

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

TOPICAL VITAMIN C AND THE SKIN: Mechanisms of Action and Clinical Applications

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VITAMIN C IS THE MOST ABUNDANT ANTIOXIDANT IN human skin.¹ 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.² Therefore, we rely entirely on external supplementation, such as topical application in the case of cosmeceuticals.³ 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.³ L-ascorbic acid is a hydrophilic and unstable

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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.⁴ 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.⁴ 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 3.5.⁵

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.⁶

Examples of other stable, esterified derivatives of vitamin C are disodium isostearyl 2-O L-ascorbyl phosphate, ascorbic acid sulphate, and tetraisoalmitoyl 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.⁴

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.⁴ Studies have shown that a concentration above 20 percent does not increase its biological significance and, conversely, might cause some irritation.⁴ 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.³

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."⁷⁻⁹ 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.¹⁰ 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.¹⁰ *In-vitro* studies have also shown that vitamin C inhibits the biosynthesis of elastin.¹¹ In animal studies, application of 5% ascorbic acid two hours

prior to UV exposure was found to reduce skin wrinkling.¹² 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.¹³ 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.¹⁴ However, the effect of oral supplementation of vitamin C remains controversial.¹⁵

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.¹⁶ Vitamin C-containing topical solutions have been shown to prevent the reduction of CD1a-expressing Langerhans cells upon UV radiation.¹⁷

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).¹⁸ 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.¹⁹ In clinical studies, vitamin C-containing solutions have been shown to reduce UV-induced thymine dimers, thereby potentially reducing the risk of photocarcinogenesis.²⁰

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.²¹ 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.¹⁰ 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.²²

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.¹⁰ Several clinical studies have proved the synergistic antioxidant effect of vitamins C and E in photoprotection.^{23–25}

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.^{26,27} 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.²⁸ Although vitamin C has been shown to suppress melanin

production, its clinical effects may not be as effective as other topical products containing hydroquinone.²⁹

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 transepidermal 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.^{30–32} 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.^{5,15}

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.^{33–37}

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

1. Manela-Azulay M, Bagatin E. Cosmeceuticals vitamins. *Clin Dermatol*. 2009;27:469–474.
2. Zetterström R. Nobel Prize 1937 to Albert von Szent-Györgyi: identification of vitamin C as the anti-scorbutic factor. *Acta Paediatr*. 2009;98(5):915–919.
3. Farris PK. Cosmetical vitamins: vitamin C. In: Draelos ZD, Dover JS, Alam M, eds. *Cosmeceuticals. Procedures in Cosmetic Dermatology*. 2nd ed. New York: Saunders Elsevier; 2009:51–56.
4. Pinnell SR, Yang H, Omar M, et al. Topical L-ascorbic acid: percutaneous absorption studies. *Dermatol Surg*. 2001;27(2):137–142.
5. Lin FH, Lin JY, Gupta RD, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. *J Invest Dermatol*. 2005;125(4):826–832.
6. Lupo MP. Antioxidants and vitamins in cosmetics. *Clin Dermatol*. 2001;19:467–473.
7. Tyrrell RM. Solar ultraviolet A radiation: an oxidizing skin carcinogen that activates heme oxygenase-1. *Antioxid Redox Signal*. 2004;6(5):835–840.
8. Godic A, Poljšak B, Adamic M, Dahmane R. The role of antioxidants in skin cancer prevention and treatment. *Oxid Med Cell Longev*. 2014;2014:860479.
9. Hanson KM, Simon JD. Epidermal trans-urocanic acid and the UV-A-induced photoaging of the skin. *Proc Natl Acad Sci*. 1998;95:10576–10578.
10. Chen L, Hu JY, Wang SQ. The role of antioxidants in photoprotection: a critical review. *J Am Acad Dermatol*. 2012;67(5):1013–1024.
11. Farris PK. Topical vitamin C: a useful agent

