

Antioxidants Used in Skin Care Formulations

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The formation of free radicals is a widely accepted pivotal mechanism leading to skin aging. Free radicals are highly reactive molecules with unpaired electrons that can directly damage various cellular structural membranes, lipids, proteins, and DNA. The damaging effects of these reactive oxygen species are induced internally during normal metabolism and externally through various oxidative stresses. The production of free radicals increases with age, while the endogenous defense mechanisms that counter them decrease. This imbalance leads to the progressive damage of cellular structures, and thus, results in accelerated aging. Antioxidants are substances that can provide protection from endogenous and exogenous oxidative stresses by scavenging free radicals. Topical antioxidants are available in multivariate combinations through over-the-counter skin care products that are aimed at preventing the clinical signs of photoaging.

Skin aging is a complex process involving various genetic, environmental, and hormonal mechanisms. One can differentiate between intrinsic, chronologic aging and extrinsic, "environmental" aging; both processes occur in conjunction with the other and are superimposed on each other. Free radicals play a central role in the course of both intrinsic and extrinsic aging. During the chronologic aging process, free radicals are formed naturally through normal human metabolism, whereas, in the extrinsic aging process, they are produced by exogenous factors, such as UV exposure, cigarette smoking, and alcohol consumption. At least 50% of UV-induced damage to the skin is estimated to be attributable to the UV-induced formation of free radicals.¹ Harman, et al. first proposed this "free radical theory of aging" in 1956, and today it is one of the most widely accepted theories used to explain the cause of aging.^[2]

Free radicals are highly reactive molecules with an odd number of electrons that are generated from oxygen;^[3] they can damage various cellular structures, such as DNA, proteins, and cellular membranes. In addition, free radicals may lead to inflammation, which seems to play an additional role in skin aging.^[4]

The body possesses endogenous defense mechanisms, such as antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic antioxidative molecules (vitamin E, vitamin C, glutathione, ubiquinone), protecting it from free radicals by reducing and neutralizing them.^[5] Some of these antioxidant defense mechanisms can be inhibited by ultraviolet (UV) light.^[6] Moreover, as part of the natural aging process endogenous defense mechanisms decrease, while the production of reactive oxygen species increases, resulting in accelerated skin aging.

It is intuitive to hypothesize that the topical application of antioxidants may neutralize some of the resulting free radicals, and consequently lessen or prevent the signs of aging skin. At present, topical antioxidants are marketed to prevent aging and UV-induced skin damage, as well as to treat wrinkles and erythema due to inflammation (e.g., post laser resurfacing). However, currently, only vitamin C can actually treat wrinkles by influencing collagen formation through a mechanism other than antioxidation. For other products, their ability to improve wrinkles is either due to swelling or hydrating effects, or to other formulary constituents, such as retinol and vitamin C. Hence, antioxidants can prevent wrinkles, but not treat them.

For topically administered antioxidants to be effective in preventing skin aging, a couple of considerations should be made when formulating them:

- Product stabilization is crucial. Because antioxidants are very unstable, they may become oxidized and inactive before reaching the target.

- They must be properly absorbed into the skin, reach their target tissue in the active form, and remain there long enough to exert the desired effects.

Many antioxidants have been used for centuries in ancient and modern cultures around the world for various diseases.^[7] In addition to their antioxidant activity, most of them possess numerous other biologic properties, e.g., they can be anticarcinogenic and anti-inflammatory. This article will discuss antioxidants that are currently marketed in cosmetic formulations and will focus on their antioxidant activities.

Vitamin E (tocopherol) is a lipid-soluble antioxidant that is present in the skin and found in various foods, such as vegetables, seeds, and meat.^[8] There are 8 active isoforms that are grouped into tocopherols and tocotrienols. Of the 4 tocopherols (α -, β -, γ - and δ -), α -tocopherol (AT) has the highest activity. In animals, a topical application of α -tocopherol has been shown to exert photoprotective effects by reducing the number of sunburn cells,^[9] reducing ultraviolet B (UVB)-induced damage,¹⁰ and inhibiting photocarcinogenesis.^[11] In humans, tocopherol 5%-8% cream that was applied to the face improved signs of photoaging when compared with placebo.^[12] Furthermore, application of vitamin E (5%) to human skin under light-tight occlusion 24 hours before UV treatment was shown to inhibit human macrophage metalloelastase, a member of the matrix metalloproteinase family involved in the degradation of elastin.^[13]

Newer studies suggest that the combined application of various antioxidants can increase their potency when compared with 1 antioxidant alone, and consequently can provide superior photoprotection, as has been shown for the combination of vitamins E and C.^[14] Topical application of vitamin E has been linked with various cutaneous side-effects, including contact dermatitis.^[15-17]

