

Clinical Evidence of Dermal and Epidermal Restructuring from a Biologically Active Growth Factor Serum for Skin Rejuvenation

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ABSTRACT

Background: Topical skin care products use various technologies to promote skin repair. Growth factors of human, animal, and plant-derived origins have clinically demonstrated the ability to repair skin by promoting collagen, elastin, and glycosaminoglycan (GAG) production to reconstruct and reinforce skin's extracellular matrix (ECM). Human skin cells respond to instructions from highly specialized proteins or hormones referred to as growth factors. These growth factors initiate cellular communication that instigates cellular replication, production, or proliferation. The production of elastin and collagen dermal connective fibers slows, and, with age, the regenerative rates of GAGs become delayed. These biological issues can be exacerbated by extrinsic factors such as sun exposure, pollutants, and various other factors. Growth factor-based products have become important topical treatment modalities for addressing signs of skin aging such as fine lines, deep wrinkles, dryness, laxity, and textural irregularities.
Objective: The aim of a 12-week clinical trial of a growth factor composition was to assess its effectiveness at restoring skin health through dermal and epidermal restructuring of aged skin.
Results: Data from expert grading, and from corneometer and cutometer evaluations, as well as 2D and 3D image analysis, reflected significant improvements in facial skin appearance, firmness, elasticity, and hydration. Elements that improved most dramatically in investigators' assessments included radiance, firmness, tactile elasticity, textural smoothness, overall appearance, and crow's feet. Ultrasound imaging showed continual increases in dermal and epidermal restructuring throughout the study duration. Subject assessments reflected positive product tolerability and positive perception across a broad range of efficacy attributes through 12 weeks of usage.
Conclusion: The results verified the ability of a multi-modal plant and enzymatically derived growth factor-based product to achieve skin rejuvenation improvements by stimulating dermal ECM and fibrous tissue regeneration to reduce fine lines and coarse wrinkles, and improve skin firmness and elasticity, while restoring skin to a properly hydrated state.

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INTRODUCTION

As skin ages, problems emerge, including fine lines, deep wrinkles, sagging, dryness, and rough or uneven texture. It is further known that sun exposure, pollution, and lifestyle choices (such as smoking) exacerbate skin stress, causing collagen degradation, chronic inflammation, and other manifestations that can contribute to visual signs of aging. Meanwhile, the body's intrinsic restorative mechanisms slow as we age, leading to faster collagen and elastin denaturation, increased inflammation, and loss of skin firmness and density.[1]

Growth factors can regulate several important processes to treat and prevent the signs of skin aging. Key examples include cell replication, collagen production, and the reduction of inflammation.[2,3] In clinical studies, applying growth factors topically has been shown to strengthen the skin's ECM, reduce signs of photoaging by stimulating collagen and elastin, and trigger the skin's innate ability to heal.[3-7]

Advances in genomics and molecular biology have unveiled multiple pathways and methods of intervention in which aged and damaged skin health can be restored. Growth factors of multiple origins have been clinically proven to augment many of the biological pathways that naturally occur in the skin to restore aged and damaged skin. The use of plant-derived or enzymatically derived stem cells can offer preferred options, as they can be more sustainably cultivated versus human or animal-derived stem cells and are not inherently susceptible to the presence of disease-causing contaminants.

Dermal cells are primarily responsible for the production of the structural framework within skin, which is primarily com-

posed of a network of collagen and elastin fibers. To maintain the integrity of these fibers, the ECM must also be maintained in a balanced state to ensure proper hydration. If the homeostatic state of the ECM becomes altered by intrinsic or extrinsic factors, the integrity of collagen and elastin becomes compromised, leading to the onset of various signs and symptoms of skin aging.

Skin in a healthy state is characterized as being firm, smooth, strong, hydrated, and free of disease. To achieve all of these clinical endpoints requires comprehensive treatment options that are capable of simultaneously initiating multiple restorative biological pathways. The aim of this research was to assess the ability of a multi-modal topical treatment enabled by a combinatorial system of plant-derived and enzymatically derived stem cell technologies to restore skin to optimal health.

