Skin
Beneficial Roles of Citrus
Executive Summary

Filomena Valim and Sandy Barros

The skin is the largest organ in man, consisting of different layers of epidermis and dermis. Its primary physiological function is to be a barrier between the body and the external environment, protecting against mechanical damage, radiation, toxic compounds and microorganisms. Skin plays a role in the regulation of body temperature and is involved in body water homeostasis

Skin is constantly exposed to pro-antioxidant environmental stresses from an array of sources, such as air pollutants, solar ultraviolet (UV) light, chemical oxidants, microorganisms, cigarette smoking and ozone

Reactive oxygen species (ROS) have been implicated in the ethiology of several skin disorders including skin cancer, and photo aging ROS are generated constantly in the skin, and are rapidly neutralized by non-enzymatic and enzymatic antioxidant substances. If the antioxidant defense is exhausted, cell damage can occur. Diets rich in bioactive compounds such as vitamins C and E, β-carotene, lycopene, Zinc (Zn) and Selenium (Se) have also demonstrated the photo protective effect against solar irradiation in human subjects.

In order to be active in skin, dietary bioactive compounds must be able to cross the intestinal barrier and reach the blood circulation. Vitamin C and Dehydroascorbic acid are readily, rapidly and efficiently absorbed from the upper part of the small intestine into the blood circulation.

Nutritional contribution against skin damage from sunlight is emerging as a topic of interest in public health and preventive medicine. The benefits provided by food nutrients reach beyond topical and temporary coverage through the use of sunscreen. While protection from these dietary nutrients in terms of sunlight damage may be low or even marginal, the cumulative effect receives increasing attention.

It is important to note that the nutritional aspect is complementary to topical photo-protection, and these two concepts of prevention should certainly not be considered mutually exclusive. One major aspect regarding dietary photo protection is the time frame. There is a time of approximately eight to ten weeks until protection against erythema (skin redness) formation becomes significant, whereas protection by topical sunscreen is practically instantaneous.

Whereas the photo-protective properties of carotenoids, vitamin E, and vitamin C have largely been attributed to their antioxidant activities, these micronutrients may also offer protection by other mechanisms.

Florida citrus/juices are sources of vitamin C, carotenoids and flavonoids that may have a protective effect against skin disorders such as sunburn, photo-damage and skin cancer, caused by UV radiation, which is an issue concerning a person's entire lifespan.

For a more detailed and referenced review of this topic, please continued reading below

Skin

Beneficial Roles of Citrus

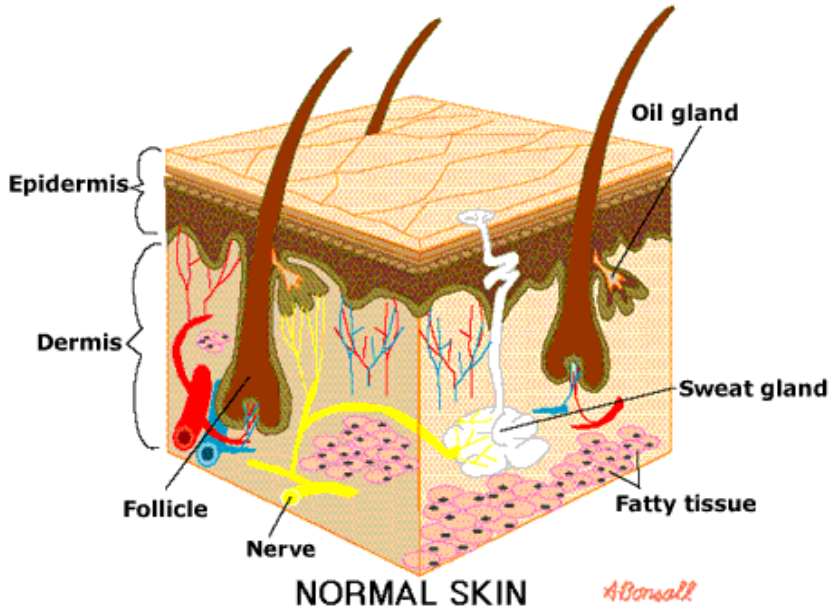
Literature Review

Filomena Valim and Sandy Barros

1- Introduction:

The skin is the largest organ in man, consisting of different layers of epidermis and dermis. Its primary physiological function is to be a barrier between the body and the external environment, protecting against mechanical damage, radiation, toxic compounds and microorganisms. Skin plays a role in the regulation of body temperature and is involved in body water homeostasis (Richelle et al., 2006).

