COSMECEUTICALS FOR THE ATTENUATION OF EXTRINSIC AND INTRINSIC DERMAL AGING

Suzanne Bruce MD

President, Suzanne Bruce and Associates, PA; The Center for Skin Research, Houston, TX

Abstract

Since the term "cosmeceutical" was coined over 2 decades ago, the number of products in this category that claim to combat dermal aging has grown dramatically. Topical retinoids remain the mainstay for treating photoaging given their proven efficacy in both clinical and histologic outcomes. In addition to retinoids, many other cosmeceutical agents are now available. The proliferation of products can cause confusion among consumers, who often ask their dermatologist for advice as to which antiaging products they should choose. Ideally, the antiaging claims of cosmeceutical formulations and their components should be demonstrated in controlled clinical trials. In order to provide appropriate recommendations to their patients, dermatologists must become familiar with the available data on currently marketed products and gain experience with antiaging regimens. This review discusses the efficacy of a number of currently marketed drug products with proven photoaging benefits and cosmeceutical products that claim similar benefits. Among the agents discussed are single-entity and combination products containing hydroquinones, retinoids, topical antioxidants, and minerals.

Introduction

The Food, Drug, and Cosmetic Act of 1938 clearly defines and distinguishes between drugs and cosmetics.[1] A drug is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," and is "intended to affect the structure or any function of the body..."[1] A cosmetic is a product intended to be "rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance" of the skin.[1] While for the most part products in these categories are mutually exclusive, in dermatology a group of products has evolved that has characteristics of both. First called "cosmeceuticals" by Albert Kligman, MD, 2 decades ago,[2] these topical products contain biologically active ingredients, but are sold to improve appearance, not for therapeutic purposes. Some drug products and many cosmeceuticals are marketed as agents that attenuate the effects of aging on the skin.

Topical Drugs with Demonstrated Activity against Dermal Aging

The efficacy of several chemical agents for the prevention and treatment of dermal aging is well established. Among preventive therapies, sunscreens are recognized as the most important drug-product class. In addition to reducing erythema associated with acute ultraviolet B (UVB) exposure, sunscreens with adequate UVA and UVB protection can also prevent melanin production and collagen and elastin degradation. After sunscreens, topical retinoids are the second most important drug class to combat and reverse dermal aging. With over 2 decades of experience, there is a vast amount of evidence that regular retinoid use over several months results in clinical improvement in skin texture, wrinkles, and pigmentation.[3] The main drawback to retinoid use is local irritation and erythema; however, this usually subsides after several weeks of use or by reducing the frequency of application from once daily to every other day.

Hydroquinones and related compounds are also used to reverse dermal aging. Hydroquinones suppress melanocyte metabolic processes, including pigment production. These agents primarily address dyspigmentation related to photoaging and lighten skin and even out skin tone. They are often used as adjuncts to topical retinoids and other treatments.[4-7] Compared with retinoids there are very few data substantiating the efficacy of hydroquinones for dermal aging. Recently, as part of their ongoing review of over-the-counter drug (OTC) products, the US Food and Drug Administration (FDA) proposed a ban on OTC hydroquinones that would reverse their generally regarded status as safe and effective and require any marketed hydroquinone product to submit a New Drug Application (NDA) for continued marketing.[8] The change in rulemaking stems from new toxicology and carcinogenesis data on orally administered hydroquinone. However, some dermatologists[9] consider the proposed ban and NDA requirements for topical OTC hydroquinones to be excessive.

Cosmeceuticals for Dermal Aging

The aging of the baby boomer population has given rise to increased consumer interest in maintaining a youthful appearance throughout middle age. The cosmetic and pharmaceutical companies have responded with a broad array of products containing "active" ingredients that claim to improve the appearance of lines and wrinkles (Figure 1). Given the number of products available, it can be difficult for consumers—and even dermatologists—to distinguish those products that genuinely produce benefits from those that do not.

