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Vitamin C in dermatology

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Abstract

Vitamin C is a potent antioxidant drug that can be used topically in dermatology to treat and prevent changes associated with photoageing. It can also be used for the treatment of hyperpigmentation. Because it is unstable and difficult to deliver into the dermis in the optimum dosage, research is being directed to find stable compounds of Vitamin C and newer methods of delivery of Vitamin C into the dermis.

Keywords: Collagen synthesis, depigmentation, drug formulations, L–ascorbic acid, photo-ageing, Vitamin C

INTRODUCTION

Vitamin C (Vit. C) is one of the naturally occurring antioxidants in nature.[1,2] Most plants and animals are able to synthesise Vit. C *in vivo* from glucose. Humans and certain other vertebrates lack the enzyme L-glucono-gamma lactone oxidase required for *in vivo* synthesis of Vit. C;[3] hence, they must acquire it from natural sources such as citrus fruits, green leafy vegetables, strawberries, papaya and broccoli.[3,4] The word “Ascorbus” means no Scurvy. Traditionally, Vit. C-rich foods like lemons were carried by sailors on long journeys to avoid Scurvy, a disease of bleeding gums. In 1937, Dr. Albert Szent Goyrgi was awarded the Nobel Prize for his work in isolating the Vit. C molecule from red peppers and identifying its role in Scurvy.[4]

L-ascorbic acid (LAA) is the chemically active form of Vit. C. In nature, Vit. C is found in equal parts as LAA and D-ascorbic acid. These are essentially isomeric molecules and are mutually interchangeable.[4] However, only LAA is biologically active and thus useful in medical practice.[2] The absorption of Vit. C in the gut is limited by an active transport mechanism and hence a finite amount of the drug is absorbed despite high oral dosage.[3] Furthermore, bioavailability of Vit. C in the skin is inadequate when it is administered orally.[1,2] The use of topical ascorbic acid is therefore favored in the practice of dermatology.[5]

BIOCHEMISTRY OF VITAMIN C

Vit. C has a 5-hydrocarbon ring similar to that of glucose. With an attached hydrogen ion, LAA becomes a weak sugar acid, similar to other alfa hydroxy acids used in dermatology. With a metal ion, it forms a mineral ascorbate. There is a marked interest in synthesis of physiologically active and chemically stable ascorbate molecules as LAA is unstable in nature, especially when exposed to light.

MECHANISM OF ACTION OF VITAMIN C WITH REFERENCE TO DERMATOLOGY

Vit. C as antioxidant

Vit. C, the most plentiful antioxidant in human skin, forms a part of the complex group of enzymatic and non-enzymatic antioxidants that co-exist to protect the skin from reactive oxygen species (ROS). As Vit. C is water soluble, it functions in the aqueous compartments of the cell.[4] When the skin is exposed to UV light, ROS such as the superoxide ion, peroxide and singlet oxygen are generated. Vit. C protects the skin from oxidative stress by sequentially donating electrons to neutralize the free radicals. The oxidised forms of Vit. C are relatively non-reactive.[4] Furthermore, they can be converted back to Vit. C by the enzyme dehydro ascorbic acid reductase in the presence of glutathione. Exposure to UV light reduces the availability of Vit. C in the skin.

UV light, reactive oxygen species (ROS) and skin damage - Vit. C and photoprotection

As mentioned above, the exposure of skin to UV light generates ROS.[3] These radicals have a potential to start chain or cascade reactions that damage the cells. The harmful effects of ROS occur as direct chemical alterations of the cellular DNA, the cell membrane and the cellular proteins, including collagen.

Oxidative stress also triggers certain cellular events mediated by transcription factors such as ROS upgrade transcription factor activator protien-1 (AP-1) that increases matrix metalloprotienase (MMP) production, leading to collagen breakdown.[3] Oxidative stress induces nuclear transcription factor kappa B (NFkB). This produces a number of mediators that contribute to inflammation and skin ageing.[3] ROS also increase the elastin mRNA level in dermal fibroblasts. This may explain the elastotic changes observed in photoaged skin.[2]

