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CoffeeBerry: A New, Natural Antioxidant in Professional Antiaging Skin Care

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CoffeeBerry: A New, Natural Antioxidant in Professional Antiaging Skin Care

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Damage caused by excess free radicals on the skin surface and within skin cells may clinically manifest as fine lines, wrinkles, dyschromia (especially hyperpigmentation), and loss of skin tone. Topical antioxidant skin care products may repair as well as protect against these changes induced by oxidative stress, commonly called environmental damage (photoaging and photodamage). Data from 2 randomized, clinical trials, including a proof-of-concept study and a comparative study, of a new daily skin care regimen (RevaléSkin™) containing the superpotent antioxidant CoffeeBerry® were presented for a roundtable discussion. The data indicated that the regimen improved signs of photoaging and photodamage and increased skin barrier function. Longer-term clinical trials of this regimen are planned.

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The importance of oxidative stress in photoaging and as a mechanism of environmental and UV light damage in the skin is widely acknowledged. The potential of topical antioxidant skin care products to repair and prevent signs of photoaging and photodamage was the topic of a recent roundtable discussion among expert dermatologic clinicians and researchers. Data from 2 randomized, clinical trials on the efficacy and safety of RevaléSkin™, a unique skin care product line containing the potent antioxidant CoffeeBerry, were presented. This article summarizes these data.

ANTIOXIDANTS IN SKIN CARE

The processes of photoaging and photodamage of the skin are intimately related to oxidative stress caused by reactive oxygen species. The sources of free radicals affecting the skin are both intrinsic cellular metabolic processes (eg, production and breakdown of adenosine triphosphate) and extrinsic, or environmental, factors (eg, UV light exposure, ozone and other pollutants, smoking, poor dietary habits, stress, illness, and physical inactivity).[1] The epidermal layer and stratum corneum contain natural antioxidants, including vitamins C and E, ubiquinones, carotenoids, uric acid, and glutathione.

These compounds act synergistically as a cooperative network to intervene in harmful oxidative processes and maintain equilibrium within the cell. When the antioxidant system is overwhelmed by intrinsic or extrinsic factors, oxidative damage to lipids, proteins, and DNA results.[2]

In particular, free radical–induced DNA mutations alter expression of enzymes that affect collagen levels, as well as the expression of collagen itself. Damaged collagen and elastin weaken the dermal connective tissue so that the epidermis is not supported, resulting in skin wrinkling, laxness, and fragility. In addition, production and turnover of new skin cells are slowed, so old cells stay on the surface longer. These deficits result in a dull, lifeless appearance in older skin.

Another outcome of oxidative stress is melanocytic overproduction of melanosomes that are not evenly distributed throughout the skin because of slow cell turnover, resulting in mottled pigmentation and distinct dark spots. DNA mutations may also produce abnormal keratinocytes that cause disorganized epidermal structure and even malignant degeneration.

Topical antioxidants have the potential to oppose the deleterious effects of oxidative stress by quenching free radicals on the skin surface before they penetrate through cell membranes. Lipid-soluble compounds with antioxidant activity may also penetrate cell membranes to protect interior portions of the cells from free radical–induced damage.[1] In addition, topical antioxidants may increase the natural antioxidant capacity through synergism within the cooperative antioxidant network.[2,3] Thus, the oxidative effects of natural aging, as well as those of environmental damage, may be reversed and future damage prevented through the use of topical antioxidants. Restorative effects of topical antioxidants include reductions in fine lines and wrinkles, decreased dyschromia, and smoothing of irregular or rough texture. Preventive effects include quenching of free radicals before damage occurs and defending against environmental factors, especially UV light exposure.[1]

Many dermatologists may be aware of the protective benefits of antioxidant ingredients in skin care products but less aware of the potential for reparative effects on aging skin. In contrast to the copious literature on sunscreens and retinoids, for example, many data on the effects of antioxidants on skin are not found in general dermatology journals. Consequently, there may be confusion about how antioxidants function and what characteristics are most important to dermatologists and patients. In addition, exactly how and when topical antioxidants should be incorporated into skin care regimens for maximum effectiveness may not be well understood.