The epidermis (outer layer of the skin) is mostly made up of flat, scale-like cells called squamous cells. Under the squamous cells are round cells called basal cells. The deepest part of the epidermis also contains melanocytes. These cells produce melanin, which gives the skin its color. The dermis (inner layer of skin) contains blood and lymph vessels, hair follicles, and glands. These glands produce sweat, which helps regulate body temperature, and sebum, an oily substance that helps keep the skin from drying out. Sweat and sebum reach the skin's surface through tiny openings called pores.



Skin is constantly exposed to pro-oxidant environmental stresses from an array of sources, such as air pollutants, solar ultraviolet (UV) light, chemical oxidants, microorganisms, cigarette smoking and ozone (Thiele et al, 1997; Cross et al, 1998).

Exposure to UV radiation, the major cause for skin disorders such as sunburn, photodamage, and skin cancer, is an issue concerning the entire life span. It has recently become clear that, interestingly, the predominant exposure of UV light occurs under everyday circumstances. The human skin is exposed to a large degree (about two/thirds of the cumulative UV dose/year) inadvertently, when no topical protection is used. Contrary to previous assumptions, recent analysis of UV exposure data shows that Americans actually get less that 25% of their lifetime UV dose by the age of 18. Three forth of lifetime exposure is delivered during adulthood and older age (Godar, et al, 2003).

Upon light exposure, a cascade of photo-induced chemical and biological reactions takes place in the skin. (Davies, et al, 2001, Girotti, 2001, Pinnell 2003). Initially light interacts with suitable chromophore (a naturally occurring pigment that selectively absorbs light at certain wavelengths). The chromophore may be damaged directly or may act as photosensitizer initiating subsequent chemical reactions. In the present of oxygen, secondary reactive oxygen intermediates are generated (Sies et al, 2004).

Reactive oxygen species (ROS) have been implicated in the ethiology of several skin disorders including skin cancer, and photo aging (Perchellet & Perchellet, 1989; Dalle & Pathak, 1992; Emerit, 1992; Guyton & Kensler, 1993). ROS are generated constantly in the skin, and are rapidly neutralized by non-enzymatic and enzymatic antioxidant substances. If the antioxidant defense is exhausted, cell damage can occur. In the case of skin, there are two methods of antioxidant administration. Topical application is the classical route, however has some drawbacks mainly dealing with antioxidant stability and its ability to penetrate the skin. The second method of administration is oral. Its advantages are that antioxidants are metabolized and then presented to the entire skin potentially in their active forms. In addition, the blood continuously replenishes the skin with these antioxidants, with are distributed to all skin compartments in with they could exert a biological activity.

Photoprotection by endogenous compounds provided from components in the diet via endogenous delivery to the skin has become of major interest. (Sies et al, 2004).

Because most of the annual UV dose is encountered in the absence of topical sun protectants (Godar, 2001), a dietary approach to improve endogenous defense may represent a viable method in the prevention of the damaging effects of sunlight (Heinrich et al, 2006).

Diets rich in bioactive compounds such as vitamins C and E, β-carotene, lycopene, Zn and Se have demonstrated photo protective effect against solar irradiation in human subjects (Richelle et al, 2006).

This white paper addresses the concept of human photo protection by dietary compounds, especially related to compounds found in citrus.

