Review Article

Photodamage of the skin: protection and reversal with topical antioxidants

K E Burke

River Court, New York, USA

Summary

Controversy exists as to whether topical antioxidants can be effective in protecting against and reversing photodamage to the skin. Topical vitamins C and E, as well as topical selenium, protect skin against sunburn, suntan and skin cancer and also reverse the mottled pigmentation and wrinkles of photoageing. However, only certain forms of these labile antioxidants are stable and active after percutaneous absorption. For effective topical application, vitamin C must be non-esterified, acidic and optimally at 20% concentration; vitamin E must be the non-esterified isomer D-α-tocopherol at 2–5% concentration. Selenium is only percutaneously absorbed and active when applied topically as L-selenomethionine, optimally at 0.02–0.05%.

There are two great advantages in applying an active formulation of topical antioxidants to the skin.

First, the skin attains far higher levels of each antioxidant than can be achieved by only taking these vitamins orally. The level of vitamin C attained in the skin by topical application is 20–40 times that achievable with oral vitamin C. With topical application, the concentration of vitamin E in the skin increases by a factor of 10.6 and selenium by a factor of 1.7.

Second, topical application arms the skin with a reservoir of antioxidants that cannot be washed or rubbed off, a protection which stays in the skin for several days after application.

Keywords: photoageing, photoprotection, selenium, skin cancer, topical antioxidants, vitamin C, vitamin E

Introduction

More than ever before, our generation enjoys the luxury of travel and leisure time for outdoor sports, markedly increasing our exposure to solar radiation. Exposure is increased at high altitudes and with reflection from surfaces covered with snow, sand, water or concrete. Our skin suffers the greatest damage – both acutely (with erythema and sunburn) and chronically (with photoageing and skin cancer).

Certainly, sunscreens are absolutely essential for protection, but they are not enough. The most significant inherent limitations are inadequate application (too little, too infrequently) and incomplete spectral protection. Because the skin naturally uses nutritional antioxidants to protect itself from photodamage, sun protection can be enhanced with effective formulations of topical antioxidants. The challenge is to create stable formulations that give effective transcutaneous absorption of the active form.

This article reviews the efficacy of the major antioxidants proven to be effective: vitamin C, vitamin E and selenium.

Correspondence: Karen E Burke, River Court, 429 East 52nd Street, New York, NY 10022, USA, E-mail: heather.nolan@gs.com

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Vitamin C

Vitamin C (L-ascorbic acid) is the body's major aqueous-phase antioxidant and is absolutely vital for life. All animals make their own vitamin C, except for humans and other primates, one species of bat and the guinea pig. In fact, a

130 lb goat synthesizes 13 g of vitamin C per day, almost 200 times the American FDA requirement.[1] Not only do other animals make hundreds of times the vitamin C we ingest, but also, when stressed, they can make more than 10 times their normal amount of vitamin C (not possible in humans).[1]

Our skin suffers from environmental free-radical stress of sunlight, pollution and smoking. Furthermore, these actually deplete the level of vitamin C in skin. Even minimal UV exposure of 1.6 MED decreases the level of vitamin C to just 70% of the normal level, and exposure to 10 MED decreases the vitamin C to only 54%.[2] Exposure to 10 p.p.m. of ozone in city pollution decreases the level of epidermal vitamin C by 55%.[3]

Effective topical formulation

Fortunately, this detrimental loss of vitamin C from the skin can be effectively corrected by topical application. Topical absorption of vitamin C was proven by radioactive-labelling studies in pigs: after treatment with 10% vitamin C cream, 8.2% was found in the dermis, and 0.7% in the blood.[4] Formulations containing 5, 10, 15, 20, 25 or 30% vitamin C were tested: the highest levels in the skin were achieved by application of 20%.[5]

To optimize percutaneous absorption and full activity of vitamin C, the precise formulation is of the utmost importance. Because L-ascorbic acid is an inherently unstable molecule, making it an excellent antioxidant, creation of an effective topical delivery system is crucial. Many products contain stable derivatives which are not metabolized by the skin (such as ascorbyl-6-palmitate or magnesium ascorbyl phosphate) and therefore have little or no activity.[5] Other formulations do not result in measurable absorption of active vitamin C because they are not at the correct pH. Delivery of L-ascorbic acid (pK_a = 4.2) depends upon removing the ionic charge – achieved optimally at a pH of 3.5.[5]

