CASE SERIES

Wrinkle + Texture Repair

12-WEEK USAGE RESULTS IN SIGNIFICANT IMPROVEMENT IN VISIBLE SIGNS OF AGING

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INTRODUCTION:

The negative psychological impact of aging, specifically skin aging, and the beneficial reward offered by cosmetics is a topic that proliferates in medical literature.[1] Aging of the skin is believed to be a by-product of a multi-factorial process that includes aggregation of damage arising from both external and intrinsic sources. Oxidative stress triggered inflammation is considered to be the commonality shared by both internal and external sources of damage.[2,3] Age-related accumulation of oxidative stress leads to chronic inflammation, which damages the extracellular matrix of the dermis and disrupts its structural integrity.

Proper organization of the dermal extracellular matrix is fundamental in regulating cellular differentiation, adhesion, migration and tissue remodeling. Collagen networks are vital in maintaining proper organization, as they are responsible for trapping macromolecules such as hyaluronic acid and inducing intracellular signaling pathways.[23] Under ideal conditions, cutaneous tissue maintains normal architecture which promotes proper regulation of cellular function and sustained homeostasis. As skin ages, collagen degradation begins to outpace the rate of new collagen synthesis, resulting in an accumulation of collagen fragments. Over time, this leads to abnormal changes in the dermal extracellular matrix architecture, reducing both cellular function and hyaluronic acid synthesis, which cumulatively manifest as visible signs of aging.

Aging of facial skin is regarded as the most visible sign of aging. The aging skin phenotype is characterized by noticeable textural changes, increased fragility and pronounced formation of fine lines and wrinkles.[24] Any effective way to topically treat aging skin must include a multi-modal approach that combines symbiotic ingredients to ameliorate cutaneous damage.

Topical formulations of retinoic acids, their effects on human skin having been studied extensively, are widely used in dermatology for management of skin aging. Retinoic acid plays a vital role in blocking collagenase activity, thus inhibiting collagen degradation. This appears to be the primary mechanism of retinoic acid action responsible for the observed anti-aging efficacy at the molecular level.[4] Despite its known anti-aging effects, retinoic acid treatment is known to cause substantial skin irritations, limiting its acceptance by patients and physicians.[5]

Retinol, a precursor of retinoic acid, is well known as an effective anti-aging treatment. It works by inducing epidermal thickening and by enhancing expression of cellular retinoic acid-binding proteins, closely emulating the effects of retinoic acid.[6] Studies have shown that retinol-induced epidermal thickening enhances the expression of cellular proteins similar to those created by retinoic acid.[7] In clinical studies, topical retinol treatment significantly improves fine wrinkles and other markers of photoaging.[8, 9] Additionally, retinol treatment has also consistently resulted in fewer signs of erythema and skin irritation as compared to retinoic acid.[10]

ZO® Skin Health has developed a new topical formula that targets the underlying pathophysiology of skin aging. This product was specifically formulated with retinol, glycerin, water, dextran, caprooyl tetrapeptide-3, Melilotus officinalis extract, Buddleja davidii meristem cell culture, phospholipids, hydrolyzed sericin, bisabolol, and beta-glucan to support the visible improvement of skin's texture and color tone, while reducing the appearance of fine lines and wrinkles in moderate to severely photodamaged skin.

Furthermore, the technology behind the delivery vehicle of this product has advanced substantially, allowing ZO® scientists to formulate this product as a microemulsion delivery system. Microemulsion delivery system is key to the product's efficacy, as it allows for greater skin penetration and for rapid release of active ingredients.[12] As a result, active ingredients are able to penetrate into deeper layers of the skin to achieve the desired outcome.

The intent of this clinical study was to evaluate the effect of a novel topical product formulation on the facial skin of female subjects. The objectives were chosen to demonstrate the clinical tolerability and efficacy of this topical formulation in female subjects presenting with a moderate photoaging phenotype.

METHODS AND MATERIALS:

This clinical study complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Allendale Institutional Review Board. All patients were required to provide their written informed consent in agreement with Title 21 Code of Federal Regulations (CFR) 50.25.

Test materials

All test materials and support products were provided by ZO® Skin Health, Inc. The active topical test product was formulated with retinol, glycerin, water, dextran, caprooyl tetrapeptide-3, Melilotus officinalis extract, Buddleja davidii meristem cell culture, phospholipids, hydrolyzed sericin, bisabolol, and beta-glucan. In order to standardize the clinical assessment, all subjects were also provided with supportive products Gentle Cleanser, Broad-Spectrum SPF 50 and Hydrating Crème. The following protocol included the following instructions:

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Clinical Assessment

Forty-nine healthy subjects (female; ages 42-67 years; Fitzpatrick II-IV) were initially enrolled into this study. Forty-three (n=43) successfully completed the study. Six subjects discontinued study participation for personal reasons that were judged to be unrelated to the study treatment.

