and a proprietary blend of naturally derived extracts showed a rapid reduction in redness in both upper eyelids as well as under-eye area as early as 2 wks. Continuous improvements were observed at week 12. A, Female, 51 y old, Caucasian. B, Female, 37 y old, East Indian. Standardized clinical photographs were taken at baseline, week 2, and week 12 using VISIA CR

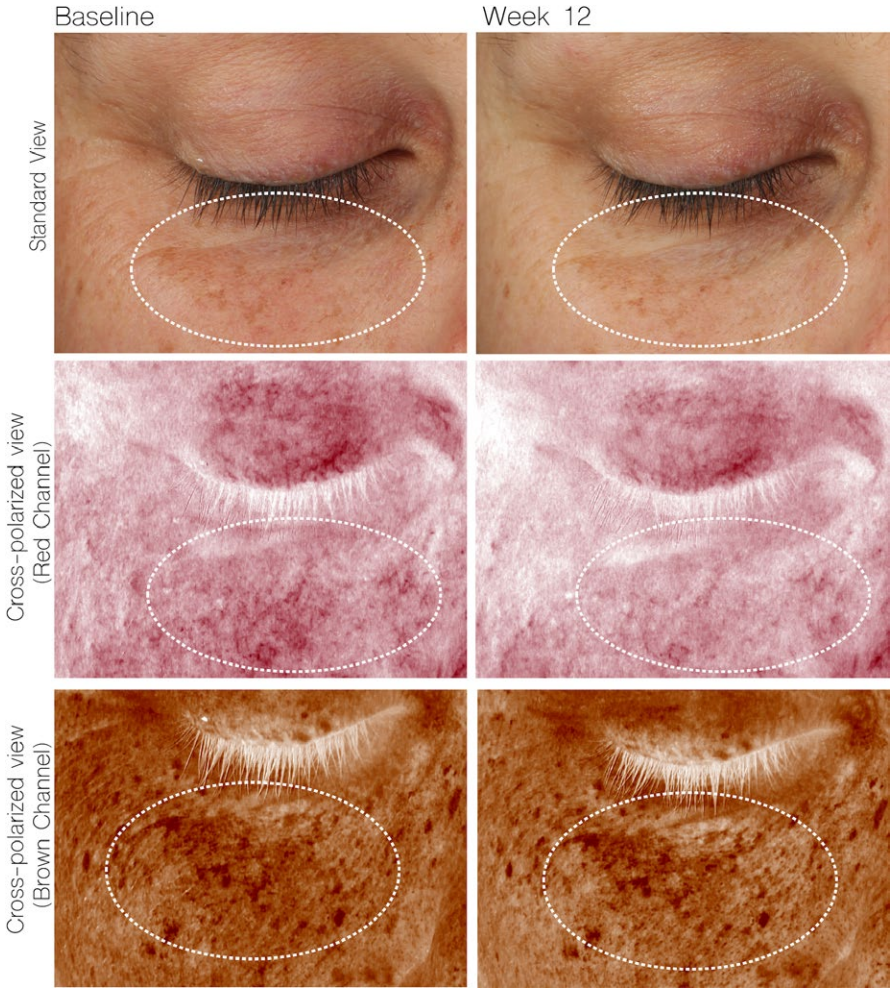

FIGURE 2 An eye cream containing LMW-HS and a proprietary blend of naturally derived extracts improved vascular conditions and hyperpigmentation (12 wks). Female, 50 y old, Caucasian. Standardized clinical photographs were taken at baseline and week 12

FIGURE 3 A cosmetic cream containing LMW-HS and a proprietary blend of naturally derived extracts improved lines and wrinkles around the eyes and on the upper eyelids as early as 4 weeks. Female, 54 y old, Caucasian. Standardized clinical photographs were taken at baseline and week 4 and 12

observed at week 12, suggesting no plateau effect (Figures 1 and 2). Brown periorbital discoloration, frequently associated with an excess of melanin, was decreased by the test product (Figure 2), significantly improving the overall appearance of the under-eye area (week 12). It is important to remark that different pigments/colors will be resolved with different kinetics, as their mechanisms are diverse. Improvements in under-eye pigmentation reported by the clinical data were ratified by the subjects' self-assessments in which 93% of the participants reported an improvement in the appearance of dark circles (Figure 5B). Based on investigator assessments (Figure 6B), 53% of the subjects showed improvement in under-eye dark circles by one grade or higher.

