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Review

Dietary proanthocyanidins prevent ultraviolet radiation-induced non-melanoma skin cancer through enhanced repair of damaged DNA-dependent activation of immune sensitivity

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ABSTRACT

Numerous plant products have been used to prevent and manage a wide variety of diseases for centuries. These products are now considered as promising options for the development of more effective and less toxic alternatives to the systems of medicine developed primarily in developed countries in the modern era. Grape seed proanthocyanidins (GSPs) are of great interest due to their anti-carcinogenic effects that have been demonstrated using various tumor models including ultraviolet (UV) radiation-induced non-melanoma skin cancer. In a pre-clinical mouse model supplementation of a control diet (AIN76A) with GSPs at concentrations of 0.2% and 0.5% (w/w) significantly inhibits the growth and multiplicity of UVB radiation-induced skin tumors. In this review, we summarize the evidence that this inhibition of UVB-induced skin tumor development by dietary GSPs is mediated by a multiplicity of coordinated effects including: (*i*) Promotion of the repair of damaged DNA by nuclear excision repair mechanisms, and (*ii*) DNA repair-dependent stimulation of the immune system following the functional activation of dendritic cells and effector T cells. Dietary GSPs hold promise for the development of an effective alternative strategy for the prevention of excessive solar UVB radiation exposure-induced skin diseases including the risk of non-melanoma skin cancer in humans.

1. Introduction

Natural products from plants, herbs and shrubs have been consumed by humans as foods and spices based on their perceived health benefits, rather than simply for nutritional reasons, for centuries. In addition, natural products have been used with the specific purpose of preventing and treating many different diseases from ancient times. They play a central role in the Unani, the Chinese and the Indian Ayurvedic systems of medicine. There is now a renewed interest in the use of natural plant products, also known as phytochemicals, as complementary and/or alternative medicine strategies for the prevention and treatment of diseases including malignancies of different organs. Realization of this potential, however, requires an improved understanding of the therapeutic effects of the plant products and identification of their mechanisms of action and molecular targets. This must be based on rigorous identification and characterization of the plant products, optimization of their administration either in dietary or non-dietary forms, and development of informative, standardized protocols and models for preclinical testing of safety and efficacy. Future clinical application requires detailed knowledge of the mechanisms of action and molecular targets of the specific phytochemical in terms of the attenuation or reduction of the risk of specific malignancies.

The incidence of cutaneous malignancies, including melanoma and non-melanoma skin cancer, is equivalent to the incidence of malignancies in all other organs combined [1]. Non-melanoma skin cancer is the most common type of malignancy in the United States, accounting for about 40% of all newly-diagnosed cancer cases. The fact is that fair-skinned people, for example Caucasians, are at the higher risk against UV light induced skin cancer. It is well established that the fair skin is more susceptible to photodamaging effects. It means that not only USA, but also those countries which have Caucasian population, they are prone to the risk of non-melanoma skin cancer. This cutaneous

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malignancy comprises squamous cell carcinoma and basal cell carcinoma. The cost of treatment of cutaneous malignancy has been estimated to be approximately $3.0 billion annually in USA [2]. Therefore, new and promising approaches/strategies are urgently needed to alleviate the burden of this major public health problem. The incidence of skin cancer is most common in fair skinned individuals or Caucasians. Chronic exposure of the skin to ultraviolet (UV) radiation is a well-recognized etiological risk factor for the skin cancer. As phytochemicals are emerging candidates for the prevention and/or treatment of many diseases including cancers, the use of proanthocyanidins specifically is encouraging for the prevention of skin cancer. In this review article, we have attempted to summarize the information available in the literature on the chemopreventive effects of dietary grape-seed proanthocyanidins (GSPs) on solar UV radiation-induced non-melanoma skin cancer development. It should be noted that chemopreventative strategies are used over the life-time of an individual; therefore, these agents should not only be effective but also have a low toxicity profile as well being easy to use and readily affordable.

2. Solar UV spectrum, wavelengths and the skin

The skin is the largest organ of the body and protects the internal organs by acting as a barrier against the many detrimental effects of the environment and xenobiotic agents. Although, several xenobiotic and environmental factors can contribute to the initiation and development of cutaneous diseases, excessive exposure of the skin to solar UV radiation is considered to be an important contributing event.

The solar UV spectrum is subdivided into three main segments based on the wavelength of the light:

(i) UVC (200–290 nm) is also known as short-wave solar radiation. Light with the UVC wavelengths is largely absorbed by the atmospheric ozone layer and therefore rarely reaches the earth's surface. UVC radiation can penetrate the skin (60–80 μm), can damage DNA and is mutagenic in nature.

(ii) UVB (290–320 nm) is also known as mid-wave solar UV radiation. UVB radiation comprises about 5% of the total UV spectrum. It can penetrate the skin to a depth of approximately 160–180 μm. It can induce both direct and indirect adverse biological effects, which include oxidative stress, inflammation, DNA damage, suppression of the immune system, and premature photoaging [3–5]. UVB is mainly responsible for the UV-induced risk of melanoma and non-melanoma skin cancers. This spectrum has the ability to act as a tumor initiator, tumor promoter and as a complete carcinogen [6–8].

