# Efficacy of a Natural-Based Bleaching Cream Versus Hydroquinone 4% Bleaching Gel in the Treatment of Hyperpigmentation

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Hyperpigmentation is a cosmetically important condition that can arise from a variety of sources, including exposure to UV light or photosensitizing agents. Although topical hydroquinone (HQ) has been the gold standard of treatment for hyperpigmentation, it is associated with potential carcinogenicity and has irritative properties that can complicate treatment. Accordingly, alternate depigmentation formulations that do not contain hydroquinone are becoming of increasing interest.

This study was undertaken in an effort to determine whether a non–HQ-containing formulation could provide depigmentation comparable with or better than a formulation containing HQ. Accordingly, this paper reports on a study comparing a natural-based, HQ-free, physician-dispensed bleaching cream with an HQ 4% bleaching gel in a blinded, split-face study over an 8-week period for depigmentation.

Twenty-one women, aged 20 to 75 years, were randomized to receive either a natural-based bleaching cream that did not contain HQ or an HQ 4% bleaching gel. Subjects were given samples labeled A and B, which were randomly assigned to either the left or the right side of the face. The subjects were instructed to apply the products twice a day, in the morning and evening, for 8 weeks. Subjects were required to use a cleanser prior to applying either product and were instructed to apply sunscreen following product application in the morning only.

Subjects were evaluated by an expert grader for fine lines, wrinkles, skin roughness, and reduction in hyperpigmentation at baseline (week 0) and at weeks 4 and 8 after study initiation. Digital photographs were also taken at these time points to perform red/brown image analysis. Skin pigmentation was assessed by the expert grader on a 3-point scale, with −1 indicating unfavorable darkening change; 0 indicating no change; and +1 indicating favorable lightening change.

Review of the images, along with expert grading, revealed decreased hyperpigmentation in 89% of subjects using the natural-based bleaching cream and 83% of subjects using the HQ 4% bleaching gel. Average scores were 0.83 for the natural-based bleaching cream and 0.78 for the HQ 4% bleaching

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gel. Qualitative assessment of fine lines, wrinkles, skin roughness, and hyperpigmentation by the expert grader corroborated these trends. For the entire 8-week study period, the reduction in hyperpigmentation was 70% for the cream and 63% for the gel. Similar trends with regard to reduced hyperpigmentation were observed in another study (n=12) at a different site.

On the measure of skin roughness, there was a 61% reduction with the natural-based bleaching cream compared with 66% with the HQ 4% bleaching gel. Image analysis for erythema (redness) indicated that 67% of subjects using the natural-based bleaching cream experienced irritation, compared with 83% of subjects who used the HQ 4% bleaching gel. Average scores, based on the 3-point scale previously mentioned, were −0.56 for the natural-based bleaching cream and −0.67 for the HQ 4% bleaching gel.

The results indicate that the natural-based bleaching cream produced a more pronounced reduction in hyperpigmentation compared with the HQ 4% bleaching gel. Furthermore, erythema was not as positively affected with the HQ 4% bleaching gel. This study suggests that the natural-based bleaching cream is equal to or better than the HQ 4% bleaching gel, both in terms of reducing hyperpigmentation and with regard to greater tolerability.

American culture places great importance on having skin that appears healthy and youthful.[1] Correction of photodamage is a common goal of cosmesis because exposure to UV light induces visual changes of dyspigmentation, fine wrinkles, and tactile roughness.[2] Of these, dyspigmentation of the skin is one of the primary cosmetic concerns voiced, especially by middle-aged and older, light-skinned people and by people of all ages with skin of color.[3,4]

Hyperpigmentation, in particular, is a very common concern among patients and it is important to determine its cause in order to select the optimal treatment.[5,6] Hyperpigmentation may arise from exogenous sources (eg, UV exposure or exposure to cosmetics, drugs, or photosensitizing agents) or skin disorders (eg, melasma, erythromelanosis follicularis, linea fusca, poikiloderma of Civatte, Riehl melanosis).[3] Other causes of hyperpigmentation include Addison disease, hemochromatosis, liver disease, pituitary tumors, and pregnancy. Hyperpigmentation can also occur in response to inflammation arising from any number of sources, including trauma, chemical peels, laser therapy, or acne.[3,6]

While hyperpigmentation associated with such common conditions as melasma and lentigines can be of concern to members of all ethnic groups, people with skin of color (ie, Asian, Mediterranean, African American, Hispanic) are typically more concerned about uneven skin tone because photodamage commonly presents as hyperpigmentation, such as postinflammatory hyperpigmentation (PIH), which is of greater concern in this population than wrinkles.[4,7,8]

