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How to Prevent Photoaging?

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There are several theories on photoaging and its etiology. At this time, however, the only defenses commonly believed to prevent photoaging are the use of sunscreens to reduce the amount of ultraviolet (UV) that reaches the skin, the use of retinoids to prevent production of collagenase and stimulate collagen production, and the use of antioxidants to reduce and neutralize free radicals. The Pinnell paper in this issue of the *Journal of Investigative Dermatology* that examines ferulic acid combined with vitamins C and E shows that this formulation seems to provide two of the above defenses: a sunscreen effect, and an antioxidant effect. Not all sunscreens confer an antioxidant effect and not all antioxidants yield a sunscreen effect (Pinnell *et al*, 2005b). For example, Kang *et al* (2003) showed that although genistein and *N*-acetyl cysteine exhibit antioxidant activity, they produced no effect on ultraviolet-induced erythema.

UV exposure results in skin damage through several mechanisms including sunburn cell development, thymine dimer formation, collagenase production, and the provocation of an inflammatory response. Sunburn cells, or UV-induced apoptotic cells, have long been used to assess skin damage due to ultraviolet exposure. UV-induced apoptosis is mediated by caspase-3 (Lin *et al*, 2005). Activation occurs in a pathway that involves caspase-7 (Pinnell *et al*, 2005a). It is believed that caspase-3 levels are good indicators of the presence of cellular apoptosis (Kang *et al*, 2003; Philips *et al*, 2003; Lin *et al*, 2005; Yao *et al*, 2005). Theoretically, the fewer sunburn cells present, less the "skin damage" from UV exposure. At this time, sun avoidance and use of sunscreens are the only defenses against sunburn cell formation. Sunscreens and sun avoidance can also protect against thymine dimer formation.

Antioxidants protect the skin from free radicals through several mechanisms in the early stages of elucidation. Free radicals can act directly on growth factors and cytokine receptors in keratinocytes and dermal cells, leading to skin inflammation. Kang *et al* have shown that free radical activation of the mitogen-activated protein (MAP) kinase pathways results in production of collagenase, which leads to degradation of collagen (Saliou *et al*, 2001; Greul *et al*, 2002; Kang *et al*, 2003; Papucci *et al*, 2003; Passi *et al*, 2003; Middelkamp-Hup *et al*, 2004a, b; Sime and Reeve, 2004; Katiyar, 2005). Blocking these pathways with antioxidants is thought to prevent photoaging by preventing the production of collagenase. This theory has been buttressed by re-

search on human skin performed by Kang *et al*. In this study, investigators showed that when human skin was pretreated with the antioxidants genistein and *N*-acetyl cysteine, the UV induction of the cJun-driven enzyme collagenase was inhibited.

Many antioxidants are now available in oral and topical preparations. Studies such as the one by Pinnell suggest that combinations of various antioxidants may have synergistic effects, yielding formulations with greater efficacy than any of the individual antioxidant compounds used alone. Each antioxidant is endowed with various properties that distinguish it from other antioxidants. Some examples of popular antioxidants and their characteristics will be briefly discussed.

Pycnogenol is a trademark name for a standardized extract of the bark of the French maritime pine plant, which is rich in procyanidins, also called proanthocyanidins. These potent free-radical scavengers can also be found in grape seed, grape skin, bilberry, cranberry, black currant, green tea, black tea, blueberry, blackberry, strawberry, black cherry, red wine, and red cabbage. In one study (Sime and Reeve, 2004), Pycnogenol concentrations of 0.05%–0.2% were applied to the irradiated dorsal skin of Skh:hr hairless mice exposed daily to minimally inflammatory solar-simulated UV radiation. Mice pretreated with Pycnogenol demonstrated a concentration-dependent reduction of the inflammatory sunburn reaction (edema). In a study (Saliou *et al*, 2001) evaluating the capacity of pine bark extract to protect human skin against erythema induced by solar radiation, 21 volunteers received oral supplementation of Pycnogenol. During supplementation, the UVR level necessary to reach one minimal erythema dose (MED) was significantly elevated, suggesting that oral pine bark extract supplementation mitigates the effects of UV radiation on the skin, lowering erythema. The mechanism of action of Pycnogenol may transcend its free-radical scavenging activities, as suggested by its anti-inflammatory effects, which are partially ascribed to the fact that Pycnogenol inhibits IFN- γ -induced expression of ICAM-1 (Bito *et al*, 2000).