FIGURE 4 Early and continuous improvement in the appearance of coarse wrinkles and under-eye crepiness by an eye cream containing LMW-HS and a proprietary blend of naturally derived extracts. A, Male, 55 y old, Hispanic. B, Male, 56 y old, Caucasian. Standardized clinical photographs were taken at baseline, week 2, and week 12

A significant improvement in the appearance of lines and wrinkles around the eyes and on the upper eyelids (Figures 3 and 4) was also observed. These changes occurred between weeks 2 and 4 and are probably due to significant improvements in skin hydration (deep and superficial hydration). The test product contains LMW-HS, which rapidly promotes skin hydration by binding water, as well as multifunctional emollients such as dimethicone, caprylic/capric triglyceride, *Olea europaea* and Helianthus *Helianthus annuus* seed oil unsaponifiables, among other ingredients of vegetable origin. The combination of these ingredients delivered instant and long-term hydration while being gentle to the delicate skin around the eye, minimizing potential irritation. Instant hydration was validated by the subjects' questionnaires and self-assessments, in which 93% of the subjects stated that their skin was hydrated after the application of the test product (Figure 5C). Significant improvements in coarse wrinkles and under-eye crepiness were also observed (Figures 3 and 4). In addition, 67% of the subjects reported improvements in coarse wrinkles (Figure 5B) at week 12 after using the test product. Investigator's assessment at week 12 (Figure 6B) reported that 50% and 87% of the subjects showed improvement in the appearance of coarse wrinkles and fine lines, respectively.

Under-eyes puffiness or mild swelling becomes more prominent as we age due to intrinsic changes in the physiology and anatomy of skin. Application of the test product resulted in a rapid decrease in under-eye puffiness (Figure 5A, non-standardized photography from an independent case study). Seventy-three percent (73%) of subjects in this study reported improvement in under-eye puffiness (Figure 5B) at week 12. Finally, Investigator's global improvements assessments of fine lines and wrinkles, coarse wrinkles, under-eye puffiness, and dark circles indicated that 40% of the subjects showed mild improvements in these conditions, while 27% and 20% of the subjects showed moderate and marked improvements, respectively (Figure 6A). In addition, product satisfaction was highly graded by all the participants, as