Regardless of cause, hyperpigmentation is determined by the size, number, and distribution of melanosomes, not by the density of melanocytes.[9] Increased pigmentation results from increased melanin deposition, which can result either from elevated melanin synthesis or, less often, from an increased number of melanocytes.[5] The degree and type of dyschromia are determined by the location of the melanin deposition in the epidermal layer (brown discoloration), the dermal layer (blue-gray), or both (brown-gray).[5] Therapeutic goals for hyperpigmentation include promoting melanosome degradation, inhibiting melanosome formation, and retarding proliferation of melanocytes (Figure 1).[5]

Hyperpigmentation disorders can be difficult to treat and may be especially challenging in people with skin of color. The goal of therapy is to reduce the level of pigmentation without significant irritation or unwanted hypopigmentation. Because exposure to sunlight can reverse gains made by treatment, the first priority in these patients is the application of a broad-spectrum sunscreen in tandem with a phenolic agent (eg, hydroquinone [HQ]) or with nonphenolic substances, such as tretinoin, kojic acid, or azelaic acid.[10]

The gold standard in topical skin lightening agents has been HQ for a number of years. In the United States, HQ is available over the counter in strengths up to 2%.[3] However, the use of HQ in cosmeceuticals is growing increasingly controversial and has already been discontinued in

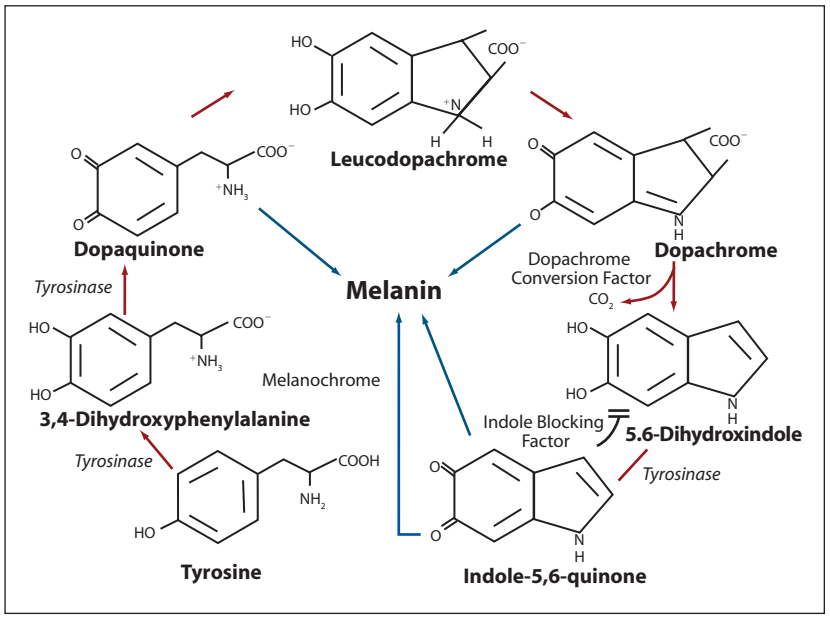


**Figure 1.** Melanin biosynthesis pathway. Illustration courtesy of David H. McDaniel, MD, and Joseph DiNardo, MS.

Europe and in parts of Asia.[11] The concern arises from both its midterm effects (eg, leukomelanoderma en confetti, exogenous ochronosis) and long-term consequences (eg, potential carcinogenicity).[12,13]

Due to the rapid uptake and distribution of HQ when applied to the skin, it has been speculated that the risks associated with topical application are probably higher than those associated with pulmonary or oral exposure.[13] There is less detoxification with topical application as the liver is partially circumvented. Detoxification is an important consideration because HQ is a metabolite of benzene; research suggests that the known carcinogenicity of benzene is associated with its metabolites and not with the parent compound.[13]

Additionally, high concentrations of HQ have been reported to cause skin irritation. This can be of particular concern in persons with darker skin because they are more likely to develop PIH.[14] Individuals with lighter shades of dark skin (eg, Asians) are particularly susceptible to PIH, while those with darker shades may experience hyperpigmentary reactions, hypopigmentary reactions, or both. Therefore, a product with decreased potential for irritation may prove safer and more effective in this population. An alternative to HQ is also desirable for African Americans, who have been observed to develop exogenous ochronosis after prolonged exposure to this skin-lightening agent. Typically, ochronosis has been seen in patients using high concentrations of HQ, but cases have also been reported in patients using HQ 2% solutions.[6]

Accordingly, alternatives to HQ are a subject of intense interest at this time. The current focus is on formulations that contain natural ingredients (derived from plant and microbial species). These substances may be less irritating and have fewer adverse effects.