Important characteristics of an ideal antioxidant skin care formulation include stability in the presence of light and oxidative conditions, lack of allergenic and irritative qualities, and cosmetic elegance. In addition, the ideal formulation should be well tolerated to avoid stimulating or aggravating sensitive skin conditions, such as rosacea, or compromising use of retinoids. With these features, several kinds of dermatologic patients may benefit from topical antioxidants. Fair-skinned patients who have had considerable lifetime sun exposure and now exhibit the cosmetic effects of photoaging or smoking are an important consideration. Darker-skinned patients, who may have fewer problems with fine lines and wrinkles but more problems with hyperpigmentation that is worsened by sun exposure, may also be appropriate candidates for topical antioxidants. Patients who are unable or unwilling to use retinoids may also be considered for antioxidants. In particular, concomitant antioxidant therapy may improve the tolerability of retinoids for some patients. Finally, patients who have had skin cancer may benefit from the photoprotective activity of topical antioxidants.

CLINICAL EFFECTIVENESS OF ANTIOXIDANTS IN SKIN CARE

Clinically, the effects of antioxidants on skin may be assessed by serial photography, including standard-light, cross-polarized, parallel-polarized, and UV techniques. Biopsy samples are also used for measuring changes in classic histology and immunofluorescent markers. Finally, changes in gene expression assessed from studies of in vitro polymerase chain reactions may be used to measure levels of important proteins in skin (eg, collagens, metalloproteinases, collagenases, and inflammatory markers) during incubation with antioxidant compounds.

Additional methods exist for measuring antioxidant efficacy for protection against free radicals and comparing the antioxidant capacity of specific substances. The most important of these methods is the oxygen radical absorbance capacity (ORAC) assay on antioxidant capacity. The ORAC assay, developed in 1993,[4] is accepted by the United States Department of Agriculture for comparing the activity of natural substances against reactive oxygen species.[5] The ORAC assay measures how well water-soluble and lipid-soluble components of a natural substance protect a standardized target from oxidation by peroxyl radicals and generates a score based on comparison with an antioxidant control. This method allows direct comparison of the substances in question and has been widely

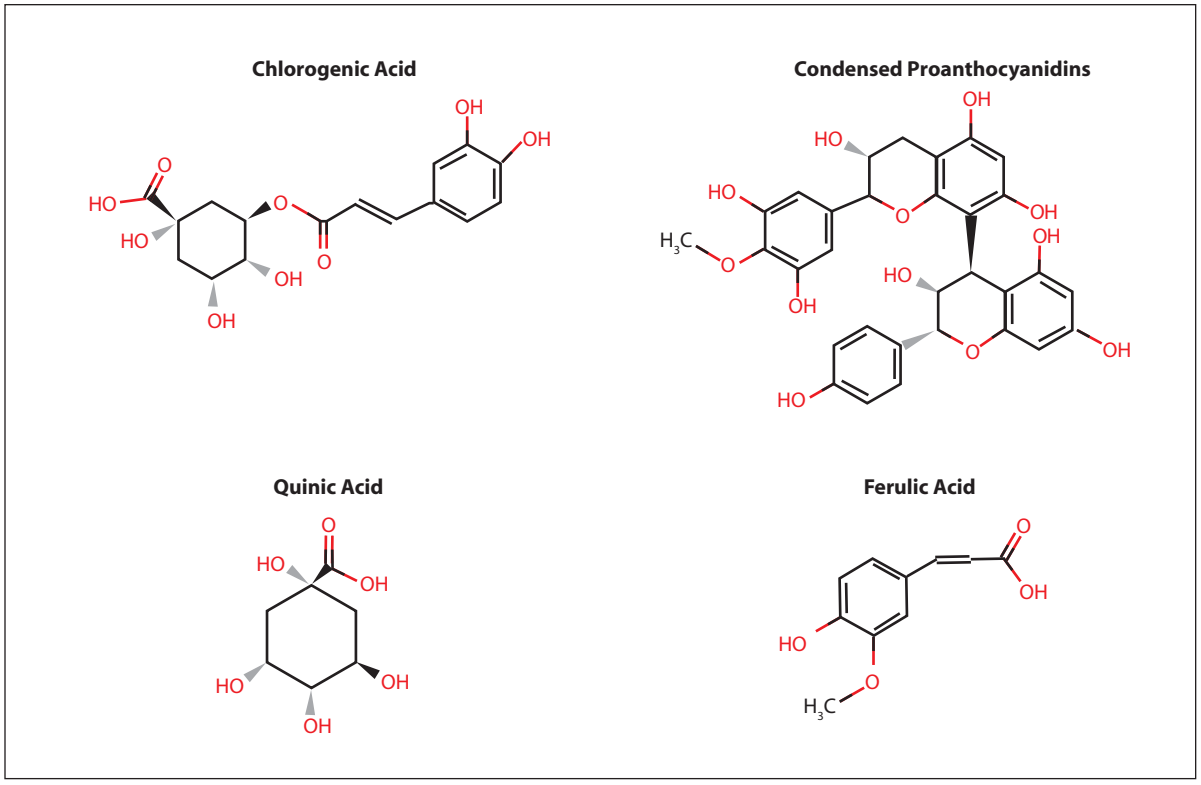

Figure 1. Structures of natural polyphenolic antioxidants found in CoffeeBerry.