(iii) UVA (320–400 nm) is also known as long-wave solar radiation or the "aging ray." This fraction of UV light comprises about 90–95% of total UV spectrum. UVA radiation can penetrate deeper in the skin (up to 1000 μm). Skin exposure to UVA induces the generation of reactive oxygen species, such as singlet oxygen and hydroxyl free radicals, which can damage cellular macromolecules, such as DNA, lipids and proteins, *etc.* [9]. Overexposure of UVA results in premature aging of the skin or photoaging of the skin in the form of wrinkling or skin sagging [10].

3. Grape seed proanthocyanidins, source and composition

Proanthocyanidins are natural compounds that are widely distributed in vegetables, fruits, seeds, flowers, bark and nuts. Grape (*Vitis vinifera*) seeds are rich source of proanthocyanidins and account for approximately 60% to 70% of whole seeds. The grape seeds are available as byproducts of the industrial production of grape juice and wine. Proanthocyanidins are composed of dimers, trimers, tetramers and oligomers of monomeric epicatechins or catechins [11–13, Fig. 1]. Proanthocyanidins are synonymous with condensed tannins, also known as pycno-genols or leukocyanidins, oligomeric proanthocyanidins or oligomers [11]. The proanthocyanidins that consist of mainly epicatechin monomers are designated as procyanidins, which are the most abundant type of proanthocyanidins. The less common proanthocyanidins containing epigallocatechin subunits are called prodelphinidins [14]. Grape seed extract provides a concentrated source of polyphenols, many of which are proanthocyanidins. Red wine is rich in the complex polyphenols, the proanthocyanidins. Proanthocyanidins share common properties with other polyphenols, in particular their reducing capacity and ability to chelate metal ions. The authors of this review have investigated the chemopreventive effects of dietary GSPs on UV radiation-induced skin carcinogenesis extensively using *in vitro* and *in vivo* animal models. The major ingredients found in the GSPs are: total proanthocyanidins (89%), which are found in the form of dimers (6.6%), trimers (5.0%), tetramers (2.9%) and oligomers (74.8%) of monomeric catechins. The major monomeric catechins are: (+)-catechins and (+)-epicatechins. Monomeric flavanols are detected at the level of 6.6% in the GSPs preparations [11,12,15,16].

4. Bioavailability and toxicity of proanthocyanidins

The bioavailability and toxicity of GSPs are an important issue. Investigations have revealed that proanthocyanidins are poorly absorbed as such in the gut or digestive system [17]. Dimerized proanthocyanidins have been detected in human plasma but their absorption is less than that of the monomeric subunits [18,19]. It has been found that long-term consumption of GSPs in the form of a supplemented diet by laboratory animals did not result in apparent signs of toxicity [20]. Consumption of proanthocyanidin-rich foods, such as red wine and grape seed extracts, has been shown to have beneficial effects by increasing the plasma antioxidant capacity and promote effects on vascular function in humans [21]. GSPs have been subjected to limited toxicity testing in an animal model. Genotoxicity tests have included tests for the induction of gene mutation in bacteria and induction of chromosomal aberrations in a mammalian cell *in vitro* system as well as a micronucleus test using an animal model. The results from these tests indicate that GSPs have low toxicity and show no genotoxic activity [22].

5. Anti-non-melanoma skin cancer activity of dietary GSPs

In most of the *in vivo* studies in which the anti-skin cancer effects of GSPs have been evaluated, the GSPs were administered by mixing them into an AIN76A control diet. Mittal et al. [15] demonstrated for the first time that dietary administration of GSPs (0.2 and 0.5%, w/w) for 24 weeks (entire duration of photocarcinogenesis protocol) prevents UV radiation-induced skin tumor development in SKH-1 hairless mice in terms of tumor incidence (percent mice with tumors), tumor multiplicity and growth or size of the tumor. Dietary GSPs also prevent malignant transformation of papillomas to carcinomas in mice. The process of transformation from papillomas to carcinomas requires constant tumor promoting events, such as inflammatory mediators and oxidative stress, *etc.* [23]. Additionally, genetic and epigenetic alterations play significant roles in cancer/tumor development as well as in malignant transformation [24–26]. These observations suggest that dietary GSPs possess the ability to protect the skin from the adverse effects of UV radiation *in vivo* in an animal model. It is important to mention that in majority of studies conducted in author's laboratory, 0.5% (w/w) GSPs-supplemented diet was used in animal experiments.

6. Anti-skin cancer activity of GSPs: molecular and cellular targets

The molecular targets and mechanism of action that have been shown to be involved in the prevention of UV-induced skin tumor development by dietary GSPs in animal models are summarized below. In this review, we emphasize on the more recent and valuable