

CRANBERRY FOR A HEALTHY HEART

Background

Atherosclerosis is the primary cause of cardiovascular disease (CVD), particularly heart disease and stroke, and is the leading cause of death in the United States (1,2). Atherosclerosis is described as the deposition of plaques containing lipids and cholesterol on the arterial walls. A number of studies have shown that flavonoids, phytonutrients found in fruits and vegetables, exhibit a number of CVD protective effects primarily attributed to their antioxidant properties. A diet rich in antioxidants is associated with a reduced risk of CVD and has been observed in studies with vitamin E (3) and total dietary flavonoid intake (4). Given the rich and unique profile of cranberry flavonoids, recent studies have looked specifically at the distinct protective effects of this fruit.

The complex etiology of atherosclerosis is thought to begin with the oxidation of low-density lipoprotein (LDL) cholesterol and its subsequent aggregation in the vascular subendothelial space known as the intima. Modified LDL trapped in the intima initiates an inflammatory response that ultimately causes more oxidation to occur, leading to lipid laden foam cells and lesions on the arteries known as fatty streaks. As lesions progress, they grow to interfere with arterial endothelial function and ultimately block arteries to restrict arterial blood flow. Total occlusion by atherosclerotic plaques can lead to ischemic heart disease, angina and acute myocardial infarctions. Plaques can also rupture and cause thrombosis, leading to the complete cessation of blood flow that causes the majority of CVD-related deaths (5,6).

Cranberry's Flavonoid Rich Profile

There are several distinct classes of flavonoids found in cranberries, all with antioxidant properties and each having potential physiologic benefits in CVD. Cranberry flavonoids include anthocyanins, the pigments that give cranberries their rich red color, flavonols, and proanthocyanidins (7). Of particular interest to researchers, proanthocyanidins isolated from cranberries exhibit an antiadhesion effect on certain bacteria. This antiadhesion effect is the mechanism by which cranberries help maintain urinary tract health (8), and possibly even help prevent periodontal disease (9) and the formation of certain ulcers (10).

According to the research, the postabsorptive protective effects of the many cranberry-specific flavonoids may act to: defend against oxidation of low-density lipoproteins (LDL), the first step in atherogenesis; inhibit atherogenic inflammation; and, possibly enhance reverse cholesterol transport to lower LDL in hypercholesterolemic individuals (2). In an extensive review article of cranberry flavonoids and cardiovascular health, Reed (2) suggested that the similarities between the classes of flavonoids found in cranberry juice and the more widely studied grape juice and red wine, may prove cranberries will have similar effects in promoting vasodilation and inhibiting the formation of blood clots.

Antioxidant Effects

A number of studies have demonstrated that flavonoids and their related polyphenolic compounds inhibit oxidation of LDL *in vitro* (11). Of the three classes of cranberry flavonoids, proanthocyanidins have shown

Key Points:

- A diet rich in antioxidants such as those found in fruits and vegetables is associated with a reduced risk of CVD and has been observed in studies that measured total dietary flavonoid intake.
- Compared with other common fruits, cranberries have one of the highest concentrations of antioxidant polyphenols, which include flavonoids and related phenolic acids.
- While more research is required to better understand cranberry's unique contribution to cardiovascular health, many of the flavonoids found in this fruit are proven to have potent antioxidant protective effects.



the highest inhibitory effect on the copper-induced oxidation of LDL *ex vivo* (12,13). Wilson et al (14) subsequently demonstrated the LDL protective effects of the antioxidants in cranberry are not due solely to the mild metal binding capacity flavonoids display (15) but to the free radical scavenging abilities of cranberry's components. Findings indicated concentrations of pure cranberry juice as dilute as 1:10,000 exhibited significant LDL antioxidant activity when exposed to a non-metal initiated oxidizing agent. Another study showed cranberry polyphenolic extracts could enrich LDL+VLDL in plasma and protect these isolated lipoproteins from oxidation (16).

Quercetin, a flavonol found in high concentrations in cranberry (17), also has strong *in vitro* antioxidant activity (18). As well, quercetin is readily absorbed into the bloodstream of humans and approaches the *in vitro* concentrations with proven antioxidant effects (19). Flavonols present in cranberries also spare the *in vitro* oxidation of vitamin E, an important nutrient proven to inhibit LDL oxidation *in vivo* (20). The anthocyanins in cranberries have also demonstrated high antioxidant capacity in *ex vivo* studies (21) and are also readily absorbed into the bloodstream of humans as shown in a human feeding study using elderberry anthocyanins (22).

The exact mechanism by which flavonoids exhibit their antioxidant effects in vascular cells has yet to be determined. In a recent review article, Reed (2) hypothesized that, based on existing research, cranberry-specific flavonoids may act to scavenge the free radicals within LDL that cause oxidation and/or inhibit the endogenous oxidative enzymes (such as 15-lipoxygenase) present in the macrophages, endothelial cells and smooth muscle cells involved in plaque formation.