used to evaluate the antioxidant activities of foods and other natural substances.[5]

It should be noted that the ORAC score may be used to evaluate the antioxidant activity of active ingredients in skin care products and does not provide information on potential allergenic or irritative qualities of a new formulation. However, given similar secondary characteristics of the final formulation (eg, moisturizing and sunscreen capacity), the ORAC score may be used to compare antioxidant skin care products to indicate a formulation that provides superior efficacy for protection against free radical–induced sun and environmental damage.

COFFEEBERRY: A NATURAL ANTIOXIDANT

CoffeeBerry is a proprietary extract of the subripe berry of the plant *Coffea arabica*, from which the familiar ripened and roasted coffee bean is also derived. The harvest time of the berry is crucial to obtaining the maximum antioxidant activity and avoiding contamination with mycotoxins that often occurs later in the ripening process. The entire berry is crushed and processed specifically for its antioxidant compounds.

CoffeeBerry is rich in natural polyphenolic antioxidants, including condensed proanthocyanidins and chlorogenic, quinic, and ferulic acids (Figure 1).[6] Polyphenolic antioxidants help to prevent damage caused by free radicals and oxidative stress.[6,7] In addition, polyphenols may interact directly with cellular receptors to alter signal transduction pathways that affect the redox status of the cell.[8] Ferulic acid is the most familiar of these compounds for skin care because of its known photoprotective properties.[9]

Comparison of natural CoffeeBerry with other antioxidant-containing formulations and antioxidant compounds according to the ORAC score showed

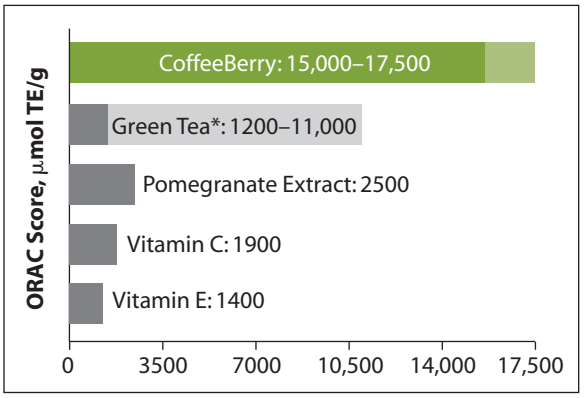

Figure 2. Oxygen radical absorbance capacity (ORAC) scores of CoffeeBerry and other common sources of antioxidant activity. Asterisk indicates commercially available green teas are included.

Protocol for Use of CoffeeBerry Products in Clinical Trials

- RevaléSkin Day Cream and Night Cream with 1% CoffeeBerry once daily in the morning and evening, respectively
- RevaléSkin Facial Cleanser with 0.1% CoffeeBerry once in the morning and once in the evening, before application of the Day Cream or Night Cream
- Use of any soap, facial cleanser, topical medications, or moisturizer on the face other than those provided for the study was prohibited
- Procedures to the face (eg, facials, microdermabrasion, laser treatments) were not permitted during the study
- Subjects were not permitted to apply cosmetics before study visits
- Sunbathing, use of tanning beds and sunlamps, and excessive exposure to UV light were prohibited during the study
- Products were self-applied; subjects were to avoid contact of the products with eyes and all mucous membranes and wash their hands after each application

that water-soluble and lipid-soluble components of CoffeeBerry had substantially more capacity to scavenge free peroxyl radicals (Figure 2).[10-14]

CLINICAL EFFICACY AND SAFETY

A unique formulation of natural CoffeeBerry was studied in a new antiaging skin care line. The daily 3-step system consists of a facial cleanser containing 0.1% CoffeeBerry, a day cream containing 1% CoffeeBerry and sunscreen with a sun protection factor of 15, and a night cream containing 1% CoffeeBerry.

