International Journal of Wine Research

Dovepress
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SHORT REPORT

Recent advance on the antitumor and antioxidant activity of grape seed extracts

This article was published in the following Dove Press journal:
International Journal of Wine Research
8 May 2015
Number of times this article has been viewed

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Abstract: The grape pomace (including seeds and stems) poses potential disposal and pollution problems along with loss of valuable biomass and nutrients. The utilization of grape seeds processing as a source of functional ingredients is a promising field. Grape seed extract provides a concentrated source of polyphenols. Grape seed extract is known as an effective antioxidant that protects the body from premature aging and disease. A number of phytochemicals including resveratrol, proanthocyanidins, etc, have demonstrated significant benefits in cancer chemoprevention. In this review, we summarize the existing knowledge on the antitumor and antioxidant activity of grape seeds polyphenols.

Keywords: grape seed, antitumor activity, antioxidant activity, polyphenol, proanthocyanidin

Introduction

Grapes, the berries of *Vitis vinifera* L. ssp *sativa*, are one of the most valued conventional fruits in the world.[1] Grape has attracted increasing interests in recent years as many studies have revealed that it might be involved in disease preventive and health promotive activities. Grape pomace is primarily composed of seeds, skins, and stems.[2] Grape seeds are increasingly being used to obtain functional food ingredients such as natural antioxidants and dietary supplements.[3] Grape seeds contain high levels of phytopharmaceuticals, which have been correlated with a decreased risk of chronic diseases. In the grape berry, phenolic compounds and the proanthocyanidins are mainly located in seeds.[4] Pyranoanthocyanins are important pigments for the color stability of red wines and are known to be formed after berry crushing, during vinification and wine aging.[5] Grape seeds are a rich source of monomeric phenolic compounds, such as (+)-catechins, (−)-epicatechin, and (−)-epicatechin-3-*O*-gallate, and these compounds act as antimutagenic and antiviral agents.[6] Indigestible compounds are the main constituents of grape peel and seed accounting for about 80% of sugar-free dry matter.[7] The digestible fraction is made up of oil, protein, and minerals.[8]

The aim of this review is to address recent research findings on the antitumor and antioxidant activity of polyphenols from grape seeds.

Grape seed polyphenols

Grape seed polyphenols have been reported to exhibit a lot of biological properties.[9] Resveratrol had cancer chemopreventive activity in assays representing three major stages of carcinogenesis.[10] Grape seed proanthocyanidins have been reported to have potent antioxidant properties.[11] The procyanidins identified in grape seeds can range

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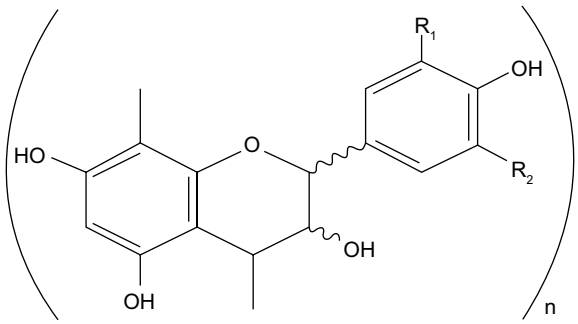
in size from monomers to long-chain polymers, such as catechin, epicatechin, and procyanidin B2 (one of dimers) (Figure 1).[12] The dimers are the most widely distributed in grape seeds; dimer and trimer are the most active part of the procyanidins.[13] A large number of investigations have demonstrated a broad spectrum of pharmacological and therapeutic benefits of grape seed proanthocyanidins against oxidative stress and degenerative diseases including cardiovascular dysfunctions, acute and chronic stress, gastrointestinal distress, neurological disorders, pancreatitis, various stages of neoplastic processes, and carcinogenesis including detoxification of carcinogenic metabolites (Figure 2).[14]

