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REVIEW ARTICLE

Oxidative Stress and Skin Cancer: An Overview

R. T. Narendhirakannan · M. Angeline Christie Hannah

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Abstract Skin is the largest body organ that serves as an important environmental interface providing a protective envelope that is crucial for homeostasis. On the other hand, it is a major target for toxic insult by a broad spectrum of physical and chemical agents that are capable of altering its structure and function. There are a large number of dietary contaminants and drugs can manifest their toxicity in skin. These environmental toxicants or their metabolites are inherent oxidants and/or directly or indirectly drive the production of a variety of reactive oxidants also known as reactive oxygen species. These are short-lived entities that are continuously generated at low levels during the course of normal aerobic metabolism. These are believed to activate proliferative and cell survival signaling that can alter apoptotic pathways that may be involved in the pathogenesis of a number of skin disorders. The skin possesses an array of antioxidant defense mechanisms that interact with toxicants to obviate their deleterious effect. The "antioxidant power" of a food is an expression of its capability both to defend the human organism from the action of the free radicals and to prevent degenerative disorders. Plants like olive trees have their own built-in protection against the oxidative damage of the sun, and these built-in protectors function as cell protectors in our own body. Although many antioxidants have shown substantive efficacy in cell culture systems and in animal models of oxidant injury, unequivocal confirmation of their beneficial effects in human populations has proven elusive.

R. T. Narendhirakannan (✉) · M. A. C. Hannah
Department of Biotechnology, School of Biotechnology and Health Sciences, Karunya University (Karunya Institute of Technology and Sciences), Karunya Nagar, Coimbatore 641 114, Tamil Nadu, India
e-mail: bionaren_phd@yahoo.co.in; rtnkannan@gmail.com

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Introduction

Skin is a major environmental interface for the body, which accidentally or occupationally gets exposed to a number of chemical mutagens and carcinogens. Skin cancer represents a major and growing public health problem [1]. It accounts for ~40 % of all new cancer diagnosed [2]. 80 % of skin cancers result from basal cell carcinomas (BCC); another 16 % are squamous cell carcinomas (SCC), and 4 % are melanomas [3].

Reactive Oxygen Species

In the last two decades there has been an explosive interest in the role of oxygen-free radicals, more generally known as "reactive oxygen species," (ROS) and of "reactive nitrogen species" (RNS) in experimental and clinical medicine [4]. ROS and RNS: are generated during irradiation by UV light, X-rays and gamma rays, they are the products of metal-catalyzed reactions, they are present as pollutants in the atmosphere, ROS are produced by neutrophils and macrophages during inflammation and they are the by-products of mitochondria-catalyzed electron transport reactions and other mechanisms [5].

Free radicals can be defined as molecules or molecular fragments containing one or more unpaired electrons. The presence of unpaired electrons usually confers a considerable degree of reactivity upon a free radical. The radicals derived from oxygen represent the most important class of such species generated in living systems [6].

Skin contains antioxidant defenses, which nullify ROS including free radicals, but these defenses will be overwhelmed if the dose of UV light is high enough, and this result in free radical damage to cellular components such as proteins, lipids and DNA [7, 8]. ROS induced by oxidative stress can ultimately lead to apoptotic or necrotic cell death [9]. Especially, the accumulated ROS plays a critical role in the intrinsic aging and photo-aging of human skin in vivo, thus suggested to be responsible for various skin cancers and other cutaneous inflammatory disorders [10, 11].

UVB radiation is a complete carcinogen and causes excessive generation of ROS thus resulting in an oxidative stress in the skin [12, 13]. Studies have shown that UVB radiation produces a variety of adverse effects that includes DNA damage [14, 15], mutations in key regulatory genes [16], inflammation [17, 18], immuno-suppression [19, 20], photo-aging and skin cancer [21, 22]. UVB is directly absorbed by cellular DNA leading to the formation of DNA lesions primarily cyclobutane pyrimidine dimers and pyrimidine (6-4)-pyrimidone photoproducts [13, 23].

