A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial of a Novel Nutritional Supplement Product to Promote Healthy Skin

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ABSTRACT

Background: Despite an abundance of nutritional supplements, very few well-controlled trials have assessed their beneficial effect on the skin, such as hydration, antioxidant levels, texture or appearance. The objective of the following placebo-controlled, double-blind study was to determine the effects of the Skin Health Experimental Product (SHEP) on skin health.

Methods: The study enrolled healthy men and women aged 30 years or older. Subjects were randomized to receive a twice-daily regimen of SHEP or placebo. The effects SHEP had on overall skin appearance and health were assessed by measuring improvements in: (1) skin hydration using a closed-aperture transepidermal water-loss moisture meter and a vapometer; (2) skin texture using silicon profilometry; (3) skin carotenoid concentration using Raman spectrometry; and (4) reported self-image assessments using the Global Aesthetic Improvement Scale (GAIS).

Results: SHEP-treated subjects demonstrated a significant reduction in fine lines compared to the placebo-treated group. Raman spectroscopy showed that SHEP increased carotenoids at some measurement sites. Based on the GAIS, SHEP-treated subjects were three times more likely to perceive an improvement in their appearance compared to placebo-treated subjects (P>0.049).

Conclusion: The orally-administered SHEP nutritional supplement improves skin texture, carotenoid levels in specific areas of the hand, and improves patients’ perception of skin health.


INTRODUCTION

While the saying “we are what we eat” is a familiar one, to what degree is it true and to what extent does it actually affect our appearance? The impact diet has on health and wellness is gaining increased popular interest and research focus. Many sectors of society consume an imbalanced diet with insufficient quantities of a variety of nutrients, leading to risk for a wide range of diseases.1 Current evidence suggests that diets high in antioxidants, low in saturated and trans fats, and rich in omega-3 fatty acids are associated with increased lifespan and decreased incidence of cardiovascular disease.2 Unfortunately, transforming this information into a vitamin or nutritional supplement has not been a simple task. The results of clinical trials that enrolled individuals already suffering from illness have demonstrated the beneficial effects of omega-3 fatty acids,3,4 calcium,5 vitamin D,6 and vitamin E;7,9 however, it has been suggested (although not proven) that certain nutrients are associated with increased mortality rates, such as high-dose vitamin E and A supplementation.10,11

Fueled by a $26.9 billion dollar industry with a relatively low barrier to entry, there has been a steady increase in the number of available nutritional products geared to promote increased vitality. Similarly, there is growing interest in potential benefits that nutritional supplementation may confer on the health and appearance of the skin, but few well-designed studies support these claims. Much of our current understanding of nutrition,
for the skin in particular, has been obtained through research of deficiencies and excesses in nutrition and their associated cutaneous manifestations. The result is a strong body of literature that focuses on the impact of poor diets on health outcomes. The potential benefits of nutritional supplements for people with non-deficient diets remains to be fully examined.

Multiple studies reveal the benefits that antioxidants have, both topically and orally, on reducing the minimal erythema dose following exposure to ultraviolet (UV) light, a well-known oxidizer and accelerator of skin age. Sunbathing and tanning are frequent practices that make exposure to the oxidizing effects of UV radiation a common part of everyday life. It therefore becomes clear that nutritional antioxidant supplements composed of vitamins and minerals known to be highly concentrated in the skin would aid skin health and possibly appearance in healthy individuals.

The effects of oral nutritional supplementation on skin hydration, antioxidant levels, skin texture and appearance has not been assessed in well-controlled, randomized, double-blinded research studies. The great promise of fruits and vegetables to lower disease risk and support health has not been realized in prospective studies with individual vitamins, suggesting that the complexity of food is a significant contributor.

The Skin Health Experimental Product (SHEP) is a natural, whole food-based nutritional supplement containing omega-3 fatty acids, ascorbic acid, beta-carotene, zinc, lutein, pyridoxine, pantothenate, niacin, choline, and coenzyme Q10. The objective of the following nine-month placebo-controlled, double-blind study was to determine the effects SHEP on skin health.