Biological activity of grape seed extracts

Antitumor activity

Many of the phytochemicals present in plants are generally accepted as contributors toward these health positive effects.[15] Grapes and grape-based products are one such class of dietary products that have shown cancer chemopreventive potential and are also known to improve overall human health.[16] Bomser et al examined the antitumor promoting activity of a polyphenolic fraction from grape seeds in CD-1 mouse skin epidermis. The final number of tumors per mouse in the 5, 10, and 20 mg grape seeds polyphenolic-treated animals was decreased 63, 51, and 94%, respectively, compared to controls. These studies indicate that grape seed polyphenolic extract possesses antitumor promoting activity when applied to CD-1 mouse skin.[17] Aluyen et al performed a systematic review to determine whether resveratrol is effective as an anticancer agent. The major mechanisms of actions in which resveratrol works include proapoptotic, anti-proliferation, and anti-inflammation. In conclusion, resveratrol appears to have anticancer effects.[18] In one study, Del Follo-Martinez et al investigated the anticancer activity of resveratrol and quercetin in combination (1:1 ratio) in HT-29 colon cancer cells. Moreover, gallic acid, a natural polyphenol present in a wide range of fruits and vegetables, has been of potential interest as an anticancer agent.[19] Kaur et al evaluated the efficacy of grape seed gallic acid in androgen-independent DU145 and androgen-dependent-22Rv1 human prostate cancer cells. Gallic acid decreased cell viability in a dose-dependent manner in both DU145 and 22Rv1 cells largely via apoptosis induction.[20] Zhang et al investigated the synergistic antitumor effect of grape seed proanthocyanidin and doxorubicin both in vitro and in vivo. Approximately 100 mg/L proanthocyanidin 12.5 mg/L inhibited proliferation of K562, A549, and CNE cells in vitro in a time- and concentration-dependent manner. These results suggest that proanthocyanidin enhances the doxorubicin-induced antitumor effect and its mechanism is attributed to the promotion of doxorubicin-induced apoptosis through increasing intracellular doxorubicin, Ca2+ and Mg2+ concentrations, and reducing pH value and mitochondrial membrane potential.[21] In another study, Ye et al assessed the cytotoxicity of grape seed proanthocyanidin extract against MCF-7 human breast cancer cells, A-427 human lung cancer cells, CRL-1739 human gastric adenocarcinoma cells, and K562 chronic myelogenous leukemic cells. Concentration- and time-dependent cytotoxic effects of grape seed proanthocyanidin extract were observed on the MCF-7 breast cancer, A-427 lung cancer, and gastric adenocarcinoma cells. These data demonstrate that grape seed proanthocyanidin extract exhibited cytotoxicity toward some cancer cells, while enhancing the growth and viability of the normal cells which were examined.[22] Zhao et al assessed the antitumor-promoting effect of a polyphenolic fraction isolated from grape seeds and employed the 7,12-dimethylbenz[a]anthracene-initiated and 12-*O*-tetradecanoylphorbol 13-acetate promoted SENCAR mouse skin two-stage carcinogenesis protocol as a model system. The observed antitumor-promoting effects of grape seed proanthocyanidin extract were dose-dependent and were evident in terms of a reduction in tumor incidence (35 and 60% inhibition), tumor multiplicity (61 and 83% inhibition), and tumor volume (67 and 87% inhibition), respectively. Procyanidin B5-3′-gallate showed the most potent antioxidant activity with an IC_{50} of 20 microM in an epidermal lipid peroxidation assay. The results show that grape seed polyphenols possess high antitumor-promoting activity due to the strong antioxidant effect of procyanidins present therein. In summary, grape seed polyphenols in general, and procyanidin B5-3′-gallate in particular, should be studied in



R_1 = H: R_2 = OH: Procyanidins
R_1 = OH: R_2 = OH: Prodelphinidins
R_1 = H: R_2 = H: Propelargonidins

Figure 1 The structure of procyanidins.

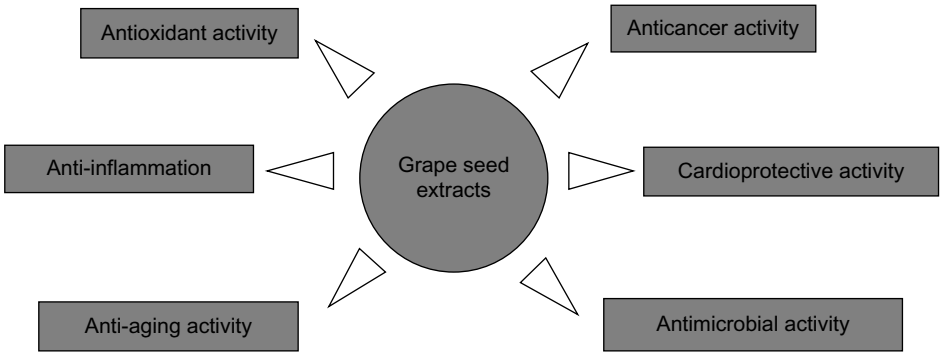


Figure 2 The biological activities of grape seed extracts.