2- Antioxidants:

2.1- Vitamin C:

Vitamin C present in vegetables and citrus fruits, is not synthesized by the human body and is the most important antioxidant in extracellular fluids and in many cellular activities (Keller & Fenske, 1998), and is also an essential cofactor in numerous enzymatic reactions. It comprises two major forms: L-ascorbic acid, the reduced form, and L-dehydroascorbic acid, the oxidized form. In man, plasma ascorbic acid concentrations are maintained between 1-15 micrograms/mL and any excess of the vitamin is excreted by the kidney (Fuchs & Podda, 1997). Ascorbic acid acts as an antioxidant by scavenging and quenching free radicals and by regenerating vitamin E from its radical form.

UV radiation generates free radicals that damage cell membranes, various enzymes, and DNA. Therefore the antioxidant vitamin C may effectively interfere with UV-induced generation of ROS, because it reacts with or suppresses the superoxide anion, the hydroxyl radical, and singlet oxygen (Scarpa et al., 1983; Cabelli & Bielski, 1983; Chou & Khan, 1983).

By replenishing vitamin E, vitamin C indirectly inhibits lipid peroxidation (Wefers & Sies, 1988; McCay, 1985). In mice, Dunhan et al. (1982) found that increases in dietary vitamin C reduced UV induced tumors.

In a study on the cooperative activity of both Vitamins E and C against UV-induced erythema over a period of 50 days, four treatment groups were investigated: Vitamin E (α-tocopherol 2g/day) and Vitamin C (ascorbate 3g/d) as single components, a combination of α-tocopherol and ascorbate (2 and 3g/d respectively), and controls without treatment (Futch et al., 1998). Upon treatment with the combination the sunburn threshold was significantly increased. The single compounds provided moderate but statistically not significant protection.

Short time intervention with high doses of both vitamin E and C also yields some protection. When vitamins were ingested at doses of 1000 IU D-α-tocopherol together with 2 g ascorbic acid/d over

a period of eight days, there was a minor increase in the erythema threshold (Eberlein-Konig et al., 1998).

Vitamin C is critical in wound healing, acting as a co-factor for several enzymes, which stabilize collagen. In vitamin C deficiency, fibroblast produce unstable collagen, providing a weak framework for repair, thus wound healing. Phillips & Pannell (1994) found that ascorbic acid counteracted a reduced proliferative capacity of elderly dermo fibroblast in vivo. Finglas et al (1993) reported lower concentrations of plasma ascorbic acid in the elderly (age 64 – 74 years) compared with healthy adults (age 20 - 64 years).

Vitamin C levels are commonly low in older patients, which may contribute to slower and more difficult wound healing (Phillips & Pannell, 1994; Fenske & Lober, 1986; Leibovitz & Siegel, 1980).

2.2- Carotenoids:

Carotenoids are lipophilic molecules that are well placed to act as chain-breaking antioxidants in the skin protecting epidermal PUFA (polyunsaturated fatty acid) from peroxidation by ROS. Carotenoid deposition in skin is not equal throughout the body (Richelle et al, 2006). Carotenoids exhibit a concentration gradient with a higher amount in the dermis and lower amounts in the stratum corneum (the outermost layer of the epidermis).

In addition, subcutaneous adipose tissue is rich in carotenoids, which could be a storage site of carotenoids for skin (Ribaya-Mercado et al, 1995).

Major carotenoids in the human body are β-carotene, α-carotene, lycopene, phytoene, and phytofluene as well as the xanthophylls lutein, zeaxanthin, and α- and β-cryptoxanthin (Khachik et al, 1997, Stahl et al, 1993).

Carotenoids are among the most efficient natural scavengers of singlet molecular oxygen. At low oxygen tension, carotenoids are also able to scavenge peroxyl radicals (Sies et al, 2004).

Carotenoids are present at the target sites of light-induced damage, the skin and the eye. The dermal pattern of carotenoids resembles that of plasma and the absolute levels vary between different skin areas. They contribute significantly to human skin color, in particular the appearance of yellowness. (Sies et al, 2004).