**MATERIALS AND METHODS**

**Subjects**
Men and women over 30 years of age were enrolled in the nine-month study. Subjects were excluded if they had any active or chronic skin disease, used prescription wrinkle therapies, had undergone procedures based on active dermal response within six months, used any facial augmenting therapy or aesthetic facial surgical therapy within nine months, had cancerous or precancerous lesions on the face, or had used any investigational product 30 days prior to enrollment. Subjects taking dietary supplements were required to abstain from using them for 30 days prior to enrollment and for the duration of the study. In addition, a cohort of 50 age-matched subjects was recruited to serve as controls.

**Study Intervention**
The Skin Health Experimental Product (SHEP) is a proprietary food-based mixture of ascorbic acid (as Camu Camu - *Myrciaria dubia*), omega-3 fatty acids, mixed carotenoids (from *Blakeslea trispora*), zinc rice chelate, lutein, pyridoxine, pantothenate, niacin, and coenzyme Q10. The amount of each component of SHEP is within levels known to be safe for human consumption.

**Study Design**
Subjects were randomized to receive two capsules containing SHEP or an identical-appearing placebo twice daily with their morning and evening meals for 270 days.

**Efficacy Measures**

**Skin Profilometry**
Major and minor skin lines were measured by topographical analysis utilizing silicon profilometry analysis (BioNet, Inc., Spring, TX). Individual silicon profilometry replicas of the periorbital skin were analyzed using a set of 10 parallel lines of equal length running across the skin replica and parallel to the direction of the lighting. Variations in luminance are indicative of skin roughness. A second analysis of the skin replica image area was performed by subdividing it into 10 bands of equal width. Average maximum difference in luminance (Rz), average deviation of the luminance curve about the mean luminance (Ra), distance between markers placed on the lines at luminance changes (FSpace), and the number of markers per millimeter that are placed on the lines at luminance changes (FNum) were measured for the various study visits to analyze changes in the spacing, breadth, shadows, and number of wrinkles in the periorbital area. Silicon profilometry of the periorbital skin was obtained at study baseline, day 60, day 90, day 180, and day 270.

**Carotenoid Measurement**
Resonance Raman spectroscopy was performed at 270 days (DeltaNu, Laramie, WY). Carotenoid skin levels were measured in samples of the stratum corneum obtained from the palm and four interdigital webs of the hand. All measurements were made on the subject's dominant hand to ensure consistency in measurement. Prior to use, the spectroscope was calibrated against a polystyrene standard to ensure accuracy using a piece of polystyrene which has a peak of 1001.4 cm⁻¹. Each subject's hand was cleaned with an alcohol pad and allowed to air dry. Integration time was set to 20.0 seconds and the laser level was set to high for each measurement. For each location, the peak area for Raman intensity and the peak area ratio, as defined by the peak area for the carotenoid scan divided by the peak area for the Raman sapphire window scan, was analyzed. The analysis was carried out for the three wave lengths (cm⁻¹) that are specific for carotenoids, 1015, 1159, and 1524 cm⁻¹.

**Global Aesthetic Improvement Scale**
The Global Aesthetic Improvement Scale (GAIS) is a commonly used and efficacious tool that measures subjective changes in ap-
The GAIS is used to measure aesthetic improvement and consists of a categorical assessment using five responses: worse, no change, improved, much improved, or very much improved. Frontal facial photography was performed using a Nikon N90 Digital SLR Camera (Nikon, Tokyo, Japan). Prior to photography, all cosmetics on the face and hands were removed using tap water and a gentle cleanser. Images were printed onto paper for analysis using the GAIS. Both the investigator and subject were asked to grade aesthetic improvement using the GAIS by comparing the current visit photograph to the baseline photograph. The GAIS was performed on study days 60, 90, 180, and 270.

Physiological Measures

Transdermal water loss (TEWL) was determined to be the mean of three readings during a 10 second period using the VapoMeter (Delfin Technologies Ltd, Kuopio, Finland). Readings were obtained from the volar arm region of the subject’s dominant hand. The area was cleansed using an alcohol pad and allowed to air dry prior to measurement. TEWL measurement was performed at study entry and on study days 60, 90, 180, and 270.

