# MECHANISMS AND EFFECTS OF APPLYING VITAMIN C AT THE SKIN LEVEL

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**Summary**

*The skin is the largest multi-functional organ in the body, its appearance generally reflecting the general health status. Normal skin contains high levels of vitamin C, with levels comparable to other body tissues and well above plasma levels. Vitamin C is involved in the formation of the skin and collagen barrier in the dermis and plays a physiological role in the skin against oxidation, in the fight against wrinkles and protection against UV radiation. Vitamin C can be applied topically, although its effectiveness depends on the formula of the cream or serum used, the concentration and the condition of the skin at the time of application.*

***Keywords**: vitamin C, topical, aging, UV protection.*

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## Introduction

The skin is the largest multi-functional organ in the body, its appearance generally reflecting the health status. The skin has many functions, but its fundamental role is to provide a protective interface between the external environment and a person's tissues, providing protection against mechanical and chemical threats, pathogens, ultraviolet radiation and even dehydration.

The nutritional status, both from the point of view of the macronutrients and the micronutrients, is important for the health and appearance of the skin, and also the nutritional status is vital for maintaining the normal functioning of the skin during collagen synthesis and keratinocyte differentiation (1).

Often, food nutrients cannot easily reach the cells in the outermost layers of the epidermis, and these cells receive little nutritional support (2). Nutrients can be provided by skin application, however, the corneal layer acts as a barrier that prevents the passage of many substances, and nutrients delivered by topical application are unlikely to penetrate easily into the deep layers of the dermis (3).

The human body is unable to synthesize vitamin C, because of the absence of the enzyme L-glucono-gamma lactone oxidase. Despite high doses of oral supplementation, only a small percentage of vitamin C will be biologically available and active at skin level (4).

### Mechanisms of vitamin C actions at the skin level

Vitamin C (ascorbic acid) is a simple low molecular weight carbohydrate, essential for the

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body as a water soluble vitamin. Although vitamin C is an important antioxidant, people get vitamin C only from the diet, because they do not have the ability to synthesize it (5).

Normal skin contains high levels of vitamin C, with levels comparable to other tissues in the body and well above plasma concentrations, suggesting active accumulation in the circulation. Vitamin C levels are lower in aging or photolysed skin. Excessive exposure to oxidant stress by pollutants or UV irradiation is associated with much lower levels of vitamin C in the epidermal layer (6,7).

The content of ascorbic acid in the epidermis is 425% higher than the content in the dermis and there is a concentration gradient of ascorbic acid in the epidermal keratinocytes (8).

It is known that there are two transport mechanisms of ascorbic acid in the skin and these depend on the sodium-ascorbate-1 transporter and the sodium-absorbent-2 transporter. Sodium-ascorbate transporters, sodium-specific vitamin C transporters, exist in various tissues and organs for the uptake and transport of vitamin C. Dermal fibroblasts have two transport mechanisms of vitamin C (high-affinity and low-affinity) related to plasma concentrations of ascorbic acid or stress states, demonstrating that the transport particularities of vitamin C in the skin may be associated with healing, anti-oxidation and antitumor effects (9).

Vitamin C is involved in the formation of the skin barrier and collagen in the dermis and plays a physiological role in the skin against oxidation, in the fight against wrinkles and in the signaling pathways of growth and differentiation of cells, which are linked to the appearance and development of various skin diseases (10).

**Topical application of vitamin C**

Vitamin C can be applied topically, although its effectiveness depends on the formula of the cream or serum used. Vitamin C, as a water-soluble molecule, is rejected by the physical barrier of differentiated epidermal cells. When the pH level is below 4 and vitamin C is present as ascorbic acid, some penetration occurs, but it is not known if this increases the level of vitamin C in the metabolic layer (11).

Great efforts have been made for the development of ascorbic acid derivatives for topical application. The derivatives must ensure the stabilization of the molecule from oxidation and be able to overcome the skin barrier. Vitamin C is available in several active forms, of all forms, L-ascorbic acid is the most biologically active and most studied (12).

L-ascorbic acid is a hydrophilic, unstable and charged molecule, resulting in poor skin penetration due to the hydrophobic character of the corneal layer (13). Reducing the acidity of L-ascorbic acid to a pH below 3.5 is an effective method for improving its stability and permeability, and the addition of ferulic acid helps both to stabilize the molecule and achieve acidity with a pH below 3.5 (14). Other two topical formulations of vitamin C include ascorbyl-6-palmitate and magnesium ascorbate phosphate, both being lipophilic, esterified vitamin C forms, stable at neutral pH (15).

Recent studies suggest that encapsulation in a lipospheric form may help transport to the deeper layers of the epidermis and may lead to increased absorption. However, the most relevant for the effectiveness of the topical application is probably the plasma level of the individual: if the plasma level is saturated, then it appears that the topical application does not increase the vitamin C content at the skin level (16).

