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Review

# Proanthocyanidins, anthocyanins and cardiovascular diseases

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ABSTRACT

Fruit and vegetable flavonoids, including proanthocyanidins, anthocyanidins to an extent and anthocyanins (anthocyanidins with sugar moieties attached to the hydroxyl groups) are found in reasonably high quantities in cocoa, berries, cinnamon and red grapes and have proved to be protective against many cardiovascular risk factors. After summarising the biokinetic properties of anthocyanins and proanthocyanidins, we review basic science and clinical evidence for the effectiveness of these flavonoids against cardiovascular disease and discuss the possible mechanisms of action and cellular signalling pathways involved in this effect.



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## 1. Introduction

Consumption of fruit and vegetables decreases the risk of developing cardiovascular diseases (CVD) (Bazzano, Serdula, & Liu, 2003; Ness & Powles, 1997). Flavonoids form part of the polyphenol family and consist of a large group of water-soluble compounds, responsible for the many shades of yellow and red in flowers, fruit and leaves (Bravo, 1998). To date, several studies investigating the effect of flavonoid intake and the risk of cardiovascular diseases suggest that flavonoids may protect against CVD (Hertog, Feskens, & Kromhout, 1997; Knekt, Jarvinen, Reunanen, & Maatela, 1996). Two flavonoid classes (flavonols and flavones) have been particularly well researched and found to contribute significantly to promoting health (Peterson, Dwyer, Jacques, & McCullough, 2012). Some of the other flavonoids on the other hand, including anthocyanins (anthocyanidins with sugar moieties), anthocyanidins and flavan-3-ols (contributing to proanthocyanidins) have been evaluated in relatively few studies (Arts, Hollman, Feskens, Bueno de Mesquita, & Kromhout, 2001; Arts, Jacobs, Harnack, Gross, &

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Folsom, 2001; Knekt et al., 2002; McCullough et al., 2012; Mink et al., 2007), despite their potential protective effects on human health (de Pascual-Teresa, Moreno, & Garcia-Viguera, 2010; Santos-Buelga & Scalbert, 2000). Although anthocyanins are predominant in foods, anthocyanidins may also be present, but in a limited capacity, as they do not have sugars to stabilise the charge (Wrolstad, Skrede, Lea, & Enersen, 1990). In this review, the term anthocyanins will be used, which refer to both anthocyanins and anthocyanidins, unless otherwise specified.

Epidemiological studies have shown that plant-based diets may improve human health and protect against CVD (Hu & Willett, 2002; Mink et al., 2007; Williams et al., 1999; Williamson & Manach, 2005). Plant-based diets contain fibre, vitamins, and polyphenols as well as phytosterols, sulfur compounds, carotenoids, and organic acids — all of which contribute to the positive health effects. Polyphenol intake drew attention when epidemiological studies at the nutritional and biochemical levels started to focus on the French paradox, a phenomenon describing the low incidence of cardiovascular disease amongst the French population, despite the high fat content of their diet (Renaud & de Lorgeril, 1992). It was suggested that the daily consumption of red wine, rich in polyphenols, is the primary cause of the protective cardiovascular effects reported (Renaud & de Lorgeril, 1992). Flavonoids are now increasingly regarded as definite contributors to health benefits. Specifically, flavonoids (in general) have the ability to inhibit low density lipoprotein (LDL) oxidation, platelet aggregation and adhesion, as well as the enzymes involved in lipid and lipoprotein metabolism (Basu, Rhone, & Lyons, 2010; Chu & Liu, 2005; Reed, 2002). Flavonoids also have the ability to induce endothelium-dependent vasodilation and increase reverse cholesterol transport whilst decreasing total and LDL-cholesterol (Reed, 2002).

Most epidemiological studies focus on specific fruits or on flavonoids in general, and are unable to specify which of the flavonoids actually produce beneficial effects. Nonetheless, the role of fruits high in proanthocyanidins and anthocyanins are receiving increased attention. One specific epidemiological study investigating the effect of strawberry and blueberry intake in postmenopausal woman showed a significant reduction in CVD mortality over a 16 year follow-up period (Mink et al., 2007). The researchers of this study attributed the positive effects of berry consumption to anthocyanins, although it is known that these fruits contain other flavonoids too (see Table 1). A follow-up of the 93,600 women between the ages of 25 to 42 from the Nurses' Health Study II also revealed an inverse association between higher intake of anthocyanins (blueberries and strawberries) and risk of myocardial infarction (MI), a relationship independent of established dietary and non-dietary CVD risk factors (Cassidy et al., 2013).