As physicians, dermatologists have been trained to select treatments for their patients based on evidence gained through adequate and well-controlled trials. With drug products and devices, the FDA ensures that such trials are performed before new drugs can be approved or devices can be marketed; however, cosmeceuticals are not required to undergo the same rigorous testing prior to marketing. When

conducted at all, clinical trials for most of these agents have been very small, open-label evaluations, often lacking an appropriate comparator. Another main concern is that, while the active ingredients may have been shown to provide an antiaging benefit *in vitro* or *in vivo*, often they are not evaluated in the final formulation.[10] This is a serious omission, since factors such as concentration, vehicle and other formulation components, and skin penetration may affect product performance.

Thornfeldt[11] has recommended some basic tenets for evaluating cosmeceuticals. First, a biologically sound rationale should exist for the cutaneous effects claimed by the ingredient. Second, the therapeutic concentration range of the ingredient should be known, and the cosmeceutical product should contain an amount of the ingredient that is known to be therapeutically meaningful. Third, formulation science should produce a final product in which the active ingredients are stable. Similarly, formulation science should ensure that the active ingredient(s) penetrate the stratum corneum. With respect to clinical trials of cosmeceuticals, such trials should have the following characteristics: have a double-blind, a prospective design, use the final marketed product, use visible end points for evaluation, enroll a sufficient number of subjects to determine clinical and statistical significance, and be performed by third-party researchers.

More recently, companies appear to be responding to dermatologists' insistence for evidence backing their claims, and there is a trend toward improved clinical trial data for cosmeceutical products. Following is a discussion of some studies conducted with final marketed cosmeceutical products.

Figure 1. Some topical cosmeceutical ingredients touting antiaging claims.