Changes in the moisture content of the stratum corneum were determined to be the mean of three 10 second readings using the MoistureMeter SC (Delfin Technologies Ltd, Kuopio, Finland). Readings were obtained from the volar arm region of the subject’s dominant hand. The area was cleansed using an alcohol pad and allowed to air dry prior to measurement. Stratum corneum moisture measurement was performed at study entry and on study days 60, 90, 180, and 270.

Statistical Analysis

Data were assessed for normal distribution and skewed data were normalized using a natural log transformation. Significant differences in categorical demographic data were determined using Chi-squared analysis. Significant differences in the scale variables Compliance, MoistureMeter SC, VapoMeter and skin replica values were analyzed across the entire study period with repeated-measures ANOVA for between-subject effects of time, treatment, and time by treatment. The number of responses for each GAIS category was recorded and compared using a paired t-test. The data were then reassessed to evaluate differences in respondents reporting “no change” or “worse” with those who reported “more improvement” for each treatment. The replicate data was analyzed using repeated-measures ANOVA on log-transformed data for both major and minor line parameters. Raman-derived carotenoid values were compared between both treatment groups and for those “control” subjects who had not received either the placebo or active treatment. The data was analyzed at each of the five individual sites on the hand, and the combined data for the hand. Data are presented as Peak Area and Peak Area Ratio following log transformation and analyzed using a one-way ANOVA. Comparisons for all pairs used the Tukey-Kramer Honestly Significant Difference test omitting outliers greater than three standard deviations from the mean. The above analyses only included data from subjects who completed the entire 270-day study.

RESULTS

One hundred and eighteen (118) subjects were enrolled in the study and 76 subjects completed it, including 61 women and 15 men aged 30-77 years (mean: 52 ± 12 years). Subject race and ethnicity were Caucasian (n=51; 67%), African American (n=12; 16%), Hispanic (n=10; 13%) and Asian American (n=3; 4%). There were no significant between-group differences with respect to demographic profile.

Skin Profilometry

Table 1 shows mean (SD) values for skin replica data for parameters that assess both major and minor lines around the periorbital area. In analysis of minor lines, the number of wrinkles decreased (P=0.0194). In addition, there was a non-significant trend for Shadows (P=0.0823) for a time and treatment interaction. All measures had significant time interactions (P<0.001) and no significant treatment only interactions. No significant associations were found in assessment of major lines over the duration of the study; however, time-dependent interactions were observed for the parameters of Rz, Ra, spacing, shadows, and number of wrinkles (P<0.001). FSpace showed a non-significant trend for time only interaction (P=0.07).

Carotenoid Measurements

The data derived from the Raman analysis are presented in Table 2. Data for each site are presented as the peak area for Raman intensity and the peak area ratio, as defined by the peak area for the carotenoid scan, divided by the peak area for the Raman sapphire window scan. Of the three peaks specific to carotenoids (1015, 1159, and 1524 cm⁻¹), only peaks at 1159 cm⁻¹ and 1524 cm⁻¹ were detectable. These correspond to the two strongest carotenoid peaks found in human skin. There was a significant difference between the non-treated control group and the placebo and active treatment groups for Raman intensity peak area and peak area ratio for Site 1 (interdigital web between the thumb and index finger) (P<0.0001).

In addition, there were significant findings for Site 2 (interdigital web between the index and third finger) between the placebo and active treatment group, with the active treatment seemingly having a higher Raman intensity peak area (P=0.0375). A non-significant trend also was observed between the non-treat-
ed control group and the placebo treatment group ($P=0.0753$), suggesting non-treated controls also had higher Raman intensity peak areas than did placebo-treated subjects. The Raman intensity peak area ratio for this site indicated significant differences between the non-treated control and placebo-treated control groups ($P=0.007$) and between active-treated and placebo-treated subjects ($P=0.0127$).