Antioxidants are necessary for neutralizing the ROS formed due to UV exposure.[2] It is important to note that Vit. C is equally effective against both UVB (290-320 nm) and UVA (320-400 nm).[2,5] Repeated small doses of UVA penetrate 30-40-times deeper into the dermis as against UVB, which mostly affects the epidermis. UVA mutates and destroys collagen, elastin, proteoglycans and other dermal cellular structures.[2] Thus, UVA causes skin ageing and possibly melanoma formation. UVB causes sunburn, ROS, epidermal mutations and skin cancer. Sunscreens when properly applied prevent UV-induced erythema and thymine dimer mutations that contribute to cutaneous carcinogenesis. However, sunscreens block only 55% of the free radicals produced by UV exposure. Photoageing can be prevented by prevention of UV-induced erythema, sunburn cell formation and inducing collagen repair.[2] To optimize UV protection, it is important to use sunscreens combined with a topical antioxidant. Vit. C does not absorb UV light but exerts an UV-protective effect by neutralizing free radicals, while this effect is not seen with sunscreens. Under laboratory conditions, it has been shown that application of 10% topical Vit. C showed statistical reduction of UVB-induced erythema by 52% and sunburn cell formation by 40-60%.[3]

Although Vit. C alone can provide photoprotection, it works best in conjunction with Vitamin E (Vit. E), which potentiates the action of Vit. C four-fold. Hydrophilic Vit. C helps regenerate Vit. E, a liphophilic antioxidant.[1,3,5,6] Thus, Vit. C and Vit. E together protect the hydrophilic and lipophilic compartments

of the cell, respectively. Vit. C and Vit. E synergistically limit chronic UV damage by significantly reducing both cell apoptosis and thymine dimer formation.[3,6]

A combination of 0.5% ferulic acid (a potent antioxidant of plant origin) with 15% Vit. C and 1% Vit. E can increase the efficacy of Vit. C eight-fold.[3] It was noted that this triple combination was very useful for the reduction of acute and chronic photodamage, and could be used for prevention of skin cancer in the future.[3]

Vit. C and collagen synthesis

Vit. C is essential for collagen biosynthesis. It has been proposed that Vit. C influences quantitative collagen synthesis in addition to stimulating qualitative changes in the collagen molecule.[2] Vit. C serves as a co-factor for the enzymes prolysyl and lysyl hydroxylase, the enzymes that are responsible for stabilizing and cross-linking the collagen molecules.[2] Another mechanism by which Vit. C influences the collagen synthesis is by stimulation of lipid peroxidation, and the product of this process, malondialdehyde, in turn stimulates collagen gene expression.[2]

Vit. C also directly activates the transcription of collagen synthesis and stabilizes procollagen mRNA, thereby regulating collagen synthesis.[2,3] Signs and symptoms of Scurvy, a deficiency disease of Vit. C, are due to impaired collagen synthesis. Clinical studies have shown that the topical use of Vit. C increases collagen production in young as well as aged human skin.[3,6]

Vit. C as a depigmenting agent

When choosing a depigmenting agent, it is important to differentiate between substances that are toxic to the melanocyte and substances that interrupt the key steps of melanogenesis. Vit. C falls into the latter category of depigmenting agents. Vit. C interacts with copper ions at the tyrosinase-active site and inhibits action of the enzyme tyrosinase, thereby decreasing the melanin formation. Vit. C also acts on the perifollicular pigment.[5,7,8] However, Vit. C is an unstable compound. It is therefore often combined with other depigmenting agents such as soy and liquorice for better depigmenting effect.[7]

Anti-inflammatory action of Vit. C

As stated earlier, Vit. C inhibits NFkB, which is responsible for the activation of a number of pro-inflammatory cytokines such as TNF-alfa, IL1, IL6 and IL8.[2,3] Therefore, Vit. C has a potential anti-inflammatory activity and can be used in conditions like acne vulgaris and rosacea. It can promote wound healing and prevent post-inflammatory hyperpigmentation.[2,3]

TOPICAL FORMULATIONS OF VITAMIN C

Vit. C is available in the market as a variety of creams, serum and transdermal patches. Of these, only the serum contains active Vit. C in an almost colorless form. It is unstable and, on exposure to light, gets oxidized to Dehydro Ascorbic Acid (DHAA), which imparts a yellow color. The stability of Vit. C is controlled by maintaining a pH of less than 3.5. At this pH, the ionic charge on the molecule is removed and it is transported well across the stratum corneum.[3,5,9]

