

Effects of Topicals on the Aging Skin Process

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KEYWORDS

- Topicals • Skin aging • Retinoids • Retinoic acid • Glycolic acid • Ascorbic acid • Vitamin C
- Peptides

KEY POINTS

- Retinoids are the most extensively studied skin topicals, and have been found to significantly improve the appearance of mild to moderate photodamage.
- Glycolic acid speeds up the process of exfoliation and skin cell turnover by weakening the intercellular cohesion of the stratum corneum, and appears to improve skin dyspigmentation better than fine wrinkles.
- Ascorbic acid is thought to act as an antioxidant and to also stimulate the production of procollagen types I and III.
- Peptides used in topical antiaging products have multiple applications and can be categorized into 4 groups based on their modes of action:
 - Carrier peptides
 - Signal peptides
 - Enzyme-inhibitor peptides
 - Neurotransmitter-inhibitor peptides

INTRODUCTION

Skin aging is a product of two processes:

1. Intrinsic, or chronologic aging, which is mainly genetic
2. Extrinsic aging from environmental stressors such as sun exposure or smoking

The resulting skin changes include dyschromia, roughness, and fine rhytids followed by persistent deeper folds. Structurally this is explained by dermal atrophy, decreased collagen, loss of subcutaneous fat, loss of inherent elasticity, and increased melanogenesis.¹

Topical antiaging products were estimated to be a \$2 billion industry in the United States in 2000,²

largely due to people seeking to find cost-effective, noninvasive methods to reverse aging. However, the Food and Drug Administration (FDA) does not oversee these products, whose efficacy is largely unproved.

This article presents the supporting evidence for the some of the most popular topical antiaging products. The evidence is taken from the literature and the primary author's research, comprising previously published data and new results from ongoing projects.

RETINOIDS

The effect of retinoids has been extensively studied in humans and animals. Retinoic acids

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have specific retinoic acid receptors with DNA-binding domains, and accomplish their effects in the skin through regulated gene expression.³ Retinoids are thought to increase fibroblast growth and procollagen synthesis, as well as inhibit the production of matrix-degrading metalloproteinases. These changes are made at the mRNA, protein, and enzyme activity levels.⁴

In the literature, there is conclusive evidence that retinoids improve the appearance of mild to moderate photodamage, thus giving the skin a more youthful appearance. A Cochrane review including 12 double-blind randomized controlled trials (RCTs) comparing tretinoin cream with placebo showed that tretinoin cream in concentrations of 0.02% or higher significantly improved fine and coarse wrinkles, roughness, freckles, and pigmentation.⁵

Tazarotene, a selective retinoic acid receptor agonist, and isotretinoin are less researched retinoids, but they have also been shown to significantly improve fine wrinkling and mottled hyperpigmentation. Kang and colleagues⁶ compared the effect of 4 different concentrations of tazarotene with 0.05% tretinoin and placebo in an RCT. The investigators found that after 24 weeks of daily application, tazarotene of all concentrations (0.01%–0.1%) and 0.05% tretinoin cream showed significant improvement of fine wrinkling in comparison with the vehicle cream. However, for mottled hyperpigmentation, only 0.1% tazarotene cream and 0.05% tretinoin cream showed significant improvement over the vehicle cream. Isotretinoin 0.1%, when applied for 36 weeks, was also shown to significantly improve fine wrinkling and mottled pigmentation in patients with moderate to severe photodamaged skin when compared with placebo.⁷

Author Research on Topical Tretinoin

The authors' research evaluated the effects of topical 0.05% tretinoin cream on the dorsal skin of nonirradiated hairless mice. Profilometric evaluation showed significant effacement of wrinkles, with a decrease in roughness texture factor as well as a decrease in fine and coarse lines. Histologic evaluation showed significantly increased epidermal width and increased nuclear volume in the granular, spinous, and basal layers. An immunohistochemical evaluation of epidermal proliferating cell nuclear antigen (PCNA) showed an increased proliferation index of epidermal keratinocytes.^{8,9}

Risks and Side Effects in Retinoid Use

Although the advantages of retinoids are well documented, the use of retinoids is not without

risk. Adverse effects of retinoids include erythema, scaling, dryness, and irritation. Most adverse effects peak during the first 2 weeks of application and decrease with time. Of the 12 RCTs included in the evaluation of tretinoin cream the attrition rates were 7% to 25%, which is likely due to these undesirable side effects. Higher doses are associated with more adverse events, and the studies with the highest concentrations of tretinoin (0.1%) had the highest attrition rates.

