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Cranberries (*Vaccinium macrocarpon*) and Cardiovascular Disease Risk Factors

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*The American cranberry (*Vaccinium macrocarpon*) is one of the three commercially important fruits native to North America. Cranberries are a particularly rich source of phenolic phytochemicals, including phenolic acids (benzoic, hydroxycinnamic, and ellagic acids) and flavonoids (anthocyanins, flavonols, and flavan-3-ols). A growing body of evidence suggests that polyphenols, including those found in cranberries, may contribute to reducing the risk of cardiovascular disease (CVD) by increasing the resistance of LDL to oxidation, inhibiting platelet aggregation, reducing blood pressure, and via other anti-thrombotic and anti-inflammatory mechanisms. Research regarding the bioactivity of cranberries and their constituents on risk factors for CVD is reviewed.*

Key words: cranberry, *Vaccinium macrocarpon*, flavonoid, proanthocyanidin, cardiovascular disease

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INTRODUCTION

The American cranberry (*Vaccinium macrocarpon*) is a low-growing, vining, woody perennial plant native to the northeastern part of North America, from eastern Canada to the US state of North Carolina. The edible red fruit, or cranberry, is one of only three commercially important fruits native to North America, along with the blueberry and Concord grape. Approximately 500–700 million pounds of cranberries are commercially produced worldwide, primarily across the northern United States (85%) and Canada (15%), with smaller amounts produced in Chile.[1] Products of the cranberry industry include fresh fruit (5%), juices (60%), and sauces, dried fruit and ingredients (35%), such as frozen fruit, juice concentrates, and spray-dried powders.[1,2]

Cranberries were used by Native New Englanders for food, fabric dye, and in poultices to treat wounds and blood poisoning. Early American sailors, including whalers and mariners, consumed cranberries as an anti-scorbutic agent during ocean voyages.[3] Today, health benefits attributed to cranberries include the prevention of urinary tract infections[4-6] and stomach ulcers[7,8] as well as improved oral hygiene.[9,10] These benefits appear to be due principally to the ability of cranberries to interfere with the adhesion of some bacteria to select cell types and surfaces. For example, cranberries can prevent pathogenic P-fimbriated *Escherichia coli* from adhering to uroepithelial cells, thereby reducing their ability to proliferate in the urinary tract. Similarly, cranberries can prevent the adhesion of *Helicobacter pylori*, the causative agent of most gastric and duodenal ulcers, to gastrointestinal mucosa, and inhibit the adhesion of oral pathogens such as *Streptococcus mutans* to tooth hydroxyapatite. Cranberries and cranberry constituents have also been shown to possess antibacterial,[11,12] antiviral,[13] antimutagenic,[14] anticarcinogenic,[15] antitumorigenic,[16] antiangiogenic,[17] and antioxidant activities.[18]

Recently, research on the effects of cranberries and their components has also focused on their use in the prevention and treatment of cardiovascular disease (CVD). Epidemiological studies have consistently shown that the consumption of fruits and vegetables is inversely associated with the risk of developing CVD[19] and stroke.[20] The phytochemical constituents of these foods appear to contribute substantially to this benefit.[21,22] Cranberries are a particularly rich source of phenolic phytochemicals. Among the 20 most commonly consumed fruits in the American diet, cranberries have the highest total phenol content.[18] These phenolic compounds have a wide range of biological effects including the ability to serve as antioxidants, modulate enzyme activity, and regulate gene expression. Experimental in vitro studies suggest phenolics may affect the pathogen-

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esis of CVD by increasing the resistance of low-density lipoproteins (LDL) to oxidation,[23] preventing platelet aggregation and thrombosis, reducing blood pressure, and/or inhibiting inflammation.[24–26]