Clinical assessments were conducted in the summer (May 2019 – August 2019), a notoriously difficult season to treat the skin due to the confounding effect of extended sun exposure. This was done in order to provide extra rigor and further validate the study results. All subjects were initially evaluated at baseline and subsequently after 2, 4, 8 and 12 weeks of product use.

Subjects were required to report to the testing facility for the baseline visit with a clean, freshly-washed face. After allowing subject 15 minutes to equilibrate to the internal environment, an expert grader visually evaluated the appearance of skin texture, radiance, evenness of skin tone, global fine lines, global wrinkles and crow's feet fine lines/wrinkles on the facial region. The expert graded all skin attributes based on an ordinal 10-point scale (0=no issues present, 9=extreme severity). Subjects were asked to complete a product satisfaction questionnaire at each study visit.

Bio-Instrumental Assessment

Bio-instrumental analyses were conducted utilizing state of the art cutaneous imaging equipment. Tewameter® (Courage + Khazaka, Germany) was utilized for facial measurements of each subject's skin barrier function (TEWL). To document the clinical results, digital photographs were taken of the face of each subject using the Visia CR® 2.0 (Canfield Scientific, Fairfield, NJ). Bio-instrumental analysis was performed by a trained technician and conducted on all subjects at all study timepoints.

Statistical analysis

All data points collected were compared against baseline visit results. This allowed for an evaluation of clinical improvement for each subject at each subsequent study visit. The summation of the different results was analyzed using the Wilcoxon Signed-Rank Test. A response was considered statistically significant from baseline when the p-value was < 0.05.

	Week 1	Weeks 2–7	Weeks 8–12
	AM PM	AM PM	AM PM
Gentle Cleanser	√ √	√ √	√ √
Wrinkle + Texture Repair	Every other day in the PM	√	√ √
Hydrating Crème	as needed	as needed	as needed
Broad-Spectrum SPF 50	√	√	√

RESULTS:

After 12 weeks of ZO® Skin Health's Wrinkle + Texture Repair application, significant improvement in all expert graded skin attributes was determined via a comprehensive analysis of the gathered data. The visual benefits achieved by the subjects completing the study is displayed in Figure 1. No significant adverse events were reported during the study. Overwhelming patient satisfaction was determined following an analytical review of patient questionnaire responses. (Table 1)

Expert clinical grading results demonstrated that after 12 weeks of product use, statistically significant improvement was noted in Skin Texture, Skin Radiance, Skin Tone, Fine Lines, Wrinkles, Crow's Feet and Overall Appearance. (Graph 1) This significant improvement in expert graded skin attributes is further substantiated by the observation that, at a minimum, 93% of all subjects showed improvement at the conclusion of the study.

Results from bio-instrumental analysis further validate the superior clinical performance of Wrinkle + Texture Repair. Instrumental analysis is a vital component of any clinical study as an unbiased confirmation of expert graded clinical improvement. Tewameter measurement demonstrated a 25.7% improvement in skin barrier function. Likewise, this remarkable improvement in skin barrier function was seen in 95% of all subjects. Taken together with the expert grader results, the bio-instrumental analysis further supports the observed clinical improvement in skin texture, radiance, tone, fine lines and wrinkles.