As the population continues to grow and diversify, cosmetic procedures of all kinds will only increase. Further growth of cosmesis is ensured not only by the ever-increasing awareness of the effects of age and sunlight on facial appearance but also by the escalating number of consumers with skin of color who are turning to cosmetic procedures that address their unique needs for skin care.[15]

The natural-based bleaching cream used in this study is a physician-dispensed depigmentation product. Its formulation encompasses an array of functional classes of ingredients, including antioxidants, botanicals, emollients, emulsifiers, humectants, and vitamins. Several of the ingredients in the natural-based bleaching cream are known skin depigmentation and lightening agents, such as magnesium ascorbyl phosphate, glycolic acid, *Glycyrrhiza glabra* (licorice) root extract, and soy isoflavones. The functional skin-lightening ingredients found in the natural-based bleaching cream are provided in the Table.

The natural-based bleaching cream formulation was developed with an understanding of the importance of adherence in hyperpigmentation therapy. Formulations containing HQ can be accompanied by a disagreeable odor, and HQ may oxidize and turn brown over time, which patients may interpret as spoiling. These characteristics may hinder adherence. However, the natural-based bleaching cream does not change color over time and is engineered to feel and smell pleasant on the skin.

This article reports on an 8-week, randomized, split-face clinical study comparing a natural-based bleaching cream with an HQ 4% bleaching gel for visible depigmentation and adverse effects.

## MATERIALS AND METHODS

### Study Design

This trial, performed at 2 sites, was a randomized, double-blind, split-face study of a natural-based bleaching cream used on one side of the face (also randomized) compared with an HQ 4% bleaching gel used on the other side of the face. Expert grader evaluations were made at baseline (week 0) and at weeks 4 and 8. This study was conducted in accordance with guidelines recommended in current Good Clinical Practices.

## Principal Skin-Lightening Components of a Natural-Based Bleaching Cream

| INCI Name |
|---|
| Allantoin glycyrrhetinic acid |
| Butylated hydroxytoluene |
| Bisabolol |
| Butylene glycol |
| *Camellia oleifera* (Japanese green tea) leaf extract |
| Cerasin |
| Diazolidinyl urea |
| Dimethicone |
| Disodium EDTA |
| *Foeniculum vulgare* (fennel) seed extract |
| Glycerine |
| Glyceryl stearate |
| Glycolic acid/ammonium glycolate |
| *Glycyrrhiza glabra* (licorice) root extract |
| Hydroxyethylcellulose |
| Iodopropynyl butylcarbamate |
| Isohexadecane |
| Lycopene |
| Magnesium aluminum silicate |
| Magnesium ascorbyl phosphate |
| Methyl dihydroxybenzoate |
| Methylparaben |
| *Morus alba* (mulberry) bark extract |
| Olive leaf extract |
| PEG-100 stearate |
| Polysorbate 20 |
| Propylparaben |
| Purified water |
| Retinol |
| Sorbitan stearate |
| Soy isoflavones |
| Squalane |
| Steareth-2 |
| Sucrose cocoate |
| Superoxide dismutase |
| Tocopherol |
| *Vitis vinifera* (grape) seed extract |
| Xanthan gum |

Abbreviation: INCI, International Nomenclature of Cosmetic Ingredients.

Volunteers were recruited from a pool of healthy men and women aged 20 to 75 years with moderate pigmentation of the face. Inclusion criteria were as follows: individuals 18 years of age or older who were not pregnant or lactating; individuals with moderate hyperpigmentation of the face who were willing to cooperate with the study requirements, including willingness to use the products twice a day for 8 weeks and not to start using any new skin care product(s) during the course of testing; and individuals in general good health, taking no medications that might mask or interfere with the results of the study.

All candidates were required to use the sponsor-provided sunscreen for the duration of the study. Subjects were also required to stop using products containing retinoids for 3 days prior to study initiation.

### Treatment Regimen

Subjects were randomly assigned samples labeled A and B to be applied to either the left or right side of the face. The contents of the 2 formulations were blinded to both the investigators and subjects. The formulation that included HQ 4% also contained purified water, glycolic acid and ammonium glycolate, HQ, SD alcohol 40-B, hydroxyethylcellulose, ascorbic acid, magnesium ascorbyl phosphate, disodium EDTA, sodium metabisulfite, and methylparaben.