Coenzyme Q10 (CoQ10), or ubiquinone, is a fat-soluble antioxidant that is found in all human cells as a component of the respiratory chain, as well as in food, e.g., fish and shellfish. Up to 95% of the body's energy requirements seem to be provided by CoQ10.¹⁸ In vitro studies showed that CoQ10 suppressed the expression of collagenase following ultraviolet A (UVA) irradiation.¹⁹ In human skin, few studies exist on the topical effect of CoQ10. Nevertheless, CoQ10 is a popular topical antioxidant included in several over-the-counter (OTC) cosmetic products. No side-effects with topical application of CoQ10 have been reported to date.

A The synthetic analog of coenzyme Q10 is called idebenone, which has been demonstrated to be stronger than CoQ10 and other well known antioxidants.^[20] In humans, a study with a topical skin care formulation containing idebenone showed positive effects on photodamaged skin (i.e., reduction in skin roughness/dryness, reduction in fine lines/wrinkles).^[21] However, the effects on wrinkles were most likely due to hydration or skin irritation. There is 1 report of contact dermatitis attributed to idebenone 0.5% in a cream.^[22] However, the authors have seen many patients who developed contact dermatitis from skin care products containing idebenone.

Lycopene, a powerful antioxidant, is a carotenoid found in red fruits and vegetables. It is, in fact, responsible for their red color.^[23] Its chemopreventive effects against photo-induced tumors have been proven in mouse models.²⁴ Despite very little clinical data, lycopene is included in various skin care products.

In humans vitamin C (ascorbic acid) can be obtained solely from food, such as citrus fruits. Sunlight and environmental pollution can deplete vitamin C present in the epidermis^[25] and because vitamin C is a potent antioxidant, enhancing its levels in the skin seems reasonable. Vitamin C predominantly exists in its reduced form, ascorbic acid. Its oxidized form, dehydro-L-ascorbic acid can be found in trace quantities and can revert back to ascorbic acid. However, if the lactone ring irreversibly opens, diketogulonic acid is formed, which is no longer active. This happens when vitamin C preparations are oxidized, rendering them ineffective and useless.^[26] Thus, vitamin C preparations should be kept in airtight, light-resistant containers to avoid exposure to UV rays or the air.

Topical vitamin C as a photoprotectant has been studied *in vitro* and *in vivo*, demonstrating its effects in preventing sun damage by reducing sunburn cells and decreasing erythema when exposed to both UVA and UVB irradiation.^[27] The

addition of topical vitamin C to either a UVA or UVB sunscreen was shown to improve sun protection when compared with sunscreen alone.^[28] Furthermore, adding topical vitamin C to “after-sun” products has been shown to scavenge UV-induced reactive oxygen species.^[29]

Ascorbate is required for collagen synthesis^[30] and the addition of ascorbic acid increases collagen production in human skin fibroblasts.^[31] At the same time it may reduce production of elastin by an unknown mechanism.^[32] Two studies in humans have shown an improvement in the appearance of wrinkles upon topical application of vitamin C.^[33,34] However, more clinical trials are necessary to unravel all the effects of vitamin C on skin and aging. Thus, vitamin C preparations are useful in preventing or lessening the detrimental effects of UV radiation. Some patients experience minimal discomfort (stinging and mild irritation) from topical application.

C **Green tea** is a very popular beverage as well as an antioxidant, that is extracted from the plant *Camellia sinensis*. There are 4 major polyphenolic catechins, of which Epigallocatechin 3-gallate (EGCG) is the most abundant and biologically active. **The green tea polyphenols (GTP) possess not only antioxidant activity, but they also act as anti-inflammatory and anticarcinogenic agents. GTP can be administered either orally or topically.^[35] With various *in vitro* and *in vivo* studies, green tea is probably the most studied antioxidant. In vivo topical application of GTPs has been shown to suppress chemo- and photocarcinogenesis in mice,^[36] and prevent UV-induced oxidative damage and induction of matrix metalloproteinases.^[37] In human skin, GTPs reduced UV-induced erythema, the number of sunburn cells, immunosuppression, and DNA-damage.^[38] In spite of the limited data in humans, there are numerous OTC products containing green tea, and using them every morning for photoprotection in combination with a sunscreen makes sense.** As with most of the antioxidants, no controlled clinical trials exist and the concentration of phenols in the various products is not standardized.