NUTRIENT AND PHYTOCHEMICAL CONSTITUENTS

The US Department of Health and Human Services/US Department of Agriculture 2005 Dietary Guidelines for Americans,[27] as well as dietary recommendations issued by the American Heart Association[28] promote the daily consumption of fresh fruit and 100% fruit juices as part of a healthy eating plan to reduce the risk of chronic diseases, particularly CVD, type-2 diabetes, osteoporosis, and some forms of cancer. Whole fruits like cranberries are naturally low in calories, fat, and sodium, contain no cholesterol, and are a good source of dietary fiber[29] (Table 1). Dried cranberries, cranberry juice, and juice cocktail similarly contain little sodium and fat. The predominant type of fatty acids present in cranberries and cranberry products are polyunsaturated, and include α-linolenic acid, 18:3n-3, which is present in the seed oil (22 g/100 g fatty acids).[30] A diet composed of foods low in saturated fat and cholesterol, that also includes ω-3 fatty acids, has been shown to have a positive effect on plasma lipid profiles. Fiber intake, especially soluble fiber like the pectin present in cranberries,[31] is also an established part of "heart healthy" diets. Further, the high ratio of potassium to sodium in cranberries and cranberry products may contribute to the promotion of lower blood pressure.

Specific cranberry products, i.e., dried sweetened cranberries and cranberry juice cocktail (27% juice), have been recognized by the American Heart Association as "heart healthy" based on their nutrient composition. One serving of either product contains <0.6 g total fat, <0.05 g saturated fat, and no cholesterol or trans fat. In addition, dried cranberries provide $>10\%$ of the daily value of fiber and cranberry juice cocktail contains $>100\%$ of the daily value of vitamin C. With the exception of cranberry juice cocktail, to which vitamin C is added during processing, none of the cranberry products listed in Table 1 is particularly high in the antioxidant vitamins C or E or the mineral selenium, a cofactor for glutathione peroxidase. Thus, the reported antioxidant activity of cranberries is due to their constituent phenolics and carotenoids.

Cranberries contain a higher amount of total phenols per serving (507–709 mg gallic acid equivalents/100 g) than other common fruits including blueberries (258–531 mg/100 g), apples (185–347 mg/100 g), red grapes (175–370 mg/100 g), and strawberries (132–368 mg/100 g).[18,32,33] Chen et al.[34] reported a total of 413 mg/L in freshly squeezed cranberry juice and 51 mg/L in a 27% cranberry juice cocktail. Vinson et al.[35] found a higher concentration (870 mg catechin equivalents/100 g total phenols) in dried cranberries. Most of the phenolics in cranberries are present in a soluble free form (91.3–96.2%).[18,32] Cranberries are one of the few fruits containing a large proportion of free phenolics, the others being avocados, honeydew melons, and oranges.

The two major classes of phenolics identified in cranberries are phenolic acids and flavonoids (44% and 56%, respectively, in freshly squeezed juice[34]) (Table 2). The most abundant phenolic acid identified by Zuo et al.[2] was benzoic acid (4.7 g/kg fresh weight), followed by the hydroxycinnamic acids *p*-coumaric (0.25 g/kg fresh wt), sinapic (0.21 g/kg), caffeic (0.16 g/kg), and ferulic acids (0.088 g/kg). Quantities of these and other phenolic acids in cranberry juice have been reported by Zhang and Zuo.[36]

Table 1. Nutrient Content of Cranberries and Select Cranberry Products

Nutrient	Whole raw (1 c or 95 g)	Dried sweetened (0.33 c or 40 g)	Juice, unsweetened (1 c or 253 g)	Juice (27%) cocktail (1 c or 253 g)
Energy (kcal)	44	123	116	137
Water (g)	83	6	220	218
Protein (g)	0.37	0.03	0.99	0.00
Carbohydrate (g)	11.59	32.94	30.87	34.21
Total lipid (g)	0.12	0.55	0.32	0.25
Fiber (g)	4.4	2.3	0.3	0
Potassium (mg)	81	16	194	35
Sodium (mg)	2	1	4	5
Selenium (μg)	0.1	0.2	0.4	0.5
Vitamin A (μg RAE)	3	0	6	0
Vitamin C (mg)	12.6	0.1	23.6	107.0
Vitamin E (mg α-tocopherol)	1.14	0.43	3.04	0.56
β-Carotene (μg)	34.2	0.0	68.3	13.0
Lutein + zeaxanthin (μg)	86.45	13.40	172.67	33.00

