Over-the-Counter Topical Skincare Products: A Review of the Literature

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ABSTRACT

Topical "anti-aging" products, with their seemingly limitless list of ingredients, make extensive claims to reduce wrinkles, fine lines, and sun damage, among others. Sales in the United States alone for cosmeceutical products are expected to increase by 7.4% per year to $8.2 billion by 2012. However, in this enormous industry, there has been a significant lack of rigorous controlled trials of efficacy. It is difficult for both dermatologists and consumers to make informed decisions in a market that is yet to be clearly defined and regulated. We elucidate the scientific basis for, as well as the literature behind, common active ingredients found in products intended to reverse photoaging, discuss some interesting new activities, and provide a review of several comprehensive studies on over-the-counter (OTC) products.

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INTRODUCTION

Ultraviolet (UV) radiation generates reactive oxygen species (ROS) in the skin that can oxidize nucleic acids, lipids, and proteins. This oxidative stress in the skin is associated with photoaging and skin cancer.[1] UV radiation also has been shown to induce matrix metalloproteinases (MMPs), which degrade dermal collagen and elastin. One of the ways skin naturally protects itself against UV damage is with antioxidants that neutralize the ROS that cause damage.[1] Based on this scientific evidence, the cosmetic skin care industry has popularized anti-aging creams and serums, many with added vitamins and other antioxidants. We provide a synopsis of many of these ingredients as well as an evaluation of the literature discussing their use in the treatment of photoaged skin.

Common Cosmeceutical Active Ingredients

Retinoids and Vitamin A

There is extensive literature on the use of topical retinoids, which are derivatives of vitamin A, a naturally occurring antioxidant in the skin. Tretinoin, or all-*trans* retinoic acid, is the biologically active form of vitamin A and one of the few therapeutic agents proven to repair photodamage.[2] It has been shown to improve fine facial wrinkles, mottled hyperpigmentation, and skin roughness.[3] However, tretinoin is often associated with skin irritation and is available only in prescription formulations. Retinoids available in OTC formulations, which include retinol, retinaldehyde, and retinyl palmitate, are less potent than tretinoin.

Retinol

Retinol is oxidized into retinaldehyde and then into retinoic acid, the biologically active form of vitamin A. A 2000 study found that treatment with 1% retinol reduces MMP expression and stimulates collagen synthesis in both sun-protected and photoaged skin.[4] Also, randomized controlled trials found significant improvement in fine wrinkles after 12 and 24 weeks of treatment, respectively.[5-7] Retinol is one of the best-studied active in OTC products and consistently has been shown to improve photoaged skin.

Retinaldehyde

Retinal or retinaldehyde is the aldehyde form of vitamin A. Retinaldehyde is often an intermediate during the conversion of retinol to retinoic acid.[8] Studies have shown that retinaldehyde can produce significant improvement in the appearance of both fine and deep wrinkles.[9,10]

Retinyl Palmitate

Retinyl palmitate is the ester of retinol and palmitic acid. Although retinyl palmitate has not yet been proven to be an effective anti-aging agent, it has been shown to inhibit the formation of thymine dimers in the presence of UVB rays.[11] It also is one of the active ingredients in an OTC product that was shown to produce significant fibrillin-1 deposition in a clinical study.[12]

α-Hydroxy Acids

α-Hydroxy acids (AHAs) are a class of compounds that consist of a carboxylic acid substituted with a hydroxyl group on the adjacent carbon. They are commonly seen on many OTC product labels as glycolic acid, malic acid, lactic acid, citric acid, α-hydroxyethanoic acid, α-hydroxyoctanoic acid, hydroxycaprylic acid, α-hydroxycaprylic acid, and hydroxyl fruit acids.

AHAs acids also are the agents used in chemical peels. Although physicians can use high concentrations of AHAs, OTC products must have less than a 10% concentration.

