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Mini-review

Multi-targeted prevention and therapy of cancer by proanthocyanidins

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Abstract

In recent years, a considerable emphasis has been focused on the importance of the naturally available botanicals that can be consumed in an individual's everyday diet and that can also be useful as a chemopreventive or chemotherapeutic agent for certain diseases, including cancers. A wide variety of botanicals, mostly dietary flavonoids or polyphenolic substances, have been reported to possess substantial anti-carcinogenic and antimutagenic activities because of their antioxidant and anti-inflammatory properties. Proanthocyanidins are considered as one of them, and are abundantly available in various parts of the plants, such as fruits, berries, bark and seeds. Their modes of action were evaluated through a number of *in vitro* and *in vivo* studies which showed their potential role as anti-carcinogenic agent. We summarize and highlight the latest developments on anti-carcinogenic activities of proanthocyanidins from different sources, specifically from grape seeds, and their molecular targets, such as NF-κB, mitogen-activated protein kinases, PI3K/Akt, caspases, cytokines, angiogenesis and cell cycle regulatory proteins and other check points, etc. Although the bioavailability and metabolism data on proanthocyanidins is still largely unavailable, certain reports indicate that at least monomers and smaller oligomeric procyanidins are absorbed in the gut. The modulation of various molecular targets by proanthocyanidins *in vitro* and *in vivo* tumor models suggests their importance, contribution and mechanism of action to the prevention of cancers of different organs.

Keywords: Proanthocyanidins; Cancer prevention; Interleukin; Matrix metalloproteinases; Ultraviolet radiation

1. Introduction

Proanthocyanidins are naturally occurring compounds that are widely found in fruits, vegetables, nuts, seeds, flowers and bark. They are a class of phenolic compounds that take the form of oligomers or polymers of polyhydroxy flavan-3-ol units, such as (+)-catechin and (−)-epicatechin [1]. These compounds are mostly found in pine bark, grape

Abbreviations: GSPs, grape seed proanthocyanidins; IL, interleukin; MAPK, mitogen-activated protein kinases; MMP, matrix metalloproteinases; NF-κB, nuclear factor-kappaB; UV, ultraviolet.

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seed and red wines. However, bilberry, cranberry, black currant, green tea, black tea and other plants also contain these flavonoids. The seeds of the grape (*Vitis vinifera*) are particularly rich source of proanthocyanidins. The grape seed proanthocyanidins (GSPs) are mainly dimers, trimers and highly polymerized oligomers of monomeric catechins [2,3]. GSPs have been shown to be potent antioxidants and free radical scavengers, being more effective than either ascorbic acid or vitamin E [4,5]. In addition to have antioxidant activity, GSPs have been shown to have anti-carcinogenic activity in different tumor models [6–8]. GSPs were subjected to a limited toxicity testing which included acute and subchronic toxicity in rats, and genotoxicity testing, comprising test for induction of gene mutation in bacteria, test for induction of chromosomal aberrations in mammalian cell *in vitro*, and mouse micronucleus test *in vivo*, the results of which indicate that these compounds are of a low toxicity and have no genotoxic potential [1]. As there has been considerable interest in the use of botanicals for the prevention of various diseases, phytochemicals might be of interest as protective agents for various cancers. Research on proanthocyanidins is however limited and many questions still remain to be answered. The present review highlights the latest developments and knowledge on the cancer chemopreventive and/or chemotherapeutic effects of proanthocyanidins including molecular targets, *in vitro* cell culture and *in vivo* animal studies, clinical trials and bioavailability and metabolism.

2. Chemistry of proanthocyanidins

Proanthocyanidins are synonymous with condensed tannins, and also known as oligomeric proanthocyanidins, pycno-genols or leukocyanidins, oligomers or polymers of flavan-3-ols and these units are linked mainly through C4→C8 bond, but the C4→C6 linkage also exists (Fig. 1). These linkages are called B-type linkages. An additional ether bond between C2→C7 resulting in doubly linkage of the flavan-3-ol units is called an A-type linkage. The most common types of compounds and linkages are shown in Fig. 1. The proanthocyanidins that exclusively consist of epicatechin units are designated procyanidins, the most abundant type of proanthocyanidins in plants. The less common proanthocyanidins containing epigallocatechin subunits are called prodelphinidin. The flavan-3-ol subunits may carry acyl substituents like gallic acid or glycosyl substituents like the sugars both of which may be linked at the C3 or C5 position of the oligomers [9]. The knowledge about the distribution and nature of proanthocyanidins in foods has until recently very limited; however the reported content of proanthocyanidins in various food items varies due to different analytical methods or to the nature of the samples analyzed, variety, stage of ripeness, part of the food, level of processing, etc. [9]. Most of the plant-based foods, like fruits and berries, but also nuts, beans, some cereals foods, such as barley and sorghum, spices curry and cinnamon, wine and beers were found to contain exclusively the homogeneous B-type procyanidins. A-type proanthocyanidins was only determined in curry, cinnamon, cranberry, peanut and plums etc. [10].

3. Molecular targets of proanthocyanidins

The extensive investigations with the proanthocyanidins have identified various molecular targets that can potentially be used for the prevention or treatment of cancers of various organs (Fig. 2). Here, we will summarize the latest developments on chemopreventive and/or chemotherapeutic effects of proanthocyanidins in general and with particular emphasis on grape seed proanthocyanidins (GSPs) which were extensively investigated against the risk of cancers *in vitro* and *in vivo* models. Moreover, the GSPs that have been used in the author's laboratory was obtained from Kikkoman Corporation (Noda, Japan), and commercially known as 'Gravinol'. Its chemical composition has been described elsewhere [6,8].

3.1. NF-κB and its target proteins

The activation of NF-κB has been involved in inflammation, cell proliferation and oncogenic processes and its activation depends on the phosphorylation and subsequent degradation of IkappaB proteins [11]. A number of studies have shown that GSPs exert their anti-cancer effects through the suppression of NF-κB. *In vitro* treatment of human epidermoid carcinoma A431 cells with GSPs downregulates the constitutive expression or basal level of NF-κB/p65 and IKKα in these cells and simultaneously inhibits the degradation of IκBα protein, a regulator of NF-κB [12]. Irradiation of normal human epidermal keratinocytes to ultraviolet (UV) radiation results in activation of NF-κB and IKKα.