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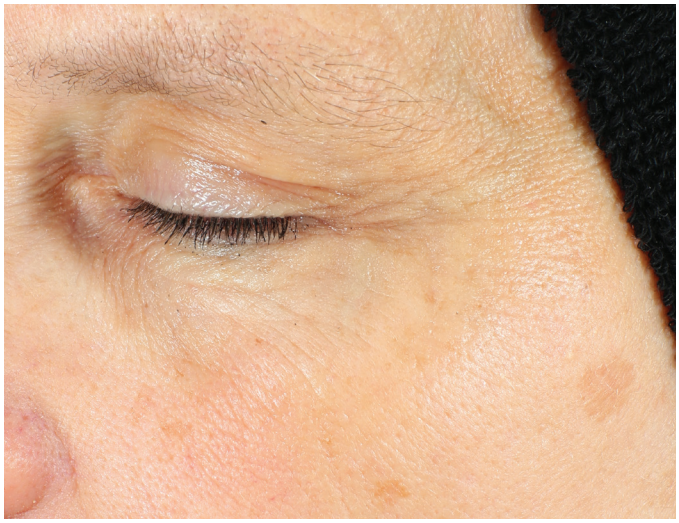
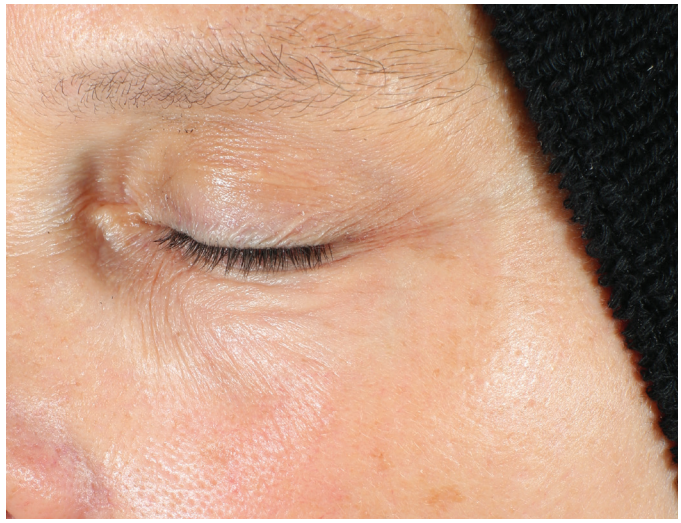
FIGURE 1. Visual benefits of Wrinkle + Texture repair from baseline to week 12



BASELINE



WEEK 12

Images were captured and analyzed using Clarity 2D Research System

PROTOCOL: A 12-week independent third-party clinical study of 43 subjects to assess the efficacy potential of Wrinkle + Texture Repair. Subjects represent females, ages 42–67, with Fitzpatrick skin types II–IV. Supported with use of Gentle Cleanser, Broad-Spectrum Sunscreen SPF 50 and Hydrating Crème during the study.

BASELINE

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DISCUSSION:

The active topical test product used during the study was specifically formulated with ingredients that exhibit potential to activate the skin's natural regenerative process, decrease inflammation and boost cutaneous collagen and fibronectin production. Combining these ingredients in one formulation allows the product to offer a multi-faceted approach to treating aging skin. Melilotus officinalis has previously been shown to have extensive anti-inflammatory properties.[13, 14] Bisabolol has a wealth of scientific literature attesting to its powerful anti-inflammatory and antioxidant properties, and to its efficacy in cosmetic applications.[16, 17] Buddleja davidii meristem cell culture and hydrolyzed sericin are newer cosmetic ingredients that have shown great promise to support the skin's regenerative properties.[15] Furthermore, Buddleja davidii Meristem Stem Cell culture and hydrolyzed sericin have exhibited potential to enhance the attachment of cultured human skin fibroblasts.[20] This attachment and ensuing proliferation of fibroblast cells has been shown to play a critical role in skin's ability to repair its underlying structure.[21]) Retinol, another mainstay of topical formulations, continues to demonstrate tremendous clinical efficacy in reducing wrinkles, as well as in promoting a smooth and even skin tone. The molecular mechanism of action behind retinol primarily involve an increase in the production of collagen and a decrease in extracellular matrix-degrading metalloproteinases, leading to an increase in epidermal thickness.[11, 18, 19] Finally, the proper selection of ingredients would be futile without a delivery vehicle properly formulated to protect its stability and to allow for rapid release in the targeted tissue. For this reason, the tested topical vehicle was formulated in a microemulsion vehicle to optimize the controlled release of the ingredients throughout the skin.

This rigorous clinical study, utilizing expert grading, bio-instrumental analysis and subject questionnaires, confirmed the exceptional clinical safety and efficacy of ZO® Skin Health's Wrinkle + Texture Repair. The combined assessment tools utilized in the study were specifically designed to mitigate the possibility of research bias while simultaneously promoting achievement of balanced and reproducible results. All subjects were assigned the same support products for at-home use to minimize the obfuscating impact that differing regimens can have on study results. The noted efficacy is further validated by the fact that the study was conducted during the summer months, the most difficult season to treat aging skin, and hence the results attained in this controlled clinical study have profound potential for real-world utilization.