Table 2. Major Classes of Phenolic Phytochemicals Identified in Cranberries

Class	Subclass	Compound
Phenolic acid	Benzoic acid	
	Hydroxycinnamic acid	p-Coumaric
		Sinapic
		Caffeic
		Ferulic
	Ellagic acid	
Flavonoids	Flavonols	Quercetin
		Myricetin
	Flavan-3-ols	Proanthocyanidins
		Epicatechin
	Anthocyanins	Cyanidin
		Peonidin
Stilbenes		Resveratrol

The predominant flavonoids present in cranberries include the anthocyanins, flavonols, and flavan-3-ols (particularly proanthocyanidins). In cranberries, the six major anthocyanins are peonidin-3-galactoside, cyanidin-3-galactoside, cyanidin-3-arabinoside, peonidin-3-arabinoside, peonidin-3-glucoside, and cyanidin-3-glucoside. Quantities of these anthocyanins were reported in cranberry juice cocktail to be 2.8, 2.0, 1.4, 1.1, 0.3, and 0.2 ppm, respectively.[1,37,38]

Quercetin, myricetin, and their glycosides are the major flavonols present in cranberries.[39-41] Chen et al.[34] reported that quercetin accounted for 75% of the total flavonoids detected in their analysis of acid-hydrolyzed cranberry juice. Acid hydrolysis prior to high performance liquid chromatography analysis yielded 175 mg/L quercetin and 47 mg/L myricetin from freshly squeezed 100% cranberry juice, while 12 mg/L quercetin and 2.9 mg/L myricetin were found in canned cranberry juice cocktail (27% juice). Without acid hydrolysis, quercetin was not detected in freshly squeezed juice, whereas myricetin was present at only 8.3 mg/L. According to the US Department of Agriculture Database for the Flavonoid Content of Selected Foods[42] the quercetin content of whole cranberries is 14.0 mg/100 g, myricetin is 4.3 mg/100 g, and kaempferol is 0.1 mg/100 g.

Proanthocyanidins, also called condensed tannins, are ubiquitous in plants, with fruits being the major source in the diet.[43] Procyanidins, a subclass of proanthocyanidins, are mixtures of oligomers and polymers consisting of catechin and epicatechin units linked mainly through B-type bonds.[44] In experimental studies, procyanidins possess a variety of activities, including antioxidant, antimicrobial, antiallergy, and antihypertensive actions.[45] The procyanidins in cranberries contain more epicatechin than catechin (46.5% vs. 7.4% of terminal units) which, unlike most other procyanidin-containing foods, are predominantly linked via A-type bonds.[44,46,47] The A-type linkage is a structural feature that appears to be responsible for the unique antiadhesion action and some of the antioxidant properties of cranberries.[4,6,46,48,49]

Hammerstone, et al.[50] calculated the procyanidin content of cranberry juice to be 31.9 mg/8 oz serving (0.14 g/L) by adding together the individual concentrations of dimers through decamers. These authors also reported that the most prevalent proanthocyanidins were the oligomers (0.13 of 0.14 g/L total procyanidins). In comparision, a 3.5 oz serving of red wine contains 22.0 mg of proanthocyanindins, with a much higher proportion present as monomers (0.05 of 0.21 g/L total procyanidins). However, Hammerstone et al.[50] did not account for the polymeric proanthocyanidin content reported by Gu et al.,[44] who analyzed freeze-dried cranberry material and found the concentration of higher oligomers (>10 mers) to be 20.58 of 32.65 mg/g total procyanidins. Taking the polymeric proanthocyanidins into account, the total proanthocyanidin contents of whole cranberries and cranberry juice cocktail have been reported as 418.8 mg/100 g fresh weight and 85.5 mg/L (54.7 mg/8 oz serving), respectively, which consist entirely of proanthocyanidins with the A-type linkage.[51] The distribution of proanthocyanidin monomers, dimers, trimers, oligomers, and polymers in these cranberry products is listed in Table 3.[51]