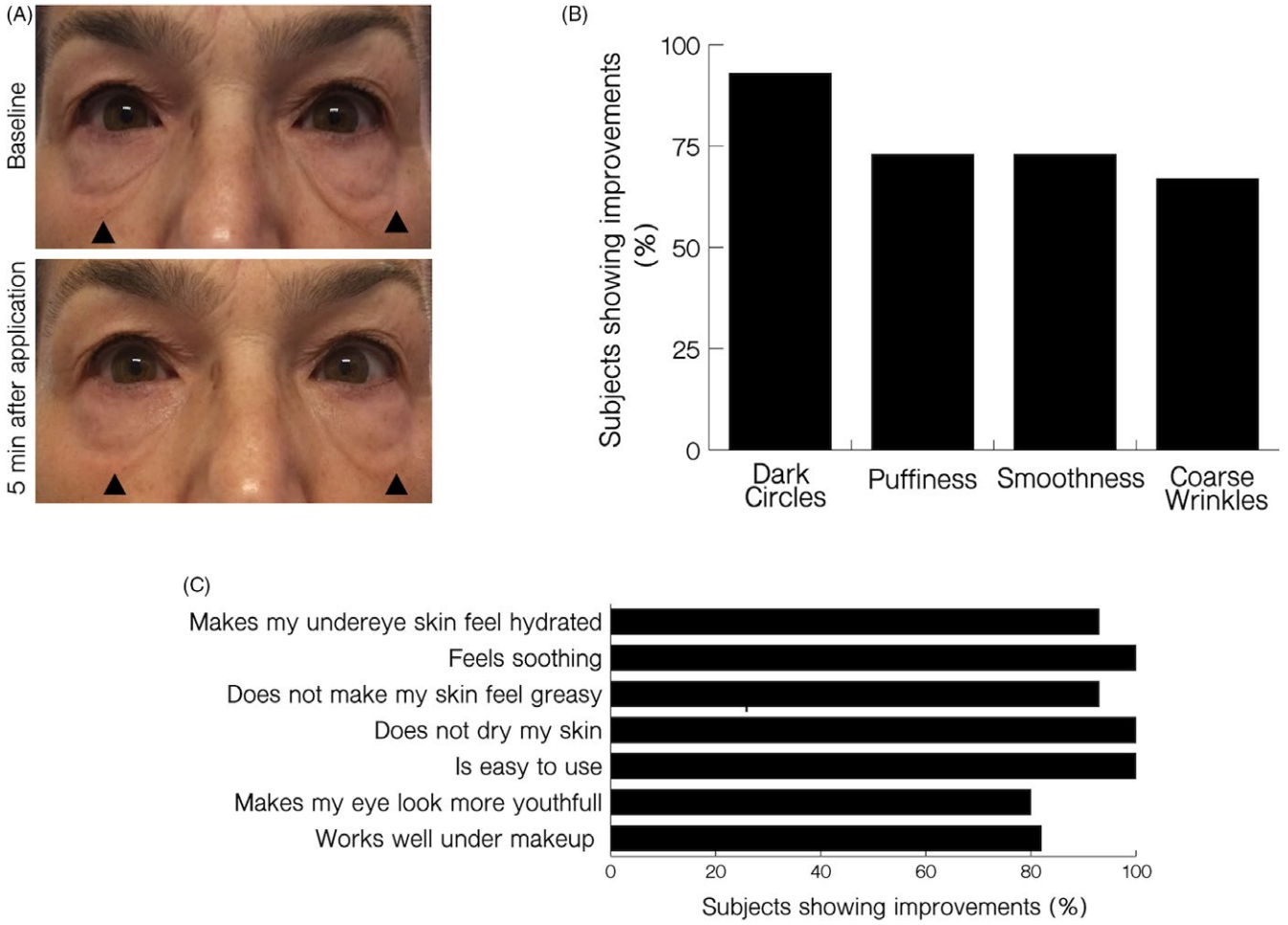

FIGURE 5 A, Case study shown using non-standardized photography. It is important to remark that clinical improvements in under-eyes puffiness cannot be assessed using standardized photography as the closing of the eye (a requirement for safe picture taking) results in improvements in the appearance of puffiness. Female, 63 y old, Caucasian, showed improvements in under-eye puffiness 5 min after application of an eye cream containing LMW-HS and a proprietary blend of naturally derived extracts. B, Subjects' self-assessments and C, product performance evaluations at week 12

100% of subjects agreed that the test product was easy to use, did not dry the skin, and felt soothing (Figure 5C).

4 | DISCUSSION

Skin aging, regardless of whether its origin is chronological or environmental, results in visible deterioration of the skin's condition and loss of its functionality.[6] Environmental aging, which is triggered by solar radiations (UVA, UVB, IR, and visible light), pollution, and other stressors, is characterized by lines and wrinkles, dyschromia, dry skin, leathery appearance, sallow complexion, and changes in skin tone and texture.[7-11] Signs of aging notoriously appear earlier around the periorbital area than in other parts of the face due to a unique combination of thin skin (the eye contour has the thinnest skin of the facial area), perpetual movements (over 10 000 blinks per day in addition to 22 muscles in constant motion), decreased amount of subcutaneous fat, and the lack (or extremely small amount) of sebaceous glands. Aging of the eye area usually starts manifesting around the third decade of life. Major patient concerns fall into three categories: periorbital hyperpigmentation, puffiness, and lines and wrinkles. In this study, we reported early and long-term improvements in all these periorbital concerns by a cosmetic cream formulated with LMW-HS and a proprietary blend of naturally derived extracts.

