



# Cosmeceuticals: The Evidence Behind the Retinoids

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## Abstract

A wide range of cosmeceutical products are available on the market currently, but evidence to support their use is often lacking in the literature. Specifically, there is a substantial amount of evidence supporting the efficacy of tretinoin in photoaging, but the evidence supporting retinoid-based cosmeceuticals remains sparse. The authors review the current data in the literature related to vitamin A–derived cosmeceutical products and conclude that cosmeceuticals containing retinaldehyde have been shown in large randomized, controlled trials to have the most beneficial effect on aging skin.

## Keywords

cosmeceuticals, cosmetic medicine, photoaging, tretinoin, retinaldehyde

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Vitamin A and its derivatives, also known as retinoids, are commonly used in topical antiaging preparations. These cosmeceutical products may be classified as either natural or synthetic derivatives (Table 1) and may be purchased over the counter without a medical prescription. Certain formulations, however—such as tretinoin, isotretinoin, alitretinoin, tazarotene, and adapalene—are classified as prescription medications (and therefore do not qualify as cosmeceuticals). For the purposes of this review, we explore only the cosmeceutical products.<sup>1</sup>

## MECHANISMS OF ACTION

Retinoids are commonly used in cosmetic products due to their effectiveness at regulating epithelial cell growth and differentiation. Retinoids, which are lipophilic molecules, exert this effect by their ability to diffuse through cellular membranes. Once they are inside the cells, they bind to specific nuclear receptors and modulate expression of the genes involved in cellular proliferation and differentiation.<sup>2</sup> Retinoids naturally occur in the skin, with retinol and retinyl esters being the most abundant form. Retinol is produced in the small intestine via one of two mechanisms: hydrolysis of retinyl esters or oxidation of carotenoids. Conversion of retinol to the active form involves oxidation to retinaldehyde, which is then oxidized to form the active tretinoin.<sup>2</sup>

**Table 1.** Natural and Synthetic Vitamin A Derivatives

Natural	Synthetic
Retinol	<i>Tazarotene</i>
Retinyl-palmitate	<i>Adapalene</i>
Retinyl-acetate	
Retinaldehyde	
<i>Tretinoin</i>	
<i>Isotretinoin</i>	
<i>Alitretinoin</i>	

Prescription-only preparations (which are not addressed in this article) have been italicized.

## Genomic Actions

The genomic actions of active retinoid are mediated via binding to a cellular retinoic acid binding protein (CRABP),

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which transports the retinoid to the nucleus. There are currently two recognized types, CRABP-1 and CRABP-2. CRABP-2 is highly expressed in the epidermis. Six specific nuclear retinoic acid receptors (RAR) have been found: RAR- $\alpha$ , RAR- $\beta$ , RAR- $\gamma$ , and the retinoid X receptors (RXR) RXR- $\alpha$ , RXR- $\beta$ , and RXR- $\gamma$ . Retinoic acid bound to an RAR directly binds to retinoic acid response elements in the DNA and modulates transcription of specific genes.<sup>3</sup> The actions include prevention of matrix metalloproteinase activation, oxidative stress, and regeneration of the extracellular matrix. Retinoids also inhibit keratinocyte differentiation and stimulate epidermal hyperplasia.<sup>2</sup>

### Nongenomic Actions

Retinoids may also exert a biological effect independent of their binding to nuclear receptors.<sup>2</sup> These nongenomic actions include ultraviolet (UV) absorption, as well as antimicrobial, antioxidant, and pigment activities.

#### Ultraviolet filter

Retinoid molecules contain a side chain with conjugated double bonds that appears to absorb UV light. Animal studies have shown natural retinoids to be effective in preventing UVB-induced apoptosis and DNA photodamage. Antille et al<sup>4</sup> used a retinoid vehicle (topical retinyl palmitate 2%) and sun protection factor (SPF) on the buttocks of six individuals and exposed them to UVB. In this nonrandomized small clinical trial, results showed that retinyl palmitate was as efficient as SPF 20 in preventing UVB-induced erythema and thymine dimmer formation.