MATERIALS AND METHODS

The Growth Factor test product's multi-modal technologies included the following:

- Growth Factor 1: A plant-derived fermented red ginseng extract rich in ginsenosides. Ginsenosides have been shown in bioassay testing to induce transforming growth factor beta-1 (TGF-β1) expression and upregulation of Type I collagen production in normal dermal fibroblasts to provide for anti-aging skin effects.[8]

- Growth Factor 2: Disodium acetyl glucosamine phosphate is an enzymatically derived form of N-acetyl glucosamine that, when tested on human skin, has shown the ability to boost GAG production through enhancement of CD44 expression in the basal layer.[9] In the same series of experiments, in-vitro testing also demonstrated the ability of this technology to increase fibroblast proliferation.[9]

- Proprietary (ZPRO™) sericin is a biomimetic protein. Sericin has demonstrated the ability to upregulate the production of collagen and hyaluronic acid.[10-12]

- Dipeptide diaminobutyroyl benzylamide diacetate is a neuropeptide that acts as an antagonist of the muscular nicotinic acetylcholine receptor (nAChR), which prevents binding of acetylcholine to the receptor, so it remains closed. In a closed state, the uptake of sodium ions (Na+) is impeded and muscles stay relaxed. In human clinical testing, this technology demonstrated substantive benefits in reducing forehead wrinkles and crow's feet.[13]

- *Angelica polymorpha sinensis* root extract, commonly known as dong quai, is a technology that has been shown in in-vitro models to prevent cells from entering terminal senescence, stimulate ECM deposition, and inhibit the pro-inflammatory enzyme cyclooxygenase-2 (COX-2).[14,15] In a cosmeceutical preparation tested on diabetic skin, it was proven to improve skin structure, directly translating into clinical improvement of elasticity, dryness, and appearance, as well as wound healing.[14]

- *Buddleja davidii* meristem cell culture is a plant stem cell inherently rich in polyphenol content, specifically verbascoside, that mitigates inflammatory response and oxidative stress. Verbascoside has been shown to have a dose-dependent ability to decrease interleukin-8 (IL-8) expression on primary cultures of human keratinocytes.[16] In a human pilot clinical trial, verbascoside's antioxidant capacity demonstrated significant protection of skin lipids from oxidative stress, and a significant increase of the antioxidant resistance of the skin.[16]

- Beta glucan is a natural polysaccharide commonly found in yeast, fungi, bacteria, and plants. An alternative to conventional beta glucan is a highly purified variant β-1,6-branched-β-1,3-glucan extracted from a unique fungal strain. The branched structure has shown higher immune-enhancing activity compared with other conventional β-1,3-glucan. Branched beta glucan has been shown in in-vitro models to achieve proliferation of human fibroblast cells, along with collagen synthesis.[17] Testing on human skin showed superior skin hydration effects in comparison to hyaluronic acid.[17]

Study Design

An Institutional Review Board (IRB)-approved, independent, open-label clinical study empaneled 44 subjects, of which 41 subjects completed the study. Those who completed the study ranged in age between 41 and 70 years, with a mean of 65.29 years. The proportions of patients who had skin types II, III, and IV were 41.5%, 48.8%, and 9.8%, respectively. All subjects were predetermined by expert grading as exhibiting moderate to severe fine lines and coarse wrinkles in the crow's feet, and moderate to severe skin laxity/lack of firmness in the facial region. Subject questionnaires revealed that most subjects classified themselves as having at least moderate severity concerns regarding skin sagging, dryness, dullness, and roughness, as well as crow's feet, fine lines, laugh lines, and deep wrinkles.

Patients were instructed to apply a new topical formulation (ZO Growth Factor Serum) primarily composed of growth factors derived from plant and enzymatic sources twice daily for 12 weeks. Trained clinical researchers measured results through standardized objective clinical measures. A range of bioinstrumental measures (including a corneometer, a cutometer, high-resolution ultrasound, and 2D and 3D imaging analyses) were also employed. Additionally, subjective assess-

ments were compiled through an administered questionnaire.

The study protocol was approved by an independent IRB to ensure the protection of the rights, safety, and well-being of subjects. Prior to study initiation, the IRB reviewed and approved the study protocol and subsequent amendments, as well as the methods and materials used in obtaining and documenting informed consent of the subjects. The study was conducted in accordance with U.S. Food and Drug Administration (FDA) Good Clinical Practice and International Conference on Harmonization guidelines in as much as they apply to cosmetic research.