Site 4 (interdigital web between the ring finger and the little finger) demonstrated significantly higher peak areas noted in the placebo-treated subjects compared to the non-treated controls ($P=0.0151$). Furthermore, higher peak areas were observed in the active-treated subjects compared to the non-treated controls ($P=0.0297$). There was also a non-significant trend observed between the active-treated subjects with higher peak area ratios and those present in the non-treated controls ($P=0.0762$).

No significant observations were noted for Site 3 (interdigital web between the third and ring fingers) or Site 5 (palm). Summation of all five sites only demonstrated non-significant trends, with active-treated subjects having higher peak areas and peak areas ratios compared to non-treated controls ($P=0.0723$).

**Global Aesthetic Improvement Scale**

The responses for subject and investigator responses to the GAI are summarized in Table 3. Significantly more subjects responded “worse” for the placebo group than active group ($P=0.019$). Active treatment subjects were significantly more likely to experience improvement as indicated by a response of “Improved,” “Much Improved,” or “Very Much Improved” than patients receiving placebo ($P=0.04$). No significance between groups was noted for the investigator GAI evaluation.

**Physiological Measures**

Table 4 indicates the mean (SD) for all subjects who completed the study for both placebo and active treatment groups for each visit of the study. The data relate to compliance, MoistureMeter SC, and Vapometer measures. No significance between treatment groups was noted for any of the physiological measurements.

**DISCUSSION**

It has previously been shown that the health and appearance of skin can be improved by eating foods rich in antioxidants, providing a strong rationale for the use of nutritional supplements to improve skin health. The lack of promising results from studies with individual vitamin supplementation suggests that a more complex mixture of ingredients may be required. This is supported by a strong body of evidence for the synergistic effect of combining pools of antioxidants such as vitamin E, vitamin C, and carotenoids with zinc — an important cofactor in many biological processes — on improved skin health. Due to the complexity of skin metabolism, it is unreasonable to expect a single nutrient to be the sole driver of dermal health. This provides a strong rationale for the multiple components used in SHEP. Most research of the interactions of nutrition and skin health has been done with study of diets rather than supplementation and have focused on strictly quantitative measures that represent skin health, but do not address overall aesthetic appearance. This study described here characterized the impact of specific nutrients and their impact on appearance as well as skin health.

The results of this double-blind, randomized, placebo-controlled trial suggest long-term oral administration of a whole food based nutritional supplement may improve the health and appearance of the skin.

Oxidative damage to skin is a by-product of aging caused by the accumulation of reactive oxygen species (ROS) produced by normal oxygen metabolism. These include free radicals and molecules that behave as free radicals such as hydrogen peroxide and singlet oxygen. A variety of factors such as poor diet, smoking, and excessive sun-exposure can lead to greater levels of ROS production and increased levels of skin damage. Exposure to ultraviolet (UV) light results in an accumulation of ROS, which causes oxidative damage to the skin and depletes antioxidant levels, a process described as photoaging. UV irradiation can also produce ROS which damage proteins, lipids and DNA mutations. By excluding genetic causes, studies in twins have shown that skin aging is greatly affected by excess sun exposure and exposure to high levels of oxidizing agents has been shown to severely age skin.

The existing evidence demonstrates that antioxidants are a critical component for the maintenance of skin health by combating the detrimental effects of oxidative damage. Hence, it is likely that higher concentrations of antioxidants in the skin will lead to improvements in skin appearance. One of the challenges with nutritional supplementation is providing sufficient nutrients in an acceptably small dosage form. The dosing of SHEP was designed to achieve an adequate level of targeted food-based nutrients within a minimal number of capsules. Doses of individual nutrients were at or below those used in the literature with the idea that synergy of action and contribution of the diet as a whole would have more benefit than isolated high-dose nutrients. Patients were prescribed two capsules of SHEP twice daily with meals.

