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ORIGINAL CONTRIBUTION

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Evaluation of an Onion Extract, Centella Asiatica, and Hyaluronic Acid Cream in the Appearance of Striae Rubra

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ABSTRACT

This study evaluated the effect of an onion extract cream with Centella asiatica and hyaluronic acid in improving the appearance of striae rubra (SR). Women participants with bilateral, outer aspect of the thigh SR were randomized to apply a quarter-sized amount of the onion extract cream twice daily for 12 weeks to the randomized left or right, outer aspect of the thigh. No treatment was administered to the contralateral side. Participants were evaluated at weeks 2, 4, 8, and 12. Primary efficacy endpoints included color, texture, softness, and overall appearance of SR by the participant and investigator at week 12. The treated thigh demonstrated a statistically significant difference in the mean change in participant and investigator evaluations in overall appearance, texture, color, and softness compared with the untreated thigh at week 12. No adverse events occurred during the study. The onion extract cream was well tolerated and significantly improved the appearance of SR in women. (*SKINmed*. 2010;8:80–86)

Stretch marks, also known as striae distensae, are a common concern for post-pubertal men and women patients seeking dermatologic care. They appear as linear thinned skin most often found on the breasts, abdomen, hips, and thighs.[1] Stretch marks may appear due to the rapid hormonal changes and growth associated with puberty, during pregnancy, or with medical diseases, such as Cushing syndrome. Under the microscope, they appear as dermal atrophy accompanied by loss of the rete ridges, a finding similar to scar tissue.[2,3] The development of striae distensae has been described as similar to that of wound healing or scar formation.[2,3] Earlier stage or immature striae distensae, also known as striae rubra, appear pink or red in color and over time become white, flat, and depressed, known as striae alba.[2] There is no clear consensus as to the cause of striae distensae.[2]

The treatment for stretch marks is limited.[2] The most invasive therapies for stretch marks involve physician administered laser surgery. Improvement in stretch marks (ie, diminution of the signs for striae) with laser therapy is accomplished by wounding the scarred skin and hoping that the newly healed skin will have a more normal, cosmetically acceptable appearance.[4] Medical reports of Nd:YAG laser,[5] radiofrequency devices,[6] and fractional photothermolysis,[7,8] have shown some degree of stretch mark appearance improvement, but not resolution. Topical tretinoin is the best studied topical stretch mark pharmaceutical product, however, some trials have yielded variable results.[9–14] Camouflage is often selected as the best option for treatment to hide the scars.[15]

In addition to physician administered stretch mark therapies, a variety of over-the-counter products can be purchased for improving stretch mark appearance. These products contain cocoa butter, emu oil, vitamin E, and other oils to apply while massaging the stretch marks. Many dermatologists recommend massaging the stretch mark in a circular motion with oil on the finger to reduce friction and make the skin more pliable, improving appearance—although no evidence exists for this recommendation. Researchers published on the lack of evidence for topical ointments and creams in stretch mark improvement (ie, diminution of the signs for striae).[2]

Red, immature stretch marks are more amenable to treatment than those that have matured to a silvery white. This is because the reddish stretch marks are still healing and the healing can be modified by intervention. One botanical ingredient that has been studied in the treatment of scars is onion extract. Onion extract possesses *in vitro* antiinflammatory properties due to cepanes, a flavonoid unique to onions.[16] In addition, onion extract contains sulfur in the form of thiosulfinates accounting for its *in vitro* antiinfective properties,[16] fibrinolytic effects,[17] and antimicrobial activity against Gram-positive bacteria.[18,19] A proprietary onion extract gel has been shown to

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improve the appearance of post-surgical shave excision scars.[20] Another botanical with *in vitro* and *in vivo* efficacy in scars[21,22] and stretch marks (data on file, Merz Pharmaceuticals, LLC) is Centella asiatica. Centella asiatica, also known as Indian pennywort, is a plant found in Asia, Africa, and North and South America used widely in Indian naturopathic medicine for ulcer healing. It contains asiaticoside, which is purported to increase the production of collagen I enhancing wound healing and scar maturation. The leaves are harvested, dried, and 95% ethanol extracted to obtain the medicinal botanical.

This research evaluated the effect of a formulation containing onion extract and Centella asiatica on newly formed striae rubra on the proximal aspect of the thighs of women. The botanical extracts are contained in a moisturizing emollient vehicle containing hyaluronic acid, a potent humectant aiding in the water holding capacity of the skin and previously studied in wound healing.[23]

METHODS

Materials

All participants applied the study onion extract cream (Mederma for Stretch Marks, Merz Pharmaceuticals, LLC, Greensboro, NC) to one randomized thigh and no treatment to the other thigh. No placebo cream was utilized in this study. Adverse events were captured for the safety analysis.

