Vitamin-Based Cosmeceuticals

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Vitamins are popular ingredients in many over-the-counter (OTC) cosmeceuticals that are designed to improve various aspects of the skin's appearance. In this article we aim to validate the clinical efficacy of vitamin-based skin care products, with a focus on vitamins A, C, B_3, E, and K. We also provide a general overview of the cosmeceutical development process to promote a better understanding of product testing and the inherent limitations of the products. Ultimately, this information will help to elucidate the most beneficial vitamin-based cosmeceuticals that are supported with well-designed clinical studies.

Cosmet Dermatol. 2012;25:405-410.

An increasing desire to maintain a youthful appearance has led to rapid growth in the antiaging skin care market. The cosmeceutical industry has capitalized on this consumer interest through the development of antiaging skin care products with vitamin-based cosmeceuticals as a popular choice among patients. In this article we review the vitamins in cosmeceuticals, specifically vitamins A, C, B_3, E, and K, with an emphasis on sound scientific data supporting the clinical efficacy of available cosmeceutical vitamin formulations. We also provide a general overview of the cosmeceutical development process and testing methods used to establish efficacy claims. Understanding how these products are developed, including their regulatory requirements (or lack thereof), sheds light on the inherent limitations in confirming their clinical effectiveness. As dermatologists, we should be familiar with the cosmeceutical formulations that are supported with well-designed, placebo-controlled clinical studies in humans, which allows us to put exaggerated advertising claims in a more realistic context for our patients.

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Drs. Jacob and Baker report no conflicts of interest in relation to this article. Dr. Farris is an advisory board member for Beiersdorf Inc and L'Oréal; spokesperson for Guthy-Renker; and consultant for The NeoStrata Company, Inc.

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PRODUCT DEVELOPMENT AND TESTING

The vast pool of botanicals and vitamins that generally are accepted as safe for human consumption are a rich source of compounds for cosmeceutical ingredients. The US Food and Drug Administration (FDA) generally accepts that any substance fit for human consumption, including plant extracts, also is fit for topical application. In fact, cosmeceuticals, which are sold as cosmetics, come under the purview of the Federal Trade Commission (FTC) and are not overseen by the FDA in any way.[1] The FTC may investigate any advertising claims made by manufacturers of over-the-counter (OTC) products that suggest pharmaceutical-like properties; however, there is little oversight in the development of these products.[2] Because many cosmeceutical ingredients are derived from existing food products and supplements that already are considered to be fit for human consumption, further safety testing often is deemed unnecessary. Instead consumers must rely on the safety testing done by the manufacturer in the company's own self-interest to maintain a sound reputation. Prior to marketing the product, reputable companies often use patch testing to

evaluate possible active ingredients for irritancy and allergic potential.

Reputable companies hoping to develop new active ingredients often will first test a promising extract or vitamin on a fibroblast gene array chip to assess for modification of any key cellular events.[3,4] If preliminary tests are encouraging, the compound then undergoes in vitro testing on cultured fibroblasts and subsequently on murine models before it is incorporated into an appropriate vehicle for application to human skin. Cosmeceutical testing in humans typically is performed using the final formulation of the product, making it difficult to substantiate statements on the active ingredient. Higher-quality studies will compare the active formulation to a group using only the vehicle; however, this practice is not commonplace. In most cases, biopsies and other invasive procedures are not performed during manufacturer-sponsored trials, as positive changes might indicate a pharmaceutical effect, which would subject the potential active ingredient to more rigorous standards under the oversight of the FDA.[3,4]

Several noninvasive techniques are used to measure treatment outcomes and serve as the basis for clinical efficacy claims. Evaporimetry is used to evaluate transepidermal water loss, providing an assessment of the overall barrier function of the skin. Profilometry assesses changes in skin texture and depth of rhytides. Silicone casts of the skin's surface are analyzed using advanced photographic techniques to assess the degree of irregularity.[5,6] Chromatometry involves the use of a special camera to assess pigmentary changes to substantiate claims of improved skin tone and radiance.[7] Doppler flow imaging measures the amount of blood flow in the skin and extrapolates information about the level of erythema and inflammation. Changes in skin thickness often are assessed with A-scan ultrasound images.[8] Subjective improvements noted by study participants and investigators also are heavily relied on to document clinical change from baseline.