Subjects were instructed to apply the products twice a day, in the morning and evening, for 8 weeks. Subjects were required to use the sponsor-provided cleanser prior to sample product application for both the morning and evening treatments and the sunscreen after sample application in the morning only. The sunscreen used was a broad-spectrum UVA/UVB lotion containing titanium oxide.

### Outcome Measures

Expert grader evaluations at both sites were based on qualitative assessment and comparison of both sides of the subject's face for the following parameters: fine lines, wrinkles, skin roughness, erythema, edema, and hyperpigmentation at baseline and at weeks 4 and 8 poststudy initiation. In both studies, the principal investigator conducted the expert grader evaluations.

Digital, standardized images at baseline and at weeks 4 and 8 posttreatment of the full face, as well as right and left oblique images, were taken using standard lighting, cross-polarized UV fluorescence, and parallel polarized light. Image analysis was done by using color analysis (site 1), by the expert grader (site 2), or both. The image analysis software applies an algorithm to skin images obtained from digital cameras using various imaging modalities (eg, UV, polarized imaging) to create red and

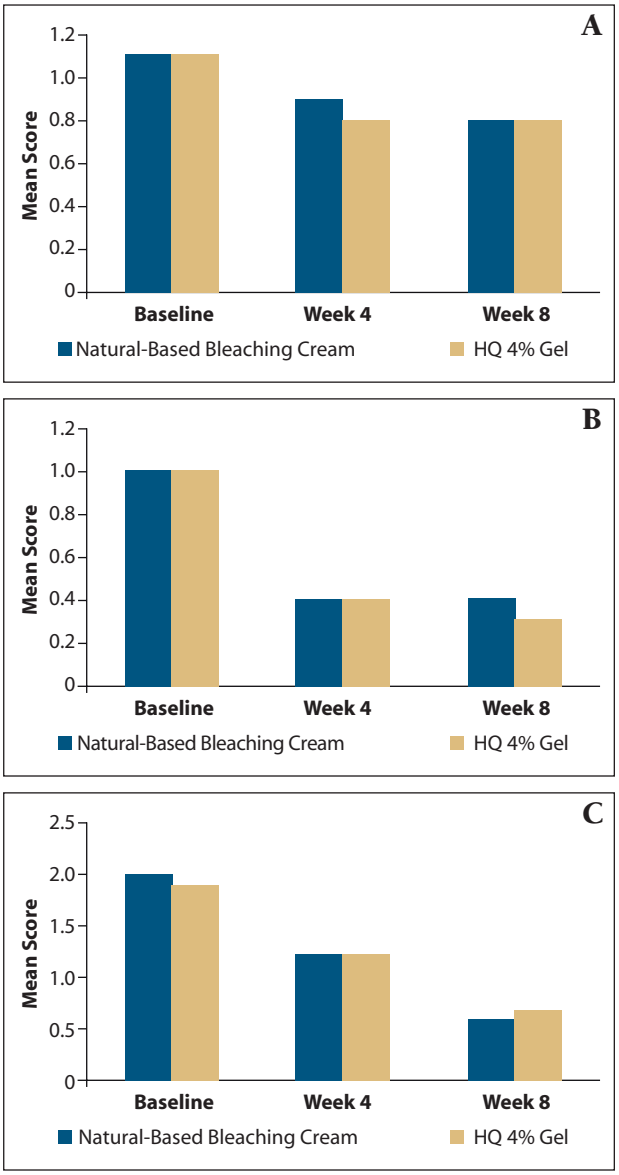


**Figure 2.** Results after an 8-week, randomized, split-face clinical study comparing a natural-based bleaching cream with a hydroquinone 4% bleaching gel, with expert grader evaluation of fine lines and wrinkles (A), skin roughness (B), and hyperpigmentation (C) at study site 1 based on a scale where 0=none; 1=slight; 2=moderate; 3=marked; and 4=severe.

brown area maps, representing vascularity and pigmentation, respectively. Computed severity scores provide quantitative measures for vascularization and hyperpigmentation.[16] Expert grader scoring of the images was done on a scale, with 0 indicating no change; 1 indicating change for the better; and −1 indicating change for the worse.

## Adverse Events

Adverse events were classified as either serious adverse events (SAEs) or nonserious adverse events. An SAE was any experience indicating a medically significant hazard. All nonserious adverse events and SAEs were evaluated by the investigator with regard to their relationship to the trial product and were documented, whether or not they were considered to be related to the treatment regimen.