Protection against photodamage

Topical vitamin C protects against solar damage primarily as an intracellular antioxidant that deactivates ultraviolet (UV)-induced oxygen free radicals. Vitamin C is itself not a sunscreen, though applying vitamin C definitely decreases erythema and sunburn even when applied *after* sun exposure. Histological examination confirms this protection: treatment with topical 10% vitamin C decreases the number of abnormal 'sunburn cells' by 40–60%[4] and reduces UV damage to DNA by 62%.[4]

Topical vitamin C is also directly anti-inflammatory. When vitamin C is applied to the skin before and after laser surgery, there is decreased redness after only 2 months (in contrast to the normal 3–4 month healing without treatment).[6] Topical vitamin C also effectively treats the inflammation of rosacea.[7]

The main action of vitamin C on the skin is direct stimulation of collagen synthesis. Vitamin C is an essential cofactor for the two enzymes required in collagen synthesis, prolyl hydroxylase (which makes the collagen molecule stable) and lysyl hydroxylase (which cross-links the collagen to give structural strength).[8] Recent research has further demonstrated that vitamin C acts directly on DNA to increase the transcription rate and to stabilize the pro-collagen messenger RNA, thus regulating and maintaining intercellular levels of collagen.[9]

Another important action of topical vitamin C is increased synthesis of several specific skin-surface lipids.[10] Not only does this mean that vitamin C helps the natural moisturization of the skin, but it also enhances the protective barrier function of the skin.

Reversal of ageing and photodamage

Exciting experiments on vitamin C have demonstrated that it also has anti-ageing effects: studies *in vitro* compared newborn with elderly (80–90 years old) fibroblasts.[11] The *in vitro* elderly fibroblasts proliferate at only 1/5 the rate of newborn cells. However, when vitamin C is added, the elderly cells actually proliferate better than normal newborn fibroblasts. Even the newborn fibroblasts enhance proliferation by a factor of 4 when exposed to vitamin C.[11]

Not only do fibroblasts increase proliferation, but they also synthesize more collagen in the presence of vitamin C. Newborn fibroblasts synthesize a larger percentage of collagen than elderly cells, but when elderly cells are exposed to vitamin C *in vitro* tissue culture, they produce more collagen than the normal, newborn fibroblasts.[11] The newborn cells double the collagen synthesized.[11]

Vitamin C further reverses the adverse appearance of photoageing by inhibiting tyrosinase,[12] thereby fading unattractive solar lentigos. Because L-ascorbic acid may inhibit elastin biosynthesis[13] it may reduce the solar elastosis of photoaged skin.

The remarkable reversal of photoageing can be appreciated in Fig. 1. After 6 months of once-daily treatment with 15% topical vitamin C, wrinkles were clearly reduced and mottled pigmentation resolved in both of the subjects shown. The skin acquired a healthy, more youthful glow.

Vitamin E

Natural vitamin E is the most important lipid-soluble, membrane-bound antioxidant in the body. Vitamin E is

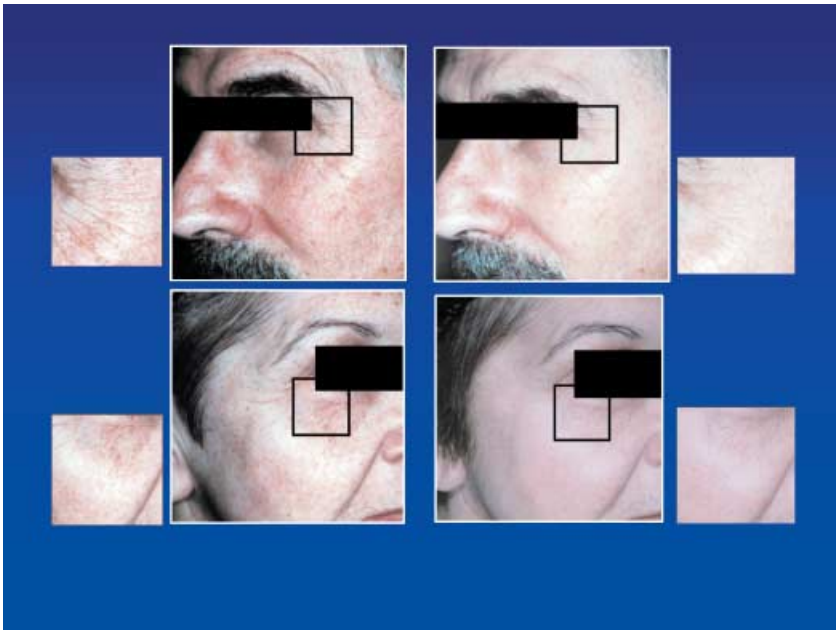
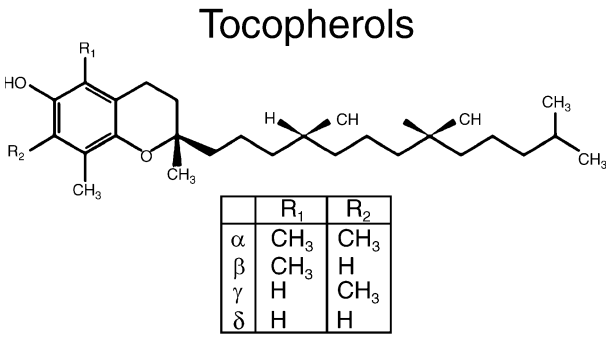