Companies marketing a finished cosmeceutical product have no obligation to perform any of these tests, but the FTC does require some form of substantiation for advertising claims boasting certain effects to protect consumers from blatant false advertising. The savvy dermatologist must realize that none of the aforementioned steps are required by law in the United States. As such, we should become familiar with the products that have been appropriately tested to ensure their safety and efficacy.

VITAMIN-BASED COSMECEUTICALS

Vitamin A

Topical vitamin A derivatives now comprise the most diverse group of cosmeceutical vitamins on the market today, with retinol, retinaldehyde, retinyl esters, and oxoretinoids being the most common.[9] The lipophilic nature of vitamin A derivatives ensures their penetration beyond the stratum corneum to reach their intended targets. To exert their effects, vitamin A derivatives must be converted to the bioactive form of vitamin A, known as tretinoin or all-*trans*-retinoic acid. Endogenous enzymes in the epidermis convert retinol and retinaldehyde to all-*trans*-retinoic acid, while retinyl palmitate and retinyl acetate, the esterified forms of topical vitamin A, do not undergo this enzymatic conversion. As such, these compounds have shown little efficacy against photoaging.[10,11] Although they are converted into biologically active tretinoin, OTC formulations do not produce the same level of tretinoin in the epidermis as pharmaceutical-grade retinoids. Retinol, for instance, produces ten times less active vitamin A in the skin in vivo than tretinoin,[12] which likely explains in part why clinical results generally are less impressive for cosmeceutical retinoids compared to prescription retinoids.

Once it passes through the epidermis, tretinoin interacts with nuclear receptors, increasing production of types I and III procollagen and modulating genes that regulate epidermal proliferation and differentiation, such as cellular retinoic acid binding protein 2, *CRABP2,* and heparin-binding epidermal growth factor–like growth factor, *HBEGF.*[12-15] Tretinoin also inhibits matrix metalloproteinases, reducing degradation of existing collagen.[13] These actions account for the antiaging effects of retinoids, with increased collagen deposition, epidermal thickening, increased deposition of glycosaminoglycans, and proliferation of fibroblasts translating to clinical improvements in wrinkles and skin texture.[16]

Although the effectiveness of prescription retinoids in improving skin appearance has been well established, the relative efficacy of various nonprescription cosmeceutical retinoids is less certain. Of the available options, retinol appears to be the preferred choice.[9] The effectiveness of retinol has been confirmed via randomized controlled trials, with substantial improvements in fine lines and wrinkles seen after 24 weeks of treatment.[17,18] One split-face study comparing tretinoin emollient cream 0.05% to a hydroquinone cream 4% containing retinol 0.3% showed equivalent efficacy in reducing periocular fine lines, roughness, and melasma severity after 16 weeks of use.[19] One of the first studies to compare the efficacy and tolerability of a nonprescription retinoid formulation (triretinol cream 1.1%) versus a prescription retinoid (tretinoin cream 0.025%) found these products to be equally effective in improving the appearance of photodamaged skin.[20] Although prescription retinoids are still considered the gold standard for improving the signs of photoaging,

OTC formulations have demonstrated clinical effectiveness and are an alternative for patients who are unable to tolerate prescription retinoids.

Vitamin C

Vitamin C, or L-ascorbic acid, is a naturally occurring antioxidant that acts as a free radical scavenger and functions as a protective agent against oxidative stress in human skin. Humans are unable to synthesize vitamin C due to a loss of L-gulonolactone oxidase and must rely on dietary intake to meet physiologic needs. The concentration of L-ascorbic acid in the skin is limited by gastric uptake, with higher levels obtained only via topical application.[21] Topical forms of vitamin C include L-ascorbic acid, ascorbyl palmitate, and magnesium ascorbyl phosphate. Because L-ascorbic acid is water soluble, its epidermal absorption is somewhat limited. Ascorbyl palmitate and magnesium ascorbyl phosphate are esterified derivatives of vitamin C with enhanced lipophilicity, resulting in better absorption into the stratum corneum and increased stability in emulsions and solutions.[22] The concentration and acidity of the formulation also impacts stability and delivery. The percutaneous absorption of L-ascorbic acid has been demonstrated to be best in concentrations less than 20%, with higher concentrations failing to increase absorption.[21] Because the ionic charge on the ascorbic acid molecule must be removed to penetrate the stratum corneum, a pH of less than 3.5 is necessary.[9]