Addressing periorbital skin rejuvenation is a complex process that involves improvements in periorbital hyperpigmentation, under-eye puffiness, fine lines, and coarse wrinkles (Figure 7). As mentioned previously, environmental and intrinsic factors are responsible for the activation of mechanisms linked to these conditions. Periorbital hyperpigmentation (dark circles around and under the eye and upper-eyelid discoloration) is a frequent cosmetic problem, with no gold standard treatment option available. It affects many individuals and results in an undesired tired, stressed, and aged look.[12] Various causes lead to periorbital hyperpigmentation, including aging, increased skin laxity and skin thinning, tear trough depression, post-inflammatory hyperpigmentation (PIH) secondary to atopic dermatitis or allergic contact dermatitis, and post-inflammatory hemodynamic

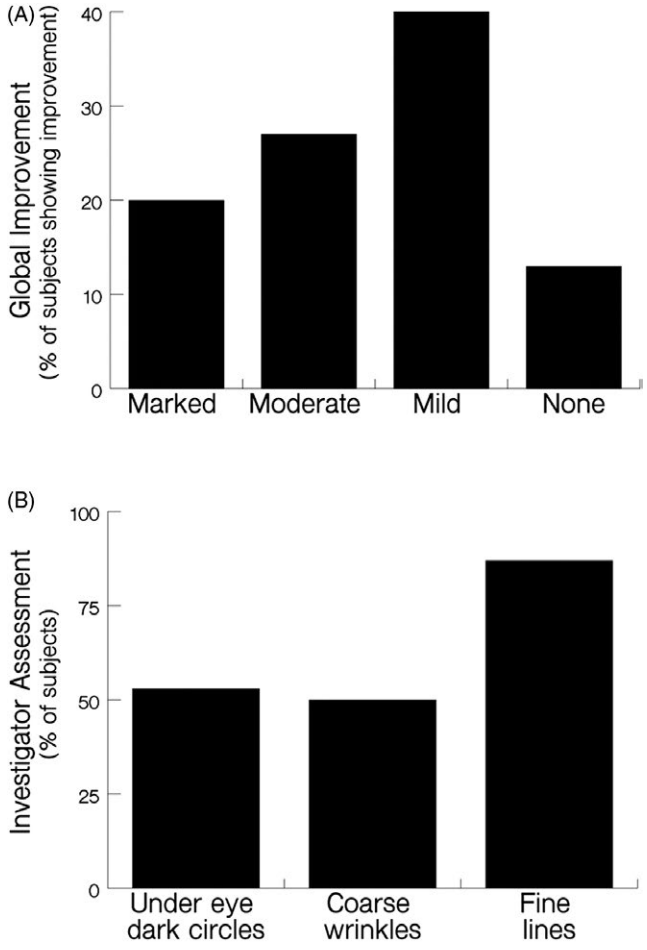

FIGURE 6 A, Investigator's Global Improvement Assessment: Overall changes in appearance of fine lines and wrinkles, coarse wrinkles, under-eyes puffiness, under-eye dark circles were evaluated at week 12. Global improvement was evaluated using a five-point scale (0 = worse, 1 = no improvement, 2 = mild improvement [~25% overall improvement], 3 = moderate improvement [~50% overall improvement], and 4 = marked improvement [~75% overall improvement]). B, Investigator's Assessment of Improvement in the appearance of under-eye dark circles, coarse wrinkles and fine lines at week 12. Subjects showing one grade of improvement or more were included in this data

congestion.[13,14] Interestingly, different pigments/colors (ie, brown, blue-gray, red-pink, and purple) are responsible for under-eye discoloration (Figure 7). One of the most common causes for under-eye hyperpigmentation is the naturally occurring thinning of the skin, which allows the visualization of vascular changes and/or muscles under the skin. Therefore, cosmetic formulations that contribute to thickening the skin around the eye may visually improve the appearance of under-eye discoloration. Clinical studies using LMW-HS in topical formulations have shown increases in skin firmness and elasticity, suggesting improvements in dermal health.[4] In addition, ex vivo data suggests that multiple applications of cosmetic creams containing LMW-HS resulted in deposit of collagens and elastin (unpublished data, not shown), further supporting a role of LMW-HS in skin thickening.