The stilbene resveratrol has also been identified in cranberries. Resveratrol has several biological effects related to cardiovascular health including quenching reactive oxygen species, inhibiting platelet aggregation, and reducing inflammation.[52] Stilbenes have also been identified in grapes, wine, and other *Vaccinium* berries.[53] Wang et al.[52] found the resveratrol content of raw cranberry juice (1.07 nmol/g) to be comparable to grape juice (1.56 nmol/g). Rimando et al.[53] reported 900 ng/g dry weight of resveratrol in freeze-dried cranberries, similar to that of highbush blueberries (*V. corymbosum*; 1074 ng/g).

Other phenolic components of cranberry include ellagic acid (120 ppm on a dry weight basis,[38] 350 μg/g dry

Table 3. Distribution of Proanthocyanidins in Cranberries and Cranberry Juice

	Degree of polymerization	
Proanthocyanidin	Raw (mg/100 g)	Juice cocktail (27%) (mg/8 oz)
Monomers	7.3	1.4
Dimers	25.9	6.9
Trimers	18.9	4.0
4–6 mers	70.3	11.6
7–10 mers	62.9	9.7
Polymers (>10 mers)	233.5	21.1

weight in cranberry pomace[54]); the lignan secoisolariciresinol (10.54 ppm on a dry weight basis);[1] and the triterpene ursolic acid.[55] Importantly, variability in the nutrient and phytochemical composition of cranberries occurs during fruit growth and ripening,[56] between cultivars,[39] under different storage conditions,[57] with environmental stresses, and during post-harvest processing.

Variations in the quantitative analyses of cranberry components may also occur with different solvent extraction and detection methodologies. Table 4 lists the average quantities of selected phytochemicals ascertained during a retail audit of cranberry juice cocktail samples (data provided by Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA, USA).

IN VITRO STUDIES

Antioxidant Capacity

Dietary antioxidants are associated with a reduced risk of CVD and hypertension.[58-60] The high concentration of phenolic compounds found in cranberries correlates with their high antioxidant capacity in vitro,[33,61] though this association varies depending on the assay used to assess this parameter. The total antioxidant capacity of whole fruit was measured by Wu et al.[33] using a variation of the oxygen radical absorbance capacity assay measuring antioxidant capacity to quench peroxyl radicals in both lipophilic and hydrophilic compartments. The total antioxidant capacity of cranberries, expressed as trolox equivalents (TE), ranked highest (94.56 μmol TE/g) among 24 commonly consumed fruits, followed closely by lowbush blueberries (92.60 μmol TE/g). Cranberry was also ranked highest in total antioxidant activity to quench peroxyl radicals in a study by Sun et al.[32] using the total oxyradical scavenging capacity assay. The values for 11 common fruits were expressed as micromoles of vitamin C equivalents/gram fresh weight and the antioxidant activity of a soluble, free phenolic extract of cranberry (177.0 μmol/g) was higher ($P<0.01$) than any other fruit tested including apple (97.6 μmol/g), red grape (64.7 μmol/g), and strawberry (64.4 μmol/g). In one study, neither 100% cranberry juice nor cranberry juice cocktail was as effective as pomegranate juice in quenching the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical.[62]

Table 4. Phenolic Phytochemical Content of Cranberry Juice Cocktail

Phenolic compound	Content (mg/8 oz serving)
Proanthocyanidins	90
Total phenolics	211
Total anthocyanins	1.23
Anthocyanins	
Cyanidin-3-galactoside	0.28
Cyanidin-3-glucoside	0.003
Cyanidin-3-arabinoside	0.13
Peonidin-3-galactoside	0.58
Peonidin-3-glucoside	0.034
Peonidin-3-arabinoside	0.20
Flavonols	
Hyperoside	5.57
Quercetin	3.12
Myricetin	1.27
Quercitrin	1.25
Avicularin	0.43
Phenolic acids	
Benzoic acid	12.0
Chlorogenic acid	2.64
4-Hydroxycinnamic acid	1.06
3,4-Dihydroxybenzoic acid	0.55
Vanillic acid	0.29
Caffeic acid	0.26