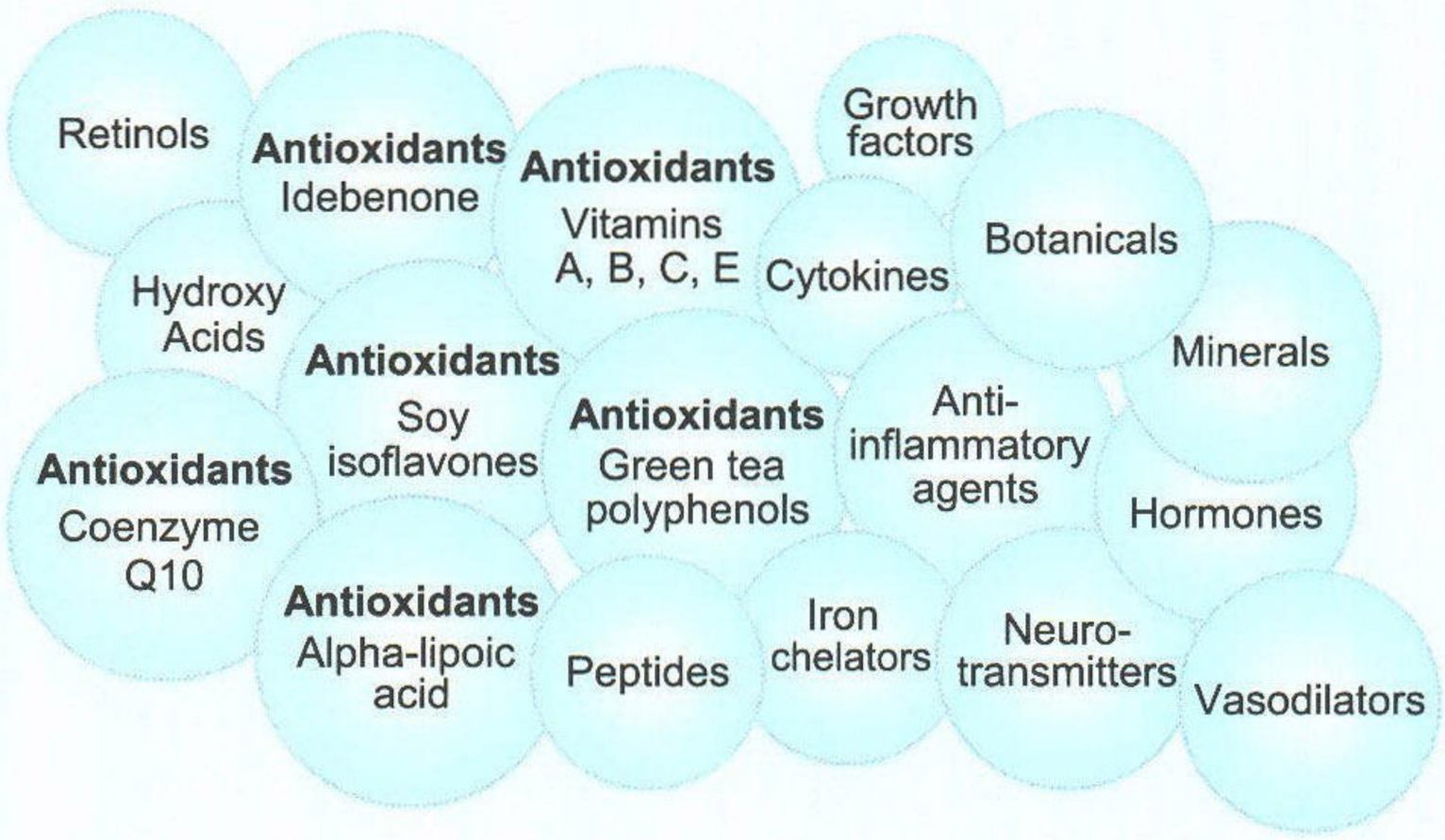
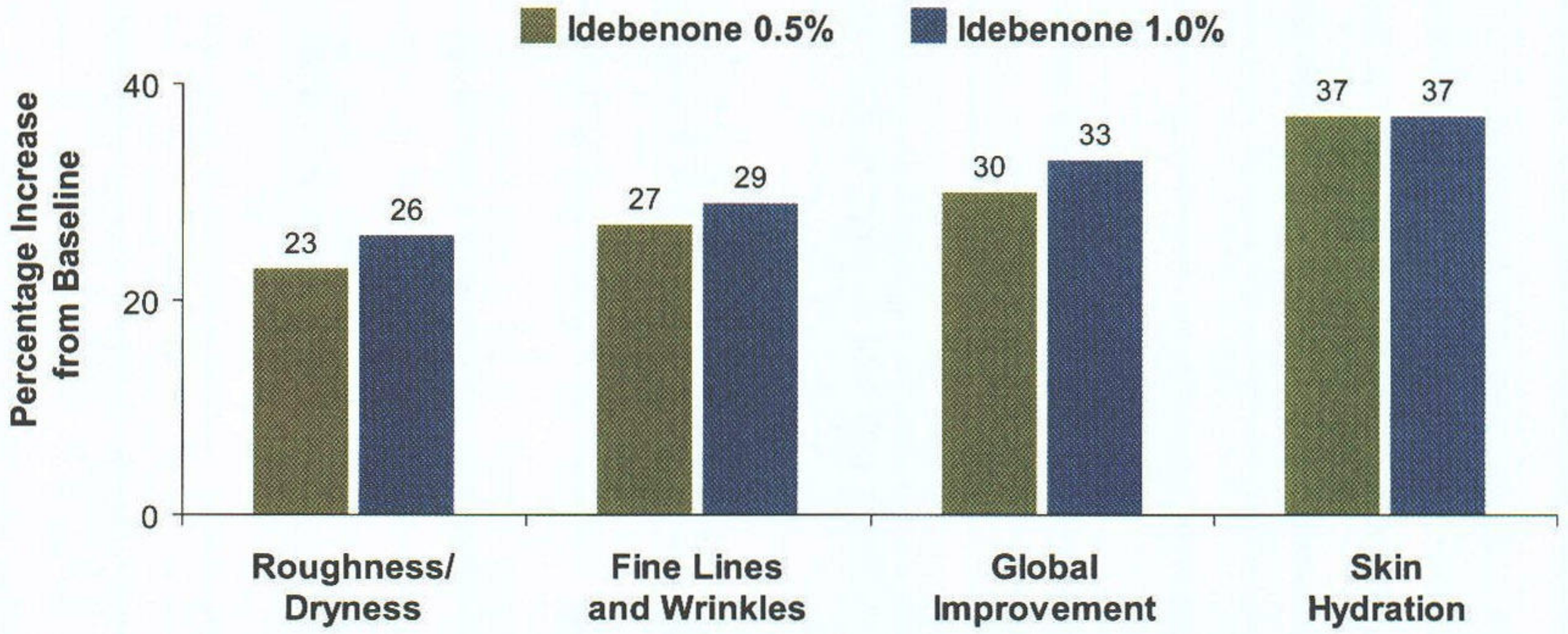