Another condition linked to periorbital discoloration is capillary leakage, which is due to inflammation, resulting in tissue accumulation/degradation of heme groups and other related pigments.[15] Free-heme groups are highly cytotoxic due to the iron atom contained in the porphyrin ring, which catalyzes an uncontrolled production of free radicals (via Fenton reaction),[16] enhancing oxidative stress, necrosis, and apoptosis. Under normal conditions, heme-oxygenase (HO) is responsible for heme degradation into carbon monoxide (CO), iron (which is sequestrated by ferritin), and biliverdin. Chronic oxidative stress and inflammation also promote the deposit of hemosiderin, a complex form of ferritin, denatured ferritin and other materials, and the accumulation of damaged proteins (which contributes to the blue-gray color of under-eye circles). Topically applied LMW-HS has been linked to a rapid decrease in erythema and uneven pigmentation as well as decreases in edema and inflammation (unpublished data).[4] In addition to LMW-HS, the test product also contains a blend of *Hieracium pilosella* and *Bellis perennis* flower extracts, which have been linked to heme-oxygenase-1 (HO-1) induction contributing to the degradation of the heme group and preventing activation of melanocytes. Thus, *E. Crustaceum plankton* extract helps to decrease vascular permeability minimizing fluid extravasation and preventing edema and puffiness.

Age-related reduction of epidermal function results in skin dehydration that can be aggravated by environmental stressors, further compromizing barrier function and increasing trans-epidermal water loss (TEWL) with the concomitant activation of cutaneous inflammation. Therefore, restoring skin hydration plays a fundamental role in controlling inflammation, which happens to be the main cause of erythema and edema. As a SuGAG, LMW-HS has the intrinsic capacity of water binding, which, in combination with its penetration profile (reaches epidermis and papillary dermis), improves skin hydration at different levels. Congenital or acquired dermal melanocytosis is another condition that can trigger the gray-blue color of dark circles.[17] Chronic environmental stress and inflammation activate melanin production, and the disruption of the circadian production of skin cortisol further affects skin homeostasis and perpetuates the inflammatory response.[18] To address cortisol imbalance, *Tephrosia purpurea* seed extract was added to the test product. This extract is enriched in stachyose, ciceritol, kaempferol-3-O-rutinoside, quercetin-3-O-rutinoside, and patuletin-3-O-rutinoside, which have been linked to normalization of cortisol imbalance while increasing β-endorphins production.[19] It is important to note that the test product in this study does not contain the typical active ingredients used to address periorbital hyperpigmentation, such as hydroquinone, tretinoin, kojic acid, azelaic acid, arbutin, growth factors, vitamin C, or sunscreen actives.[20,21] Although these active ingredients have been proven to be efficacious, they may trigger irritation, increasing the risk of PIH or worsening uneven skin tone conditions. Addressing periorbital discoloration is frequently done by a combination in-office and take-home skin care approach.[22] Thus, it would be interesting to evaluate the potential synergistic effect of the test product with in-office procedures such as pulsed light therapy, lasers, or peels.[23-25]

