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Review

Cardioprotective properties of grape seed proanthocyanidins: An update

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Background: The nutritional properties of grapes (*Vitis vinifera* L.) and derived-grape products are known for a long time. To produce those food products, the agro-industry generates great amounts of by-products. The re-use of these undervalued materials is challenging because it represents an attractive opportunity to convert them into value-added sources of natural ingredients with potential human health benefits.
Proanthocyanidins, naturally occurring polyphenolic compounds in fruits, nuts, seeds, or bark, are an important group of compounds present in grape skin and seeds.
Several studies have demonstrated the beneficial effects of grape seeds, a grape by-product, regarding cardiovascular disease.
Scope and Approach: This review aims to provide an overview on the major impact of grape seed proanthocyanidins on modulating cardiovascular disease risk markers in humans, namely blood pressure, blood lipids, endothelium and anti-inflammatory function. Therefore, current and relevant data regarding the functional properties of grape seed proanthocyanidins in cardiovascular disease was explored.
Key Findings and Conclusions: Grape seed proanthocyanidins reveal a promising potential in human health, particularly in cardiovascular disease. Nevertheless, additional long-term studies, and larger sample sizes are necessary to better understand the individual effect of those compounds and/or their synergism with other individual bioactive substances.

1. Introduction

Grape seeds contain a high concentration of polyphenols, mostly monomeric flavan-3-ols and oligomeric proanthocyanidins (Carlson, Peng, Prasain, & Wyss, 2008; Naziri, Nenadis, Mantzouridou, & Tsimidou, 2014). Grape seed proanthocyanidins (GSP) are mostly dimers, trimers and highly polymerized oligomers of monomeric catechins (Nandakumar, Singh, & Katiyar, 2008). Several clinical trials, *in vitro* and animal studies show that these compounds have a positive effect in modulating different factors associated to cardiovascular diseases (CVD), such as hypertension and dyslipidemia (Graf, Raskin, Cefalu, & Ribnicky, 2010). Epidemiological studies also strongly suggest that proanthocyanidins could protect against CVD (Blade, Arola, & Salvado, 2010).

Among non-communicable diseases, CVD are one of the major causes of morbidity and mortality and continue to rise worldwide. They occur not only in developing countries but also in low and middle-income ones, as a consequence of globalization (WHO, 2011). It is estimated that, in 2030, nearly 23.3 million people will die from cardiovascular disorders (7.1 million in 2002) (Mathers & Loncar, 2006). There are life style factors that can predispose to CVD such as a sedentary life and an unhealthy diet (WHO, 2011). Nevertheless, CVD seem to be also consequence of a complex interaction between those factors and genetics (Sarajlic & Przulj, 2014).

It is known that an adequate consumption of fruit and vegetables reduces the risk of CVD and other chronic diseases (Eilat-Adar, Sinai, Yosefy, & Henkin, 2013; Schroeter et al., 2010). Indeed, there are several products that have been pointed out as being of interest in preventing CVD, namely cocoa, tea, red wine, pine bark or grape

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seeds (Habauzit & Morand, 2012; Khan et al., 2014; Nandakumar et al., 2008; O'Keefe et al., 2013).

A great number of products derived from the grape processing can be found in the market (e.g. wine, juice, jam, raisins, and others), entailing a huge amount of agro-industrial by-products. Simultaneously, there is a huge interest in identifying and characterizing natural compounds in those products in order to provide food industry natural ingredients, ameliorate human health and increase the sustainability of the process (Georgiev, Ananga, & Tsolova, 2014).

This review aims to enlighten the possible health value of GSP associated to CVD prevention or treatment. Blood pressure, blood lipids, endothelial and anti-inflammatory function were considered are the risk markers for CVD considered in this review.

2. Review strategy

Extraction of current and relevant data was performed using electronic database Pubmed. Reviews and primary articles were searched using advanced search terms in "all fields" and with the publication type "reviews" or none, using the keywords "grape seeds" and "cardiovascular disease", "hypertension", "blood pressure", "hyperlipidemia", "blood lipids", "endothelial function", "platelet function", "coronary artery disease", "coronary heart disease", and "myocardial function" in individual searches. The same keywords were searched using in "all fields", the keyword "grape seed".

The search was limited to English language articles. The titles and abstracts were scanned to exclude any studies that were clearly irrelevant. Studies that evaluated concomitant drugs administration and/or polyherbal formulations were excluded.

3. Bioactive compounds of grape seeds

Although there are many species of grapevines, wine is usually produced from *Vitis vinifera* L. Among fruits, grape is one of the richest sources of phytochemicals. Flavonoids are the most abundant biologically active compounds present in this fruit (Georgiev et al., 2014). In general, a grape is constituted by about 2–6% stems, 5–12% skin, 80–90% juice and 0–5% seeds.