A double-blind, proof-of-concept study was initiated to establish the efficacy and safety of the formulation and protocol. A cohort of 30 women aged 30 years or older with moderate photoaging were enrolled. Subjects were required to discontinue all other photoaging products and could not have other medical conditions or be taking medications that would interfere with the study. Subjects were randomized to use the CoffeeBerry products on the whole face daily for 6 weeks (n=20) or use the products and appropriate vehicles daily for 6 weeks in a split-face design with a vehicle on one side of the face and the study products on the other (n=10; randomized to use active treatment on the left side [n=5] or right side [n=5] of the face). The protocol

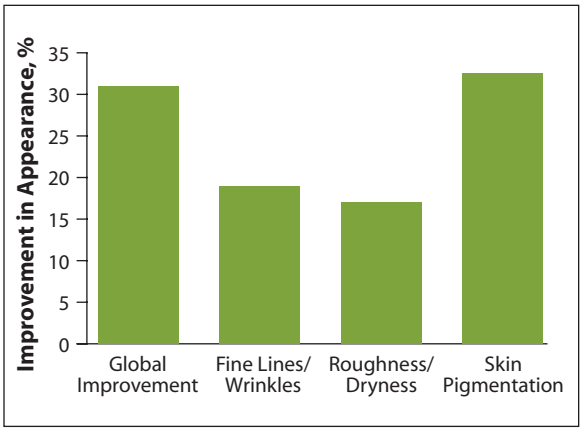

Figure 3. Blinded expert evaluation of global and specific improvement from baseline after 6 weeks of daily use of CoffeeBerry products on the full face.

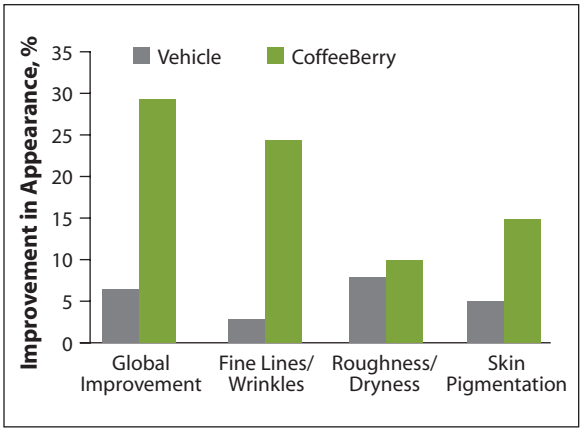

Figure 4. Blinded expert evaluation of improvement associated with daily use of CoffeeBerry products and vehicle in a split-face study design for 6 weeks.

for the use of the study products is detailed in the Table.

The end points of the trial were photography evaluation (standard-light digital and cross-polarized UV photography) and adverse events. Split-face and full-face photographs were taken at baseline and weeks 3 and 6. In addition, 4 subjects in the split-face group were recruited for biopsy studies. Biopsies were obtained from the lateral orbital area, adjacent to the hairline, on both the right and the left sides of the face and stained for standard histology, collagens I and IV, matrix metalloproteinase 1, and interleukin 1β1. Patient diaries and subjective reporting at study visits revealed adverse events.

Blinded expert evaluation of baseline and week-6 photographs from full-face subjects (n=14) showed global improvement of skin appearance, as well as improvement of fine lines and wrinkles, roughness and dryness, and skin pigmentation (Figure 3). In the split-face subjects at 6 weeks (n=10), skin treated

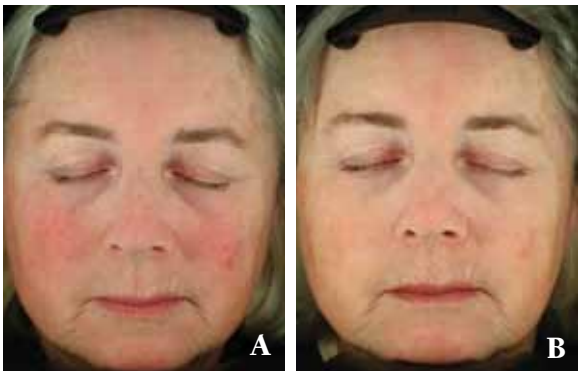

Figure 5. Patient treated with CoffeeBerry on the right side of the face and vehicle on the left at baseline (A) and after 6 weeks (B). Photographs courtesy of David H. McDaniel, MD.

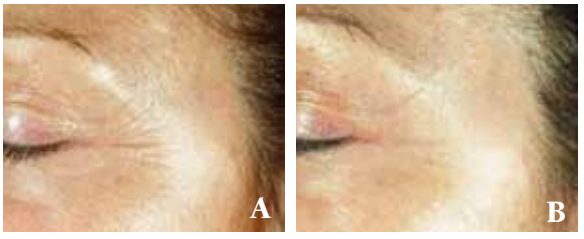

Figure 6. Appearance of crow's-feet at baseline (A) and after 6 weeks of daily use of CoffeeBerry on the left side of the face (B). Photographs courtesy of David H. McDaniel, MD.