Due to its high lipid-to-protein concentration ratio, the stratum corneum was determined to be a likely site for the intercalation of lipophilic carotenoids into the cell membranes and for their
aid in protecting against membrane damage caused by ROS resulting from UV exposure. The Resonance Raman technique has previously been shown to be an accurate measurement of carotenoids, providing a general profile of antioxidants in the skin. Based on Raman-derived carotenoid data, we demonstrated a significant increase in the level of carotenoids in the active treatment group compared to the placebo group in the interdigital web between the index finger and the third finger. While the active treatment groups had higher carotenoids peaks and peak area ratios than the non-treated group, there was no significant difference when compared to the placebo group. This may be the result of high degree of inter- and intra-subject measurement variability previously reported, making it impossible to discern a significant increase in carotenoids levels.

Decreased transepidermal water loss and increased water retention are indicative of improved skin health. Water-rich skin layers and the stratum corneum are highly conductive and act as an electric capacitor. The moisture value is proportional to the water content of the stratum corneum, with higher values correlating to a more hydrated skin surface.

### TABLE 1.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 60</th>
<th>Day 90</th>
<th>Day 180</th>
<th>Day 270</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Lines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>143 (35)</td>
<td>146 (34)</td>
<td>156 (34)</td>
<td>143 (34)</td>
<td>137 (43)</td>
<td>137 (76)</td>
</tr>
<tr>
<td>Active</td>
<td>160 (37)</td>
<td>152 (37)</td>
<td>160 (34)</td>
<td>143 (34)</td>
<td>137 (43)</td>
<td>137 (76)</td>
</tr>
<tr>
<td>Rz</td>
<td>29 (8)</td>
<td>34 (11)</td>
<td>34 (13)</td>
<td>29 (8)</td>
<td>29 (12)</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Ra</td>
<td>2.0 (0.4)</td>
<td>2.0 (0.5)</td>
<td>1.8 (0.7)</td>
<td>1.9 (0.4)</td>
<td>2.0 (0.8)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>Fspace</td>
<td>0.43 (0.1)</td>
<td>0.45 (0.1)</td>
<td>0.44 (0.2)</td>
<td>0.43 (0.1)</td>
<td>0.44 (0.2)</td>
<td>0.45 (0.1)</td>
</tr>
<tr>
<td>FNum</td>
<td>1.09 (0.7)</td>
<td>1.16 (0.6)</td>
<td>1.18 (0.7)</td>
<td>1.17 (0.6)</td>
<td>1.29 (0.7)</td>
<td>1.57 (0.9)</td>
</tr>
<tr>
<td>Spacing</td>
<td>0.23 (0.04)</td>
<td>0.24 (0.05)</td>
<td>0.26 (0.07)</td>
<td>0.26 (0.12)</td>
<td>0.24 (0.05)</td>
<td>0.26 (0.08)</td>
</tr>
<tr>
<td>Breadth</td>
<td>9.8 (5.5)</td>
<td>9.6 (6.0)</td>
<td>11.4 (7.7)</td>
<td>11.4 (8.1)</td>
<td>8.7 (4.5)</td>
<td>8.5 (6.4)</td>
</tr>
<tr>
<td>Shadows</td>
<td>146 (64)</td>
<td>129 (59)</td>
<td>134 (61)</td>
<td>130 (62)</td>
<td>115 (48)</td>
<td>98 (56)</td>
</tr>
</tbody>
</table>