Test Materials and Regimens

After the initial screening visit, participants who consented to the study protocol went through a one-week washout period, during which they replaced their usual cleanser and sunscreen with investigator-supplied study support products: a gentle proprietary cleanser (ZO Skin Health Gentle Cleanser) and a sunscreen (ZO Skin Health Oclipse Sunscreen + Primer SPF 30). Investigators instructed participants to solely use the following daily skin treatment regimen during the 12-week treatment period:

- Gentle Cleanser, AM and PM
- Growth Factor Serum, AM and PM
- Oclipse Sunscreen + Primer SPF 30, AM and reapplied as needed throughout the day

Clinical Efficacy Assessments

Visual analog scales (VAS) are used in clinical research to measure intensity or frequency of various symptoms, subjective characteristics, or attitudes that cannot be directly measured. VAS are reliable scales that are more sensitive to small changes than simple ordinal scales. When responding to VAS items, expert graders specify their level of agreement to a statement by indicating a position along a line (10 cm) between two endpoints or anchor responses. A VAS in which the ends of a 10-cm horizontal line were defined as extreme limits orientated from the left (best) to the right (worst) was used to evaluate efficacy parameters.

At each subject's baseline visit, and at follow-up visits 2, 4, 8, and 12 weeks thereafter, investigators evaluated each of the following parameters by employing VAS methodology:

- Fine lines/wrinkles (crow's feet)
- Texture/smoothness
- Radiance/luminosity
- Overall appearance
- Firmness
- Elasticity

At all study visits, researchers also used the following objective measuring tools:

- A corneometer for hydration
- A cutometer for firmness and elasticity
- Ultrasound imaging (DermaScan, Cortex Technology, Hadsund, Denmark) for skin thickness/density
- 2D clinical photos of left, right, and center views (Clarity machine vision software from JADAK, Syracuse, NY)
- A subset of 15 patients underwent 3D image/photo analysis (Antera 3D, Miravex Ltd., Dublin, Ireland) of the crow's feet.

Additionally, all patients answered a detailed questionnaire about their perceptions of the treatment benefits at all follow-up visits.

Statistical Analysis Methods

Researchers used descriptive statistics to analyze subject demographics and subjective questionnaires. For expert clinical grading, instrumentation, and Antera image analysis, they used the paired T-test (monadic). Statistical significance was set at $P<0.05$.

RESULTS

Investigator

All investigator-graded parameters showed statistically significant improvement over baseline at all follow-up visits. Week 12 results were as follows (Table 1):

Instrumental

All corneometer and cutometer measurements showed statistically significant improvement over baseline at all follow-up visits. Regarding corneometry at week 12, subjects had achieved a 40.51% mean improvement, with 85.4% of subjects showing improvement. The corresponding figures for cutometer scores were 10.09%/68.3%, respectively, for firmness, and 21.31%/65.9% for elasticity. Ultrasound measurements revealed a 33.39% mean increase in skin thickness versus baseline ($P<0.001$), with 93.8% of subjects showing improvement.

TABLE 1.

Week 12 Investigator Evaluations*		
Study Parameter	Mean % Improvement Over Baseline	Percent of Subjects Showing Improvement
Radiance/luminosity	26.71%	100%
Firmness	26.28%	100%
Elasticity (tactile)	24.08%	100%
Texture/smoothness (visual)	22.46%	95.1%
Overall appearance	19.01%	97.6%
Lines/wrinkles (crow's feet)	18.67%	92.7%

*$P<0.001$ in all analyses

2D Image Analysis

Average wrinkle severity, fine line counts, and total wrinkle counts showed statistically significant improvement at multiple time points (Table 2):

Compared to baseline, average fine line count and wrinkle severity improved significantly at week 12: -17.66% and -10.32%, with 68.3% and 82.9% showing improvement, respectively ($P<0.001$ in both analyses). Investigators also noted improvements in

TABLE 2.