Retinoids are also teratogens, and treatment of pregnant women with topical retinoids is not advised. However, the prevalence of anomalies in exposed women was not shown to be greater than the prevalence in nonexposed women. Topical tretinoin does not affect the endogenous levels of tretinoin or its metabolites, and no systemic adverse effects have been reported for topical tretinoin application.¹⁰

α-HYDROXYL ACIDS/GLYCOLIC ACID

α-Hydroxyl acids (AHAs), such as glycolic acid (GA) or lactic acid, are thought to speed up the process of exfoliation and skin cell turnover by weakening the intercellular cohesion of the stratum corneum.¹¹ At concentrations of 25%, AHAs are thought to promote increased epidermal thickness as well as increased production of collagen and hyaluronic acid. The FDA limits over-the-counter concentrations of AHAs to 10%, and peels containing 40% AHAs can only be applied by medical doctors.¹²

In the literature there is some evidence supporting the antiaging effects of AHAs. Stiller and colleagues¹³ found 8% GA to significantly improve skin sallowness in an RCT after 22 weeks of daily treatment. Lactic acid 8% in this same trial was found to significantly decrease mottled hyperpigmentation, sallowness, and roughness compared with the vehicle control. In an RCT of 75 patients comparing 5% GA with placebo, Thibault and colleagues¹⁴ found a significant change in general skin texture and discoloration, but no significant decrease in skin wrinkling. Application of a medical-strength 50% GA peel for 5 minutes weekly for 4 weeks was shown to improve mild photoaging of the skin in a double-blind, vehicle-controlled study of 41 patients.¹⁵ This study showed significant improvement in fine wrinkling and solar keratoses. Histology showed thinning of the stratum corneum, granular layer enhancement, and epidermal thickening.

Author Research on AHAs

The senior authors evaluated the effect of 12% GA gel on the dorsal skin of nonirradiated hairless

mice. Of 5 products tested (retinoic acid, GA, estrogen, vitamin C, and soy), GA caused the most dramatic thickening of the epidermis (**Fig. 1**). The epidermal thickness increased from an average of 18.3 μm to 55.5 μm , almost triple the thickness of the untreated skin. The nuclear volume of the basal layer and the spinous layer was also the highest in the GA group, and PCNA-positive cells were also markedly increased after treatment with GA.⁹

Risks and Side Effects in AHA Use

Skin erythema and flaking are listed as the major side effects of treatment with AHAs, the effects becoming more pronounced as the concentrations of the products increase. AHAs are also known to increase skin photosensitivity, and it has been shown that GA and ultraviolet-B (UVB) radiation inhibits proliferation and induces apoptosis in human keratinocytes.¹⁶

VITAMIN C/ASCORBIC ACID

Ascorbic acid is thought to affect skin aging by two mechanisms, the first of which is its antioxidant property. Ascorbic acid is an efficient water-soluble antioxidant, and is able to neutralize free radicals both intracellularly and extracellularly.¹⁷ The second mechanism is collagen synthesis. Ascorbic acid has been shown to stimulate the synthesis of procollagen types I and III in cultured human skin fibroblasts.¹⁸ Ascorbic acid is also necessary to form enzymes necessary for cross-linking collagen molecules, and therefore influences the quality of collagen produced.

In the literature, a few small RCTs support significant antiaging effects of ascorbic acid. In a double-blind study of 19 patients, Humbert and colleagues¹⁹ found a significant improvement in roughness, suppleness, and small-wrinkle scores

on comparing 5% ascorbic acid with placebo. Evaluation of skin biopsies of 10 of these patients showed evidence of repair of elastic tissue in the ascorbic acid group; however, there was no difference in melanocyte distribution. In a study of 10 patients comparing 10% ascorbic acid with placebo, Fitzpatrick and Rostan²⁰ showed a small significant decrease in the wrinkling scores of the treatment sides. However, there was no difference in pigmentation between the treated and untreated sides of the patients. Biopsies of the lateral cheeks of 4 of the patients showed increased Grenz zone collagen and increased staining for mRNA for type I collagen. A third trial including 19 patients showed significant improvement, with ascorbic acid better than the control for fine wrinkling, tactile roughness, coarse rhytids, skin laxity/tone, sallowness/yellowing, and overall features. Of all of the parameters measured, the greatest improvement was noted in the fine wrinkling.²¹ Most recently, a split-face study of 20 patients with 23.8% ascorbic acid showed significant improvement in dyspigmentation, surface roughness, and fine lines.²²