Figure 1 Correction of photoaeging after 1 year of once-daily treatment with 15% vitamin C serum. Notice the improvement of periorbital wrinkles and lightening of solar lentigoes. (Photographs courtesy of SkinCeuticals, Dallas, Texas, USA.)

especially abundant in stratum corneum, delivered there by sebum.[14] Its concentration is highest at the lower levels of the stratum corneum with a decreasing gradient outward. As the outermost defence of the body, the stratum corneum is first to absorb the oxidative stress of sunlight and pollution, depleting vitamin E in the process. Therefore, topical application is particularly advantageous.

Effective topical formulation

Several forms of vitamin E exist in natural dietary sources. The form which is found in mammalian tissues and has by far the greatest biological activity is pure, non-esterified RRR-α-tocopherol,[15] which has three methyl groups on the 6-chromal ring (Fig. 2). Humans use predominantly α-tocopherol because a specific α-tocopherol transfer protein selectively transfers α-tocopherol into lipoproteins.[16] The other natural forms are beta, gamma and delta which contain only one or two methyl groups on the 6-chromal ring. Relative to the α form, the β, γ and δ RRR-tocopherols give only 42, 72 and 40%, respectively, of the protection against post-UV oedema.[17] The synthetic form is 'DL' or 'all-*rac*', a mixture of eight stereoisomers. The synthetic isomers are usually esterified (to acetates and succinates) for use in commercial vitamins and topical formulations because the esters are far more stable. This ester must be hydrolysed before there is any biological activity, a reaction that readily occurs in the stomach after oral ingestion or in cell and organ culture, but is very slow in skin after topical



	R_1	R_2
α	CH_3	CH_3
β	CH_3	H
γ	H	CH_3
δ	H	H

Figure 2 Molecular structures of tocopherols.

application. Thus the antioxidant potential of topical esterified forms is minimal.[18,19] Furthermore, the all-*rac* form of vitamin E has been reported to cause allergic contact dermatitis[20] and erythema multiforme[21] when applied topically. No such adverse reactions have been reported with D-α-tocopherol.

Protection against photodamage

Previous studies have demonstrated protection against *acute*[22,23] UV-induced damage of inflammation and hyperpigmentation, as well as protection against the *chronic* UV-induced damage of skin cancer[22,23,24] even by the various forms of vitamin E which are less metabolically potent when applied topically than the non-esterified Eol. Topical D-α-tocopherol was shown to be far more