Ascorbic acid is essential to the proper structure and function of collagen, serving as a cofactor for both prolyl and lysyl hydroxylases during posttranslational processing of collagen. The ability of vitamin C to promote collagen synthesis via transcriptional activation of procollagen messenger RNA and to prevent collagen degradation via downregulation of collagen-degrading metalloproteinases has been histologically confirmed; these actions likely contribute to its antiaging effects.[23-25] An increase in grenz zone collagen and increased staining for messenger RNA type I collagen on skin biopsies after treatment with topical vitamin C confirms its efficacy in vivo.[25] The in vitro inhibition of tyrosinase by L-ascorbic acid likely accounts for its skin-lightening properties.[26] It also functions as an anti-inflammatory, suppressing activation of nuclear factor κB and tumor necrosis factor α.[21,27] Ascorbic acid also is capable of neutralizing free radicals, which reduces the oxidative stress thought to be a major factor in extrinsic aging.

Topical vitamin C formulations can be used as antiaging, anti-inflammatory, and skin-lightening agents. Several vehicle-controlled studies have demonstrated substantial improvements in aging skin treated with formulations containing vitamin C, including improvement in fine and deep wrinkles, skin tone, and overall texture.[24,28] The anti-inflammatory properties of vitamin C may prove beneficial for perioperative skin care. One placebo-controlled, split-face study showed substantial reductions in erythema following CO_2 laser resurfacing on the side treated with topical vitamin C.[29] Another study showed synergistic enhancement of trichloroacetic acid peels with the addition of topical ascorbic acid.[30] Its ability to suppress melanin formation via tyrosinase inhibition makes vitamin C a useful adjunctive treatment of unwanted pigmentation, with notable lightening of melasma and lentigines following application of magnesium ascorbyl phosphate.[26] Vitamin C also can be incorporated into sunscreens to enhance overall photoprotection and lessen oxidative stress following UV exposure.[31]

Vitamin B_3

Niacinamide, also known as vitamin B_3 or nicotinamide, is becoming a popular active ingredient in cosmeceuticals. Niacinamide is a precursor to the major redox coenzymes nicotinamide adenine dinucleotide phosphate and reduced nicotinamide adenine dinucleotide phosphate. These enzymes are involved in widespread biochemical reactions and play a major role in the body as antioxidants. Evidence of penetration and activity of niacinamide in the skin has been extrapolated by measuring an increase in nicotinamide adenine dinucleotide in epidermal tissue after application.[32-35]

The exact mechanisms of action for the clinical effects of niacinamide are not well elucidated. Niacinamide is thought to increase epidermal barrier function and decrease transepidermal water loss via upregulation of serine palmitoyltransferase, leading to increased epidermal synthesis of ceramides and lipids. In vitro and in vivo studies have shown an increase in differentiation of keratinocytes via effects on genes responsible for transcription of keratin 1.[36] Niacinamide also has been shown to reduce melanosome transfer from melanocytes to keratinocytes.[37]

Niacinamide functions as an antioxidant, anti-inflammatory, epidermal barrier–enhancing, and pigment-lightening agent. Its clinical efficacy in improving overall skin appearance has been proven in several well-designed placebo-controlled studies with statistically remarkable reductions in fine lines and wrinkles and improvements in roughness and surface texture.[32,38] Niacinamide has been shown to be an effective lightening agent with notable reductions in hyperpigmentation seen following topical application.[37,39] Its ability to increase ceramide synthesis translates to enhanced epidermal barrier function, improving skin hydration and resistance to irritating substances.[36] These functions are thought to contribute to its utility as an adjunctive treatment of rosacea and

disorders of barrier function, such as atopic dermatitis. The broad range of beneficial effects, safety, and tolerability of niacinamide make it a popular addition to antiaging cosmeceutical products.