Figure 2. Percentage increase/decrease from baseline in photodamage parameters after 6 weeks of idebenone applied twice daily.



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Idebenone

Idebenone is an antioxidant that is structurally related to coenzyme Q10.[12] Its safety and efficacy for improving photodamaged skin was evaluated in a clinical trial in which 50 female subjects aged 30 to 65 years with moderate photoaging were randomized to receive double-blind commercial lotions containing either 0.5% or 1% idebenone.[12] Subjects were instructed to apply the product twice daily for 6 weeks. Assessments were performed by an experienced blinded investigator evaluating before and after photographs using a 5-point scale (0=no improvement to 4=100% improvement). Results are shown in Figure 2. While both concentrations resulted in improvements from baseline, no statistical significance was reported. A placebo arm might have better demonstrated the meaningfulness of the reported percentage improvements.

Copper Zinc Malonate

The clinical effects of a physician-dispensed bimineral product containing copper zinc malonate were evaluated in a trial in which 32 female subjects aged 45 to 69 years applied a controlled amount of product (~0.25 g) to the periorbital areas twice daily for 8 weeks.[13] Except for cleanser, the use of other facial products in the areas treated was not permitted. In addition to patient assessments and photography, this study used more objective measures to evaluate outcomes. To assess skin elasticity, a Cutometer® was used to measure the speed of recoil of the skin after being pulled into a vacuum. A Corneometer® was used to assess the dielectric constant in the stratum corneum, in order to determine the moisture content of the skin. Silicone replicas were created to measure the number and depth of the wrinkles in the periorbital areas.

Over time, the speed of skin recoil increased steadily from baseline, from a 20% increase at week 2 to a 46% increase at week 9 ($P \leq .01$ at week 2 and $\leq .001$ at weeks 4, 6, 8, and 9). The dielectric constant in the stratum corneum increased 6% to 7% at weeks 2 through 6, but then returned to baseline by week 8. The normalization of moisturization suggests that other improvements were independent of skin hydration. By week 9, the mean percentage reduction from baseline in wrinkles was 16% ($P \leq .05$). Serial photography demonstrated the improvements in wrinkles over time (Figure 3).