The optimal concentration of vitamin C depends on its formula. For a product to have biological significance, it must have a vitamin C concentration of more than 8%. Concentrations above 20% do not increase the biological significance and may cause irritation. The widely available products generally have concentrations between 10% and 20% (13).

**The actions of vitamin C**

Skin aging - like the other components of the human body, the skin is subject to changes caused by the natural aging process. Skin changes are often the first visible signs of aging and this can have implications on our emotional and mental well-being. Aging can be regarded from two points of view, on the one hand the natural aging, and on the other hand the aging caused by the environment. Changes due to aging caused by the environment are usually superimposed on those that occur naturally, which often makes difficult the distinction between the two (14).

*The role of vitamin C in preventing skin aging.* The ability of vitamin C to limit natural aging is difficult to differentiate from its ability to prevent or slow down aging due to the environment, with limited information on the relationship between vitamin C levels and overall skin deterioration.

With aging, the thickness of the dermal layer is reduced, there are fewer fibroblasts and mast cells, less collagen production and reduced vascularization, more precisely, during aging, there is a gradual degradation of the extracellular components of the matrix, especially elastin and collagen (17).

Vitamin C is essential for collagen biosynthesis and is believed to have an anti-aging effect. Vitamin C also serves as a cofactor for prolyl and lysyl hydroxylase, key enzymes that cross-link and stabilize collagen fibers and collagen synthesis III. Vitamin C increases collagen gene expression and tissue inhibitor synthesis of MMP-1, which decreases collagen degradation (18,19,20). Daily application of topical vitamin C at a concentration of 3% over a four-month period has been shown to lead to a significant increase in the density of dermal papillae (21).

*Anti-pigmentation effect.* Vitamin C plays a role of anti-pigmenting agent, by interacting with copper ions in the active sites of tyrosinase and inhibits the action of the tyrosinase enzyme - the main enzyme responsible for the conversion of tyrosine into melanin - thus decreasing melanin formation (22). Topically applied 25% vitamin C caused a significant decrease in pigmentation caused by melasma after 16 weeks of treatment, however, its clinical effects may not be as effective as other topical products containing hydroquinone (23).

*Vitamin C and UV protection*. It has been established that vitamin C limits the damage caused by exposure to UV, this type of injury is directly mediated by a radical-generating process, and protection is primarily related to the antioxidant activity of vitamin C. UV light seems to deplete the vitamin C content in the epidermis. Vitamin C prevents lipid peroxidation in keratinocytes grown after exposure to UV and also protects keratinocytes from apoptosis and increases cell survival (24,25,26).

**Table. 1.** Demonstrated efficacy of vitamin C applied to the skin (29,30,31)

| *Description* | *Parameters tracked* | *Results* | *Animals / humans* |
|---|---|---|---|
| Skin application of Vitamin C and Vitamin E cream in mice, followed by UV irradiation. | Measurement of melanocyte differentiation after irradiation. Skin color change - tanning, inflammation. | UVR-induced proliferation and melanogenesis of melanocytes were reduced with vitamin C and E. Melanocyte population and confluence were reduced when vitamin C was present. | Animal studies |
| Skin application of vitamin C cream before applying the hair dye product p-phenylenediamine. | Visual evaluation of the allergic reaction after applying the patch on the skin of the volunteers (on the back). | Decreased or ablated dermatitis and allergic response due to local antioxidant action of vitamin C in cream. | Human study |
| Clinical study applying vitamin C in liposomes on human skin (abdomen), then exposure to UV irradiation. | Measurement of penetration through the skin layers, vitamin C delivery, Trolox loss, TNFalpha and Il-1beta. | Vitamin C levels increased in the epidermis and dermis with liposomes. The protection against UV radiation increased only on liposomes. | Human study |

There is a synergy between vitamin C and vitamin E, the combination being particularly effective against UV radiation; this combination also decreases the inflammation induced by excessive UV exposure (27,28). The effectiveness of topical vitamin C and other nutrients may depend on the pre-existing condition of the skin.

## Conclusions

Vitamin C is one of the most powerful antioxidants. The role of skin applications ranges from photoprotection and anti-aggregation to anti-pigmentation. Vitamin C has an excellent safety profile, and its use in cosmetics is popular. Clinical studies are still limited as to the most effective formula for topical application. The current trend is to find the most stable and penetrable formula for skin applications.

