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Efficacy and Tolerability of a Cream in Aging Skin

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ABSTRACT

Background: The clinical presentation of photodamaged and aged skin includes fine lines, wrinkles, and pigmentation changes, which are related to the amount of water in the epidermis. Use of moisturizing products can help improve signs of aging.

Methods: Twelve (12) week single-center study in participants 40 to 75 years old with sensitive skin and signs/symptoms of photodamage and skin aging (defined as mild-to-moderate wrinkles, overall photodamage, and lack of skin tone evenness on the neck and outer forearms). Participants applied a cream twice per day to the body (neck, legs, arms, and hands). Efficacy was assessed by clinical grading and digital imaging (in a subgroup of 19 participants) and standard safety assessments were performed.

Results: A total of 41 participants participated. All clinical grading parameters showed significant improvements, including crepiness (visual), skin texture/smoothness (tactile), and overall quality/appearance. In addition, density/thickness improved on both neck and limbs throughout the study. Pinch recoil measurements also improved from baseline to day 84. Tolerability assessments showed improvement of dryness and scaling on limbs vs baseline and no measurable change in any other tolerability parameters throughout the study. In addition, participants reported a positive impression of the cream on a self-assessment questionnaire.

Conclusions: The tested cream, which incorporates the ingredients mandelic acid and *Centella asiatica*, effectively improved participants' skin appearance in adults with sensitive skin and moderate signs of aging.

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INTRODUCTION

Aging skin frequently shows a decrease in skin firmness/density and may be associated with erythema or uneven skin tone.[1] Often, aging skin is accompanied by dermatoporosis or thin, fragile skin.[2,3] There is growing interest in cosmetic and aesthetic treatments that can improve and maintain the skin's appearance. However, such management can be challenging in the setting of sensitive skin since those with sensitive skin have a tendency toward stinging/burning, itching, and erythema.[1]

Recently, a cosmetic cream was formulated with mandelic acid and *Centella asiatica*. Microdosing these two well-known agents had surprisingly synergistic effects decreasing senescent cells and their inflammatory cytokines.[4] Mandelic acid, an alpha hydroxy acid, is a potent exfoliating ingredient and an antimicrobial agent that has shown benefits for hyperpigmentation and acne and has anti-aging activity.[5,6] It can also function as a preservative and contributes to optimizing the pH of the formulation.[5] *Centella asiatica* (also known as gotu kola) is a medicinal herb that has been used for centuries in parts of Asia to improve wound healing and a variety of dermatologic conditions.[7] In wound healing, the addition of *C asiatica* increases cellular proliferation and collagen synthesis and helps wounds epithelialize faster (and, in turn, heal faster).[7-9] In skin diseases, the triterpenes present in *C asiatica* contribute to beneficial effects on eczema, psoriasis, acne, and atopic dermatitis (AD).[10] In these settings, the above-mentioned effects may be beneficial as well as its antioxidant properties. Additionally, *C asiatica* has been shown to have antibacterial activity against *P acnes*[11]; in AD, *C asiatica* reduces hyperkeratosis and inflammatory cell infiltrate and has actions on several inflammatory pathways.[12,13]

Given the positive effects of these ingredients, this study was designed to test the efficacy and tolerability of the novel moisturizing cream containing mandelic acid and *C asiatica* under normal conditions in adults with sensitive skin and aging/photodamage after daily use for 12 weeks.

MATERIALS AND METHODS

This was a 12-week single-center study in participants 40 to 75 years old with sensitive skin and signs/symptoms of photodamage and skin aging (defined as mild-to-moderate wrinkles, overall photodamage, and lack of skin tone evenness on the neck and outer forearms). Participants applied a cream (Galderma Laboratories, LP, Dallas, Texas) twice per day to the body (neck, legs, arms, and hands). The study was performed according to Good Clinical Practice and all participants provided written informed consent.

Patient Population

Participants had clinically mild-moderate facial aging/photodamage (score 3-6 on a scale of 0=none to 9=severe, modified Griffiths scale[14]) in wrinkles, overall photodamage, and lack of skin tone evenness. They could be male or female and could have any type of skin (oily, dry, or combination). The population was recruited to have at least 10 participants with Fitzpatrick skin phototypes IV-VI (including 5 in the imaging subgroup). Skin sensitivity was determined at screening via a proprietary skin sensitivity questionnaire (Sensiscale) and approved by a board-certified dermatologist. Using a scale of 0-10 each, participants rated the degree of overall skin irritation and severity of skin conditions (tingling, burning, heat sensations, tautness, itching, pain, general discomfort, hot flashes, and redness) for a maximum score of 100. To qualify, participants were required to have a global score ≥5.