Author Research on Ascorbic Acid

In a comparison of the effects of 15% ascorbic acid with the effects of retinoic acid, GA, estrogen, and soy, ascorbic acid caused the smallest increase in epidermal thickness, the nuclear volumes of the different layers of the epidermis being the lowest among the 5 treatment groups. However, the expression of PCNA, which is described to play an important role in cytologic differentiation and growth, was still significantly increased in the skin of mice treated with ascorbic acid (**Fig. 2**).⁹

Risks and Side Effects in Topical Vitamin C Use

The adverse effects of topical ascorbic acid are mild compared with the effects of retinoic acid

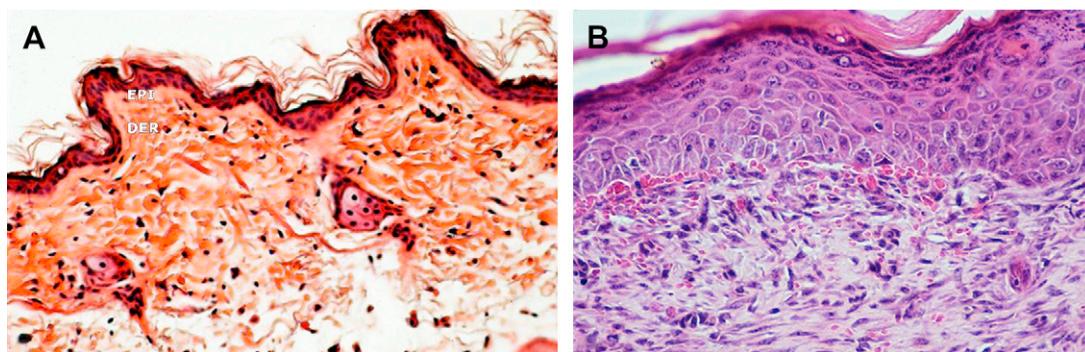


Fig. 1. (A) Histologic preparation of control mouse skin showing a thin epidermis (EPI). DER, dermis (original magnification $\times 200$). (B) Mouse skin treated with glycolic acid for 2 weeks. The epidermis is highly differentiated and a profusion of fibroblasts is observed in the dermis (original magnification $\times 200$).

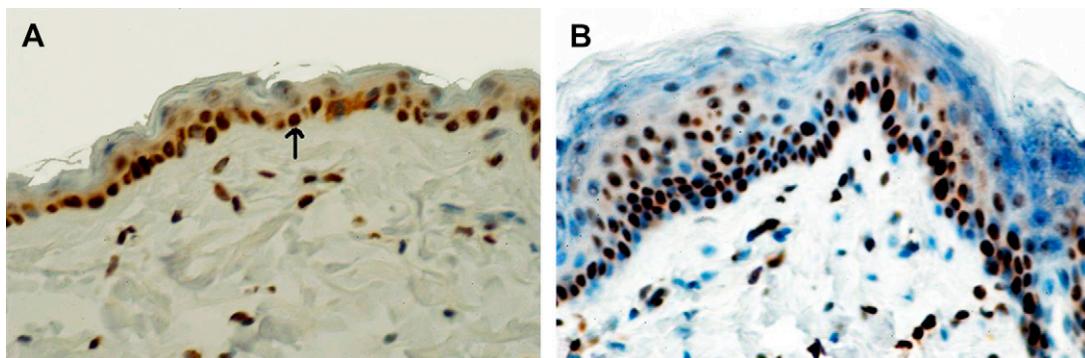


Fig. 2. (A) Control proliferating cell nuclear antigen (PCNA) reaction in mouse skin epidermis, showing dark positive cells (*arrow*) limited to the basal layer (original magnification $\times 200$). (B) PCNA reaction in a mouse treated with topical vitamin C, showing proliferation of positive cells and peripheral spread. Nonreactive cells stained with hematoxylin (original magnification $\times 200$).

and GA. Adverse effects include skin flaking and erythema. In one of the RCTs discussed earlier, patients described a unilateral stinging, making it difficult to keep the study blinded.²⁰

PEPTIDES

Peptides used in topical antiaging products have multiple applications. Gorouhi and Maibach²³ categorized topical peptides into 4 groups based on their modes of action:

1. Carrier peptides
2. Signal peptides
3. Enzyme-inhibitor peptides
4. Neurotransmitter-inhibitor peptides

Carrier peptides are short chains of amino acids with a net positive charge, which cross the cell membrane in a receptor-independent and energy-independent manner.²⁴ Carrier peptides allow the transmembrane delivery of bioactive molecules as well as the delivery of collagen and elastin into the cell. The most common application has been for the delivery of trace elements such as copper and manganese into the cells. These elements are necessary for skin healing and enzymatic processes.

