OBJECTIVE: This review article details the main mechanisms of action and clinical applications of topical vitamin C on the skin, including its antioxidative, photoprotective, antiaging, and antipigmentary effects.

DESIGN: A PubMed search for the relevant articles on vitamin C and the skin was conducted using the following key words: “vitamin C,” “ascorbic acid,” “ascorbyl-6-palmitate,” and “magnesium ascorbyl phosphate.”

RESULTS: As one of the most powerful antioxidants in the skin, vitamin C has been shown to protect against photoaging, ultraviolet-induced immunosuppression, and photocarcinogenesis. It also has an antiaging effect by increasing collagen synthesis, stabilizing collagen fibers, and decreasing collagen degradation. It decreases melanin formation, thereby reducing pigmentation. Vitamin C is the primary replenisher of vitamin E and works synergistically with vitamin E in the protection against oxidative damage.

CONCLUSION: Topical vitamin C has a wide range of clinical applications, from antiaging and antipigmentary to photoprotective. Currently, clinical studies on the efficacy of topical formulations of vitamin C remain limited, and the challenge lies in finding the most stable and permeable formulation in achieving the optimal results.

KEYWORDS: antioxidant, ascorbic acid, photoaging, photoprotection, vitamin C

ABSTRACT

Relation of Antioxidant Activity to Skin Aging

Recent studies have highlighted the role of antioxidants in skin aging. Vitamin C is one of the most abundant antioxidants in human skin. Unlike plants and some animals, humans are unable to synthesize vitamin C due to absence of the enzyme L-glucono-gamma lactone oxidase. Despite high doses of oral supplementation, only a small fraction of vitamin C will be biologically available and active in the skin. Therefore, we rely entirely on external supplementation, such as topical application in the case of cosmeceuticals.

In this article, we describe and discuss the main mechanisms of action and clinical applications of topical vitamin C on the skin, including its antioxidative, photoprotective, antiaging, and antipigmentary effects.

TOPICAL FORMULATIONS OF VITAMIN C

Vitamin C is available in a number of active forms. Among all forms, L-ascorbic acid is the most biologically active and well studied. L-ascorbic acid is a hydrophilic and unstable...
molecule, hence the poor penetration into the skin because of the hydrophobic character of the stratum corneum. L-ascorbic acid is also a charged molecule, which further limits its penetration. Reducing the acidity of L-ascorbic acid to a pH below 3.5 is an effective method of improving its stability and permeability. This has shown to greatly aid its penetration, largely because of the transformation from the charged to the uncharged form of the molecule. In one example of the currently available L-ascorbic acid product (SkinCeuticals, L’Oreal, New York, New York), the addition of ferulic acid aids in both stabilization of the molecule and achieving an acidity of a pH below 3.5. Two other common topical formulations of vitamin C include ascorbyl-6-palmitate and magnesium ascorbyl phosphate (MAP). Unlike L-ascorbic acid, which is hydrophilic and unstable, both ascorbyl-6-palmitate and MAP are lipophilic, esterified forms of vitamin C, which are stable at neutral pH. Examples of other stable, esterified derivatives of vitamin C are disodium isostearyl 2-0-L-ascorbyl phosphate, ascorbic acid sulphate, and tetrasopalmitoyl ascorbic acid. However, one study showed that daily application of MAP, ascorbyl-6-palmitate, and other ascorbic acid derivatives did not increase the levels of L-ascorbic acid in the skin.

The optimal concentration of vitamin C depends on its formulation. In most cases, for a product to be of biological significance, it needs to have a vitamin C concentration higher than eight percent. Studies have shown that a concentration above 20 percent does not increase its biological significance and, conversely, might cause some irritation. Reputable products of vitamin C available today are, therefore, in the range of 10 to 20 percent.

**MECHANISMS OF ACTION AND CLINICAL APPLICATIONS**

**Vitamin C as a potent antioxidant.** Environmental factors, such as solar radiation, pollution, and smoking can accelerate damage to the skin through the generation of so-called “oxidative stress”. Vitamin C is one of the most potent antioxidants in the skin. It neutralizes the oxidative stress by a process of electron transfer and/or donation. Protection against photoaging. Transurocanic acid is a by-product of fillagrin present in the skin, which acts as a chromophore for photons of solar radiation (mainly ultraviolet [UV] and, to a degree, infrared) leading to the formation of singlet oxygen. This triggers a cascade of events that lead to the formation of so-called “reactive oxygen species” or “free radicals.” Free radicals are highly toxic, unstable molecules that can cause damage to nucleic acids, proteins, and cell membranes. UV-induced reactive oxygen species also trigger the signal transduction cascade, which leads to upregulation of factors, such as activation protein–1 (AP-1) and nuclear factor–B, and downregulation of transforming growth factor–β. These proteases collectively upregulate matrix metalloproteinases (MMPs), which degrade collagen, reduce collagen production, and increase elastin accumulation. This leads to the clinical manifestations of photoaging pigmentation, telangiectasias, coarse texture, deep wrinkles, and solar elastosis.