#### Antibacterial activity

Retinaldehyde compounds are highly reactive, especially with alcohols and amines, and this may explain their antibacterial action, which is independent of nuclear receptors. Pechere et al<sup>5</sup> conducted *in vitro* and *in vivo* studies investigating the antibacterial activity of retinoids. The *in vitro* studies showed that retinaldehyde, in comparison to retinoic acid and retinol, was the only retinoid to possess antibacterial activity. *In vivo* studies revealed that 0.05% retinaldehyde applied to the forehead and forearm correlated with decreases in bacterial counts when used for two weeks. The authors concluded that this antibacterial activity was due in part to the aldehyde group in the isoprenic lateral chain.

#### Antioxidants

*In vitro* studies have shown that retinoids exert free radical scavenging activity. Sorg et al<sup>6</sup> showed that in hairless mice, topical retinaldehyde 0.05% prevented peroxidation of epidermal lipids when topical menadione was applied. However, there is a lack of clinical evidence regarding the efficacy of topical retinoids as antioxidants.

#### Pigmentation actions

Retinoids have been used as bleaching agents in certain preparations. Tretinoin, for example, has been successfully used with hydroquinone for depigmentation of skin.<sup>2</sup> Yoshimura et al<sup>7</sup> conducted a small, uncontrolled, nonrandomized clinical trial using 10% retinol, 5% hydroquinone,

and 7% lactic acid. In their 18 patients, the authors reported some improvement in 88.9% of patients, as assessed by two surgeons reviewing pre- and posttreatment photographs.

## CLINICAL EVIDENCE BEHIND RETINOID-BASED COSMECEUTICALS

A large body of evidence supports the use of tretinoin in the treatment of photoaging.<sup>3</sup> The evidence behind nonprescription retinoids that are commonly used in cosmeceuticals is, however, less abundant. A review of the literature was conducted for the different retinoids used in cosmeceuticals and a summary is provided below for each derivative.

### Retinyl-Acetate and Retinyl-Palmitate

Retinyl-acetate and retinyl-palmitate, both vitamin A ester derivatives, are considered to be the least effective topical retinoids. This may be explained by the mechanism resulting in the conversion of retinyl-palmitate to the active tretinoin. The first step involves cleavage of the ester bond, followed by conversion of the retinol to tretinoin via a two-step oxidative process.<sup>8</sup>

Green et al<sup>9</sup> investigated the clinical and histological effects of retinyl propionate cream on photoaging using a double-blind, randomized, placebo-controlled trial with 80 patients. Seventy-five patients completed the first 24 weeks of the trial and 59 completed the full 48 weeks. They noted that, despite minimal improvement, the results were not statistically significant in comparison to the placebo; no improvement was noted in subject self-assessment between treatment and placebo groups. Through clinical, histological, or profilometric measures, no significant differences were noted between placebo and retinyl propionate.

Watson et al<sup>10</sup> conducted a clinical trial comparing three commercially available creams and retinoic acid. The three creams were a moisturizer, a 2% total active complex containing peptides and antioxidants, and a 6% total active complex that also contained retinyl palmitate <0.2%. Their nine volunteers underwent punch biopsies from their forearms following 12 days of patch testing with the products. The results indicated that the 6% total active complex formulation increased deposition of fibrillin-1, comparable to that seen with retinoic acid, and also procollagen-I. They concluded that it was unclear whether these changes could be attributed solely to the presence of the retinyl palmitate.

In summary, there is no significant evidence in the literature to support the effectiveness of topical retinyl-acetate and retinyl-palmitate as antiaging agents. Topical retinyl palmitate, however, has been shown in animal and human studies to offer some degree of UV protection.

### Retinol

Retinol, a precursor to retinaldehyde and retinoic acid, is widely used in cosmetic products, but again, there is little evidence to support the efficacy of this derivative in the treatment of photoaging.

Kang et al<sup>11</sup> conducted a randomized, double-blind study comparing topical retinol, retinoic acid, and a vehicle alone. In their study, a small sample of healthy volunteers had the agents applied to their buttock skin; biopsies were taken at 0, 6, 24, and 96 hours. Clinically, application of retinoic acid induced significant erythema in comparison to retinol, which produced none or only trace erythema. Retinol was shown to cause epidermal thickening comparable to retinoic acid. Retinol also induced increased mRNA and protein levels of CRABP-2. The study also showed significant accumulation in epidermal retinyl ester with retinol application. Topical retinol, however, did not produce an increase in retinoic acid levels.