During the processing of grapes into juice, only small amounts of anthocyanins are extracted. Throughout the fermentation/maceration process other bioactive compounds, such as proanthocyanidins and oligostilbenes, are obtained (Georgiev et al., 2014). This step of the process originates grape pomace, a by-product that includes skin, pulp, stems and grape seeds, retaining more than 70% of grape polyphenols (Ratnasooriya & Rupasinghe, 2012).

Grape products (such as wine and grape juice) are also known to contain high amounts of polyphenols, particularly phenolic acids, anthocyanins and simple and complex flavonoids, as proanthocyanidins (Leifert & Abeywardena, 2008). The highest concentrations of grape polyphenols are found in stems, skin and seeds. In red grape berries, phenolic compounds are mainly present in skin and seeds (Dohadwala & Vita, 2009).

Grape seeds can be separated from the pomace, being a potential source of bioactive compounds (Kar, Laight, Shaw, & Cummings, 2006; Teixeira et al., 2014). The seeds contain fibre (40%), essential oils (16%), protein (11%) and phenolic compounds (7%), like tannins, and other substances, such as sugars and minerals (de Campos, Leimann, Pedrosa, & Ferreira, 2008). Grape seed extract is an outstanding source of polyphenols, mostly proanthocyanidins (approximately 90%) that can be found mostly in red wine (rather than in white wine) but also commercially available as capsules or tablets at different concentrations (Feringa, Laskey, Dickson, & Coleman, 2011). The health benefits of seeds or its extracts and grape-derived products, such as wine, have been attributed to its polyphenolic compounds (Graf et al., 2010; Peng et al., 2005).

Proanthocyanidins are structurally a complex subclass of polyphenolic compounds and may occur as monomers, dimmers, trimers and oligomers of 20 or more units, although higher molecular weight polymers are regularly found (Wang, Chung, Song, & Chun, 2011). Grape skin and seeds contain proanthocyanidins, most of which are water soluble, thus allowing the use of clean extraction methods for their recovery (Koyama, Goto-Yamamoto, & Hashizume, 2007; Nandakumar et al., 2008; White, 2012).

The grape skin contains anthocyanins and flavonols; hydroxycinnamates are present in the flesh and skin; seeds contain flavan-3-ol monomers and the majority of gallic acid derivatives. The flavan-3-ol subclass covers the simple monomers (+)-catechin and its isomer (−)-epicatechin, as well as oligomeric (from two to five units) and polymeric (more than five units) molecules, also known as proanthocyanidins or condensed tannins. Procyanidins, exclusively composed by catechin and/or epicatechin subunits are the most abundant type of proanthocyanidins in plants. On the other hand, the less common prodelphinidins are composed by gallocatechin or epigallocatechin subunits, and have been identified in grape skin (Tsang et al., 2005).

In the U.S.A., the estimated dietary intake of polyphenols is about 100 mg/day, distributed into 22% monomers, 16% dimmers, 5% trimmers, and 30% polymers (Choy, Jaggers, Oteiza, & Waterhouse, 2013).

Polyphenols can be naturally conjugated with sugars. Glucose is most often found due to its prevalence in plant physiology (Manach, Scalbert, Morand, Remesy, & Jimenez, 2004). These conjugates can also be linked to other phenol groups, organic acids, proteins and even lipids, that may affect their absorption (Parada & Aguilera, 2007). The type of sugar bounded to a flavonoid skeleton determines the site and the extent of absorption of the glycosylated flavonoids. Once free from the sugar, they are further metabolized and a large number of modified molecules are produced (D'Archivio, Filesi, Vari, Scazzocchio, & Masella, 2010).

To understand the effectiveness of grape seeds polyphenolic compounds in preventing CVD it is important to determine the nature and distribution of these compounds in an organic system.

The bioactive composition of grapes and its seeds is strongly determined by external factors such as the variety or stage of ripeness, geographic location, climatic conditions or cultivars (Nandakumar et al., 2008; Rathel, Samtleben, Vollmar, & Dirsch, 2007). Other aspects may influence polyphenols bioavailability, for instance, individual differences that can lead to a wide rate variation and extent of the compounds absorption. This inter-individual variability can be due to several factors, such as genetic profile, composition/activity of the gut microbiota, and diet (Rein et al., 2013).

3.1. Proanthocyanidins metabolism

Bioavailability can be defined as the proportion of a given compound that is ingested, digested, absorbed and reaches the systemic circulation (Carbonell-Capella, Buniowska, Barba, Esteve, & Frígola, 2014). In turn, bioaccessibility refers to digestive transformations, the absorption into the intestinal epithelium cells, presystemic intestinal and hepatic metabolism, tissue distribution and bioactivity (Courraud, Berger, Cristol, & Avallone, 2013). Therefore, the bioavailability strictly depends on the bioaccessibility (Palafox-Carlos, Ayala-Zavala, & Gonzalez-Aguilar, 2011). Bioaccessibility is usually determined by *in vitro* studies, accessed by simulated gastric and small intestine digestion. The