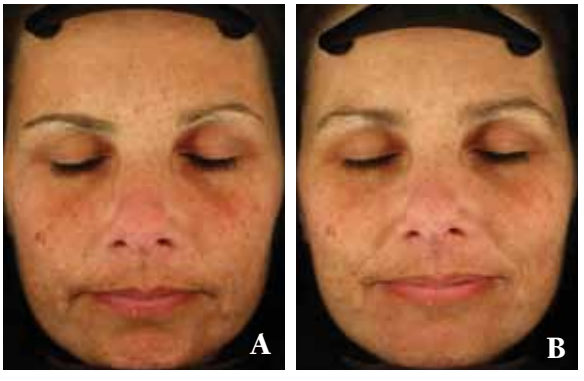

Figure 7. Appearance of pigmentation at baseline (A) and after 6 weeks of daily use of CoffeeBerry on the full face (B). Photographs courtesy of David H. McDaniel, MD.

with vehicle was compared with skin treated with the CoffeeBerry products in photographs taken at baseline and 6 weeks; greater improvement was shown on the CoffeeBerry side (Figure 4). Of interest, similar improvement of roughness and dryness was observed for both the side of the face treated with vehicle and the side of the face treated with CoffeeBerry, indicating the moisturizing effect of the vehicle and the additional benefit of daily treatment with CoffeeBerry for fine lines, wrinkles, and skin pigmentation.

Overall, the comparison of CoffeeBerry products with vehicle indicated a 3-fold improvement in skin pigmentation, a 4-fold improvement in overall skin appearance, and a 10-fold improvement in fine lines and wrinkles on the side of the face treated with CoffeeBerry. The appearance of photodamage (Figure 5) and crow's-feet (Figure 6) was reduced on the side of the face treated with CoffeeBerry, and pigmentation was improved (Figure 7) after 6 weeks of daily use of CoffeeBerry.

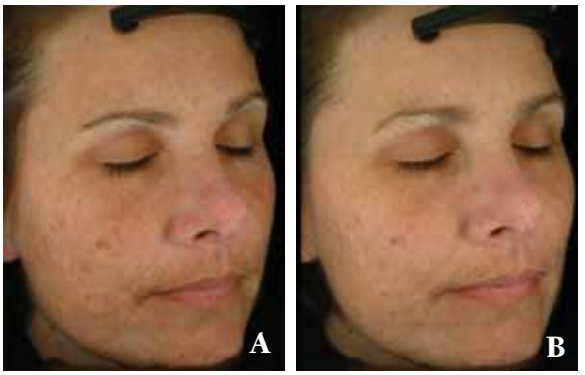

Figure 8. Standard-light photography showing erythema at baseline (A) and after 6 weeks of use of CoffeeBerry (B). Photographs courtesy of David H. McDaniel, MD.

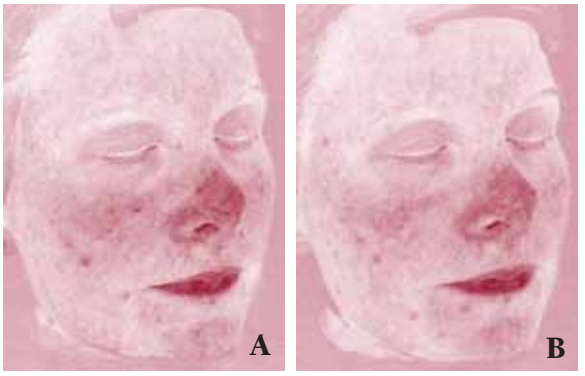

Figure 9. Polarized-light photography showing erythema at baseline (A) and after 6 weeks of daily use of CoffeeBerry (B). Photographs courtesy of David H. McDaniel, MD.

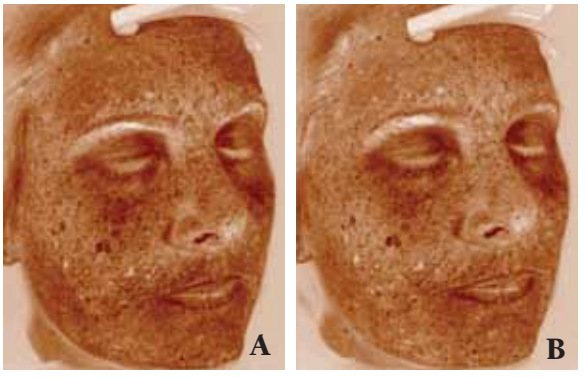

Figure 10. UV photography showing appearance of pigmentation at baseline (A) and after 6 weeks of daily use of CoffeeBerry (B). Photographs courtesy of David H. McDaniel, MD.