## Results

This article reports on two 8-week, blinded, split-face clinical studies conducted to evaluate a natural-based bleaching cream and HQ 4% bleaching gel for visible depigmentation and adverse events. Clinical trials were conducted at 2 different sites. Twenty-one healthy volunteers participated in the trial at study site 1, and 18 (86%) completed the study. Twelve subjects were enrolled at study site 2, and 10 (83%) completed the study.

Outcome measures at study site 1 included visual qualitative assessment of the face by the expert grader for fine lines, wrinkles, skin roughness, erythema, edema, and hyperpigmentation at specified time intervals after study initiation (baseline and weeks 4 and 8). At study site 2, the expert grader evaluation included scoring for erythema, edema, and hyperpigmentation. In addition to the qualitative assessments, digital photographs were taken and images were evaluated for hyperpigmentation and erythema either by the expert grader only (study site 2) or by using color analysis and expert grader evaluation (study site 1).

## Expert Grader Evaluations

Expert grader evaluation results for study site 1 are presented in Figure 2, with fine lines, wrinkles, skin roughness, and hyperpigmentation, respectively. Both the natural-based bleaching cream and the HQ 4% bleaching gel resulted in improvement of fine lines and wrinkles at the end of the study period (8 weeks). The effect increased slightly from 4 to 8 weeks (Figure 2A). Tactile roughness decreased in the first 4 weeks and remained reduced at 8 weeks (Figure 2B). The antiaging effects seen with both treatments may be partially attributable to the fact that both products contained glycolic acid. Progressive reduction of hyperpigmentation occurred with both the natural-based bleaching cream and the HQ 4% bleaching gel during the study period (Figure 2C).

At the end of the 8-week study period at study site 1, comparison by the expert grader of the side of the face exposed to the natural-based bleaching cream with the side treated with the HQ 4% bleaching gel showed a 27% reduction in fine lines and wrinkles for both products tested. There was a 66% reduction in skin roughness for the HQ 4% bleaching gel versus 61% for the natural-based bleaching cream, and a 63% reduction in hyperpigmentation was noted for the HQ 4% bleaching gel versus a 70% reduction for the natural-based bleaching cream (Figure 3).

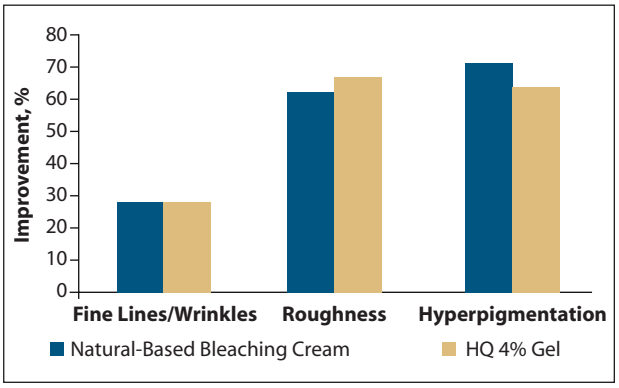


**Figure 3.** Percentage of improvement after 8 weeks of treatment with a natural-based bleaching cream versus a hydroquinone 4% bleaching gel based on expert grader evaluation of fine lines, wrinkles, skin roughness, and hyperpigmentation (study site 1).

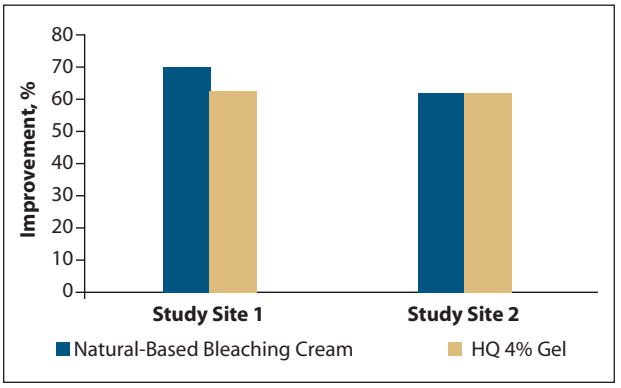


**Figure 4.** Percentage of improvement in hyperpigmentation after 8 weeks of treatment with a natural-based bleaching cream versus a hydroquinone 4% bleaching gel based on expert grader evaluation (study sites 1 and 2).