Assessments

Assessments included clinical grading of efficacy parameters, using a modified Griffiths 10-point scale (0=none, 1-3=mild, 4-6=moderate, 7-9=worst possible/severe). Parameters included visible skin density/thickness, transparency, skin color/evenness, firmness, crepiness, skin texture/smoothness, and overall skin quality/appearance. Pinch recoil measurements were performed on the forearm to assess skin resiliency. Digital imaging (Canfield IntelliStudio®, Canfield Imaging Systems, Fairfield, NJ), was performed at baseline and days 28 and 84 in a subgroup of participants, with images of at least 10 participants of the neck and 10 of the forearm. In addition, 3D imaging of wrinkle volume (Antera 3D® Imaging, Miravex Ltd, Dublin, Ireland) was undertaken. Finally, all participants completed a subject questionnaire. Tolerability evaluations were performed by a board-certified dermatologist who assessed erythema, edema, dryness, scaling, and rash on arms/legs on a scale of 0=none to 3=severe.

Statistical Methods

For evaluation parameters, a descriptive summary was provided (including N, mean, median, standard deviation, minimum, and maximum at all timepoints). The mean change from baseline

TABLE 1.

Subject Demographics and Clinical Characteristics		
	All subjects (N=41)	Imaging subgroup (N=19)
Age (y), mean (range)	62.0 (47-72)	65.6 (47-72)
Sex		
Female	36 (89%)	16 (84%)
Male	5 (12%)	3 (16%)
Race/Ethnicity		
American Indian or Alaska Native	2 (5%)	1 (5%)
Asian	5 (12%)	4 (21%)
Black or African American	7 (17%)	5 (26%)
White or Caucasian/Hispanic	5 (12%)	3 (16%)
White or Caucasian/Non-Hispanic	22 (54%)	6 (32%)
Fitzpatrick Skin Type		
I	5 (12%)	1 (5%)
II	15 (37%)	4 (21%)
III	9 (22%)	4 (21%)
IV	5 (12%)	5 (26%)
V	4 (10%)	2 (11%)
VI	3 (7%)	3 (16%)
Fitzpatrick Skin Type Subgroups		
I-III	29 (71%)	9 (47%)
IV-VI	12 (29%)	10 (53%)
Skin Type		
Combination	23 (56%)	11 (58%)
Dry	9 (22%)	5 (26%)
Normal	9 (22%)	3 (16%)
Sensiscale Global Score ≥13	33 (81%)	15 (79%)

was also calculated. The null hypothesis that the mean change from baseline was zero tested by Wilcoxon signed rank test for clinical grading, tolerability parameters, and paired t test for 3D imaging. A binomial (sign) test was used for analysis of the subject questionnaire. Analyses were performed using SAS software version 9.4 series (SAS Statistical Institute).