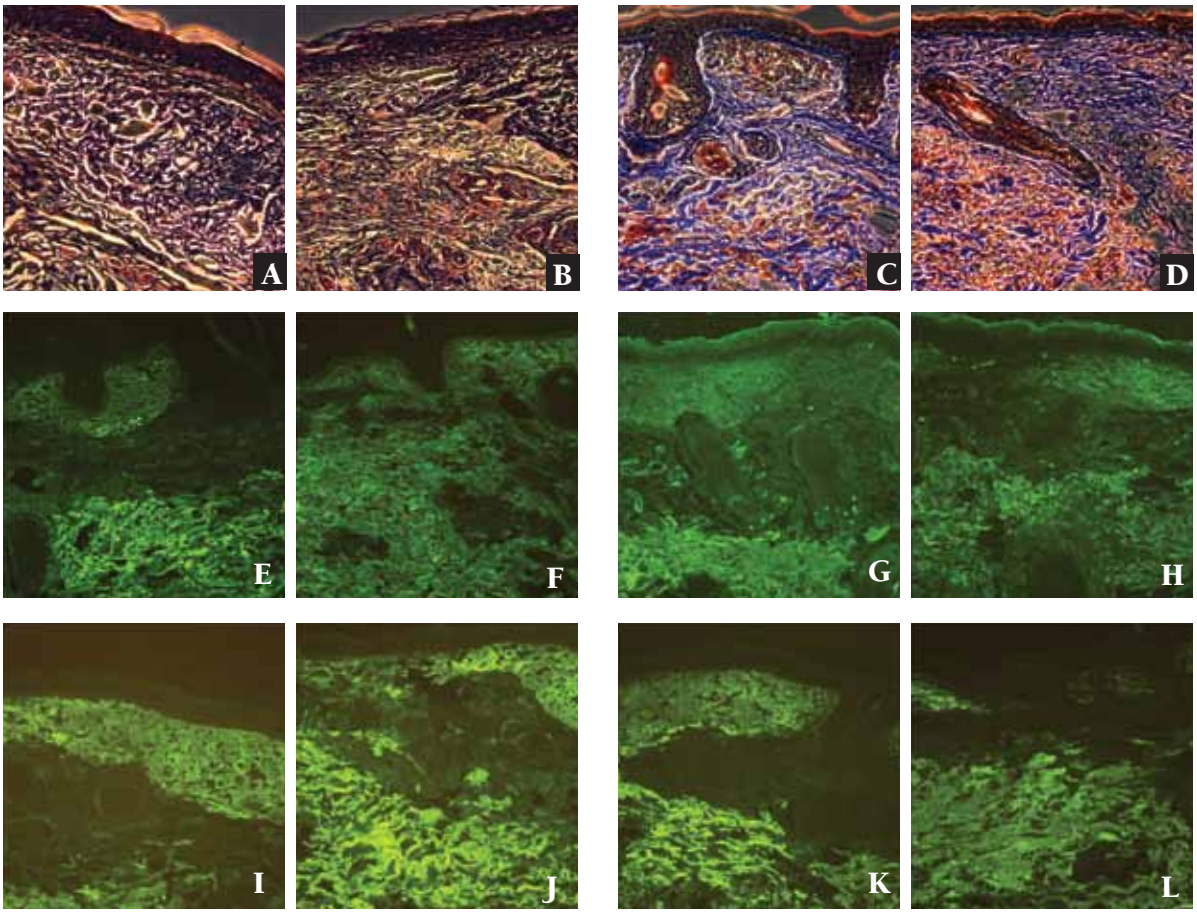

Figure 11. Histologic study of biopsy samples from a 65-year-old subject who had smoked for more than 40 years at baseline (A, C, E, G, I, K) and after 6 weeks of daily use of CoffeeBerry (B, D, F, H, J, L) using H&E staining (original magnification ×20) (A, B), high-magnification Masson staining (original magnification ×10; collagen stains shown in blue) (C, D), immunostaining for collagen I (original magnification ×10) (E, F), immunostaining for matrix metalloproteinase I (original magnification ×10) (G, H), immunostaining for collagen IV (original magnification ×10) (I, J), and immunostaining for interleukin 1β1 (original magnification ×10) (K, L). Photographs courtesy of David H. McDaniel, MD.