Similar trends related to reduced hyperpigmentation with the products tested were also observed at study site 2. Reduced hyperpigmentation was observed with both formulations. Use of the natural-based bleaching cream resulted in a 38% and a 62% reduction in hyperpigmentation after 4 and 8 weeks, respectively, compared with a 43% and a 62% reduction in hyperpigmentation for the HQ 4% bleaching gel after 4 and 8 weeks, respectively. Figure 4 presents the combined percentage of improvement after 8 weeks of treatment based on expert grader evaluation of hyperpigmentation at study sites 1 and 2.

### Digital Photograph Analysis

Digital color analysis of the right side of the face at baseline (week 0) and at study completion (week 8) at study site 1 is presented in Figure 5. Expert grader analysis of the images indicated that 89% of subjects showed improvement in hyperpigmentation with the natural-based bleaching cream compared with 83% of subjects who used the HQ 4% bleaching gel. Based on a scoring scale where 0 indicates no change; 1 indicates change for the better; and −1 indicates change for the worse, the average expert grader scores were 0.83 and 0.78 for the natural-based bleaching cream and the HQ 4% bleaching gel, respectively, after 8 weeks.

### Safety Analysis

Product tolerability was assessed from expert grader assessment of the erythema response, from analysis of the digital images, and from patient diary information in study 1. In study 1, based on expert grader qualitative assessment of erythema, both products showed slightly increased levels compared with baseline at week 4. However, there was no increase at week 8. Image analysis for erythema indicated that 67% of subjects using the natural-based bleaching cream experienced irritation compared with 83% of subjects who used the HQ 4% bleaching gel. The average score was −0.56 for the natural-based bleaching cream and −0.67 for the HQ 4% bleaching gel.

These trends in terms of safety of the 2 products were confirmed in study 2. Skin tolerance was acceptable for both products, with irritation increasing slightly from a mean of 0.3 at baseline to a mean of 0.6 for the natural-based bleaching cream and 0.7 for the HQ 4% bleaching gel after 8 weeks of product use. Based on the subject self-assessment questionnaire, subject satisfaction scores were high (strongly/somewhat agree) for both products.

## COMMENT

The number of people seeking facial treatments to alleviate the psychologic distress associated with the effects of aging and photodamage continues to grow rapidly.[15] There is a rapidly growing market for products that address


**Figure 5.** Color analysis of the right side of the face at baseline and after 8 weeks of treatment with a natural-based bleaching cream versus a hydroquinone 4% bleaching gel.

hyperpigmentation and pigment dyschromia–related conditions. The current trend is toward natural-based products. Factors contributing to this trend include concern about the safety of HQ (eg, carcinogenicity, exogenous ochronosis, and PIH), increasing levels of dyspigmentation among baby boomers due to photoaging, and changing demographics (eg, an increase in the nonwhite population). Above all, the awareness that these disorders are treatable is bringing more and more patients to the office.

Skin-lightening agents have been the subject of several reviews.[3,9-11] Examples of depigmentation agents that are either routinely incorporated into formulations or have been tested and proven effective include arbutin, ascorbic acid, azelaic acid, kojic acid, licorice extract, mequinol, *N*-acetylglucosamine, retinoids, and soy proteins.[3,11] When evaluating potential skin-lightening agents, parameters to evaluate in addition to depigmentation efficacy include melanocyte toxicity, carcinogenic potential, irritation profile, and sensitizing ability of the constituent ingredients.[11]

In this study we evaluated the effectiveness of a natural-based bleaching cream that contains an array of functional classes of ingredients targeting not only dyschromia but also fine lines, wrinkles, and skin roughness. These ingredients include antioxidants, botanicals, emollients, emulsifiers, humectants, and vitamins as a potential alternative to HQ. The natural-based product was well tolerated and performed well in reducing fine lines, wrinkles, skin roughness, and hyperpigmentation. At both study sites, there was a directionally more positive response in hyperpigmentation with the natural-based bleaching cream than with the HQ 4% bleaching gel. At study site 1, the only site reporting on measures of fine lines, wrinkles, and skin roughness, the natural-based bleaching cream performed better than or as well as the HQ 4% bleaching gel on these indices. Additionally, there was a higher directionally negative response in terms of erythema with the HQ 4% bleaching gel.

The results of this study suggest that the natural-based bleaching cream is equal to or better than the HQ 4% bleaching gel for reducing hyperpigmentation and could be a potential replacement for HQ-based topical agents in the treatment of hyperpigmentation. Additional studies are warranted to determine the efficacy and safety of the natural-based bleaching cream for extended use.

***Acknowledgment*—**Canfield Scientific, Inc, provided assistance with image processing and special equipment support.

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