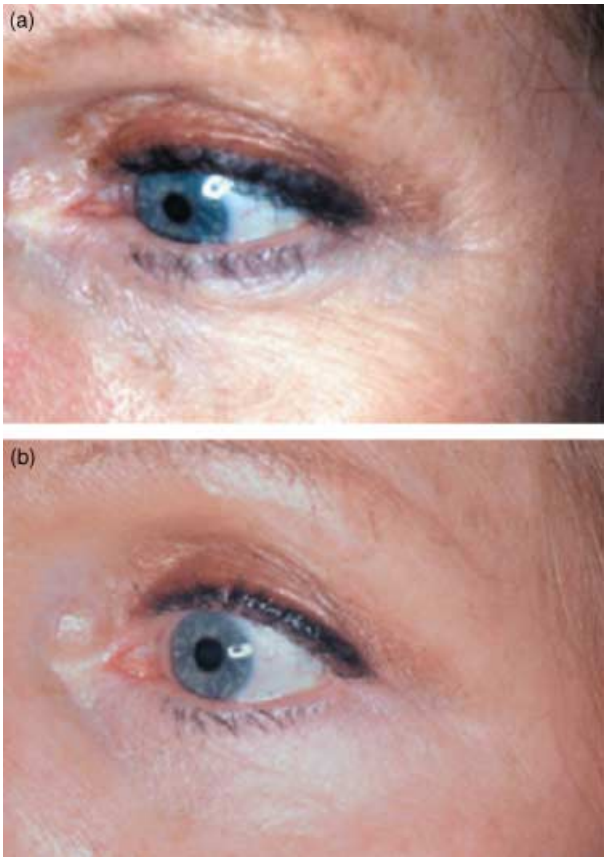


Figure 3 Correction of periorbital wrinkles after 4 months of once-daily treatment 5% D-α-tocopherol cream.

effective in protecting against all acute and chronic UV-induced damage than topical D-α-tocopheryl succinate in mice.[25] In other mouse studies, topical α-tocopheryl succinate and α-tocopheryl acetate not only failed to inhibit UVB-induced immunosuppression and carcinogenesis, but actually appeared to enhance carcinogenesis.[26] Topical α-tocopheryl acetate was less effective than α-tocopherol against UV-induced erythema in rabbits[26] and UV-induced photoageing in mice.[27]

Reversal of photodamage

Vitamin E has been shown to dramatically reverse photoageing. Figure 3 shows the dramatic decrease in periorbital rhytides in a 48-year-old woman after 4 months of daily application of D-α-tocopherol (5%). Histological confirmation of correction of the UV-induced epidermal hypertrophy with thickened stratum corneum, increased incidence of damaged 'sunburn cells' in the basal layer, and disruption of dermal collagen and elastin was demonstrated in mice after 8 weeks of similar topical treatment (Burke *et al.*, unpublished observation). Further electron microscopic analysis confirmed correction of collagen and elastin fibre damage and demonstrated repair of UV-induced disruption of the basement membrane anchoring fibrils.

Vitamin C with vitamin E

The skin uses predominantly vitamin C to protect the aqueous environment and vitamin E to protect membranes from lipid peroxidation. Because vitamin C is naturally present intracellularly in relatively high concentrations, it can regenerate oxidized vitamin E so the vitamin E need not be replaced.[28] Oral vitamin C with vitamin E in high doses protects against UV-induced erythema in humans, whereas either vitamin alone is ineffective.[29] Topical L-ascorbic acid (15%) with α-tocopherol (1%) gives fourfold protection against UV-induced erythema and thiamine dimer formation in porcine skin.[30] Fortunately, combining these hydrophilic and lipophilic antioxidants in a topical formulation stabilizes each[30] for a cosmetically attractive application.

Selenium

Selenium, an essential trace element in humans and animals, is required by the intracellular antioxidant enzymes glutathione (GSH) peroxidase and thioredoxin reductase.[31] Selenium has been shown to have other protective effects that may not involve selenium-dependent glutathione peroxidase (SeGSHpx) activity,[32] such as protecting and repairing DNA, reducing the DNA binding of carcinogens, inhibiting neoplastic transformation and suppressing gene mutations at the lysine and histidine loci.

Effective topical formulation

Topical preparations containing selenium sulphide are frequently used to treat tinea versicolor, seborrhoeic dermatitis and dandruff. However, the selenium from these preparations is not absorbed by the skin.[33] Selenium can be absorbed transdermally when applied as SeMet, giving increased skin and liver levels of selenium after topical application of 0.02% SeMet to mice.[34] This formulation increased the minimal erythema dose in humans[35] and decreased UV-induced skin damage, as demonstrated by a decrease in post-UV tanning and skin cancer in Skh:2 mice.[34]

Protection against photodamage

Selenium has been implicated in reducing carcinogenesis. In animal tumour models, moderate selenium supplementation at levels above the dietary requirements has