The excellent results attained in a controlled clinical study can only be considered impactful if there is strong reliability that patients will continue to remain compliant with their treatment. Simply stated, patients can only expect to receive benefits if they remain compliant with the treatment over the long term. Hence, the excellent patient satisfaction and complete absence of adverse events or increases in irritation, noted in this study, strengthens the expectation that patients will continue to use the tested topical product for a long time, a commonly noted problem with prolonged use of many topical retinoids.[22] Interestingly, it should also be recognized that none of the expert graded results showed any plateauing effect at the conclusion of the study, suggesting that patients may expect to see even further benefits when using the product for longer than 12 weeks. The combination of expert graded evaluations and bio-instrumental analysis overwhelmingly support the superior efficacy of ZO® Skin Health's Wrinkle + Texture Repair. Patient satisfaction, along with a lack of reported irritation and adverse events, further suggest that this product was extremely well-received and holds great potential for success.

TABLES & GRAPHS:

TABLE 1. Consumer perceived satisfaction and improvement in skin quality after 12 weeks of product use

CONSUMER PERCEIVED SKIN ATTRIBUTE	PERCENTAGE OF SUBJECT SATISFIED	PERCENTAGE OF SUBJECT DISSATISFIED
Skin texture feels improved	88.0%	7.0%
Skin appears moisturized	93.0%	5.0%
Skin appears smoother	93.0%	7.0%
Skin appears more elastic	88.0%	5.0%
Skin tone appears more even	84.0%	2.0%
Skin appears to have a healthy glow	93.0%	5.0%
Fine lines are less noticeable	84.0%	5.0%
Wrinkles are less noticeable	84.0%	5.0%
Skin appears healthier	93.0%	5.0%
Skin appears more youthful	86.0%	2.0%
Noticeable improvement in the quality of my skin	91.0%	5.0%
Noticeable improvement in the overall appearance of my skin	93.0%	5.0%

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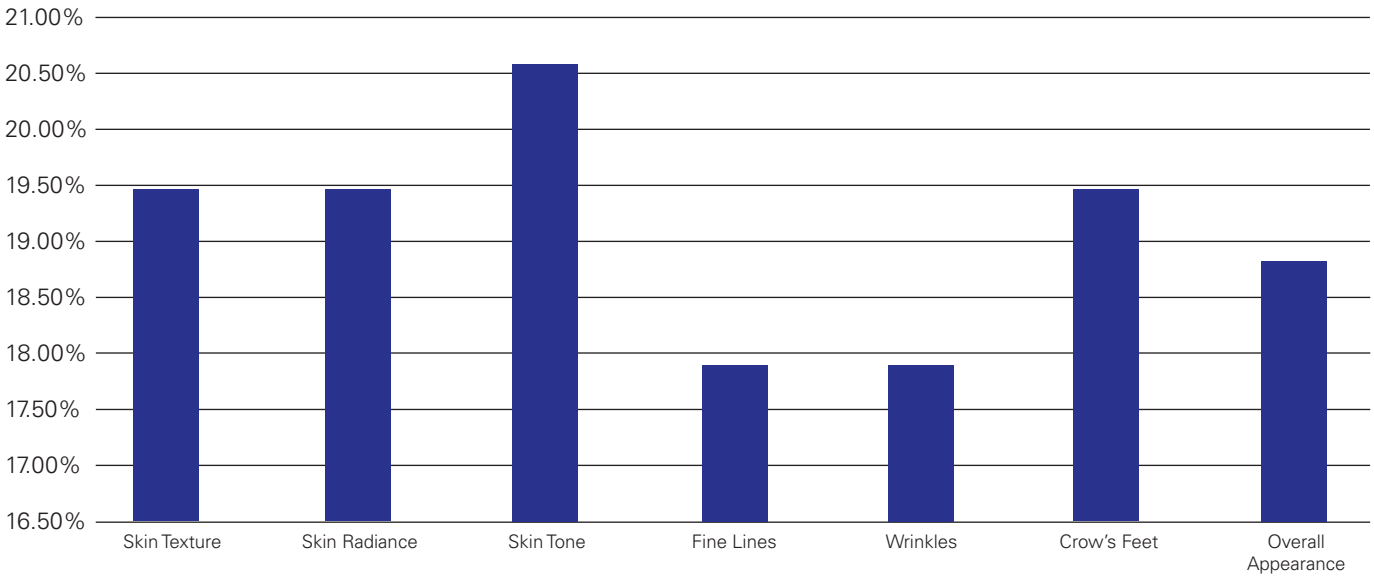
GRAPH 1. Expert graded improvement in appearance of subject facial skin after 12 weeks of product use



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