AHAs work by thinning the stratum corneum and speeding up normal skin exfoliation and regeneration.[13] A 1996 study found that a 25% AHA lotion produced significant reversal in markers of photoaging. The AHA treatment caused the epidermis to thicken, and papillary dermal changes included increased thickness, increased acid mucopolysaccharide, increased density of collagen, and improved quality of elastic fibers.[14] Also, AHAs can be effective even at the lower concentrations present in OTC formulations. A double-blind clinical trial evaluating 8% glycolic acid and 8% L-lactic acid creams found that both creams significantly improved the severity of photodamaged skin when used for a 22-week period.[15]

Ascorbic Acid

More commonly known as vitamin C, this topical has been shown to produce many beneficial effects supposedly due to its antioxidant properties. However, it must be kept in airtight, darkened bottles to prevent oxidation and inactivity.

Three in vivo studies have shown that ascorbic acid can promote type I and type III collagen synthesis when applied topically.[16-18] More recent studies have shown that topical ascorbic acid also can provide photoprotection against both UVA and UVB rays.[19,20] Finally, topical ascorbic acid has been shown to have an anti-inflammatory function because of its ability to suppress tumor necrosis factor α–induced nuclear factor κB activation.[21] Although these studies have shown various remarkable effects of vitamin C on the skin, they were limited by relatively small samples sizes.

Vitamin E

The lipid-soluble antioxidant vitamin E has been shown to have several beneficial effects when used topically. Its most biologically active form, α-tocopherol, has been shown to reduce and prevent sunburn, neutralize free radicals, and act as a humectant.[22] Recently, several studies have shown that vitamin E has a synergistic relationship with vitamin C. When the two topicals are applied simultaneously, they seem to have a strong protective effect against UV radiation when evaluated in vivo in humans. This phenomenon seems to be connected to the role of vitamin C in the regeneration of oxidized vitamin E.[23] Although vitamin E has been shown in in vitro studies to be involved in collagen and elastin breakdown through its effect on matrix metalloproteinases, no studies have definitively shown that vitamin E improves photoaged skin clinically.

α-Lipoic Acid

α-Lipoic acid (ALA) is an essential cofactor of the mitochondrial multi-enzyme complex and therefore plays an important role in energy metabolism. Topically, ALA has anti-inflammatory properties and acts as an exfoliant. In a study of 5% ALA applied topically for 12 weeks, it was shown to reduce skin roughness and fine wrinkles.[24] However, ALA has not been definitively shown to protect against UV-induced erythema.

Niacinamide

Nicotinamide or niacinamide is a potent antioxidant and is the amide form of nicotinic acid, which is vitamin B3 or niacin. Topical niacinamide improves the lipid barrier present in the stratum corneum and therefore reduces transepidermal water loss. Also, several studies have shown that topical niacinamide can significantly reduce fine lines and wrinkles.[25] It also has been shown to help eliminate hyperpigmented spots, most likely due to its role as an inhibitor of melanosome transfer.[25] Finally, recent studies have shown that niacinamide also can improve skin elasticity and reduce sallowness.[26]

N-Acetyl-Glucosamine

Glucosamine and its more stable derivative *N*-acetyl glucosamine (NAG) are amino monosaccharides with essential biochemical functions. Glucosmine and NAG also act as substrate precursors for the biosynthesis of polymers such as the glycosaminoglycan hyaluronic acid and in the production of proteoglycans. Topical glucosamine has been shown to accelerate wound healing and improve skin hydration when taken orally. It also may reduce skin wrinkles when used in conjunction with niacinamide.[27] Because of its stimulation of hyaluronic acid synthesis, glucosamine acts as an inhibitor of tyrosinase activation and therefore inhibits melanin production. Because of this role, topical glucosamine has been used to reduce hyperpigmentation.[28] Also, the combination of topical niacinamide and NAG has been shown to have a synergistic effect in reducing hyperpigmentation.[29]

Promising New Actives

Grape Compounds: Resveratrol, Flavenoids, and Grape Seed Extract

Resveratrol

This compound is a stilbenoid, a type of natural phenol produced by plants when attacked by pathogens. Resveratrol is most commonly found in the skin of red grapes and certain other fruits. The effects of resveratrol are currently a topic of numerous animal and human studies. Recently, in vitro and in vivo studies in animal models have found that topical resveratrol inhibited UV-induced carcinogenesis and photodamage.[30] It can be hypothesized that topical resveratrol also may have an effect on the visible signs of photoaging, which also is caused by exposure to UV radiation.