Participant Selection and Study Design

This randomized, controlled, investigator-blinded, institutional review board approved study (Concordia Clinical Research, Institutional Review Board, Cedar Knolls, NJ) was conducted at one site in the United States from November 2008 to March 2009. The study was performed in accordance with globally accepted standards of Good Clinical Practice (as defined by the May 1, 1996, International Council on Harmonisation E6 Guidelines for Good Clinical Practice). Women participants between the ages of 18 and 45 years having symmetrical striae rubra on the proximal aspect of the thighs were enrolled since it was felt that mature striae alba would not be amenable to improvement. Participants with known allergies or sensitivities to the study ingredients, history of keloids or hypertrophic scars, excessive sun exposure, pregnancy, breast feeding, and treatment with an investigational drug or device within a period of 30 days prior to the study were excluded. In addition, participants with any systemic or dermatologic disorder that, in the opinion of the investigator, would interfere with the study, body mass index above 30, prior surgical or prescription topical striae distensae were excluded. Participants did not apply any products to the areas of observation for 2 weeks prior to the initiation of therapy.

After successful completion of Health Insurance Portability and Accountability Act authorization, informed consent, photography consent, and investigator screening, study participants were randomized to apply a quarter-sized amount of the onion extract cream twice daily for 12 weeks to either the assigned right or left thigh. The opposite thigh received no treatment. Participants returned to the study center for evaluation at weeks 2, 4, 8, and 12. Participant and investigator assessments were obtained regarding striae rubra softness, texture, color, and overall appearance. Standardized digital photography (Nikon E3, Canfield, NJ) by the investigator with a fixed focal length and exposure of the right and left striae rubra was obtained at each visit.

Noninvasive Assessments

Skin elasticity was selected as the most appropriate noninvasive assessment parameter for striae rubra. This evaluation was included to determine if the study product modified the recoil of the skin. Skin elasticity measurements were obtained via a negative pressure suction device (DermaLab, Hadsund, Denmark). The device functioned by applying negative pressure to the skin until distended into a suction cup with a light beam across the top of the cup. When the skin was adequately distended, the light beam was interrupted, the negative suction discontinued, and the skin relaxation evaluated. This cycle was repeated and recorded to obtain 5 distention and relaxation curves.

Clinical Efficacy Parameters

Clinical efficacy was based on the unblinded participant assessments and the blinded investigator assessments comparing the treated to the untreated striae rubra both visually and tactilely. The primary efficacy parameter was the participant assessment of striae rubra softness, texture, color, and overall appearance of the untreated vs treated striae rubra at 12 weeks using a 5-point ordinal scale: 0 = no improvement, 1 = minimal improvement, 2 = mild improvement, 3 = moderate improvement, and 4 = marked improvement. The secondary efficacy outcomes included participant assessment of striae rubra softness, texture, color, and overall appearance at weeks 2, 4, and 8 using a 5-point ordinal scale; physician assessment of striae rubra using a 5-point ordinal scale at all visits; and noninvasive skin elasticity measurements.

Statistical Methodology

The safety evaluation set was the subset of randomized participants who received study treatment at least once. The full analysis set was the subset of randomized participants who received study treatment at least once and for whom at least one post-baseline value of efficacy was available. For all efficacy variables, descriptive summary statistics and paired two-sided t tests with confidence intervals were performed for each visit based on the full analysis set. The post-baseline last observation carried forward method was used to impute missing post-baseline efficacy variables. Baseline values were not imputed into follow-up visits.

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Table I. Summary of Changes From Baseline to Weeks 2, 4, 8, and 12 in Participant Assessment of Striae Rubra (FAS Population, Last Observation Carried Forward)