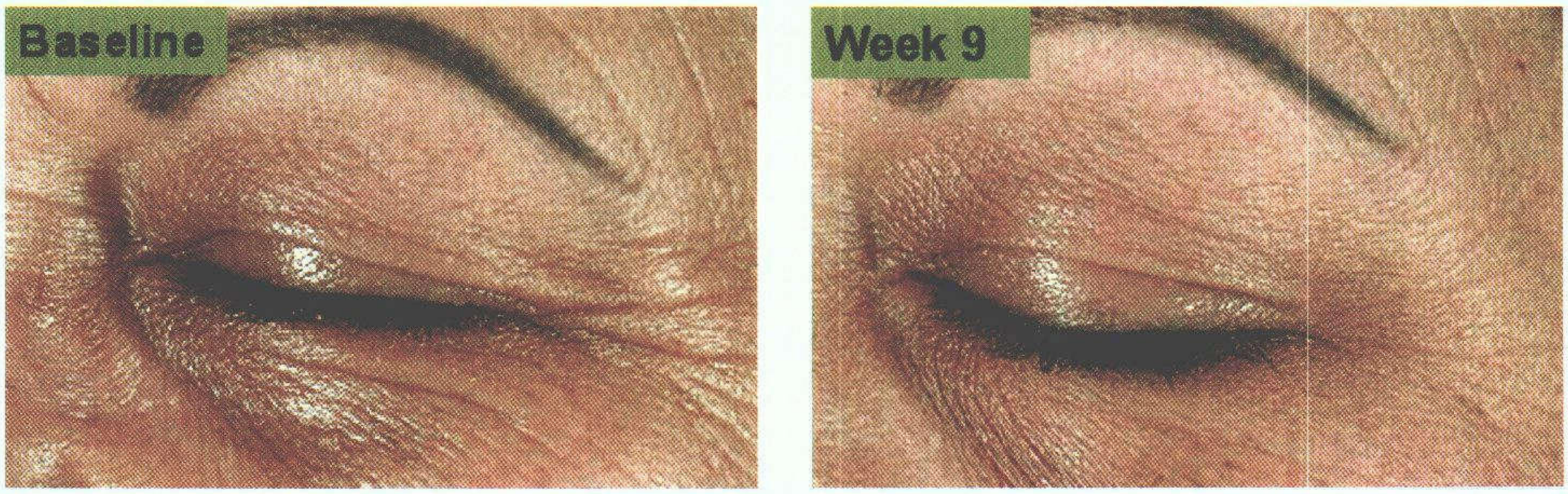
In a separate evaluation of the same copper zinc malonate eye cream in 23 subjects who applied it either once or twice daily, biopsy evaluation showed that twice-daily application was more beneficial than once-daily application in terms of increased levels of elastin and collagen.[14] Twice-daily treatment resulted in the replacement of clumped and relatively thick elastic fibers by finer, more discrete fibers; once-daily treatment was minimally effective in inducing histologic changes. Data regarding once- or twice-daily use are particularly meaningful, as proper administration will ensure the best possible outcomes and likely result in greater patient satisfaction.

Tretinoin/Hydroquinone-based System

Because hydroquinones are primarily active against skin dyspigmentation, their combination with a retinoid potentially offers a product that also treats the fine lines and wrinkles of photoaging. A large scale, 4-arm study evaluated the efficacy of a proprietary 4-step skin treatment system (cleanser, toner, and day and night creams) containing 0.1% tretinoin and 4% hydroquinone with that of regimens consisting of tretinoin plus an OTC cleanser and daily moisturizer with sunscreen, 4% hydroquinone plus the same OTC products, and the OTC products alone.[15] A total of 387 female subjects aged 38 to 65 years (at least 50% had fine perioral wrinkles) were randomized to receive one of the 4 treatments on a twice-daily regimen for 24 weeks. With the proprietary 4-step system, hydroquinone was applied twice daily and tretinoin once daily;, and with the other arms that contained these ingredients, hydroquinone and tretinoin were applied once daily. Assessments using an 11-point scale (0=no damage to 10=extensive damage) were conducted by an investigator who was blinded to the study treatment.

A total of 301 subjects completed the study. At 12 and 24 weeks, the 3 treatment arms containing tretinoin and/or hydroquinone produced numeric improvements from the

Figure 3. Improvement in appearance of periorbital lines in a 56-year-old female with a bimineral complex eye cream applied twice daily.



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baseline in investigator-assessed parameters, although improvements from the baseline were only significant with the tretinoin/hydroquinone combination system (Figure 4).[15] Improvements were more pronounced at 24 weeks than at 12 weeks. As might be expected, subjects randomized to the hydroquinone regimens reported more erythema, scaling, burning, and stinging, although mean change from baseline scores were still in the mild range.