Standard-light photography (Figure 8) and polarized-light photography (Figure 9) showed improvement of erythema. UV photography showed improvement of pigmentation (Figure 10).

These photographs showed that even older subjects in this cohort had marked improvement of the appearance of fine lines and wrinkles with daily use of the CoffeeBerry products Also, it should be noted that the potential for improvement of skin pigmentation may be understated in subjects with more hyperpigmentation because of the marked benefit observed in this cohort of subjects with little or no hyperpigmentation at baseline.

Although this cohort included subjects with sensitive skin, no allergic or irritative reactions were observed. Four subjects experienced mild erythema and burning; these reactions were transient in 3 of the subjects. One subject had mild peeling; 6 subjects reported mild acne flare-ups. Two acne flare-ups resolved with continued daily use of the study products.

Figure 11 shows a representative series of biopsy comparisons from a 65-year-old subject who had smoked for more than 40 years. These studies, which were performed on 4 subjects in the split-face group, indicated no significant changes in basic histology of the dermal layer over 6 weeks (Figure 11A and 11B). Nonspecific and specific staining for collagen showed increased collagen overall (Figure 11C and 11D) and in collagen I (Figure 11E and 11F) and matrix metalloproteinase I (Figure 11G and 11H). Further, staining for collagen IV (Figure 11I and 11J) and interleukin 1β1 (Figure 11K and 11L) was decreased.

These results were confirmed by in vitro gene expression studies, which indicated upregulation by 60% or more in the following genes during incubation of keratinocytes with CoffeeBerry: collagens 12a1, 14a1, 15a1, and 16a1; connective tissue growth factor; laminin γ1; thrombospondin 2; and vascular cell adhesion molecule 1. Further,

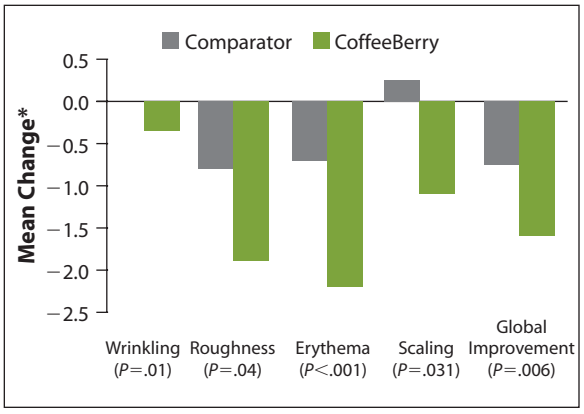

Figure 12. Blinded expert evaluation of changes from baseline after 12 weeks of daily use of CoffeeBerry or the comparator. Asterisk indicates changes based on a scale of 0–5, where 0=no change and 5=severe change.

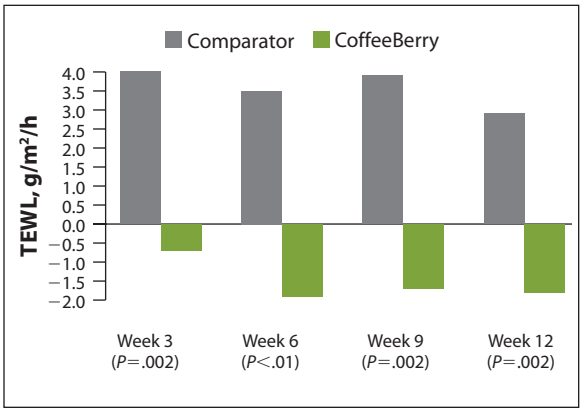

Figure 13. Comparison over time of transepidermal water loss (TEWL) in subjects who used CoffeeBerry or the comparator for 12 weeks.

incubation with CoffeeBerry resulted in downregulation of fibronectin 1, integrin α5, and matrix metalloproteinases 1, 13, and 15 in keratinocytes.

Although the clinical significance of these gene expression findings is currently under active investigation, it appears that CoffeeBerry has the ability to positively affect keratinocyte incubation gene expression consistent with its known antioxidant properties.

Clinical observations from this proof-of-concept study indicate notable improvement of fine lines and wrinkles after 6 weeks of daily use of the CoffeeBerry products in subjects with moderate photodamage. It was concluded that improvement of skin pigmentation and photodamage was not only from the effects of moisturization, as shown in the vehicle-controlled portion of the study.

A 12-week, double-blind, clinical study was performed under the leadership of Z. Draelos, MD, to compare the study products with a dual-treatment comparator containing an equivalent sunscreen component (sun protection factor of 15) similar to that of the CoffeeBerry system. The study population consisted of 50 women aged 30 years or older with moderately photodamaged skin who were randomized to use the study products as specified in the Table or the comparator system, which consisted of a mild cleansing wash and dual-treatment moisturizing lotion.