Vitamin E

Vitamin E is the major lipophilic antioxidant in the body, with α-tocopherol representing the main bioactive form. This antioxidant is solely supplied by dietary means. Vitamin E is present with the greatest density in the lowest levels of the stratum corneum where it protects cell membranes from lipid peroxidation by free radicals. As such, it is a primary defense against reactive oxygen species from UV exposure and environmental impurities. The regeneration of vitamin E back to its reduced form is necessary for its sustained action; intracellular L-ascorbic acid, glutathione, and selenium are all important for this regeneration.[40-42]

Commercial preparations most often contain synthetic forms of vitamin E, consisting of 8 stereoisomers of α-tocopherol.[9] Although the esterified forms of vitamin E are more stable, they have limited protective qualities, as there is limited hydrolyzation to active forms in the skin.[43] Murine model studies have shown that oral and topical *d*-α-tocopherol are almost equivalent in photoprotective properties, while other forms of topical vitamin E were less effective.[44] Formulations containing α-tocopherol 0.2% have been shown to increase levels of vitamin E in the stratum corneum and decrease lipid peroxidation in vivo, insuring good penetration of topical preparations.[45] The inherent instability of vitamin E requires the addition of L-ascorbic acid to any topical formulations for its ability to stabilize vitamin E against UVA degradation and regenerate vitamin E back to its active form.[46]

Topical vitamin E typically is clinically used as an adjunctive photoprotective agent, especially in combination with L-ascorbic acid. One study demonstrated a 4-fold greater protection against UV-induced erythema using a topical formulation combining 15% L-ascorbic acid, 1% α-tocopherol, and 0.5% ferulic acid compared to a 2-fold increase with either agent alone. Their use prior to UV exposure led to decreased erythema, cytokine production, thymine dimer formation, and protein p53 upregulation.[31] There is no evidence to support topical vitamin E as an effective treatment for the reduction of visible signs of photoaging when used alone.

Vitamin K

Vitamin K, also known as phytonadione, serves as a cofactor in the biosynthesis of clotting factors II (prothrombin), VII, IX, and X. The interest in topical vitamin K began when Elson[47] demonstrated faster resolution of iatrogenically induced forearm bruising and actinic purpura following treatment with a topical cream containing vitamin K. Although the mechanism of action in this case is poorly elucidated, it does not appear to be its aforementioned role as a hepatic cofactor. Activation of epidermal γ-glutamyl carboxylase has been proposed as a possible step in the role of vitamin K in bruising.[48]

The utility of topical vitamin K formulations for treating laser-induced purpura has been studied with varying outcomes. One placebo-controlled, split-face study evaluated the effect of vitamin K oxide gel on purpura following pulsed dye laser treatment. Although there were no statistically significant differences in active versus placebo scores, there was a trend toward faster resolution of purpura with vitamin K.[48] Another study demonstrated a substantial decrease in the severity of bruising when topical vitamin K was applied following laser treatment; however, pretreatment with vitamin K had no effect on bruising outcomes.[49] The paucity and inconsistency of clinical trials prohibit any recommendations regarding topical vitamin K at this time; however, preliminary data suggest that this application deserves further study.

CONCLUSION

Familiarity with the process of cosmeceutical testing and development contributes to a better overall understanding of the utility and limitations of these products and allows us to critically evaluate marketing claims of efficacy. Because in vitro findings do not always translate to clinically significant effects, it is important to choose formulations with stable active ingredients that have been tested on humans in vehicle-controlled clinical studies. Cosmeceuticals containing vitamins can be useful therapeutic adjuncts and are popular among patients who desire naturally derived active ingredients. Although more research is needed in this field, good evidence exists to support the use of topically applied vitamins for improving the overall appearance and health of the skin.

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