Hydroquinone/Stabilized Retinol Combination Product

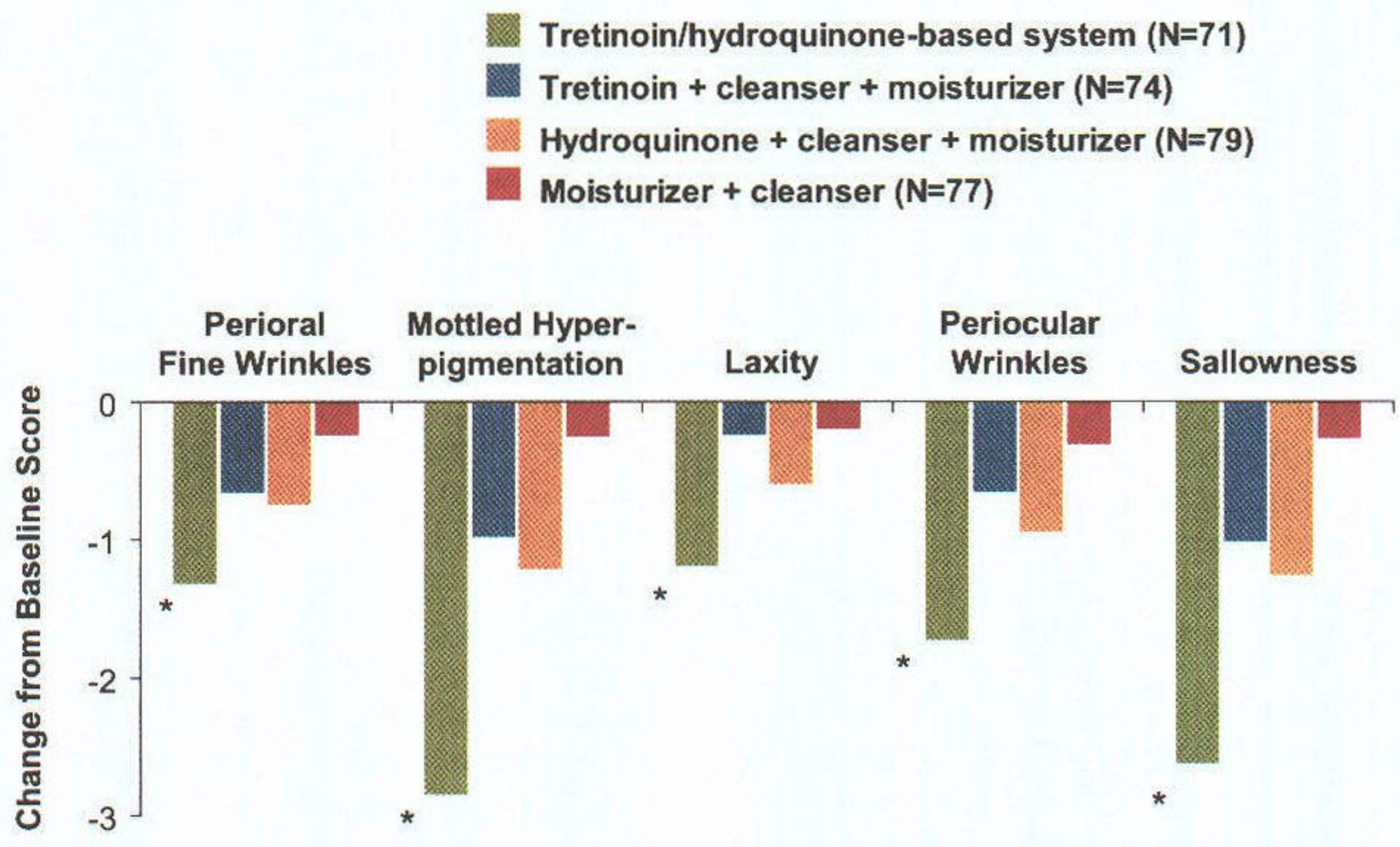
Since tretinoin can cause some unwanted dermal effects, a less irritating retinoid such as retinol has been evaluated in combination with hydroquinone. In a 16-week study, a cosmeceutical formulation containing 4% hydroquinone and 0.3% stabilized retinol in an emollient vehicle was found to be more effective in diminishing dyspigmentation, fine wrinkles, and tactile roughness in sun-damaged skin than a 0.05% tretinoin single-component emollient cream.[16]

Topical Antioxidant Formulations

Cosmeceutical formulations of the antioxidant vitamins C and E have proven to be of value in the treatment of photoaging. Interest in vitamin C to treat photoaged skin has increased based on preclinical studies demonstrating their ability to block UV-induced erythema. In addition, *in vitro* studies have shown that vitamin C stimulates collagen production by fibroblasts, and further studies indicate that it has anti-inflammatory activity and suppresses melanin formation.