Silymarin is a naturally occurring polyphenolic flavonoid compound or flavonolignans antioxidant derived from the seeds of the milk thistle plant *Silybum marianu*. The beneficial effects of silymarin are primarily the result of its main active constituent silybin, which was shown to be bioavailable in the skin and other tissues following systemic administration (Zhao and Agarwal, 1999). Topical application of silybin before or immediately after UV irradiation has been found to impart strong protection against UV-induced dam-

Abbreviations: CoQ10, coenzyme Q10; UV, ultraviolet

age in epidermal tissue by a reduction in thymine dimer-positive cells (Dhanalakshmi *et al*, 2004). A wide range of *in vivo* animal studies suggests that silymarin possesses antioxidant, anti-inflammatory, and immunomodulatory properties that may help prevent skin cancer as well as photoaging (Katiyar, 2005).

Coenzyme Q10 (CoQ10) or ubiquinone is a naturally occurring antioxidant found in fish, shellfish, spinach, and nuts. It is a fat-soluble compound also present in all human cells as part of the electron transportation chain responsible for energy production that has been recently found to exhibit antiapoptotic activity (Papucci *et al*, 2003). Researchers have identified an age-related decline of CoQ10 levels in animals and humans (Beyer and Ernster, 1990). UV light depletes vitamin E, vitamin C, glutathione, and CoQ10 from the dermis as well as epidermis of the skin; however, CoQ10 is consistently found to be the first antioxidant depleted in the skin.

Polypodium leucotomos (PL) extract is derived from tropical fern and has demonstrated potent antioxidant activity. Orally administered PL was recently shown to decrease the incidence of phototoxicity in subjects receiving PUVA treatment and in normal healthy subjects (Middelkamp-Hup *et al*, 2004a). UV-exposed keratinocytes and fibroblasts treated with PL have also exhibited significantly improved membrane integrity, reduced lipid peroxidation, enhanced elastin expression, and inhibited matrix metalloproteinases-1 (MMP-1) expression (Philips *et al*, 2003).

Using antioxidants in combination is likely to impart synergistic benefits. A randomized, double-blind, parallel group, placebo-controlled study (Greul *et al*, 2002) examining the effects of an antioxidant preparation containing vitamins E and C, carotenoids, selenium, and proanthocyanidins orally administered to subjects and then exposed to UVB showed a difference in MMP-1 production between the treatment and placebo groups ($p < 0.05$). The assessment of MED of the skin, however, did not reveal any statistically significant differences between the oral antioxidant group and the placebo group.

Although copious data have shown that both topical application and oral administration of individual antioxidants impart benefits to the skin, it is reasonable to investigate a cumulative or additive benefit derived from using oral and topical antioxidant products in combination. In a study (Passi *et al*, 2003) evaluating two groups of individuals, Group A was treated daily with a base cream containing 0.05% ubiquinone, 0.1% vitamin E, and 1% squalene. In addition, 50 mg of CoQ10 + 50 mg of d-RRR- α -tocopheryl acetate + 50 μ g of selenium were administered orally. Group B was treated with the base cream alone. Sebum, stratum corneum, and plasma levels of CoQ10, vitamin E, and squalene were measured every 15 d. The patients treated only with the topical antioxidant formulation showed a significant increase of CoQ10, d-RRR- α -tocopherol, and squalene in the sebum, with no significant changes observed in their stratum corneum or plasma concentrations. Those treated with concomitant oral administration also exhibited elevated levels of vitamin E and CoQ10 in the stratum corneum.

Antioxidants clearly play an important role in the prevention of aging. It is unknown as to which antioxidants are the most effective. Combining them both topically and orally will likely be the leading therapeutic approach in the near future. Antioxidants should be used in combination with sunscreens and retinoids to enhance their protective effects.

DOI: 10.1111/j.0022-202X.2005.23810.x

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