From a clinical point of view, it is important to note that the efficacy of the Vit. C serum is proportional to the concentration, but only up to 20%.[3] The half-life in the skin after achieving maximum concentration is 4 days. A persistent reservoir of Vit. C is important for adequate photoprotection, and can be achieved by regular 8-hourly applications.[1,5] As UV light lowers tissue Vit. C levels, topical Vit. C is best used after exposure to UV light and not prior.[1–3] A combination of tyrosine, zinc and Vit. C has been shown to increase the bioavailability of Vit. C 20-times vis-à-vis using just Vit. C.[2]

A variety of creams with Vit. C derivatives are available in the market. As a dermatologist, it is important to know that not all preparations are physiologically effective. Some are not delivered into the dermis in an adequate quantity, while others do not chemically convert to the biologically active form of Vit. C in the skin.[1,2,4]

Magnesium ascorbyl phosphate (MAP) is the most stable and preferred ascorbyl ester. This lipophilic molecule is easily absorbed into the skin, and the rate-limiting step for absorption is its release from the vehicle, and not the rate of diffusion across the stratum corneum as one might suppose. MAP has a hydrating effect on the skin and decreases transepidermal water loss. It is also a free radical scavenger that is photoprotective and increases collagen production under laboratory test conditions.[1,3] Other useful stable esterified derivatives are:

1. Ascorbyl 6 palmitate, a lipophilic free radical scavenger that hydrolyses to Vit. C and palmitic acid.[3,8]
2. Disodium isostearyl 2-0 L-ascorbyl phosphate (VCP-IS-Na), another reliable and popular derivative of Vit. C with a C8 alkyl chain attached to the stable ascorbyl moiety. This ensures increased permeability across the epidermis
3. Ascorbic acid sulfate.[1]
4. Tetraisopalmitoyl ascorbic acid, a lipophilic provitamin and sodium ascorbate, are derivatives under research.

ADVERSE REACTIONS OF TOPICAL VITAMIN C

Topical Vit. C is largely safe to use on a daily basis for long durations. It can safely be used in conjunction with other common topical anti-ageing agents such as sunscreens, tretinoin, other antioxidants and alfa hydroxy acids such as glycolic acid. Minor adverse reactions include a yellowish discoloration of the skin, hypopigmented hair and staining of clothes, which occur due to oxidative changes of Vit. C. Once applied, Vit. C cannot be fully washed or wiped off the skin. Rarely, stinging, erythema and dryness are observed after use of topical Vit. C. These can easily be treated using a moisturiser. Care must be taken while applying Vit. C around the eyes.[1,2]

Urticaria and erythema multiforme, following the use of topical Vit. C, have been documented.[1] The toxic doses of Vit. C that lead to cellular apoptosis under laboratory conditions are 100-200-times the daily recommended dose, giving Vit. C a very high safety profile.[1]

FUTURE DEVELOPMENTS

As Vit. C is hydrophilic, there is a marked interest to find methods of efficient transepidermal delivery of the stable active compound. If antioxidants could be delivered in high concentration through the stratum corneum barrier, then a dermal reservoir of protective antioxidant could be increased and thus photoprotection would be enhanced.[5] As stated earlier, the use of stable lipophilic esterified derivatives of Vit. C is being explored for the purpose.[5,8,10–13] Extensive research is underway to investigate microspheres, nanoparticles and multilayered microemulsions for graded topical delivery. Trials have been performed with Vit. C and Vit. E in the same multilayered emulsions together.[6] Both electroporation and iontophoresis have been used to enhance penetration of Vit. C into the dermis.[11,14,15] Application of Vit. C to the treated skin surface after microdermabrasion and CO_2 or Er-Yag resurfacing increases the transepidermal penetration of Vit. C 20-times.[2,16] It has also been observed that Vit. C is a good priming agent and a post-operative agent for the prevention of erythema following laser resurfacing. Smokers have been found to have low Vit. C levels in the dermis, akin to UV-damaged skin. Smoking-related skin ageing is another area where efficacy of Vit. C is being explored. Another very useful application of Vit. C may be

striae, where a study has shown that daily application of Vit. C combined with 20% glycolic acid over 3 months can significantly improve striae.[9]

CONCLUSION

To summarize, Vit. C is a naturally occurring drug with multiple desirable effects. With an excellent safety profile, it finds increasing use in photoageing, hyperpigmentation, tissue inflammation and promotion of tissue healing. Ongoing research has been directed toward improving its delivery into the dermis for stimulating collagen production and scavenging free radicals. Vit. C thus holds promise as a mainstream drug in future dermatology practice.

Footnotes

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