

# 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.<sup>1</sup>

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

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.<sup>3</sup> 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.<sup>4</sup>

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.<sup>5</sup>

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 colleagues<sup>6</sup> 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.<sup>7</sup>

#### ***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.<sup>8,9</sup>

#### ***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.<sup>10</sup>

#### ***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.<sup>11</sup> 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.<sup>12</sup>

In the literature there is some evidence supporting the antiaging effects of AHAs. Stilller and colleagues<sup>13</sup> 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 colleagues<sup>14</sup> 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.<sup>15</sup> 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

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