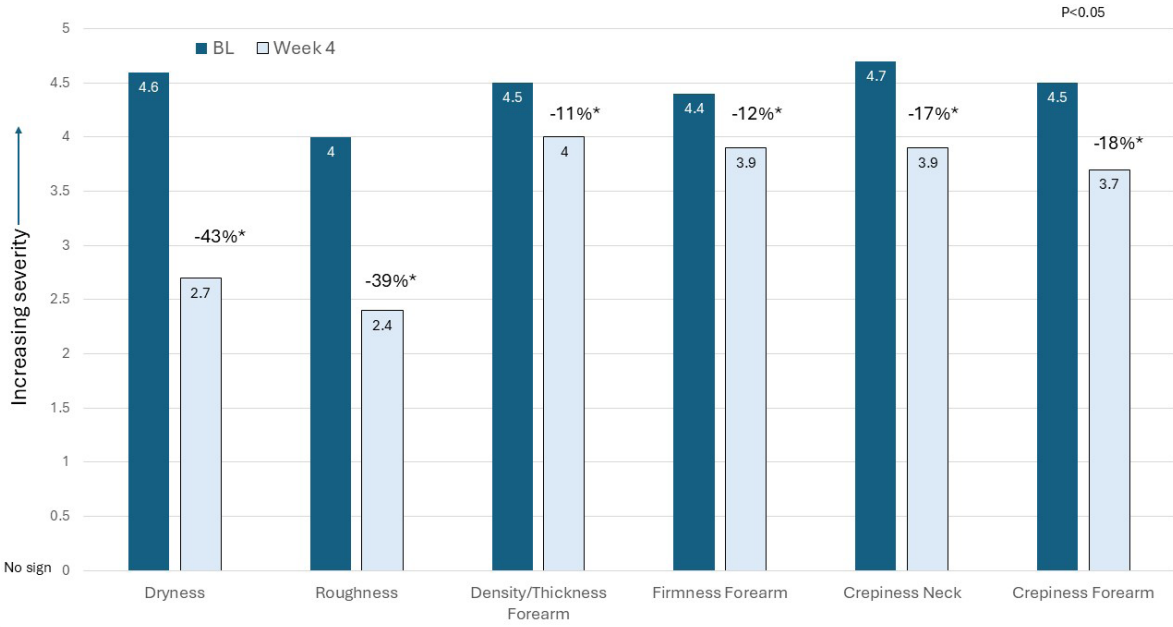
RESULTS

A total of 41 participants participated, with demographics as shown in Table 1. The majority of demographic characteristics were similar between the overall population and those who participated in the imaging subgroup (N=19).

Clinical Grading

There was a statistically significant improvement in scores for crepiness (visual), skin texture/smoothness (tactile), and overall skin quality/appearance (health) on the neck and forearms at each post-baseline timepoint (Figure 1 and Table 2). Figure 2 also shows a visual representation of the improvement of clinical grading scores via standardized photography. Additionally,

FIGURE 1. Overview of clinical grading results.



BL=baseline, *$P<0$

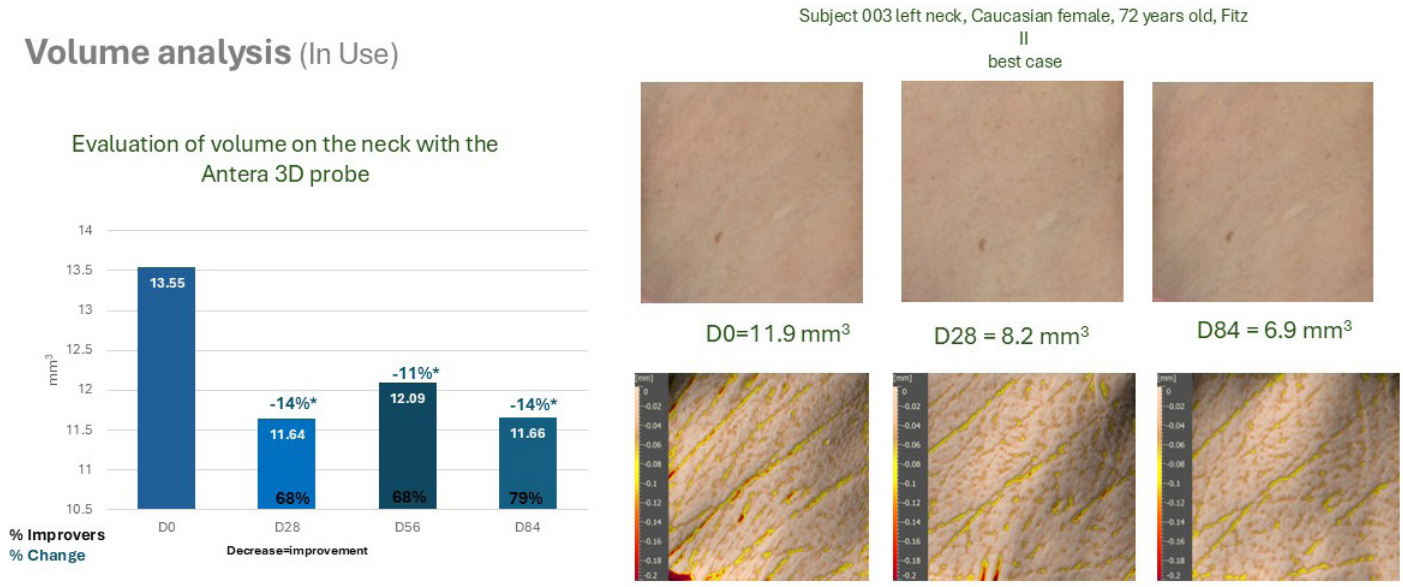
TABLE 2.