- for treating photoaging and other dermatologic conditions. *Dermatol Surg.* 2005;31(7 Pt 2):814–817.
12. Bissett DL, Chatterjee R, Hannon DP. Photoprotective effect of superoxide-scavenging antioxidants against ultraviolet radiation-induced chronic skin damage in the hairless mouse. *Photodermatol Photoimmunol Photomed.* 1990;7:56–62.
13. Fitzpatrick RE, Rostan EF. Double-blind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. *Dermatol Surg.* 2002;28(3):231–236.
14. Humbert PG, Haftek M, Creidi P, et al. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation:double-blind study vs. placebo. *Exp Dermatol.* 2003;12(3):237–244.
15. McArdle F, Rhodes LE, Parslew R, Jack CI, Friedmann PS, Jackson MJ. UVR-induced oxidative stress in human skin *in vivo*: effects of oral vitamin C supplementation. *Free Radic Biol Med.* 2002;33(10):1355–1362.
16. Toyoda M, Bhawan J. Ultrastructural evidence for the participation of Langerhans cells in cutaneous photoaging processes: a quantitative comparative study. *J Dermatol Sci.* 1997;14:87–100.
17. Matsui MS, Hsia A, Miller JD, et al. Non-sunscreen photoprotection: antioxidants add value to a sunscreen. *J Invest Dermatol Symp Proc.* 2009;14(1):56–59.
18. Meplan C, Richard MJ, Hainaut P. Redox signaling and transition metals in the control of the p53 pathway. *Biochem Pharmacol.* 2000;59:25–33.
19. Darr D, Combs S, Dunston S, Manning T, Pinnell S. Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. *Br J Dermatol.* 1992;127:247–253.
20. Murray JC, Burch JA, Streilein RD, Iannacchione MA, Hall RP, Pinnell SR. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. *J Am Acad Dermatol.* 2008;59(3):418–425.
21. Oresajo C, Stephens T, Hino PD, et al. Protective effects of a topical antioxidant mixture containing vitamin C, ferulic acid, and phloretin against ultraviolet-induced photodamage in human skin. *J Cosmet Dermatol.* 2008;7:290–297.
22. Lin JY, Selim MA, Shea CR, et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. *J Am Acad Dermatol.* 2003;48:866–874.
23. Lin FH, Lin JY, Gupta RD, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. *J Invest Dermatol.* 2005;125:826–832.
24. Austria R, Semenzato A, Bettero A. Stability of vitamin C derivatives in solution and topical formulations. *J Pharm Biomed Anal.* 1997;15(6):795–801.
25. Lee S, Lee J, Choi YW. Skin permeation enhancement of Ascorbyl palmitate by lipohydro gel formulation and electrical assistance. *Bio Pharma Bull.* 2007;30:393–396.
26. Ando H, Kondoh H, Ichihashi M, Hearing VJ. Approaches to identify inhibitors of melanin biosynthesis via the quality control of tyrosinase. *J Invest Dermatol.* 2007;127:751–761.
27. Kameyama K, Sakai C, Kondoh S, et al. Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis *in vitro* and *in vivo*. *J Am Acad Dermatol.* 1996;34:29–33.
28. Hwang SW, Oh DJ, Lee D, Kim JW, Park SW. Clinical efficacy of 25% L-ascorbic acid (C'ensil) in the treatment of melisma. *J Cutan Med Surg.* 2009;13(2):74–81.
29. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double- blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma. *Int J Dermatol.* 2004;43(8):604–607.
30. Telang PS. Vitamin C in dermatology. *Indian Dermatol Online J.* 2013;4(2):143–146.
31. Lee WR, Shen SC, Kuo-Hsien W, Hu CH, Fang JY. Lasers and microdermabrasion enhance and control topical delivery of vitamin C. *J Invest Dermatol.* 2003;121(5):1118–1125.
32. Ebihara M, Akiyama M, Ohnishi Y, Tajima S, Komata K, Mitsui Y. Iontophoresis promotes percutaneous absorption of L-ascorbic acid in rat skin. *J Dermat Sci.* 2003;32:217–222.
33. Sung YK, Hwang SY, Cha SY, et al. The hair growth promoting effect of ascorbic acid 2-phosphate, a long-acting Vitamin C derivative. *J Dermatol Sci.* 2006;41(2):150–152.
34. Kwack MH, Shin SH, Kim SR, et al. L-Ascorbic acid 2-phosphate promotes elongation of hair shafts via the secretion of insulin-like growth factor-1 from dermal papilla cells through phosphatidylinositol 3-kinase. *Br J Dermatol.* 2009;160(6):1157–1162.
35. Jagetia GC, Rajanikant GK, Mallikarjun Rao KV. Ascorbic acid increases healing of excision wounds of mice whole body exposed to different doses of gamma-radiation. *Burns.* 2007;33(4):484–494.
36. Findik RB, Hascelik NK, Akin KO, Unluer AN, Karakaya J. Striae gravidarum, vitamin C and other related factors. *Int J Vitam Nutr Res.* 2011;81(1):43–48.
37. Yun IS, Yoo HS, Kim YO, Rah DK. Improved scar appearance with combined use of silicone gel and vitamin C for Asian patients: a comparative case series. *Aesthetic Plast Surg.* 2013;37(6):1176–1181. JCAD