Flavenoids

A 2011 in vitro study showed that several antioxidant polyphenolic fractions from grapes protected human keratinocytes against UV-induced oxidative damage. The highest protective effect was for fractions rich in procyanidin oligomers and gallate esters.[31]

Grape Seed Extract

This antioxidant has been shown to speed wound contraction and closure.[32] Topically, it also has been shown to protect against UV radiation in humans.[33] Interestingly, a 2011 study found that oral use of grape seed extract was associated with a significantly decreased prevalence of squamous cell carcinoma.[34]

Although these grape compounds show promise as effective actives, in vivo studies need to be conducted to further evaluate their effects on photoaged skin.

Soy Isoflavones

These naturally occurring organic compounds in soybeans can act as phytoestrogens in mammals. Several studies have shown that oral soy isoflavones can improve skin appearance, especially in postmenopausal women. There is little literature supporting their role in improving skin appearance topically, but they have been shown to protect against UVB radiation.[35]

Tea Polyphenols

Green tea has long been thought to be associated with various health benefits ranging from decreased risk for heart disease to weight loss. Some recent research has shown that polyphenols from green tea as well as white tea can suppress carcinogenic activity from UV radiation.[36]

However, another recent study found that histopathologic analysis of sun-exposed skin treated with topical green tea polyphenols showed no statistically significant difference in photoaging parameters compared with placebo. Moreover, the green tea–treated group actually had significantly more wrinkling from baseline compared with the placebo group. Overall, there seems to be conflicting literature on the function of green tea polyphenols, and more comprehensive studies are needed.[37]

Derivatives of *Coffea arabica*

Extracts from *C. arabica* berries, which are used in the production of coffee, contain polyphenols. They have stronger antioxidant properties than pomegranate, vitamins C and E, and green tea. In a vehicle-controlled blinded study, *C. arabica* was shown to improve fine lines, skin texture, and skin pigmentation. Interestingly, extracts from the leaves (caffeine) has been used to reduce undereye puffiness and temporarily improve the appearance of cellulite.[38]

DMAE

Dimethylaminoethanol (DMAE) is an analog of choline and a precursor of acetylcholine. A 2005 study showed that a 3% DMAE facial gel applied daily for 16 weeks reduced forehead lines and periorbital fine wrinkles.[39] The formulation also improved lip shape and fullness and the overall appearance of aging skin. A more recent study in both hairless mice and human skin showed that a DMAE-supplemented formulation led to increased dermal thickness, and DMAE also induced an increase in collagen fiber thickness.[40] Formulations both with and without DMAE enhanced the stratum corneum water content in forearm skin.

Comprehensive Studies of Formulations

There are a multitude of studies evaluating specific active ingredients, yet there are few studies of OTC formulations, which are often a mixture of many ingredients. Although there is a significant lack of rigorous trials of efficacy for these products, we review the existing literature on OTC formulations below.

A 2009 study[12] evaluated the No7 Protect & Perfect Intense Beauty Serum by Alliance Boots (a water-in-silicone emulsion with glycerin, emollients, and ingredient complex comprising sodium ascorbyl phosphate, Panax ginseng, *Morus alba, Lupinus alba*, tocopherol, palmitoyl oligopeptide, palmitoyl tetrapeptide-7, *Medicago sativa,* and retinyl palmitate). This is one of very few studies evaluating an OTC cosmetic "anti-aging" product with a rigorous double-blind, vehicle-controlled trial of efficacy. This study effectively showed that an OTC product can cause fibrillin-1 deposition and may have the potential to repair and clinically improve photoaged skin.