Split-face and full-face photography and assessment of skin hydration using corneometry and analysis of transepidermal water loss (TEWL) were performed at baseline and weeks 3, 6, 9, and 12. Profilometry to assess fine wrinkles with silicone casts of the lateral orbital area was performed at baseline and weeks 6 and 12. The primary tolerability end point was investigator-assessed absence of erythema and irritation after 12 weeks of daily use of the study products The primary efficacy end point was investigator-assessed improvement of overall appearance at week 12 compared with baseline; the secondary efficacy end point was subject-assessed improvement of overall skin appearance at week 12 compared with baseline.

At week 12, blinded expert evaluation showed statistically significant changes from baseline in wrinkling, roughness, erythema, scaling, and global improvement of the subjects using the CoffeeBerry products versus the comparator (Figure 12). Analysis of effects over time of daily use of the 2 regimens showed no statistically significant differences between the groups at week 3. However, at week 6, a significant improvement of skin roughness (P=.044) and erythema (P=.003) was observed in the CoffeeBerry group; at week 9, a significant improvement of skin wrinkling (P=.010) and global assessment (P=.007) was also observed. At week 12, all criteria were significantly more improved in the CoffeeBerry group than in the comparator group. These observations indicate comparable results between the 2 groups in the moisturizing phase (through week 3) and superior results in the CoffeeBerry group in exfoliant effects in weeks 6 through 12 of the trial.

Instrumental analysis of TEWL showed that the moisturizer component of the study products was significantly more effective at reducing TEWL than the comparator at all time points (Figure 13). Corneometry measurements of skin hydration did not change from baseline and were equivalent between the groups at all time points, as expected in a cohort of subjects with normal, as opposed to dry, skin. Corneometry measurements showed that neither regimen reduced skin barrier function or induced disease during the 12-week study. No

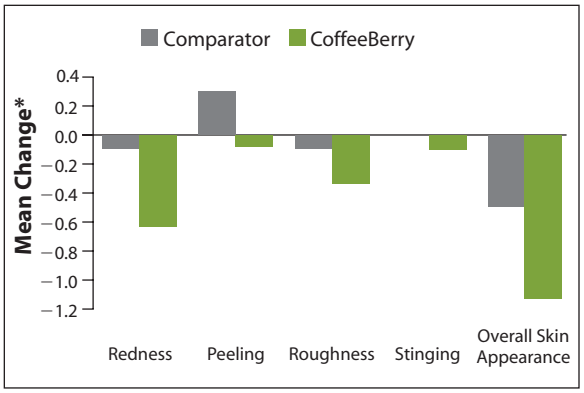

Figure 14. Subject evaluation of skin appearance after daily use of CoffeeBerry or the comparator system for 12 weeks. Asterisk indicates changes based on a scale of 0–5, where 0=no change and 5=severe change.

serious adverse events or allergic reactions were reported. Four subjects (3 in the CoffeeBerry group and one in the comparator group) had acne flare-ups that did not, however, warrant discontinuation from the study.

These data suggest that significant investigator-assessed effects of exfoliation and improvement of barrier function of the skin were found with daily use of the CoffeeBerry products for 12 weeks. Subjects also assessed their overall skin appearance, as well as redness, peeling, roughness, and stinging, as more improved in the CoffeeBerry group than in the comparator group (Figure 14). Tolerability, as assessed by absence of erythema and irritation, was satisfactory.

SUMMARY

Double-blind, proof-of-concept and comparative, clinical studies have been conducted to evaluate efficacy and safety of skin care products containing 1% CoffeeBerry. The improvement of barrier function shown with daily use of the CoffeeBerry products is an important aspect of improving skin sheen and texture and diminishing fine lines to give the skin a healthy appearance. The potential for increasing tolerability and adherence to retinoid therapy is an important consideration for future use of this antioxidant. Longer-term (6-month) studies are in progress to provide more data on the benefits of the antioxidant effects of CoffeeBerry.

CONCLUSIONS

The value of topical antioxidant skin care products for repairing and preventing signs of intrinsic and extrinsic oxidative damage is rapidly emerging. Early experience and randomized, double-blind, clinical trials have indicated that daily use of the CoffeeBerry products is well tolerated and associated with significantly enhanced skin barrier function and improvement of fine lines, wrinkles, erythema, skin texture, and pigmentation.

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