Week	Treated (Onion Extract Cream)	Untreated	Difference (Treated–Untreated)	*P* Value Paired *t* Test
Week 2	n=50	n=50	n=50	
Overall appearance, mean (SD)	0.56 (0.644)	0.10 (0.364)	0.46 (0.613)	<0.01
Color, mean (SD)	0.28 (0.701)	0.08 (0.566)	0.20 (0.452)	<0.01
Softness, mean (SD)	0.74 (0.922)	0.20 (0.670)	0.54 (0.813)	<0.01
Texture, mean (SD)	0.48 (0.814)	0.14 (0.606)	0.34 (0.626)	<0.01
Week 4	n=54	n=54	n=54	
Overall appearance, mean (SD)	1.15 (0.878)	0.15 (0.452)	1.00 (0.890)	<0.01
Color, mean (SD)	0.70 (0.882)	0.06 (0.231)	0.65 (0.894)	<0.01
Softness, mean (SD)	1.26 (0.894)	0.20 (0.528)	1.06 (1.054)	<0.01
Texture, mean (SD)	0.89 (0.883)	0.11 (0.317)	0.78 (0.945)	<0.01
Week 8	n=54	n=54	n=54	
Overall appearance, mean (SD)	0.94 (0.712)	0.20 (0.562)	0.74 (0.935)	<0.01
Color, mean (SD)	0.69 (0.773)	0.11 (0.462)	0.57 (0.924)	<0.01
Softness, mean (SD)	1.17 (0.795)	0.22 (0.538)	0.94 (0.979)	<0.01
Texture, mean (SD)	1.00 (0.777)	0.22 (0.604)	0.78 (0.984)	<0.01
Week 12	n=54	n=54	n=54	
Overall appearance, mean (SD)	1.13 (0.802)	0.20 (0.562)	0.93 (0.843)	<0.01
Color, mean (SD)	0.70 (0.792)	0.07 (0.328)	0.63 (0.784)	<0.01
Softness, mean (SD)	1.31 (0.865)	0.15 (0.408)	1.17 (0.986)	<0.01
Texture, mean (SD)	1.06 (0.856)	0.19 (0.552)	0.87 (0.848)	<0.01

Five-point ordinal scale (0 = no improvement, 1 = minimal improvement, 2 = mild improvement, 3 = moderate improvement, and 4 = marked improvement). Abbreviations: FAS, full analysis population; SD, standard deviation.

RESULTS

Fifty-five women participants between the ages of 18 and 45 years were randomized. Fifty-two participants successfully completed the trial (1 discontinued due to lack of compliance, 2 were lost to follow-up). Fifty-five participants were in the safety evaluation set population and 54 participants were in the full analysis set population.

For all of the participant assessment endpoints (overall appearance, color, softness, and texture), the difference between the striae rubra treated with the onion extract cream and the untreated side at week 12 were statistically significant using last observation carried forward imputed values (Table I). There were statistically significant differences in the mean changes from baseline to weeks 2, 4, 8, and 12 in participant assessments of overall appearance, color, softness, and texture.

The mean change from baseline in the investigator assessments were statistically significant ($P<0.01$) at all time points in terms of overall appearance, softness, and texture on the side treated with the onion extract cream than on the untreated side (Table II). At weeks 2 and 4, no significant difference in mean change from baseline in investigator assessment of color between the treated and untreated sides was present. Representative photographs of the treated and untreated sides are presented in the Figure.

A responder analysis was completed in which responders were defined as having at least a one-grade improvement from baseline in the assessment (Table III). At each visit there were more responders on the side treated with onion extract cream vs the untreated side as assessed by both the investigator and participant.

The mean baseline skin elasticity was 17.86 pounds per square inch (psi) for the side treated with the onion extract cream and 16.82 psi for the untreated side. After 12 weeks of treatment, a trend favoring the use of the onion extract was observed with mean skin elasticity

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Table II. Summary of Changes From Baseline to Weeks 2, 4, 8, and 12 in Investigator Assessment of Striae Rubra (FAS Population, Last Observation Carried Forward)

Week	Treated (Onion Extract Cream)	Untreated	Difference (Treated–Untreated)	*P* Value Paired *t* Test
Week 2	n=50	n=50	n=50	
Overall appearance, mean (SD)	0.68 (0.741)	0.10 (0.303)	0.58 (0.859)	<0.01
Color, mean (SD)	0.02 (0.247)	0.02 (0.141)	0.00 (0.286)	1.000
Softness, mean (SD)	0.74 (0.723)	0.18 (0.388)	0.56 (0.884)	<0.01
Texture, mean (SD)	0.42 (0.758)	0.04 (0.198)	0.38 (0.805)	<0.01
Week 4	n=54	n=54	n=54	
Overall appearance, mean (SD)	1.06 (0.738)	0.20 (0.451)	0.85 (0.998)	<0.01
Color, mean (SD)	0.11 (0.420)	0.00 (0.000)	0.11 (0.420)	0.0570
Softness, mean (SD)	1.09 (0.759)	0.22 (0.462)	0.87 (1.047)	<0.01
Texture, mean (SD)	0.96 (0.800)	0.19 (0.438)	0.78 (1.022)	<0.01
Week 8	n=54	n=54	n=54	
Overall appearance, mean (SD)	1.48 (0.746)	0.17 (0.423)	1.31 (1.006)	<0.01
Color, mean (SD)	0.30 (0.633)	0.0 (0.0)	0.30 (0.633)	<0.01
Softness, mean (SD)	1.61 (0.763)	0.19 (0.438)	1.43 (1.021)	<0.01
Texture, mean (SD)	1.46 (0.818)	0.15 (0.408)	1.31 (1.043)	<0.01
Week 12	n=54	n=54	n=54	
Overall appearance, mean (SD)	1.72 (0.712)	0.09 (0.351)	1.63 (0.853)	<0.01
Color, mean (SD)	0.61 (0.627)	0.00 (0.00)	0.61 (0.627)	<0.01
Softness, mean (SD)	1.87 (0.825)	0.11 (0.317)	1.76 (0.970)	<0.01
Texture, mean (SD)	1.72 (0.738)	0.07 (0.328)	1.65 (0.872)	<0.01