Clinical Grading Results by Study Visit (0=no sign to 9=worst possible)					
	Baseline	Day 7	Day 28	Day 56	Day 84
Skin dryness	4.56	3.62 (-20%)*	3.69 (-18%)*	3.13 (-32%)*	2.65 (-43%)*
Skin roughness	3.97	3.40 (-13%)*	3.18 (-19%)*	2.78 (-30%)*	2.43 (-39%)*
Skin density/thickness – Neck	4.8	4.8	4.7 (-2%)*	4.6 (-4%)*	4.3 (-9%)*
Skin density/thickness – Forearms	4.5	4.5	4.3 (-4%)*	4.1 (-9%)*	4.0 (-11%)*
Firmness – Forearms	4.4	4.4	4.2 (-4%)*	4.0 (-8%)*	3.9 (-12%)*
Transparency – Neck	2.5	2.6	2.5	2.4 (-5%)*	2.2 (-12%)*
Transparency – Forearms	4.4	4.4	4.3 (-3%)*	4.0 (-8%)*	3.9 (-12%)*
Skin color evenness – Forearms	5.0	5.0	4.8 (-4%)*	4.6 (-8%)*	4.4 (-11%)*
Crepiness – Neck	4.7	4.5 (-4%)*	4.3 (-8%)*	4.1 (-13%)*	3.9 (_17%)*
Crepiness – Forearms	4.5	4.4 (-4%)*	4.1 (-9%)*	3.9 (-14%)*	3.7 (-18%)*
Skin texture/smoothness – Neck	4.3	3.8 (-12%)*	3.5 (-17%)*	3.5 (-18%)*	3.2 (-25%)*
Skin texture/smoothness – Forearm	4.8	4.1 (-13%)*	3.8 (-19%)*	3.7 (-21%)*	3.5 (-26%)*
Overall skin quality/appearance – Neck	4.8	4.5 (-6%)*	4.4 (-9%)*	4.2 (-12%)*	4.0 (-16%)*
Overall skin quality/appearance – Forearm	5.0	4.7 (-5%)*	4.5 (-9%)*	4.4 (-12%)*	4.2 (-15%)*

*$P<0.05$

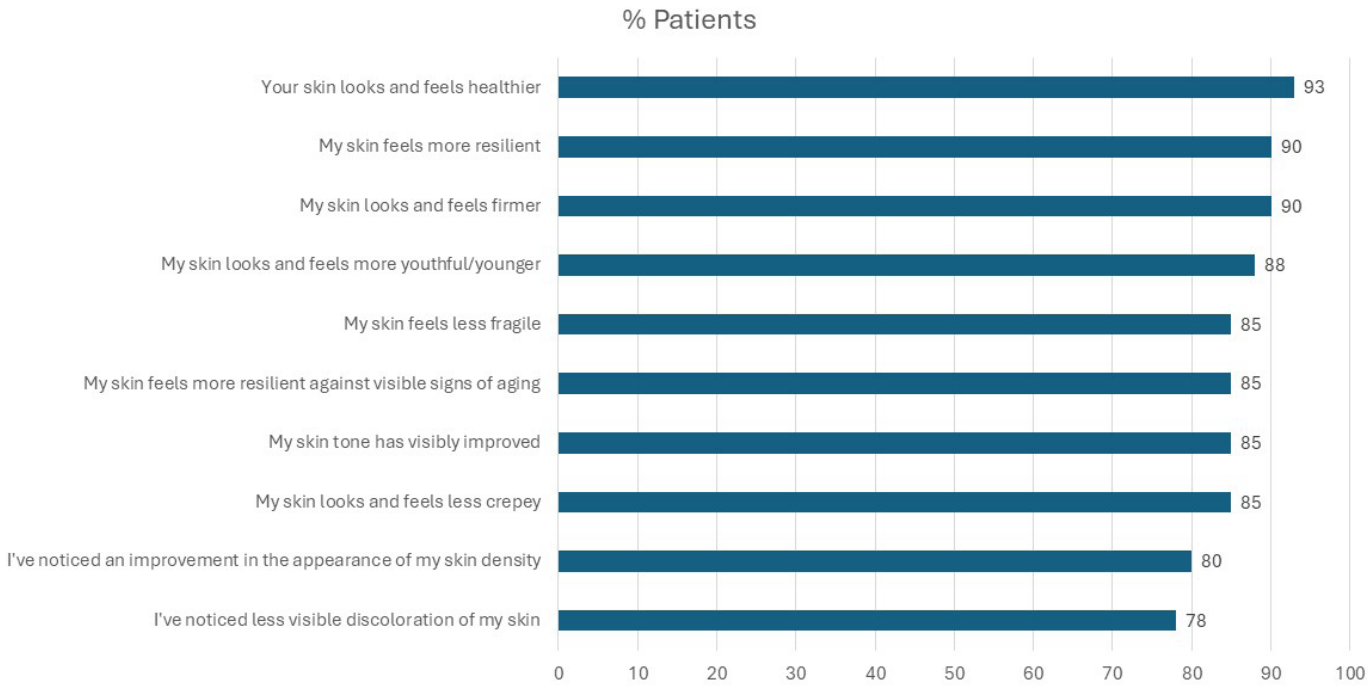
FIGURE 2. Clinical photos of participants treated with the cream.