|                  |          |        |        |         |         |     |
| **Minor Lines**  |          |        |        |         |         |     |
| Placebo          | 145 (34)| 132 (39)| 135 (27)| 134 (28)| 121 (29)| 123 (29)| 117 (36)| 120 (29)| 109 (31)| 117 (30)| NS  |
| Active           | 29 (8)  | 27 (10)| 27 (6) | 27 (7)  | 24 (7)  | 25 (7)  | 24 (9)  | 25 (8)  | 22 (8)  | 24 (7)  | NS  |
| Rz               | 1.9 (0.5)| 2.0 (0.5)| 1.9 (0.4)| 1.9 (0.5)| 1.9 (0.4)| 1.9 (0.4)| 1.9 (0.4)| 1.9 (0.5)| 2.0 (0.3)| 1.9 (0.4)| NS  |
| Ra               | 0.47 (0.1)| 0.46 (0.2)| 0.46 (0.1)| 0.47 (0.1)| 0.44 (0.1)| 0.45 (0.1)| 0.45 (0.1)| 0.45 (0.1)| 0.43 (0.1)| 0.44 (0.1)| NS  |
| Fspace           | 1.28 (0.7)| 1.51 (1.0)| 1.55 (0.8)| 1.48 (0.9)| 1.75 (0.9)| 1.56 (0.9)| 1.77 (0.9)| 1.87 (0.9)| 2.19 (1.2)| 1.78 (0.8)| NS  |
| FNum             | 0.22 (0.05)| 0.22 (0.05)| 0.20 (0.04)| 0.20 (0.05)| 0.20 (0.04)| 0.20 (0.05)| 0.20 (0.04)| 0.22 (0.06)| 0.21 (0.05)| 0.22 (0.06)| NS  |
| Spacing          | 8.7 (6.1)| 6.9 (5.4)| 5.8 (4.4)| 6.4 (4.7)| 4.2 (3.2)| 5.2 (4.3)| 3.6 (3.3)| 4.4 (4.0)| 3.8 (3.8)| 4.2 (3.7)| 0.08 |
| Breadth          | 129 (67)| 107 (69)| 92 (53)| 102 (66)| 69 (44)| 80 (52)| 60 (46)| 61 (41)| 52 (44)| 61 (42)| 0.02 |

n=38 per treatment group for each visit. Statistical analysis performed on log transformed data. P = time*treatment interaction using repeated measures ANOVA. Rz, Ra, Spacing, Shadows, and NumWr showed significant time only interactions (P<0.001), and all variables showed non-significant treatment only interactions. FSpace showed a trend towards significance for time only interactions (P=0.0722). NS, not significant.
matology and academic skin research as a valid means of measurement for transepidermal water loss. Although there was no significant difference observed in the skin hydration of the active treatment group compared to the placebo group, we believe significant changes in skin hydration may have been masked by wide inter- and intra-subject variability. Nuutinen et al. observed a coefficient of variation of 8 percent following 10 repeated measures on the volar region of the forearm and noted reproducibility values of 3-8 percent for the Vapometer instrument. Other investigators observed standard deviations of 2-5 percent for repeated individual measurements on subjects in their comparative study using the MoistureMeter SC. Similarly, the standard deviations observed in our subjects for both the MoistureMeter SC and Vapometer were at least half of the mean values observed for several of the time points from both placebo and active groups. While attempts were made to standardize testing conditions such as room temperature and humidity, environmental factors and seasonal changes could have contributed to the large variance observed.

Skin profilometry is an effective method for measuring skin topography and comparing changes over time, such as wrinkle reduction and skin appearance improvement. The sensitivity of this technique to subtle changes in the skin surface makes it a valuable tool for assessing changes in the prominence of wrinkles. The skin replica data demonstrates a significant finding in comparing the reduction of fine lines around the crow’s feet area in those subjects who received the active treatment compared to placebo-treated subjects. While the exact mechanism is unknown, the active ingredients in SHEP may affect processes at a cellular level, leading to a gradually improved environment for collagen regeneration and a decreased number of wrinkles.

Compared with control subjects, individuals treated with SHEP perceived a significant improvement in the overall appearance of their skin, as demonstrated by the GAIS data. There was a three-fold greater likelihood of participants in the active treatment group to describe their appearance as "Improved" compared to "Worse" or "No Change." Patient satisfaction is a key component of any aesthetic intervention and an improved appearance was an important finding. This is especially true where compliance is greatly dependent on subject motivation. Although our blinded evaluator did not see an improvement in GAIS, improvements in appearance are often subtle and difficult to perceive. Patients may be able to detect the subtle changes in their appearance because of greater familiarity with