## Bibliography

1. Park K. Role of micronutrients in skin health and function. Biomol. Ther. 2015;23:207-217.
2. Langton AK, Sherratt MJ, Griffiths CE, Watson RE. A new wrinkle on old skin: The role of elastic fibres in skin ageing. Int. J. Cosmet. Sci. 2010;32:330-339.
3. Baumann L. Skin ageing and its treatment. J. Pathol. 2007;211:241-251.
4. Zetterströ MR. Nobel Prize 1937 to Albert von Szent-Györgyi: identification of vitamin C as the anti-scorbutic factor. Acta Paediatr. 2009;98(5):915-919.
5. Lykkesfeldt J, Michels AJ, Frei B. Vitamin C. Adv. Nutr. 2014;5:16-18.
6. Rhie G, Shin MH, Seo JY, et al. Aging- and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. J. Investig. Dermatol. 2001;117:1212-1217.
7. Shindo Y, Witt E, Han D, Packer L. Dose-response effects of acute ultraviolet irradiation on antioxidants and molecular markers of oxidation in murine epidermis and dermis. J. Investig. Dermatol. 1994;102:470-475.
8. Weber SU, Thiele JJ, Cross CE, Packer L. Vitamin C, uric acid, and glutathione gradients in murine stratum corneum and their susceptibility to ozone exposure. J. Invest. Dermatol. 1999;113:1128-1132.
9. Butler JD, Bergsten P, Welch RW, Levine M. Ascorbicacid accumulation in human skin fibroblasts. Am. Soc. Clin. Nutr. 1991;54:1144S-1146S.
10. Ponec M, Weerheim A, Kempenaar J, et al. The formation of competent barrier lipids in reconstructed human epidermis requires the presence of vitamin C. J. Invest. Dermatol. 1997;109:348-355.
11. Pinnell SR. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. J. Am. Acad. Dermatol. 2003;48:1-22.
12. Farris PK. Cosmetical vitamins: vitamin C. In: Draelos ZD, Dover JS, Alam M, editors. Cosmoceuticals. Procedures in Cosmetic Dermatology. 2nd ed. New York: Saunders Elsevier; 2009:51-56.
13. Pinnell SR, Yang H, Omar M, et al. Topical L-ascorbic acid: percutaneous absorption studies. Dermatol Surg. 2001;27(2):137-142.
14. 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
15. Lupo MP. Antioxidants and vitamins in cosmetics. Clin Dermatol. 2001;19:467-473
16. Nusgens BV, Humbert P, Rougier A, et al. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. J. Investig. Dermatol. 2001;116:853-859.
17. Naylor EC, Watson RE, Sherratt MJ. Molecular aspects of skin ageing. Maturitas. 2011;69:249-256.
18. Chen L, Hu JY, Wang SQ. The role of antioxidants in photoprotection: a critical review. J Am Acad Dermatol. 2012;67(5):1013-1024.
19. Horodinschi RN, Stănescu AMA, Bratu OG, et al. Treatment with statins in elderly patients. Medicina 2019;55(11):721.
20. Mircescu D, Totan A, Stanescu II, et al. Periodontal disease and systemic health. Revista Medicală Română 2019;LXVI(3):195-199.
21. 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.

22. 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
23. Hwang SW, Oh DJ, Lee D, et al. Clinical efficacy of 25% L-ascorbic acid (C'ensil) in the treatment of melisma. J Cutan Med Surg. 2009;13(2):74-81.
24. Stănescu AMA, Grajdeanu IV, Stefani C, et al. Terapii adjuvante pentru îmbunătă?irea rezultatelor terapiilor farmacologice în rozacee. Revista Medicală Română 2018;LXV(4):253-257.
25. Crisan D, Roman I, Crisan M, et al. The role of vitamin C in pushing back the boundaries of skin aging: An ultrasonographic approach. Clin. Cosmet. Investig. Dermatol. 2015;8:463-470
26. Mircescu D, Titan A, Stanescu II, et al. Antioxidant Activity of Entrapped alfa-tocopherol and Lutein in PLGA Nanoparticles in Wistar Rats. Materiale Plastice 2019;56(3):520-524.
27. Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by d-alpha-tocopherol and l-ascorbic acid: A clinical study using solar simulated radiation. Free Radic. Biol. Med. 1998;25:1006-1012.
28. Stănescu AMA, Grajdeanu IV, Stefani C, et al. Rolul vitaminei D la nivel cutanat. Practica Medicală 2018;13,4(61):251-254.
29. Quevedo WC, Holstein TJ, Dyckman J, et al. Inhibition of UVR-induced tanning and immunosuppression by topical applications of vitamins C and E to the skin of hairless (hr/hr) mice. Pigment Cell Res. 2000;13:89-98.
30. Basketter DA, White IR, Kullavanijaya P, et al. Influence of vitamin C on the elicitation of allergic contact dermatitis to p-phenylenediamine. Contact Dermat. 2016;74:368-372.
31. Serrano G, Almudever P, Serrano JM, et al. Phosphatidylcholine liposomes as carriers to improve topical ascorbic acid treatment of skin disorders. Clin. Cosmet. Investig. Dermatol. 2015;8:591-599.


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