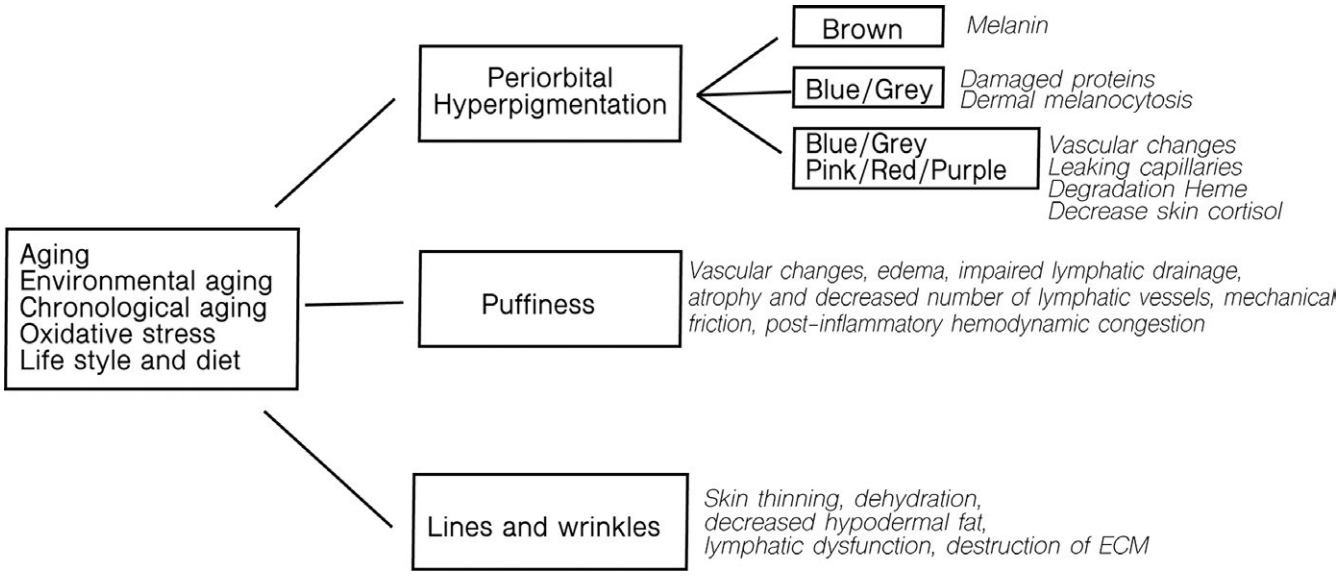

FIGURE 7 Main causes and mechanisms associated with the three major aging concerns of the periorbital area: periorbital hyperpigmentation (dark circles and upper-eyelid discoloration), puffiness, and lines and wrinkles. All these conditions are triggered by a variety of factors and therefore require a multi-factorial approach

Under-eye puffiness or mild swelling becomes more prominent as we age due to intrinsic changes in the physiology and anatomy of skin. Lifestyle (eg, smoking, alcohol, and drug consumption) and diet (eg, salty food) are strong triggers of under-eye puffiness, as are seasonal allergies and eczema. Therefore, controlling under-eye puffiness is a daily challenge. Periorbital edema, as well as erythema can be linked to rubbing and scratching the skin around the eyes (mechanical friction) or to conditions such as post-inflammatory hemodynamic congestion, inflammation (increase in capillary permeability), and impaired lymphatic circulation (Figure 7). Interestingly, aging results in gradual atrophy and a decrease in density and network complexity of the lymphatic system,[26,27] promoting water accumulation in the tissues. Furthermore, UV radiations were found to damage cutaneous lymphatic vessels,[28] contributing to the lymphatic-dependent dysregulation of adipose volume and, therefore, facial wrinkle formation.[29] We observed that the test product addressed under-eye puffiness (Figure 5A,B), contributing to the global rejuvenation of the periorbital area.

Wrinkles on the face are the most dominantly recognized sign of skin aging. Facial sites such as the corner of the eyes (crow's feet) are especially susceptible to wrinkle formation due to constant movement and skin thinning. While intrinsic aging plays a role in crow's feet formation by decreasing the thickness of the epidermis (with minimal changes in the number of cell layers) and dermis, environmental stressors (solar radiations and pollution) remain the predominant factors associated with coarse wrinkle formation as these stressors increase collagen degradation and decrease its production, diminish the amount of functional elastic fibers, and significantly alter the balance of cutaneous GAGs (Figure 7). Chronological and environmental aging trigger intense dermal and epidermal GAG remodeling, altering the ratio of abundancy of SuGAGs, which is linked to the development of solar elastosis.[30] Deposit of elastotic material not only affects the dynamics of the ECM but also increases SuGAG-linked dysfunction by sequestrating these molecules and compromizing both their biological activity and water trapping capacity, resulting in fragile and dehydrated skin that shows signs of tiredness. In addition to these changes in the dermal level, volume loss on the adipocyte layer also contributes to wrinkle formation.[31,32]

In conclusion, our clinical evaluation of an eye cream containing LMW-HS and a proprietary blend of naturally derived extracts showed total global improvements in periorbital skin condition. This test product was highly rated by subjects for efficacy and product attributes and was well tolerated. Although results of this proof-of-concept clinical study were satisfactory in both efficacy and subject satisfaction, further evaluations with a larger number of subjects would be appropriate to expand this study's findings. In addition, it would be interesting to evaluate the efficacy of this test product in combination with common in-office procedures for periorbital eye rejuvenation, such as dermal fillers, neurotoxins, lasers, and others.

CONFLICT OF INTEREST

The authors have no other conflict of interest.

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