With particular reference to proanthocyanidins, it has been found that proanthocyanidins increase plasma antioxidant capacity (Williamson & Manach, 2005), as well as protect the intestinal mucosa against oxidative stress in humans. Proanthocyanidin supplementation also has a positive effect on vascular function and reduces platelet activity (Williamson & Manach, 2005). Virtually no data from human subjects are available on the effects of proanthocyanidins and anthocyanins exclusively. The only studies with particular reference to anthocyanidins and proanthocyanidins have investigated the consumption of red wine in men with coronary heart disease — moderate consumption correlates well with a decrease in CVD (Graziano, Buring, & Breslow, 1993; Klatsky, 1994; Rimon, Giovannucci, & Willett, 1991).

It is important to keep in mind that epidemiological studies are mainly based on dietary assessments without independent validation by objective methods that do not depend on an individual's memory. This review therefore aims to highlight aspects of dietary intake, such as the concentration of specific flavonoids and their metabolism on the potential for active metabolites to be present in plasma or target tissue. The main mechanisms proposed for positive effects are the flavonoids' ability to scavenge free radicals, their nitric oxide (NO)-endothelium-dependent effect, their anti-inflammatory, and their metabolic and anti-ischemic effect — effects that will be discussed in detail in the third section of the review.

## 2. Dietary intake, food sources and biokinetic properties

Virtually all fruits, vegetables, herbs and spices, dry beans and grains contain flavonoids with the more colourful components of the food (like the skin of fruits) often containing the highest concentration (Manthley & Grohmann, 1996, 2001). Many contain several classes of flavonoids, including the flavonols, flavanols, anthocyanidins and anthocyanins, and proanthocyanidins (Renaud & de Lorgeril, 1992; Scalbert & Williamson, 2000).

The processing of food sources may concentrate or dilute the polyphenol content, whilst addition of only small quantities to a dish may render the actual polyphenol content negligible. For example, the fermentation of grapes has a large influence on the type and level of phenolic compounds in the wine (Yilmaz & Toledo, 2004). The proanthocyanidins are extracted from the seed and proanthocyanidins and anthocyanins from the skin into the red wine, whereas white wine is only made from the juice of the grapes (without the skin) (Hertog, Feskens, Hollman, Katan, & Kromhout, 1993; Hertog, Hollman, & van de Putte, 1993; Yilmaz & Toledo, 2004). In addition, one has to consider that the levels depend on cultivar, geographic origin, growing season and agricultural practice for all fruit/vegetables (Chun et al., 2010).

### *2.1. Proanthocyanidin food sources*

The total proanthocyanidin intake in the diets of American adults range from 96 to 137 mg per day (mg/d) (Gu et al., 2004), whereas those reported for Spanish or Finnish adults was 189 mg/d (Santos-Buelga & Scalbert, 2000) and 128 mg/d proanthocyanidins (Saura-Calixto, Serrano, & Goni, 2007), respectively. A recent study however, recorded the mean daily intake in American adults to be 95 mg/d (Wang, Chung, Song, & Chun, 2011), an amount that was previously seen as the lower end of intake, whilst others report even higher values than that seen by Gu et al. (2004) (Cassidy et al., 2011; Cassidy et al., 2013). These studies report intake only, based on a subject's recall and do not refer to bioavailability and metabolism. Proanthocyanidins in food are without sugar moieties which may simplify biochemical analysis. However, proanthocyanidin content in food differs in terms of distribution of monomers (the flavan-3-ols), oligomers and polymers (units containing multiple, usually >10, flavan-3-ol monomers), and their interflavan linkages (Prior & Gu, 2005). In two comprehensive studies, one by Gu et al. (2004) and the other by Hellstrom, Torronen, and Mattila (2009), the mean daily intake of oligomeric and polymeric proanthocyanidins was estimated to be higher than that of monomeric flavan-3-ols, and twice as high as the combined overall intake of other flavonoids (Gu et al., 2004; Hellstrom et al., 2009).

Table 1 presents different food sources containing anthocyanidins or proanthocyanidins, or both. Where both are present, the Table illustrates that their content can be quite different. With specific reference to chocolate, the proanthocyanidin content differs depending on the type of chocolate consumed. Proanthocyanidins exist naturally in cacao, but because they do taste bitter, they are often removed — even in the case of dark chocolate (Lancet, 2007).

### *2.2. Anthocyanin food sources*

According to the Oregon State University Linus Pauling Institute, there are more than 300 different anthocyanins found in natural products (Wrolstad, 2001), with the daily consumption ranging between 3 and 215 mg/d (Chun, Chung, & Song, 2007; Wu et al., 2006). In a study by Zamora-Ros et al. (2011), the daily intake of anthocyanidins was investigated in 3 different regions (south, central and north) of Europe (Zamora-Ros et al., 2011). For men, the total anthocyanidin mean intake ranged from 19.3 to 64.88 mg/d, whereas