Intervention studies on UV-protection effects of carotenoids have shown protection against UV-induced erythema after dietary intervention, as opposed to supplementation with isolated compounds. Ingestion of the equivalence of 16mg lycopene/day over a period of 10 weeks let to

elevated serum levels of lycopene and although there was no significant protection found after 4 weeks of ingestion, erythema formation was significantly lower after 10 weeks.

In animal studies, carotenoids proved to be useful agents to prevent skin cancer, and the incidence of nommelonoma skin cancers was inversely related to β-carotene serum levels (Kune et al., 1992). **However, at present there is no clear evidence from epidemiological or interventional studies that β-carotene or other carotenoids contribute to the prevention of any type of skin cancer in humans.**

2.3- Polyphenols:

Flavonoids, a subclass of polyphenols, are secondary plant metabolites found in many commonly consumed fruits and vegetables and, as such, are abundant in a plant-rich human diet (Ross et al, 2002).

Many flavonoids are efficient antioxidants in vitro, and the in vitro antioxidant capacity of a number of fruits and vegetables can be attributed, in part, to its flavonoid constituents (Proteggenta et al, 2002, Middleton at al, 2000). In addition to their antioxidant capabilities, flavonoids can modulate enzyme activity, influence anti-inflammatory pathways, and affect cell division (Dell'Agli et al. 2004).

Animal studies have provided evidence that tea polyphenols, when given orally or topically, ameliorated adverse skin reactions following UV exposure, including skin damage, erythema, and lipid oxidation (Kim et al., 2001, Mukhtar, 2003).

3.0- Summary:

Nutritional contribution to systemic photoprotection is emerging as a topic of interest in public health and preventive medicine (Sies et al., 2004).

The concept of endogenous skin protection is to provide a maintenance level at sensitive dermal targets sites, beyond those reached by topical, and temporary coverage through the use of sunscreen. While the endogenous protection in terms of sun protection factor may be low or even marginal, the cumulative effect receives increasing attention. Lifelong inadvertent sunlight exposure is important (Godar et al., 2003).

It is important to note that the nutritional aspect focused in this white paper is complementary to topical photoprotection, and these two concepts of prevention should certainly not be considered mutually exclusive. One major aspect regarding dietary photoprotection is the time frame: as noted in

the studies showed here. There is a time of approximately eight to ten weeks until protection against erythema formation becomes significant. Skin turnover and skin biochemistry therefore require this time frame, whereas protection by topical sunscreen is practically instantaneous (Sies et al., 2004).

Whereas the photoprotective properties of carotenoids, vitamin E, and vitamin C have largely been attributed to their antioxidant activities (F'guyer et al., 2003), these micronutrients may also offer protection by interfering with cellular signaling in UV-dependent responses to tissues (Ross et al., 2002).

Florida citrus/juices are sources of vitamin C, carotenoids and flavonoids that may have a protective effect against skin disorders such as sunburn, photodamage and skin cancer, caused by UV radiation, which is an issue concerning a person's entire lifespan.

References:

Richelle, M., Sabatier, M., Steiling, H., Williamson, G. (2006). Skin bioavailability of dietary vitamin E, carotenoids, polyphenols, vitamin C, zinc and selenium. British J Nutr, 96:227-238.

Scarpa, M., Stevenato, R., Viglino, R.A. (1983). Superoxide ion as active intermediate in the autoxidation of ascorbate by molecular oxygen: effect of superoxide dismutase. J Biol Chem, 258:6695-6697.

Cabelli, D.E., Bielski, B.H.J. (1983). Kinetics and mechanism for the oxidation of ascorbic acid/ascorbate by HO2/O2 radicals: a pulse radiolysis and stopped flow photlysis study. J Phys Chem 87:1805-1812.

Chou, P.T., Khan, A.U. (1983). L-ascorbic acid quenching of singlet delta molecular oxygen in aqueous media: generalized antioxidant property of vitamin C. Biochem Biophys Res Common 115:932-937.