more detail to be developed as cancer chemopreventive and/or anti-carcinogenic agents.[23] Recently, Tyagi et al identified procyanidin B2 3,3″-di-*O*-gallate as the most active constituent of grape seed extract for efficacy against prostate cancer. Both B2 3,3″-di-*O*-gallate preparations inhibited cell growth, decreased clonogenicity, and induced cell cycle arrest and apoptotic death, comparable to each other, in various human prostate cancer cell lines.[24]

Antioxidant activity

Grape seed extract is derived from the grape seeds that is extracted, dried, and purified to produce polyphenolic compound-rich extract that also has well documented antioxidant, antimicrobial, and anti-inflammatory properties.[25] Jayaprakasha et al evaluated the antioxidant activity of grape seed extracts using β-carotene-linoleate model system and linoleic acid peroxidation method. The results showed that different extracts had 65%–90% (scavenging rate) antioxidant activity at 100 ppm concentration. The present work indicated grape seed extracts may be exploitable for the preservation of food products as well as for health supplements and nutraceuticals.[26] Shaker evaluated the antioxidative effect of red grape seed and peel ethanolic extracts on primary and secondary lipid oxidation in sunflower and conjugated sunflower oils. After 6 days, a high antioxidative effect was found for the secondary oxidation products in conjugated sunflower for peel extract followed by seed extract.[27] In one study, Kim et al evaluated the effect of heating and physical conditions of grape seeds on the antioxidant activity of their extracts. The results indicated that antioxidant activity of grape seed extract was affected by heating conditions and physical conditions of grape seeds at the time of heat treatments.[28] Brannan and Mah determined the antioxidant effect of grape seed extract by assessing the bleaching of pyrogallol red by peroxynitrite or iron/ascorbate, and the formation of lipid hydroperoxides and thiobarbituric acid substances in raw or cooked ground muscle during refrigerated or frozen storage. In this model, grape seed extract was more effective than gallic acid in inhibiting oxidation. These results show that grape seed extract at concentrations as low as 0.1% is a very effective inhibitor of primary and secondary oxidation products in various muscle systems and has potential as a natural antioxidant in raw and cooked meat systems.[29] Furiga et al investigated the effect of a grape seed extract on two oral anaerobes closely associated with periodontal diseases and its antioxidant action. The evaluation of antioxidant activity was based on the capacity of a sample to scavenge the ABTS radical cation as compared to a standard antioxidant (Trolox). It significantly decreased the formation of biofilm. High Trolox equivalent antioxidant capacity was registered and this extract exhibited greater antioxidant capacity than vitamins C and E.[30] Moreover, Sung and Lee evaluated the antioxidant and antiproliferative activities of grape seeds from ten different cultivars. The antioxidant activity of the grape seeds was determined by radical scavenging activities and reducing power. Both the polyphenol and flavonoid contents were positively correlated with radical scavenging activity ($R^2 > 0.9$). These results may provide basic information about health-beneficial effects of grape seeds.[31] Jara-Palacios et al evaluated the antioxidant potential of white grape pomaces from nine different varieties. Grape pomaces exhibited different quantitative phenolic profiles and different antioxidant activities, with significant differences ($P < 0.05$).[32] The mechanism of antitumor activity might be associated with free radical production inhibition and regulation.

Conclusion and future prospective

Completed studies from various scientific groups conclude that both grapes and grape-based products are excellent sources of various anticancer agents and their regular consumption should thus be beneficial to the general population. Further studies are needed, however, with individual phenolic

compounds of grape seeds to elucidate the different antioxidant mechanisms and possible synergism. Moreover, further research involving electrostatic spray and nanoscale delivery of the active components present in these grape seed extracts and using them as a component in multiple hurdle approach would enhance the food safety and quality in addition to providing alternative "green" solutions to the food processors.

Acknowledgments

This research was supported by National Natural Science Foundation of China (project code: 31470542) and Natural Science Foundation of Hebei Province, People's Republic of China (project code: C2014407059).

Disclosure

The authors have declared that there is no conflicts of interest.

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