### TABLE 2.

<table>
<thead>
<tr>
<th>Raman Carotenoid Values*</th>
<th>Non-treated</th>
<th>Placebo</th>
<th>Active</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Area</td>
<td>15816 (10285)</td>
<td>4392 (4430)</td>
<td>5617 (4082)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak Area Ratio</td>
<td>0.025 (0.024)</td>
<td>0.007 (0.008)</td>
<td>0.009 (0.007)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Site 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Area</td>
<td>11383 (7943)</td>
<td>8593 (6517)</td>
<td>12567 (9720)</td>
<td>0.0375 (0.0753)</td>
</tr>
<tr>
<td>Peak Area Ratio</td>
<td>0.015 (0.012)</td>
<td>0.010 (0.007)</td>
<td>0.015 (0.011)</td>
<td>0.0070; 0.0127</td>
</tr>
<tr>
<td><strong>Site 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Area</td>
<td>10844 (11439)</td>
<td>16730 (8442)</td>
<td>17139 (10834)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak Area Ratio</td>
<td>0.017 (0.021)</td>
<td>0.022 (0.012)</td>
<td>0.026 (0.021)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Site 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Area</td>
<td>10111 (9503)</td>
<td>15993 (11249)</td>
<td>18517 (12183)</td>
<td>0.0151; 0.0297</td>
</tr>
<tr>
<td>Peak Area Ratio</td>
<td>0.013 (0.012)</td>
<td>0.023 (0.018)</td>
<td>0.027 (0.018)</td>
<td>0.0762</td>
</tr>
<tr>
<td><strong>Site 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Area</td>
<td>10681 (7286)</td>
<td>13510 (11077)</td>
<td>15001 (11866)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak Area Ratio</td>
<td>0.015 (0.010)</td>
<td>0.026 (0.036)</td>
<td>0.051 (0.169)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Combined Sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Area</td>
<td>11649 (5548)</td>
<td>11843 (5124)</td>
<td>13768 (6287)</td>
<td>0.0827</td>
</tr>
<tr>
<td>Peak Area Ratio</td>
<td>0.017 (0.009)</td>
<td>0.018 (0.011)</td>
<td>0.026 (0.036)</td>
<td>0.0723</td>
</tr>
</tbody>
</table>

* Subjects completing the study by treatment group for wavelength 1159 cm⁻¹ at each of five sites on the hand and also combine. Outliers greater than 3 standard deviations were excluded. NS, not significant.
aesthetic details of their own face. Alternatively, improvements in the patient-reported GAIS might also be attributed to changes in the patient self-esteem or mood. While improved GAIS rating support the hypothesis that SHEP improved the health and appearance of the skin, it is also possible that the SHEP intervention resulted in improvements in the subject’s psyche, making them feel better about their skin. In some respects, this may be one of the most critical findings of our study. Since changes in objective aesthetic measures are difficult to identify, statistically significant improvements in GAIS among SHEP-treated subjects is a relevant finding.

Conducting clinical studies to determine the benefits of a nutritional supplement on the skin has several limitations. Patient compliance with the treatment cannot always be verified, possibly reducing the actual sample size and statistical robustness. Additionally, the Investigator GAIS scores may have been skewed by the use of a single evaluator.

Summary
The results of this double-blind, randomized, placebo-controlled trial suggest long-term oral administration of a whole food based nutritional supplement may improve the health and appearance of the skin. Further research and commitment

<table>
<thead>
<tr>
<th>TABLE 3. Subject and Investigator GAIS Number of Responses for Each Effect Over the 9-Month Duration</th>
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</thead>
<tbody>
<tr>
<td>Subject GAIS</td>
</tr>
<tr>
<td>Worse</td>
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<tr>
<td>No Change</td>
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<tr>
<td>Improved</td>
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<td>Much Improved</td>
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<td>Very Much Improved</td>
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<td>No or less improvement</td>
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<tr>
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NS, not significant

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<tr>
<td>N</td>
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<td>Placebo</td>
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<tr>
<td>Compliance (%)</td>
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<tr>
<td>Moisture (a.u)</td>
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<tr>
<td>Vapometer (g/m^2h)</td>
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<tr>
<td>Active</td>
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<tr>
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to understanding the role of oral nutritional supplements on health and appearance of the skin is warranted.

**DISCLOSURES**

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