FIGURE 3. Wrinkle volume analysis with 3D imaging (change indicates filling of fine lines).



Left = mean change, right top = clinical photography and top bottom = imaging.

FIGURE 4. Results of participant self-assessment questionnaire at week 12.



participants reported their skin felt soothed and looked/felt firmer. Skin density/thickness and firmness on forearms were significantly improved from day 28 to the end of the study and from day 56 onwards for the neck. Finally, the evaluation of skin resiliency ("bounce back") following a pinch recoil test improved from 0.94 seconds at baseline to 0.83 (-12%, $P<0.05$) at day 84.

Volume Analysis

Analysis of 3D imaging (N=19) showed significant improvement in wrinkle volume (mm^3) on the neck at each post-baseline compared to baseline (Figure 3, $P<0.05$).

Questionnaire results and correlation with improvements in clinical grading (Figure 4).

Safety

Tolerability evaluations showed that dryness on extremities improved at each study visit compared to baseline. There was no significant increase or decrease in tolerability scores for any other parameter at any study visit. The Sensiscale evaluation indicated a significant improvement in the degree of overall skin irritation and severity of tingling, burning, heat sensations, tautness, itching, pain, general discomfort, hot flashes, and redness. The global Sensiscale score also improved at each evaluated timepoint vs baseline. The tested cream was associated with good safety and there were no AEs reported during the duration of the study.

DISCUSSION

The results of this study demonstrate that the mandelic acid/*C asiatica* moisturizing cream was effective in improving the cosmetic appearance of skin conditions on the neck and outer forearm, with statistically significant improvements in scores for crepiness, skin texture and smoothness, and overall appearance. In addition, the cream filled in fine lines in tested areas, which is likely related to improvement in skin thickness. It was very well tolerated and had a favorable rating from participants with pre-existing sensitive skin.

Utilization of a moisturizer with *C asiatica* that enhances collagen synthesis may confer marked benefits in aged, fragile, and sensitive skin.[1,15] With age, collagen fibers thin, fragment, and separate from each other, creating extracellular matrix disorganization.[1] Production of collagen by fibroblasts decreases while matrix metalloproteinases increase the breakdown of collagen.[1] In addition, the role of reactive oxygen species (ROS) is important in aging and sensitive skin, underscoring the benefits of incorporating antioxidant ingredients to neutralize ROS such as *C asiatica*.[1] Aging is associated with a depletion of exogenous antioxidants and the skin has a reduced protective system against ROS.[1] In addition, a major aspect of aging involves cellular senescence, inflammation, and decreased function of fibroblasts in producing collagen, elastin, and hyaluronic acid.[16] A formulation that impacts this functionality would be expected to produce improvements in crepiness, texture,

wrinkle volume, and recoil as demonstrated in this study. The pigmentation normalization activities of mandelic acid help to reduce uneven skin tone, as shown in this study. For those with aging and sensitive skin, it is very important to employ products that improve or are neutral on sensations of burning/stinging, and itching. We showed no increased tolerability problems and improvement in skin dryness. Improvement in skin elasticity, also important in aged skin, was shown by shorter pinch recoil time.

Our findings agree with an earlier proof of concept study complementing it with hydration improvement.[4] Our conclusion supports the use of a moisturizer containing specifically designed ingredients to impact skin condition and aging.

DISCLOSURES

All authors are employees of Galderma Laboratories.

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