Anti-inflammatory Effects

A number of flavonoids, such as those found in cranberries, inhibit the atherogenic inflammatory response in the intima, induced by the presence of oxidized LDL (23), by blocking a number of key kinase enzymes necessary for immune cell activation (24-26). Certain flavonoids can also inhibit cytokine-induced gene expression, an important immune response modulator. Cellular adhesion molecules on endothelial cells, aberrantly expressed in atherosclerotic lesions, are inhibited by flavonoids such as hydroxyl flavones and, to a lesser extent, flavonols (27). These same flavonoids also inhibited the production of a number of inflammatory intermediates (28) involved in the larger inflammatory response cascade.

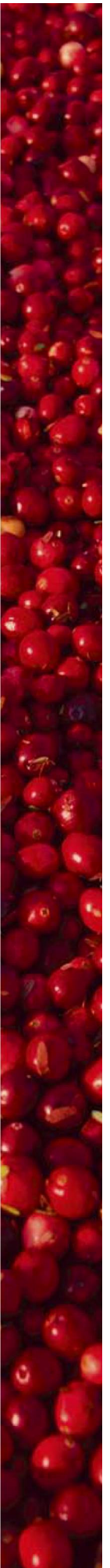
Recently, a research team at Tufts University studied the antioxidant and inflammatory inhibition properties of blueberry and cranberry polyphenol extracts, specifically the anthocyanins and hydroxycinnamic acids found in these fruits (29). Results demonstrated that these polyphenols were able to localize in human microvascular endothelial cells and effectively reduce oxidative stress in the cells. These berry extracts also suppressed the induction of various inflammatory mediators involved in recruiting leukocytes to damaged areas of the endothelium. Researchers concluded the polyphenols in cranberries and blueberries protect endothelial cells from oxidative and inflammatory injury, providing benefits that may reduce the initiation and development of vascular disease.

Enhanced Cholesterol Transport

A small, preliminary animal study found cranberry juice powder (CJP) significantly decreased LDL in swine with familial hypercholesterolemia (FH) (12). Blood was taken at weekly intervals for four weeks. At baseline, FH sows had seven times the amount of total cholesterol versus normal sows and 11 times the LDL of normal. Four weeks of feeding 150 g/day of CJP lowered total cholesterol and LDL levels in FH sows, decreasing LDL levels 22 percent from the baseline measurement. Researchers hypothesized the proanthocyanidins in CJP may be increasing reverse cholesterol transport and enhancing cholesterol excretion by the liver. These researchers also concluded their results indicated humans with hypercholesterolemia may benefit from adding cranberry juice to their diets.

Other Possible Protective Benefits

In a 2002 review article (2), Reed cited relevant research using flavonoids from different sources, primarily grapes, but in the same class as those found in cranberries, suggesting the cranberry may offer other cardiovascular benefits. Although cranberry-specific research is necessary, impaired arterial vasodilation characteristic of CVD may also benefit from flavonoids present in cranberries. Nitric oxide (NO), produced in the endothelial cells, mediates vasodilation by acting on the adjacent smooth muscle cells lining the vascular membrane (30). Research suggests the oligomeric proanthocyanidins found in wine improves vasodilation by stimulating endothelial NO production *in vitro* (31,32). As well, studies have shown that proanthocyanidin oligomers in certain fruits interfered with the production of angiotensin II, a potent vasoconstrictor that can aggravate atherosclerotic symptoms (33-35).



Cranberry's flavonoid arsenal may also prove to effect platelet activity in advanced atherosclerosis. The damaged atherosclerotic endothelium can cause platelets to adhere to the walls of the coronary arteries and aorta and incorporate into the growing lesion (36). Thrombosis can occur when platelets aggregate in the narrow areas of the coronary artery, stopping the flow of blood and inducing myocardial infarctions (37). Researchers have studied the effects of drugs, notably aspirin, and food components, such as flavonoids, in platelet downregulation in an effort to decrease the risk of heart attacks and strokes in atherosclerosis (38). Not surprisingly, *in vivo* animal studies (39) and an *ex vivo* human study (40) found grape juice can have beneficial effects on platelet aggregation. Flavonols, anthocyanidins and proanthocyanidins are the flavonoids most common in grapes (2) and, notably, cranberries (41).

Conclusions

Epidemiological studies have long associated flavonoid rich diets with a decreased risk for many diseases, including CVD (4). While more research is required to better understand cranberry's unique contribution to cardiovascular health, many of the flavonoids found in this fruit are proven to have potent antioxidant protective effects. With the highest fresh-weight flavonoid content of 20 common fruits tested (16), incorporating cranberries into a healthy diet can help protect cardiovascular health by providing a rich source of dietary flavonoids and antioxidants.

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