Figure 4. Improvement in skin parameters after **a)** 12 weeks and **b)** 24 weeks of 4 different topical treatment regimens.

a.



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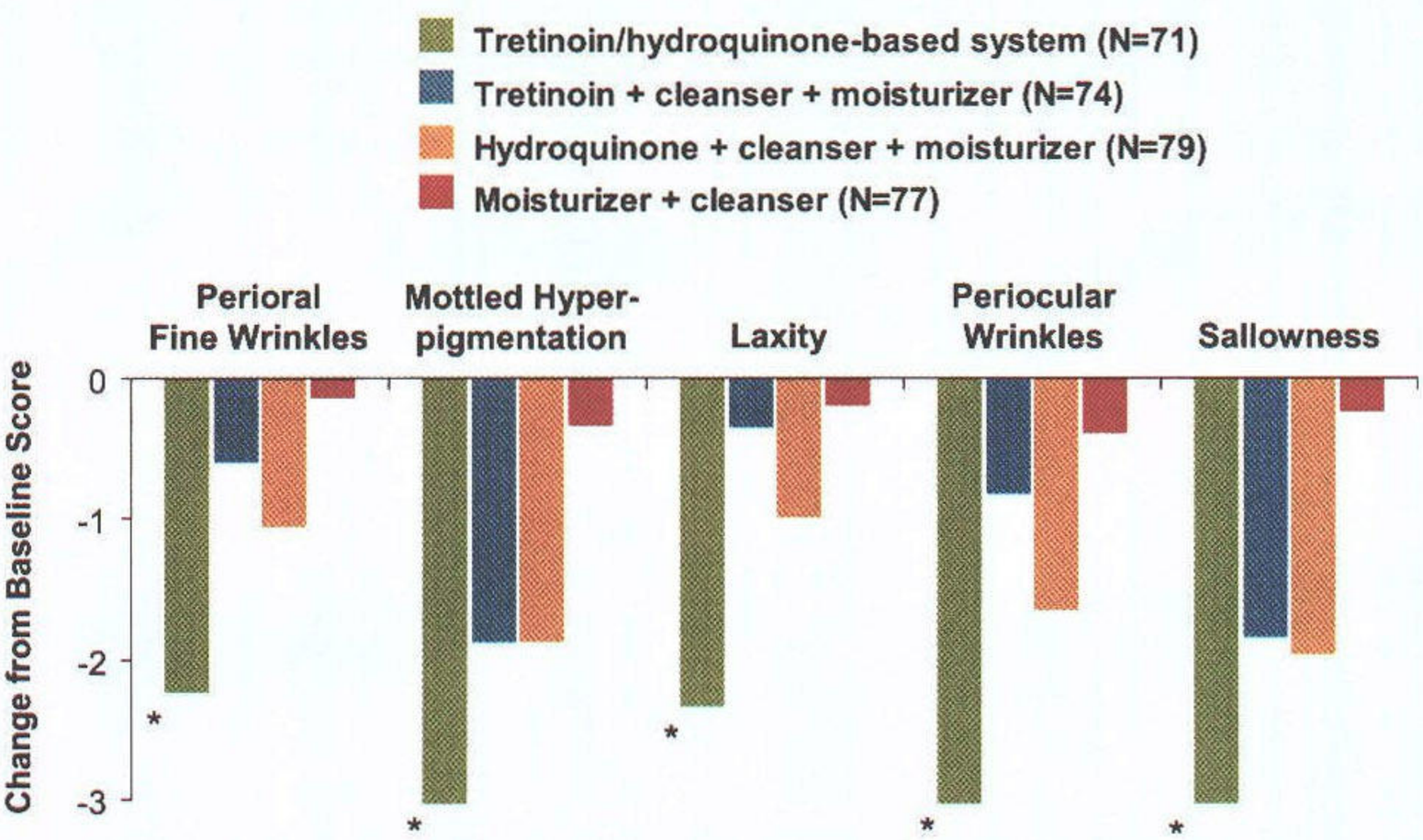

*$P \leq .05$ versus other regimens.