Signal peptides are aimed at stimulating matrix-protein production, collagen, and elastin synthesis. The effects of palmitoyl KTTKS (palmitoyl pentapeptide), a signal peptide, are documented in the literature. Palmitoyl pentapeptide is a subfragment of type I collagen, and is thought to promote synthesis of type I collagen by upregulating transforming growth factor β and maintaining the stability of mRNA.²⁵ In a double-blind RCT with 93 patients, topical 3 ppm palmitoyl pentapeptide was found to significantly reduce the length of fine wrinkles within 12 weeks.²⁶

An example of an enzyme-inhibitor peptide is soy protein, which inhibits proteinases and is frequently used as an antiaging skin moisturizer. A double-blind, placebo-controlled study applying 2% soy extract to the forearms of 19 volunteers showed a significant increase in the papillae index (number of papillae per area) in the soy-extract group.²⁷ This increased interdigitation of the epidermis and dermis is thought to be a sign of rejuvenation, as the papillae index normally decreases with age.

Neurotransmitter-inhibitor peptides inhibit acetylcholine release at the neuromuscular junction. Subsequent paralysis of the muscles smoothes the overlying skin and prevents wrinkling secondary to facial animation. Botox is an example of such a neurotransmitter-inhibitor, and is also available as a topical gel. In a randomized, placebo-controlled study evaluating the effect of RT001 botulinum toxin type A topical gel on moderate to severe lateral canthal lines, 89% of 45 subjects achieved significant reduction in their lateral canthal lines at 4 weeks.²⁸

Author Research on Peptides

The authors studied the effects of a peptide lotion with pentapeptides and hexapeptides. After daily application to the dorsal skin of the hairless mouse, the total dermis thickness was noted to be significantly higher than the control, with an almost equal effect as that with retinoic acid. A discernible improvement was also noted in the surface profile, with a pronounced reduction in surface-roughness factor. In further studies, a statistically significant reversal of epidermal edema caused by chronic UVB radiation with topical application of a peptide cream, and a vitamin C preparation was observed in an experiment with a mouse model (Bhattacharyya and colleagues, in preparation, 2012) (**Fig. 3**).

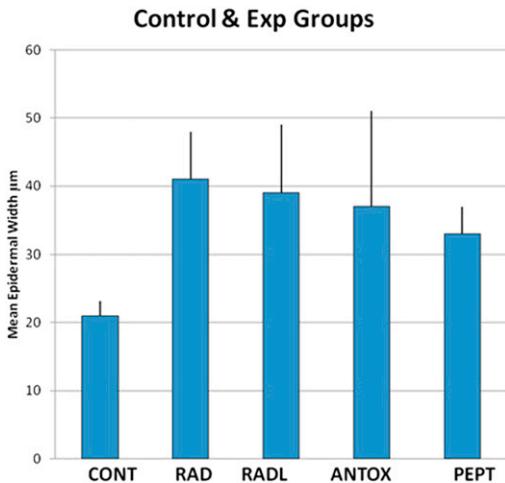


Fig. 3. Epidermal width in control (CONT) and experimental groups (mean \pm SD). RAD, animals exposed to chronic ultraviolet-B radiation (8 weeks); ANTOX and PEPT, radiated skin topically treated with antioxidant solution and peptide cream, respectively, for 4 weeks; RADL, skin adjacent to treated areas and left alone for 4 weeks for comparison.

The authors also studied the effects of soy cream on the dorsal skin of the hairless mouse. The beneficial effect of soy on the skin microrelief (reduction of fine lines and wrinkles, roughness) was almost equal to that of retinoic acid. The total dermis thickness, however, did not increase as much as in the skin treated with retinoic acid.⁸

Risks and Side Effects in Topical Peptide Use

There are few data in the literature concerning adverse effects of topical peptides. Palmitoyl pentapeptide appears to be extremely well tolerated. In the study of 93 patients, there was no sign of irritation (erythema, skin flakiness, stinging) in any of the patients.²⁶ However, peptides should be used with caution, as there are conceivable grave consequences of introducing materials into cells and modulating transcription factors.

SUMMARY

Topical antiaging products are very popular because people are seeking cost-effective, noninvasive methods to improve their appearance. Retinoids are the most widely researched antiaging topicals, and there are several double-blind RCTs proving that they significantly improve fine and coarse wrinkles, roughness, freckles, and pigmentation.⁵ GA also has evidence from large RCTs to support its efficacy. GA appears to be better for the reduction of pigmentation changes than reduction of fine wrinkles. Other products

such as vitamin C and peptides show promise, but lack extensive data to support their efficacy.

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