Silymarin, derived from the milk thistle plant, *Silybum marianum*, is a natural polyphenolic flavonoid. Its main component silybin (silibinin), is considered to be the most biologically active with strong antioxidant properties.^[39] *In vivo* studies have shown photoprotective effects with topically applied silybin prior to, or immediately after, UV irradiation.^[40] Thus, there is reasonable evidence to include the compound into sunscreens.

B **CoffeeBerry®** (VDF FutureCeuticals) is the proprietary name for an antioxidant extracted from the fruit of the coffee plant *Coffea arabica*. It has been shown to be a stronger antioxidant than green tea, pomegranate extract, vitamins C and E.41 It contains polyphenols, which are well known for their antioxidant properties.⁴² In 2007, a product containing CoffeeBerry® polyphenols 1% (Revaléskin™, Stiefel Laboratories) was launched. **The company claims that its use over a 6-week period can result in significant improvement of hyperpigmentation, fine lines, wrinkles, and overall appearance.** Furthermore, there have been no reports of irritation by patients with sensitive skin. However, further prospective, randomized and controlled human studies assessing the antioxidant effects of topical preparations containing CoffeeBerry® extract are needed.

The antioxidant resveratrol is a polyphenolic phytoalexin compound that is found in grapes, nuts, fruits, and red wine, among others.⁴³ *In vitro* and *in vivo* studies have shown that, when topically applied, resveratrol protects against UVB-mediated cutaneous damage and inhibits UVB-mediated oxidative stress.^[44-46] The effect of resveratrol on human skin and photoaging remains to be examined. It is included in a few products that claim to have antiaging benefits.

Grape seed is extracted from *Vitis vinifera* and is rich in proanthocyanidins, which belong to the flavonoid family. Proanthocyanidins are potent antioxidants with strong free radical scavenging activities.^[47] Grape seed extract has been shown to be an even stronger scavenger of free radicals than vitamins C and E.^[48] A possible antioxidant mechanism of photoprotection by grape seed proanthocyanidins (GSP) was suggested by Mittal, et al.^[49] GSP was shown to inhibit the depletion of antioxidant defense components induced by UVB,^[50] and topical application of grape seed extract seems to enhance the sun protection factor in humans.^[43] It is included in topical cosmetic formulations for antiaging purposes.

Pomegranate extracts can be obtained from various parts of the fruit *Punica granatum*, such as the juice, seed, and peel. In particular, the phenolic components have potent antioxidant activity.^[51] Topical application of the peel extract

was shown to restore catalase, peroxidase, and superoxide dismutase enzyme activities *in vivo*.^[52] The fruit extract has been shown to ameliorate UVA-mediated damages,^[53] and protect against the adverse effects of UVB radiation *in vitro*.^[54] Pomegranate extract is available in various skin care products.

Genistein is an isoflavone derived from soybeans with the capacity to inhibit UV-induced oxidative DNA damage.^[55] Genistein, either topically applied or orally supplemented, was shown to effectively protect human skin against UVB-induced skin photodamage.^[56,57] It is included in various products such as facial moisturizers, sunscreens, and other skin care formulations that claim to provide anti-aging effects.

Pycnogenol can be extracted from the French maritime pine (*Pinus pinaster*). It contains flavonoids and phenolic compounds, which act as potent free-radical scavengers. Immunosuppression and a reduction of the inflammatory sunburn reaction were observed in mice after topical application of pycnogenol 0.05%–0.2%.⁵⁸ The potential of pycnogenol to provide photoprotection for humans has been investigated for oral supplementation, showing that a significantly elevated UV radiation level was necessary in order to reach 1 minimal erythema dose.^[59]

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Niacinamide, or nicotinamide, is the biologically active amide of vitamin B3. Besides its antioxidant activity, it has also been shown to exhibit anti-inflammatory, depigmenting, and immunomodulant properties. The use of niacinamide has been shown to improve the texture and tone of the skin, and reduce fine lines, wrinkles, and hyperpigmentation.^[60] Topical niacinamide is well tolerated and can be found in various skin care products.

The use of topically applied antioxidants seems promising; however, there is a paucity of controlled clinical trials in humans examining the role of antioxidants in preventing or decelerating skin aging. Thus, further experimental data needs to be generated. Current research suggests that combinations of different antioxidants seem to have synergistic effects and, thus, better efficacy, when compared with 1 antioxidant used alone.^[61,62] Also, some data suggest that a cumulative or additive benefit can be derived from using oral and topical antioxidant products in combination.^[63,64] In spite of the lack of data, millions of dollars are spent annually on these products worldwide. At this point, it is important to understand that these agents are harmless when applied topically, but the exact efficacy of these products is currently unknown.

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