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Together, these functions of vitamin C contribute to its ability to reverse the appearance of photoaging. Vitamin E also exhibits activity that suggests it may be of value for the treatment of photoaging. In animal studies, topical vitamin E, in the form of D-α-tocopherol, was found to protect against acute and chronic UV-induced damage, based on inhibition of tumor formation. In clinical studies, topical vitamin E decreased wrinkles and solar lentigoes of photoaging; these benefits were confirmed by a histologic examination in mice. When used in combination, topical L-ascorbic acid (15%) with α-tocopherol (1%) gave 4-fold greater protection against UV-induced erythema, compared to 2-fold greater protection with either vitamin alone.[17]

Increasing the lipid solubility of vitamin C appears to improve its effectiveness. A double-blind, half-face study compared a vitamin C-complex formulation consisting of 10% ascorbic acid (water soluble) and 7% tetrahexyldecyl ascorbate (a lipid form of provitamin C) to vehicle. The anhydrous base allowed for a time-released delivery of the vitamin C and prevented its rapid degradation, while the lipid form of provitamin C was used for its ability to penetrate into the dermis, where it is converted to vitamin C.

After 12 weeks, results showed significant improvements in photoaging scores, with biopsies indicating an increase in collagen production. The formulation of vitamin C produced a clinically visible and statistically significant improvement in wrinkling when used topically for 12 weeks.[18]

Green tea extracts contain antioxidant polyphenols and have been promoted as a treatment for improving the appearance of photoaged skin. The efficacy of green tea extracts was evaluated in a study of 40 women with moderate photoaging who were randomized to either a combination regimen of 10% green tea cream and 300 mg twice-daily green tea oral supplementation or a placebo regimen for 8 weeks. No significant differences in clinical grading were found between the green tea and placebo-treated groups; however, an improvement in the elastic tissue content of treated specimens ($P<.05$) was observed upon histologic examination of skin biopsies.[19]

Clinical Evaluations of Cosmeceuticals in Everyday Practice

In the absence of clinical trial data, how can a dermatologist determine if a particular cosmeceutical is beneficial? One means of assessment is through individual split-face trials. Although this is not a common clinical practice, it may be of benefit for a dermatologist self-assessment of a new product or when suggesting a product to skeptical patients (by using it on one side of the face and not the other, patients can see the changes for themselves). The most important tool for assessing dermal changes is serial photography. Commonly used to assess the effect of lasers, it is helpful to show patients the effects of prescription or OTC cosmeceutical dermal antiaging regimens. The documented changes can serve as motivation for the patient to continue using the product(s). A more sophisticated photographic tool is the VISIA® Complexion Analysis System (Canfield Imaging Systems), which uses multispectral imaging and analysis to capture and measure key visual information for areas affecting complexion health and appearance, such as wrinkles, skin evenness, pores, and spots. This is a useful method for educating patients about the state of their skin and the existence of subclinical sun damage, rating it against the database of their age- and sex-matched peers. As with serial photography, the VISIA system can assess changes produced via use of cosmeceutical/topical antiaging products.

Summary

The market for antiaging dermatologic products is growing at a fast pace with cosmeceuticals leading the way. Dermatologists are a key point of contact for patients who are seeking to look younger; they are experts who can guide patients through the confusing barrage of antiaging claims by directing them to the most proven products. Clearly, cosmeceuticals can be of benefit in combating the signs of aging. An assessment of the available data to substantiate efficacy and safety is warranted, and more data are available for some products than others. Antiaging claims associated with cosmeceuticals should be substantiated with demonstrated efficacy of these ingredients in the final marketed product. Dermatologists should press companies to provide appropriate evidence, in the form of adequately designed clinical trials, to substantiate antiaging claims for their products.

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Address for Correspondence

Suzanne Bruce MD
The Center for Skin Research
1900 St. James Pl, Ste. 650
Houston, TX 77056
Phone: 713-850-2040