Sunscreens are only partially effective in blocking free radicals produced by UV exposure. Vitamin C has been shown to inhibit the activation of AP-1, which leads to a reduction in MMP production and collagen damage. In-vitro studies have also shown that vitamin C inhibits the biosynthesis of elastin. In animal studies, application of 5% ascorbic acid two hours prior to UV exposure was found to reduce skin wrinkling. The photoprotective effects of vitamin C are also seen in human clinical studies. One double-blind, placebo-controlled study on 10 subjects using 10% topical vitamin C over a 12-week period showed a statistically significant reduction in photoaged scores and improvement in wrinkling in vitamin C-treated patients as compared to placebo. A significant improvement in furrows on skin histology and clinical appearance was seen in another double-blind, placebo-controlled study using 5% topical vitamin C on 20 subjects over a six-month period. However, the effect of oral supplementation of vitamin C remains controversial.

Protection against UV-induced immunosuppression. CD1a-expressing Langerhans cells are antigen-presenting cells present in the epidermis, which act by initiating a protective immune response. Their numbers are decreased upon acute and chronic UV exposure. Vitamin C-containing topical solutions have been shown to prevent the reduction of CD1a-expressing Langerhans cells upon UV radiation.

Protection against photocarcinogenesis. UV-induced erythema and thymine dimer mutations contribute to photocarcinogenesis. In addition, UV-induced reactive oxygen species induce mutations on the p53 gene, which affect the repair of damaged deoxyribonucleic acid (DNA) and induce a process of programmed cell death (apoptosis). In laboratory studies, application of 10% topical vitamin C has been shown to reduce UVB-induced erythema by 52 percent and apoptotic sunburn cell formation by 40 to 60 percent. In clinical studies, vitamin C-containing solutions have been shown to reduce UV-induced thymine dimers, thereby potentially reducing the risk of photocarcinogenesis.
**Antiaging effect.** Vitamin C is essential for collagen biosynthesis and is thought to have an antiaging effect. More importantly, it serves as a cofactor for prolyl and lysyl hydroxylase, key enzymes that cross-link and stabilize collagen fibers. Vitamin C also directly activates the transcription factors involved in collagen synthesis and stabilizes pro-collagen messenger RNA (mRNA) that regulates type I and III collagen synthesis. In addition, vitamin C increases the gene expression of collagen and synthesis of the tissue inhibitor of MMP-1, which decreases collagen degradation. A clinical study showed that daily application of three-percent topical vitamin C over a four-month period led to a significant increase in the density of dermal papillae.

**Replenisher of vitamin E.** Aside from its antiaging and photoprotective effects, vitamin C is also known to be the primary replenisher of vitamin E. Vitamin E is a lipophilic antioxidant and has a primary role in protecting cell membranes against oxidative stress and maintaining the collagen network in the skin. Similar to vitamin C, its levels are rapidly depleted after UV exposure. Several clinical studies have proved the synergistic antioxidant effect of vitamins C and E in photoprotection.

**Antipigmentary effect.** Vitamin C also plays a role as an antipigmentation agent. It interacts with copper ions at tyrosinase-active sites and inhibits the action of the enzyme tyrosinase—the main enzyme responsible for the conversion of tyrosine into melanin—thereby decreasing melanin formation. A clinical study examining the effect of a topical formulation containing 25-percent vitamin C and a chemical penetration enhancer reported a significant decrease in pigmentation caused by melasma after 16 weeks. Although vitamin C has been shown to suppress melanin production, its clinical effects may not be as effective as other topical products containing hydroquinone.

**FUTURE DEVELOPMENTS**

Clinical studies on the efficacy of different formulations of topical vitamin C in human skin remain limited. The challenge lies with developing a stable formulation and finding the most efficient transdermal delivery method for the esterified forms of vitamin C (e.g., ascorbyl palmitate, MAP) to maximize the concentration of active vitamin C in the skin. Recent studies have shown that methods such as nanoparticles, multi-layered microemulsions for graded delivery, ultrasound, iontophoresis, laser resurfacing, and microdermabrasion, can help to enhance penetration of vitamin C. However, these studies remain small, and there are no comparative studies to determine the optimal delivery method. Also, further larger studies are needed to confirm the synergistic effect of vitamin C with other antioxidants and growth factors. Methods to deliver huge doses of vitamin C via oral and intravenous means have been explored; however, their effectiveness on the skin remains controversial.

Continuous efforts are being made to research other benefits of vitamin C, including the effects of vitamin C on hair growth, wound healing, smoking-related skin aging, scars, and striae. 

**CONCLUSION**

Vitamin C is one of the most powerful antioxidants in the skin. Due to its antioxidant, neocollagenesis, and skin-lightening properties, its clinical applications range from photoprotection and antiaging to antipigmentation. With an excellent safety profile, it has become a popular cosmeceutical agent. However, clinical studies on the efficacy of topical formulations of vitamin C remain limited, and the challenge lies in finding the most stable and permeable formulation in achieving the optimal results.

**REFERENCES**

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