Sixty photoaged subjects were recruited to a controlled trial of the test product used once daily for 6 months on the face and hands. Clinical assessments were performed at recruitment and following 1, 3, and 6 months of use. Twenty-eight subjects had skin biopsies at baseline and at 6 months of treatment for immunohistochemical assessment of fibrillin. All subjects received the test product for an additional 6 months. Final clinical assessments were performed at the end of this open period, and 27 subjects received the test product for the full 12 months.

In the clinical trial, at 6 months, 43% of subjects on the test product had an improvement in facial wrinkles, whereas only 22% of subjects using the vehicle (product without ingredient complex) had clinical improvement. After 12 months, there was a significant benefit of the test product over that projected for the vehicle. Most interestingly, there was significant deposition of fibrillin-1 in skin treated for 6 months with the test product.

However, the study had several weaknesses. First, there was no statistically significant improvement clinically in facial wrinkles. Also, only 27 subjects received the product for 12 months (when the significant benefit of the test product was seen). Also, more clinical and histological markers could have been evaluated in order to provide even more valuable information about efficacy.

Another recent study evaluated Olay Professional Pro-X: Age Repair Lotion SPF 30, Wrinkle Smoothing Cream, and Deep Wrinkle Treatment (all of the test products in the regimen contained niacinamide, the peptides Pal-KT and Pal-KTTKS, and carnosine.[41] The daytime SPF 30 lotion also contained a broad-spectrum sunscreen

and vitamins C and E. The wrinkle treatment contained 0.3% retinyl propionate). This study was particularly interesting because it effectively compared the clinical efficacy of an OTC product with that of tretinoin, which is often considered the benchmark prescription topical therapy for improving facial wrinkles.

This was an 8-week, randomized parallel-group study. A total of 196 women with moderate to moderately severe periorbital wrinkles were evaluated. A total of 99 subjects on the treatment regimen were compared with subjects using 0.02% tretinoin plus moisturizing SPF 30 sunscreen (n=97). Subject cohorts (n=25) continued treatment for an additional 16 weeks. Changes in facial wrinkles were assessed by expert grading, image analysis of digital images, and a self-assessment questionnaire.

The treatment regimen significantly improved the appearance of wrinkles after 8 weeks relative to tretinoin. Also, the treatment regimen was better tolerated than tretinoin in all of the measures. Some potential weaknesses in this study include the fact that tretinoin is more irritating to the skin than the treatment products and thus could have affected the results; subjects were not blinded, which could have affected the subjects' self-assessments; and no histological markers were evaluated.

Another interesting study from 2009 that evaluated a topical medication with rigorous trials of efficacy looked at topical fluorouracil for actinic keratoses and photoaging.[42] Although this study did not evaluate an OTC product, it still can serve as a model for other future studies.

The study evaluated gene and protein expression of molecular effectors of epidermal injury, inflammation, and extracellular matrix remodeling 24 hours after fluorouracil treatment. It also measured clinical improvement by evaluators, photography, and patient questionnaires. The study found that one day after the final fluorouracil treatment, gene expression of the effectors of epidermal injury (keratin 16), inflammation (interleukin 1β), and extracellular matrix degradation (MMPs 1 and 3) was significantly increased. Types I and III procollagen messenger ribonucleic acid were induced at week 4 (7-fold and 3-fold, respectively). Type I procollagen protein levels were increased 2-fold at week 24.

Overall, it seems that there is a great necessity for more rigorous studies of OTC skincare products. This is especially imperative because these products comprise such a significant percentage of the enormous cosmeceutical industry. The average woman in the United States uses at least 25 products containing hundreds of the ingredients on her skin daily. Very few of these OTC products, which may cost hundreds of dollars, have been subjected to rigorous controlled trials of efficacy. With the current lack of comprehensive information on these products, it is extremely difficult for both clinicians and consumers to ascertain their efficacy. Future studies can ameliorate this problem by not only evaluating products for clinical efficacy but also using histologic and gene and protein expression to ascertain their effectiveness.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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