2D Imaging Results

Assessment		Time Point	n	Mean ± SD	Mean Percent Improvement *From BL Mean*	Percent of Subjects Showing Improvement *From BL*	*P*-Value *TX vs. BL*
Lines, Wrinkles, Crow's Feet	Average Length	Baseline	41	155.15 ± 40.18	--	--	--
		Week 2	40	152.68 ± 35.39	NI	57.5%	0.584
		Week 4	41	143.87 ± 27.76	4.33%	63.4%	0.059
		Week 8	41	152.48 ± 36.25	NI	61.0%	0.581
		Week 12	41	146.46 ± 29.87	3.01%	56.1%	0.107
	Average Width	Baseline	41	25.28 ± 2.21	--	--	--
		Week 2	40	25.25 ± 1.90	NI	45.0%	0.849
		Week 4	41	25.26 ± 1.82	NI	48.8%	0.907
		Week 8	41	25.35 ± 1.70	NI	29.0%	0.798
		Week 12	41	25.19 ± 1.75	0.08%	43.9%	0.719
	Average Wrinkle Severity	Baseline	41	5652.94 ± 1177.98	--	--	--
		Week 2	40	5029.80 ± 800.56	10.45%	92.5%	<0.001*
		Week 4	41	5041.57 ± 762.11	9.76%	85.4%	<0.001*
		Week 8	41	5071.73 ± 808.56	9.32%	87.8%	<0.001*
		Week 12	41	5007.25 ± 780.33	10.32%	82.9%	<0.001*
	Total Wrinkle Count	Baseline	41	54.44 ± 12.86	--	--	--
		Week 2	40	51.10 ± 12.60	4.45%	67.5%	0.014*
		Week 4	41	53.83 ± 12.76	NI	53.7%	0.673
		Week 8	41	51.29 ± 12.51	4.11%	65.9%	0.035*
		Week 12	41	52.98 ± 10.49	NI	56.1%	0.300
	Fine Lines Count	Baseline	41	27.37 ± 8.40	--	--	--
		Week 2	40	20.73 ± 8.04	23.01%	77.5%	<0.001*
		Week 4	41	22.76 ± 8.83	14.78%	75.6%	<0.001*
		Week 8	41	21.46 ± 8.59	20.40%	78.0%	<0.001*
		Week 12	41	21.95 ± 7.64	17.66%	68.3%	<0.001*
	Deep Lines Count	Baseline	41	7.46 ± 3.29	--	--	--
		Week 2	40	5.98 ± 3.77	13.65%	65.0%	0.006*
		Week 4	41	5.93 ± 3.55	15.64%	73.2%	0.001*
		Week 8	41	6.17 ± 3.35	11.48%	68.3%	0.005*
		Week 12	41	6.49 ± 4.61	8.51%	48.8%	0.080
	Emerging Lines Count	Baseline	41	19.61 ± 9.76	--	--	--
		Week 2	40	24.40 ± 10.55	NI	22.5%	<0.001**
		Week 4	41	25.15 ± 11.01	NI	19.5%	<0.001**
		Week 8	41	23.66 ± 9.68	NI	29.3%	0.001**
		Week 12	41	24.54 ± 10.19	NI	31.7%	<0.001**

*Indicates a statistically significant improvement compared to baseline, $P\leq0.05$
**Indicates a statistically significant worsening compared to baseline, $P\leq0.05$

TABLE 3.

3D Imaging Results

Assessment		Time Point	n	Mean ± SD	Mean Percent Improvement *From BL Mean*	Percent of Subjects Showing Improvement *From BL*	*P*-Value *TX vs. BL*
Wrinkles	Indentation	Baseline	16	19.01 ± 4.42	--	--	--
		Week 2	15^	17.09 ± 4.55	9.53%	80.0%	0.007*
		Week 4	16	17.07 ± 4.38	9.72%	87.5%	0.005*
		Week 8	16	17.29 ± 3.81	7.53%	75.0%	0.025*
		Week 12	15^^	16.47 ± 3.37	13.22%	93.3%	<0.001*
	Max. Depth	Baseline	16	0.19 ± 0.05	--	--	--
		Week 2	15^	0.17 ± 0.04	10.90%	66.7%	0.032*
		Week 4	16	0.17 ± 0.05	11.89%	62.5%	0.023*
		Week 8	16	0.18 ± 0.03	4.72%	56.3%	0.179
		Week 12	15^^	0.17 ± 0.04	11.92%	73.3%	0.024*

^Subject 4 does not have data for week 2 (15 subjects analyzed).
^^Subject 8 does not have data for week 8 (15 subjects analyzed).
*Indicates a statistically significant improvement compared to baseline, $P \leq 0.05$

the week 12 deep line counts (-8.51%), and the average wrinkle length (-3.0%) and average wrinkle width (-0.08%), although these improvements did not reach statistical significance. Total wrinkle counts improved by 4.45% and 4.11% at weeks 2 and 8, respectively (P=0.014 and 0.035). Improvements in total wrinkle counts lost statistical significance at weeks 4 and 8, and emerging line counts worsened significantly throughout the study for possible reasons that will be addressed in the Discussion section.