Five-point ordinal scale (0 = no improvement, 1 = minimal improvement, 2 = mild improvement, 3 = moderate improvement, and 4 = marked improvement). Abbreviations: FAS, full analysis population; SD, standard deviation.

decreasing by 1.40 psi for the treated side vs 0.10 psi for the untreated side, but statistical significance was not reached (*P*=0.23).

There were no adverse events reported among the 55 participants who participated in this trial.

DISCUSSION

In this randomized, controlled, investigator-blinded 12-week study examining a cream containing onion extract, Centella asiatica, and hyaluronic acid, there was a statistically significant improvement in proximal aspect of the thigh striae rubra in terms of overall appearance, softness, color, and texture as evaluated by the participants and the investigator. Using participants with symmetrical striae rubra on the proximal aspect of the thighs allowed each participant to serve as their own control. Improvement in skin elasticity was not statistically significant between treated and untreated sides; however, it is envisaged that perhaps with longer use and/or an increase in the study sample size, the skin elasticity measurement might achieve statistical significance.

It is important to recognize that this study demonstrated only improvement (ie, diminution of the signs for striae) in the feel and appearance of striae rubra, not a reduction in their size or elimination of the scar tissue. Stretch marks are such a common occurrence that it is hard to classify them as a dermatologic disease, yet they are designated by an *International Classification of Diseases, Ninth Revision* code. They typically occur in women and men at or around puberty on the proximal, medial aspect of the arms, lateral aspect of the breasts, lumbar region of the torso, and proximal aspect of the thighs.[24] A second common time for the formation of striae distensae is during pregnancy, again a time of hormonal change characterized by corticosteroid secretion. During pregnancy, striae distensae

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Figure. A photographic comparison of the untreated and proprietary onion-extract-cream–treated striae rubra (week 12). Patient 1: (A) right thigh, proprietary onion extract; (B) left thigh, no treatment. Patient 2: (C) right thigh, no treatment; (D) left thigh, proprietary onion extract.

can occur in the previously mentioned locations, but also commonly on the abdomen. All of the women enrolled in this study had striae rubra on the proximal aspect of the thighs due to pregnancy.

There are some important limitations of this research. The first limitation is that the participants were not blinded to treatment, which could lead to a bias toward the treated side. Since a moisturizing vehicle by itself could induce enhanced moisturization of the skin and improve the appearance of the striae rubra, it was not possible to have a true placebo controlled study. The investigator was blinded, however the study compared some treatment to no treatment. Some of the improvement noted with the study product might be due to hydration and massage; however, it is not possible to determine if the improvement may have been solely due to these factors or due to the active ingredients in the study product. The results are probably due to a combination of all factors.

This product was designed for use in the over-the-counter market and thus was only evaluated for appearance changes and claims. It is for this reason that it could only be formulated with botanical ingredients, which contain active plant extracts. This research methodology and the study cream combining onion extract, Centella asiatica, and hyaluronic acid demonstrated improvement (ie, diminution of the signs for striae) in striae rubra appearance in women.

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Table III. Responder Analysis

Week	Investigator Assessment: Treated Side (Onion Extract Cream) Number of Responders,[a] n	Investigator Assessment: Untreated Side Number of Responders,[a] n	Participant Assessment: Treated Side (Onion Extract Cream) Number of Responders,[a] n	Participant Assessment: Untreated Side Number of Responders,[a] n
Week 2	n=50	n=50	n=50	n=50
Overall appearance	31	5	24	4
Color	18	2	17	4
Softness	2	1	10	1
Texture	34	9	25	6
Week 4	n=54	n=54	n=54	n=54
Overall appearance	46	10	43	6
Color	41	9	35	6
Softness	6	0	26	3
Texture	46	11	44	8
Week 8	n=54	n=54	n=54	n=54
Overall appearance	49	8	39	8
Color	46	7	40	8
Softness	13	0	27	4
Texture	49	9	44	9
Week 12	n=54	n=54	n=54	n=54
Overall appearance	50	4	43	7
Color	50	3	38	3
Softness	29	0	27	7
Texture	50	6	45	4

[a]A participant that has at least a one-grade improvement from baseline in the assessment.

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