UVB radiation to mammalian skin is known to alter cellular function via oxidation of macromolecules, DNA damage, generation of ROS, and alterations in signaling pathways [13]. The incidence of lipid peroxidation (LPO) in the biological membrane is a free radical-mediated event that is regulated by the availability of substrates in the form of polyunsaturated fatty acids (PUFAs), pro-oxidants which promote peroxidation [24]. LPO is highly detrimental to cell membrane structure and function, and its elevated level has been linked to damaging effects such as loss of fluidity, inactivation of membrane enzymes, increases cell membrane permeability which may ultimately lead to disruption of cell membrane potential [25].

UVB-induced leukocyte infiltration in the skin, and inflammatory leukocytes are the major source of H_2O_2 production that plays an important role in inflammatory skin diseases and skin cancer. It was clearly demonstrated that oral feeding of pomegranate fruit extract would result in reduction of the risk factors associated with UVB radiation by inhibiting UVB-mediated LPO and production of H_2O_2 [26].

Epidemiology

Epidemiological studies have reported that the incidence of it is significantly rising worldwide due to increased cumulative ultraviolet (UV) exposure. Epithelial tumors, basal cell carcinoma and squamous cell carcinoma are the most important skin tumors [2, 27]. Associated risk factors for skin cancer include childhood and chronic sun exposure, individual susceptibility with red or blond hair and fair skinned phenotype, older age, polycyclic aromatic hydrocarbon, immuno-compromised status.

Etiology

Major etiological factors for it are family history, sun sensitivity, chronic exposure to sun and occupational exposure to carcinogens and immune suppression. Whereas several efforts have been made to educate the general population about the strategies to prevent skin cancer, such as avoiding exposure to sun and use of sunscreens, additional approaches are still needed to control and prevent the occurrence of skin cancer.

Increasing incidence of skin cancer due to constant exposure to environmental carcinogens, including both chemical agents and UV radiation, provides a strong basis for chemoprevention with both synthetic and natural, and internal and topical, remedies [28].

Ultra violet radiation (UVR) is considered to be the major carcinogenic factor for all types of it. However, many other factors contribute to the initiation and promotion of skin carcinogenesis [29]. For instance, occupational exposures to chemical pollutants (e.g. polycyclic aromatic hydrocarbons), volatile organic compounds (e.g. benzene) and heavy metals (e.g. arsenic, lead) considered very potent genotoxic factors for some population groups such as steel, agriculture, petrochemical, textile and pesticide industry workers [30]. UVR and chemical agents can initiate damages to biomolecules either by direct photochemical reactions or/and via oxidative mechanisms generated by ROS [31–36].

Skin spontaneously responds to increased ROS levels, induced by UVR or chemical agents by detoxifying enzymes such as superoxide dismutase, catalase, thioredoxin reductase and low-molecular mass antioxidant molecules such as glutathione, a-tocopherol and ascorbic acid. However, this response may not be sufficient to prevent the oxidative damage of cutaneous cells after excessive or repetitive exposure to carcinogenic agents [37].

Thus, ROS may oxidize lipids, proteins and DNA leading to formation of oxidized products such as lipid hydroperoxides, protein carbonyls and 8-oxo-guanosine [32]. If these alterations occur to genes involved in normal homeostatic mechanisms that control proliferation and cell death, significant abnormalities are observed in the cell cycle, leading to the first cancer stage, initiation [33, 38].

ROS such as superoxide radical, hydroxyl radical and hydrogen peroxides are frequently generated in the biological systems either by normal metabolic pathways or as a consequence of exposure to physical, chemical and biological agents. ROS attack bio membranes and lead to

oxidative destruction of PUFAs by a chain reaction known as LPO.

ROS interfere with the structure and function of the cells, making them weak and defenseless. Overproduction of ROS within tissues can damage DNA and contribute to mutagenesis and carcinogenesis. ROS-mediated oxidative stress has been implicated in the pathogenesis of several diseases including cancer [39]. Human body has, however, an array of sophisticated antioxidant defense mechanism to combat the deleterious effects of ROS-mediated oxidative damage.

Phytochemicals, Skin Cancer and ROS

The "antioxidant power" of a food is an expression of its capability both to defend the human organism from the action of the free radicals and to prevent degenerative disorders deriving from persistent oxidative stress [40]. Plants like olive trees have their own built-in protection against the oxidative damage of the sun, and these built-in protectors function as cell protectors in our own body. The very pigments that make blueberries blue and raspberries red protect those berries from oxidative damage [41].