Kafi et al<sup>12</sup> conducted a randomized, double-blind, vehicle-controlled study investigating the effectiveness of topical 0.4% retinol in improving the signs of naturally aged upper arm skin. In their study, 23 patients completed the 24-week trial. Their results, as assessed by two blinded dermatologists, indicated clinical improvement in fine wrinkles after four weeks of treatment. Biopsies of their patients revealed increased glycosaminoglycan expression and collagen production. On the basis of their data, the authors recommended at least two to three months of treatment for significant improvement to be noted.

The literature shows that retinol has potentially beneficial effects in the treatment of aged skin. This evidence is based on small subjective clinical studies, but histological findings indicate a basis for improvement of aged skin.

## Retinaldehyde

Saurat et al<sup>13</sup> investigated the effect of varying doses of topical retinaldehyde on human skin using histological, immunohistochemical, and electronmicroscopic techniques. Healthy volunteers had application of 0.5%, 0.1%, or 0.05% retinaldehyde for one to three months on one forearm and a vehicle on the other. Biopsies were then taken from either forearm and analyzed. Biological activity was shown by induction of CRABP-2 mRNA and protein. Their study showed that the rank order for CRABP-2 increase was retinoic acid, retinaldehyde, 9 cis-retinoic acid, retinol, and  $\beta$ -carotene. In the 229 volunteers, there was a significant dose-dependent increase in epidermal thickness, keratin 14 immunoreactivity, and also the area of distribution of involucrin, transglutamine, and filaggrin immunoreactivity. At a high concentration (0.5%), the morphological changes noted were similar to those induced by 0.1% topical retinoic acid. The study also showed improved tolerance with decreasing concentration of preparation.

Creidi et al<sup>14</sup> conducted a randomized, double-blind, controlled trial comparing topical retinaldehyde (0.05%), retinoic acid (0.05%), and a vehicle. In this study, 125 patients were recruited across three centers in France. Patients were asked to apply the topical agents for 44 weeks. A review was performed at 18 and 44 weeks with profilometric techniques involving silicone molds of the crow's feet area on each patient's face. At 18 weeks, retinaldehyde and retinoic acid results showed a significant reduction in wrinkles and roughness. The effect at 44 weeks was still significant but

less pronounced. The vehicle agent showed no significant improvement at either review period. It was also noted that retinaldehyde was better tolerated and caused less irritation than retinoic acid throughout the study period.

Retinaldehyde has been shown to be effective in improving fine and deep wrinkles. The evidence supporting its use is based on larger scale studies of the previously mentioned retinoids. Retinaldehyde is well tolerated by patients, even at higher concentrations, unlike tretinoin, which can cause significant irritation. A concentration of 0.05% appears to be effective, is well tolerated, and allows prolonged use on sensitive areas such as the face.

## CONCLUSIONS

There is a substantial amount of evidence supporting the efficacy of tretinoin in the treatment of photoaging. The evidence supporting retinoid-based cosmeceuticals, however, remains sparse. There are a number of in vitro studies, with a smaller number of in vivo studies. Based on the hierarchical levels of evidence (with well-designed, randomized, controlled trials providing the highest level), retinaldehyde appears to be the only retinoid-based cosmeceutical to be effective in the treatment of photoaging. A large, randomized, controlled trial assessing retinyl propionate concluded that it had no significant effect on photoaging. There is evidence from a small, randomized, controlled trial showing that retinol has effects on human skin and supporting its potential as an agent against photoaging. However, large-scale clinical studies would need to be undertaken to investigate this further. Therefore, we conclude that products containing retinyl-acetate or retinyl-palmitate are unlikely to have a significant beneficial effect, but retinaldehyde-containing cosmeceuticals have evidentiary support for their benefits in patients with aging skin. Retinol has potential benefit, but more research is needed.

## Disclosures

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