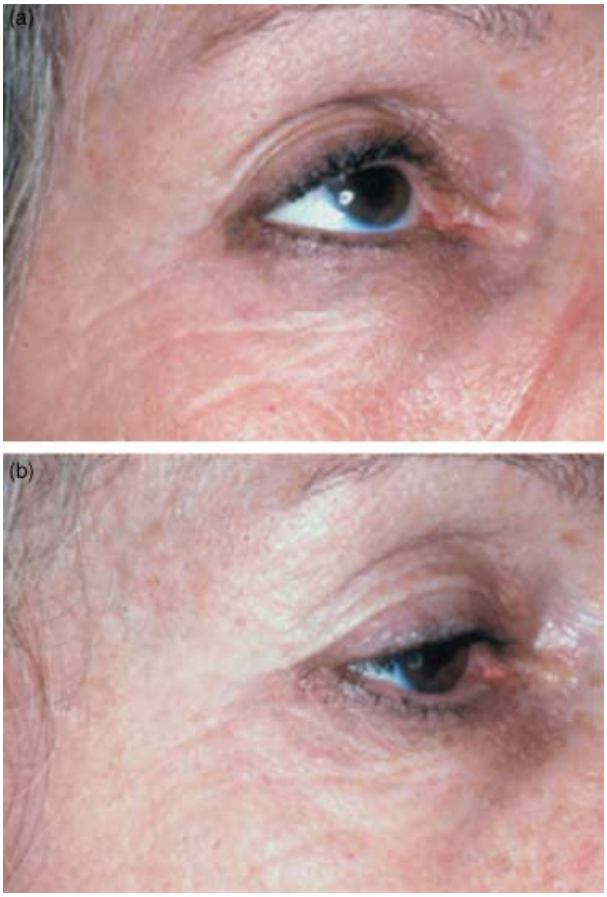


Figure 4 Correction of periorbital wrinkles after 4 months of once-daily treatment 0.05% L-selenomethionine lotion.

been shown to decrease the number of tumours induced by several chemical carcinogens and viruses and to reduce the incidence of spontaneous mammary tumours.[36] In addition, selenium supplements have been shown to inhibit the growth of human tumour cell lines *in vitro*,[37] as well as the growth of transplanted tumours in mice[36] and to decrease the mutagenic activity of several known carcinogens.[36]

Some, but not all, epidemiological studies have found a reduced risk for several kinds of cancer associated with a higher blood concentration of selenium.[38,39] A decreased selenium concentration and glutathionine peroxidase activity in blood and, interestingly, an increase of these parameters in malignant tissue was found in lung cancer patients.[39] A study of 240 non-melanoma skin cancer patients in good general health demonstrated a significantly lower mean plasma selenium concentration than control subjects without skin cancer.[40] In fact, those patients whose blood concentrations were in the lower decile had 4.4 times the incidence of skin cancer as those in the highest decile.[40]

In a 10-year prospective study of 1312 patients with a history of basal cell or squamous cell carcinomas of the skin, selenium treatment did not protect against further development of such skin cancers; however, it did reduce total cancer incidence and the incidence of lung, colorectal and prostate cancer as well as lung cancer mortality.[41]

Reversal of photodamage

Topical selenomethionine is highly effective not only in preventing, but also in reversing photoageing.[42] The significant decrease in periorbital rhytides in a 56-year-old woman after 4 months of daily application of L-selenomethionine (0.05%) is shown in Fig. 4. Histological and electron microscopic analysis confirmed repair of epidermal and dermal photoageing.[42]

Selenium with vitamin E

In many biological systems, vitamin and selenium often act synergistically. Borek *et al*.[43] demonstrated that Se and RRR-α-tocopheryl succinate (natural vitamin E succinate) act alone by different mechanisms to prevent radiogenic and chemically induced transformation *in vitro*. They further showed that there was additive protection when both were used together.

In experiments in mice comparing and combining topical L-selenomethionine with oral D-α-tocopheryl acetate and topical D-α-tocopherol[44] the topical combination was less effective than topical vitamin E alone. Both in prolonging the onset and in decreasing the incidence of UV-induced skin cancers,[44] topical L-selenomethionine with oral vitamin E was more effective than either alone; both forms of vitamin E alone were equally effective and more effective than topical L-selenomethionine alone.[44] Topical L-selenomethionine (alone or in combination with each form of vitamin E) was most effective in preventing UV-induced inflammation (100% effective!).[44]

Conclusion

Three primary antioxidants naturally are required for life: vitamin C, vitamin E and selenium. They can be applied topically to substantially increase their levels in the epidermis and dermis, thereby not only protecting the skin from acute and chronic photodamage, but also reversing the clinical and histological manifestations of photoageing.

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