Plants are rich alternative sources of natural antioxidants which can complement the antioxidants produced by the human body. Phytochemicals are defined as bioactive non-nutrient plant compounds in fruits, vegetables, grains and other plant foods that have been linked to reducing the risk of major chronic diseases. The word 'phyto-', derived from the Greek word *phyto* which means—plant [42]. The presence of these bioactive components are said to confer them with resistance against bacterial, fungal and pesticidal pathogens. Different mechanisms of action of phytochemicals have been suggested. They either act as antioxidants, or may modulate gene expression and signal transduction pathways [39, 43, 44].

Anthocyanidins and their derivatives, many found in common foods, protect against a variety of oxidants through a number of mechanisms. Cyanidins, found in most fruit sources of anthocyanins, have been found to "function as a potent antioxidant in vivo" in recent Japanese animal studies [45]. In other animal studies, cyanidins protected cell membrane lipids from oxidation by a variety of harmful substances [46]. Additional animal studies confirm that cyanidin is four times more powerful an antioxidant than vitamin E [47]. The anthocyanin pelargonidin protects the amino acid tyrosine from the highly reactive oxidant peroxynitrite [48]. Eggplant contains a derivative of the anthocyanidin delphinidin called nasunin, which interferes with the dangerous hydroxyl radical-generating system—a major source of oxidants in the body [49].

Grape seed proanthocyanidins (GSP) are potent antioxidants and free radical scavengers. GSP inhibited skin tumor formation and decreased the size of skin tumors in hairless mice exposed to carcinogenic UV radiation. Exposure to UV radiation can suppress the immune system, but GSP prevented this suppression in mice fed a diet containing GSP. Treatment of cells with GSP increased tumor cell death in a model used to study tumor promotion in skin cells [50].

Resveratrol belongs to a class of polyphenolic compounds called stilbenes. Resveratrol is a fat-soluble compound that occurs in a *trans* and a *cis* configuration. Resveratrol is a naturally occurring polyphenolic phytoalexin [51]. Foods known to contain resveratrol are limited to grapes, wine, grape juice, cranberries, cranberry juice [52, 53], peanuts, and peanut products [54]. It has shown that the roots of the weed *Polygonum cuspidatum* constitute one of the richest sources of resveratrol [55].

Topical application of resveratrol SKH-1 hairless mice prior to UVB irradiation resulted in a significant decrease in UVB-generation of H_2O_2 as well as infiltration of leukocytes and inhibition of skin edema. Long-term studies have demonstrated that topical application with resveratrol (both pre- and post-treatment) results in inhibition of UVB-induced tumor incidence and delay in the onset of skin tumorigenesis [56].

The most common flavonol in the diet is quercetin [57]. Quercetin has anti-inflammatory and antioxidant effects and act as a immunomodulator [58]. A diet rich in quercetin has been reported to inhibit the development of carcinogen-induced rat mammary cancer [59], colonic neoplasia [60], oral carcinogenesis [61], and skin tumor formation in three models of skin carcinogenesis in mice when administered by topical application [62]. Quercetin may account for the beneficial effects of dietary fruits and vegetables on mutagens and carcinogens, including metals [63]. It is present in various common fruit and vegetables, beverages, and herbs [64]. The highest concentrations are found in onion [57]. Quercetin and rutin were tested as potential topical sunscreen factors in human beings and found to provide protection in the UVA and UVB range [65].

Apigenin is a widely distributed plant flavonoid occurring in herbs, fruit, vegetables, and beverages. Apigenin was found to be effective in the prevention of UVA/UVB-induced skin carcinogenesis in SKH-1 mice [64]. Artemisia (*Artemisia inculta*) and *Cuminum cyminum* or cumin also contain apigenin and luteolin and their derivatives in addition to plants like carrot (*Daucus carota*), agrimony (*Agrimonia eupatoria*), arnica (*Arnica montana*), purple coneflower (*Echinacea purpurea*), and eyebright (*Euphrasia officinalis*)—all of which have demonstrated anti-inflammatory activity when used under the right conditions [66].