Wefers, H., Sies, H. (1988). The protection by ascorbate and glutathione against microsomal lipid peroxidation is dependent on Vitamin E. Eur J Biochem 174:353-357.

McCay, P.B. (1985). Vitamin E: interactions with free radicals and ascorbate. Annu Rev Nutr 5:323-340.

Phillips, C., Pinnell, S.R. (1994). Effects of ascorbic acid on proliferation and collagen synthesis in relation to the donor age of human dermal fibroblasts. Soc Invest Dermatol 103:228-232.

Finglas, P.M., Bailey, A., Walker, A., Loughridge, J.M., Wright, A.J., Southon, S. (1993). Vitamin C intake and plasma ascorbic acid concentration in adolescents. Br J Nutr 69:563-576.

Godar, DE, Urback, F, Gasparro, FP, van de Leun, JC. 2003. UV doses of young adults. Photochem. Photobiol. 73:621-29.

Godar, DE. 2001. UV doses of Amercian children and adolescents. Protochem Photobiol. 74:787-93.

Sies, H., Stahl, W. 2004. Nutitional Protection Against Skin Damage from Sunlight. Annu. Rev. Nutr. 24:173-200.

Davies, MJ., Truscott RWJ. 2001. Photo-oxidation of proteins and its consequesnces. Amsterdam:Elsevier.

Girotte, AW. 2001. Lipid photo-oxidative damage in biological membranes: reaction mechanism, cytotoxic consequences, and defense strategies. Amsterdam:Elsevier.

Pinnell, SR. 2003. Cuteneous phtodamage, oxidative stress, and topical antioxidant protection. J. Am. Acad. Dermotol. 48:1-19.

Khachik, F., Spangler, CJ., Smith JC., Canfield, LM., Steck, A., Pfander, H. 1997. Indentification, quantification, and relative concentrations of carotenoids and their metobolites in human milk and serum. Anal. Chem. 69:1873-81.

Stalh W, Sundquist, AR., Hunusch, M., Schwarz, W., Sies, H. 1993. Separation for b-carotene and lycopene geometrical isomers in biological samples. Clin.Chem. 39:810-14.

Kune, GA., Bannerman, S., Field, B., Watson, LF., Cleland, H, et al. 1992. Diet, alcohol, smoking, serum beta-carotene, and vitamin A in male nonmeloanocytic skin cancer patients and controls. Nutr. Cancer 18:237-44.

Ross, JA., Kasum, CM., 2002. Dietary flavonoics:bioavailabilty, metabolic effects, and safety. Annu Rev Nutr. 22:19-34.

Proeggenta, AR, Pannaia AS, Paganga, G. Van Buren, L. Wagner, E, Wiseman, S., Dacombe, C., Rice-Evans, CA. 2002. The antioxidant activity of regularly consumed fruit and vegetables reflect their phenolic and vitamin C composition. Free Radic Res. 36:217-33.

Middleton, E. Jr., Kandaswami, C., Theoharides, TC. 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev. 52:673-751.

Dell'Agli, M., Busciala, A., Bosisio, E. 2004. Vascular effects of wine polyphenols. Cardiovasc Res. 63:593-602.

Kim, J., Hwang, KS., Cho, YK., Han, V., Jenn, KH. 2001. Protective effects of (-)-epigailocatechin-3-gallat on UVA- and UVB-Induced shin damage. Skin Pharmocol Appl Skin Physiol. 14:9-11.

Mukhtaf, H. 2003. Eat plenty of green leafy vegetables for photoprotection: emerging evidence. J Invest Dermatol 121:viii.

F'guyer, S., Afag, F., Mukhtar, H. 2003. Photochemoprevention of ultraviolet B signaling and photocarcinogenesis. Mutat Res. 571:153-73.

Fuchs, J., Kern, H., 1998. Modulaton 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. 25:1006-12.

Eberlein-Konig, B., Placzek, M., Pzybilla, B. 1998. Protective effect against sunburn of comined systemic ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E). J. Am. Acad. Dermatol. 38:45-48.