3D Evaluations

For the 15 patients who underwent 3D image analysis, mean week 12 improvements in maximum indentation depth were 13.22% and 11.92%, respectively (P<0.001 and P=0.024), with 93.3% and 73.3% showing improvement, respectively (Table 3). Results reached statistical significance in all parameters at all time points, except for week 8 in maximum depth.

Subjective

Participants' perceptions of the study product and its effects were highly favorable. At week 12, 92.7% of patients said they saw the following (P<0.001 in all analyses):

- Noticeable improvement in overall skin appearance
- Visible improvement in texture and smoothness
- Skin appeared hydrated
- Skin appeared moisturized

Similarly, 87.8% of participants agreed at week 12 that their skin appeared and felt healthy, and also felt moisturized and hydrated, with visible improvement in dryness. Between 70.7% and 78% of subjects said their skin appeared and felt tighter, and also appeared more youthful, with visible improvement in density/plumpness (P<0.001 in all analyses).

DISCUSSION

To counter the signs and symptoms of facial skin aging, and to fortify skin against intrinsic and extrinsic harms, patients continue to seek safe, effective, and advanced skincare technologies. Not only did the growth factor serum studied herein achieve statistically significant improvements in most parameters assessed by experts and subjects, but these improvements generally began to appear at the earliest measurement opportunity. At week 2, investigators noted small (1.73%–3.90%) but statistically significant improvements in crow's feet, firmness, tactile elasticity, visual texture, radiance, and overall appearance. By week 4, all but one of these variables, overall appearance, reached double-digit improvements. Also, at week 2, 55%–95% of participants perceived clinically significant improvements in overall skin characteristics such as moisturization, hydration, and appearance. Corneometer and cutometer measurements showed statistically significant gains over baseline starting at week 2, while the first ultrasound measurements of dermal thickness, performed at week 4, revealed statistical significance.

In 3D analysis, the only finding that did not reach statistical significance was maximum depth at week 8 (4.72% mean improvement; P=0.179). With a 15-subject subpopulation, changes in one or two subjects may have skewed these findings. Perhaps more reliable are the indentation measurements, which gauge the smoothness of the ridge and valley, so to speak, of crow's feet at maximum depth. These figures went from a 9.53% improvement at week 8 (P=0.007 versus baseline) to 13.22% at week 12 (P<0.001).

In 2D analysis, wrinkle counts at weeks 2 and 8 and severity at all time points improved significantly, while wrinkle width and length showed no statistical improvement. It is possible that im-

provement of one deeper wrinkle can create multiple finer lines, a single elongated line, or multiple fine lines that are located so close together that the imaging algorithm reads them as the width of one wrinkle rather than of two wrinkles.

Improvements in total wrinkle count lost statistical significance at weeks 4 and 12. As with wrinkle width and length, treatment potentially could alter one deep line into multiple finer lines, thus increasing total line count.

Emerging line counts worsened throughout the study period, from 19.61 ± 9.76 at baseline to 24.54 ± 10.19 at week 12. The increase in emerging line counts may be linked to the reduction in fine line count, as analysis software may have interpreted smaller, less severe post-treatment lines as new, emerging lines.

CONCLUSIONS

Based on expert visual grading, corneometer and cutometer evaluations, and 2D and 3D image analyses, the study product resulted in significant improvements in facial skin appearance, firmness, elasticity, and hydration. Elements that improved most dramatically in investigators' assessments included radiance, firmness, tactile elasticity, textural smoothness, overall appearance, and crow's feet. Ultrasound imaging showed increased dermal thickness as early as week 4, which continued through week 12. Additionally, subject questionnaires reflected a significantly positive perception of the product's effects, and high product tolerance through 12 weeks' use. Thus, the study product demonstrated the ability to provide a safe and effective solution to address several key concerns in facial skin aging.

DISCLOSURES

Dr. Frank Barone and Dr. Sameer Bashey are actively engaged in retail sales of ZO Skin Health products.

Frederick Woodin Jr. is an employee of ZO Skin Health, Inc.

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