Silymarin is a flavonoid compound found in the seeds of milk thistle (*Silybum marianum*) [67]. Silymarin consists of the following three phytochemicals: silybin, silidianin, and silicristin. Silybin is the most active phytochemical [51]. Topical silymarin has been shown to have a remarkable anti-tumor effect. The number of tumors induced in the skin of hairless mice by UVB light was reduced by 92 %. Silymarin reduced UV-induced sunburn cell formation and apoptosis. Silymarin treatment prevents UVB-induced immune suppression and oxidative stress in vivo [68].

Curcumin (diferuloylmethane) is a yellow odorless pigment isolated from the rhizome of turmeric (*Curcuma longa*). Curcumin possesses anti-inflammatory [51, 69], antitumoral, and antioxidant properties. The inhibitory effects of curcumin were attributed to its ability to scavenge ROS. Curcumin can prevent UV irradiation-induced apoptotic changes in human epidermoid carcinoma A431 cells [69].

Vitamin E (α-tocopherol) may protect both animal and plant cell membranes from light-induced damage [70]. Topical application of these antioxidants to the skin has been shown to reduce acute and chronic photo-damage. *Triticum vulgare* oil is particularly rich in vitamin E and offers excellent antioxidant promise in topical anti-aging formulations. Also, it nourishes and prevents loss of moisture from the skin [71].

Extra virgin *Corylus avellana* (hazelnut) oil has good levels of tocopherols, as do *Helianthus annuus* (sunflower) and *Sesamum indicum* (sesame) oils. *Cucurbita pepo* (pumpkin) seed oil deserves greater recognition. With a lipid profile containing high levels of linoleic acid (43–53 %), it contains two classes of antioxidant compounds: tocopherols and phenolics, which account for 59 % of the antioxidant effects. Due to the strong, rich aroma, it is only used in small proportions in topical formulations. It (L-ascorbic acid) is the body's most important intracellular and extracellular aqueous-phase antioxidant. Vitamin C provides many benefits to the skin most significantly, increased synthesis of collagen and photo-protection [72].

Many phytochemicals are endowed with photoprotective properties, i.e., the capability to prevent the harmful effects of excessive exposure to UV light. These effects include photoaging and skin cancer, and immunosuppression. Photoprotection is endowed through two major modes of action: UV absorption or reflection/scattering; and tissue repair post-exposure. Fernblock is an all-natural antioxidant extract, administered both topically (on the skin) or orally. It inhibits generation of ROS production induced by UV including superoxide anion. It also prevents damage to the DNA, inhibits UV-induced AP1 and NF-κB, and protects endogenous skin natural antioxidant systems, i.e., CAT, GSH, and GSSR. Its photoprotective effects at a cellular level include a marked decrease of UV-mediated cellular apoptosis and necrosis and a profound inhibition of extracellular matrix remodeling [73].

Our previous studies indicates that extract of *A. marmelos* possess the polyphenol and flavonoids compounds that modulates the activity of enzymic and nonenzymic antioxidants and enhances the defense against ROS-generated damage in diabetic rats and *Cleome gynandra* leaf extract contains high content of glycosides and flavonoids and possess significant anti-arthritic activity as evidenced by mediated through its inhibiting effect on the formation of lipid peroxide and effective free radical scavenging activity [74, 75].

Conclusion

UV radiation causes skin damages. Everybody needs protection from harmful UV lights. There are many different ways to protect our skin. The best way is avoiding direct sun exposure. But sometimes, it can be impossible, especially during summer. Because of that, sunscreen products should be used. Overproduction of ROS within tissues can damage DNA and contribute to mutagenesis and carcinogenesis.

ROS-mediated oxidative stress has been implicated in the pathogenesis of several diseases including cancer. Human body has, however, an array of sophisticated antioxidant defense mechanism to combat the deleterious effects of ROS-mediated oxidative damage.

Our body may not produce adequate antioxidants so it is necessary to have fruits and minerals rich in antioxidants each day to get rid of the free radicals and thus from the oxidative stress.

Plants' ability to protect themselves from UV radiation from the sun is the main reason for the popularity of using natural ingredients in different skin care products. Plant phenolics are one candidate for prevention of harmful effects of UV radiation on the skin. Additionally, plants contain a lot of other substances which can be useful for skin care. Their potential is still undefined. It was shown that using only one natural component is not enough for skin protection. Maybe, combination of several different natural substances is a right solution. It will be ideal to make the product with natural components only, without any harmful effects.

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