The antioxidant activities of cranberry juice (from pulverized de-seeded fruit pulp) against superoxide radicals, hydrogen peroxide (H_2O_2), hydroxyl radicals, and singlet oxygen were among the highest in a study by Wang et al.[63] comparing different genotypes of cranberry, blackberry, blueberry, raspberry, and strawberry. Cold-pressed oil from cranberry seeds was shown to have scavenging activity against the radicals 2,2'-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) and DPPH.[64] Among four extracted seed oils tested (cranberry, black caraway, carrot, hemp), cranberry seed oil had the greatest DPPH scavenging activity (95% of DPPH quenched with 11.3 mg oil equiv/mL), comparable to vitamin C (8.8 mg/mL) and higher than vitamin E (21.5 mg/mL).[64] Roy et al.[17] found the oxygen radical absorbance capacity value of methanol-solubilized cranberry powder was comparable to elderberry and raspberry seed powders, but lower ($P<0.05$) than strawberry, wild bilberry, and wild blueberry powders. Antioxidant activity has also been demonstrated in the extracted flavonol,[41] procyanidin,[49] anthocyanin, and phenolic fractions[61] of cranberries.

Cranberries consistently rank high among common fruits in antioxidant activity. According to Halvorsen et al.[65] cranberries and cranberry juice also ranked high among other foods commonly found in the US diet. Using the ferric reducing ability of plasma assay (FRAP) to analyze and rank 1113 food samples according to total concentration of redox-active compounds, whole cranberries had the fifth highest concentration with 3.125 mmol/serving (95 g or 1 cup), while cranberry juice was ranked thirteenth with 2.474 mmol/serving (240 mL or 8 oz). When these same foods were ranked by antioxidant

content per 100 g sample, cranberries were ranked twenty-first with 3.289 mmol/100 g.

Several in vitro studies have demonstrated the antioxidant activity of cranberries using assays measuring linoleic acid peroxidation, diene-conjugation formation, or other end products of lipid peroxidation in LDL. Wilson et al.[66] were the first to report the LDL protective properties of cranberry juice (pressed berries) using this model. The formation of thiobarbituric acid reactive substances from Cu^{2+}-induced oxidation of LDL was suppressed at a dilution of 0.10% juice ($P<0.001$) compared to a control sample with no cranberry juice. Wilson et al.[67] also observed the inhibition of 2,2'-azobis-amidinopropane-initiated LDL oxidation by cranberry juice at a dilution of 1:5000 ($P<0.05$), indicating the antioxidant action was not mediated via chelation of Cu^{2+}. Chu et al.[68] determined the median effective dose (EC_{50}) of cranberry in a LDL oxidation model for antioxidant capacity assay to be 1.46 mg cranberry/mL indicating the antioxidant activity of 100 g cranberries is equipotent to 1012 mg vitamin C or 3700 mg vitamin E in this assay. Inhibition of LDL oxidation in vitro has also been demonstrated with cold-pressed cranberry seed oil (at 2.8 mg/g oil)[64] as well as cranberry fractions composed of proanthocyanidins,[46,48,69] procyanidins,[49] and selected flavonols and anthocyanins.[41]

Vinson et al.[18] used the phenol antioxidant index, a combined measure of quantity and quality of phenol antioxidants, to rate 20 fruits consumed in the American diet. Antioxidant quality was measured by determining the IC_{50} (concentration required to inhibit oxidation by 50%) in an assay using Cu^{2+}-induced oxidation of LDL plus very low density lipoprotein with thiobarbituric acid. Although the IC_{50} of both free (0.86 μM) and total phenols (0.75 μM) extracted from cranberry was quite potent in this assay, it was less effective than extracts from cherries, red grapes, blueberries, strawberries, and white grapes. In a comparison of dried fruits,[35] the IC_{50} of cranberries was 0.42 μM, indicating it was less potent than figs (0.23 μM), dried plums (0.23 μM), and raisins (0.29 μM). According to Vinson et al.,[35] the IC_{50} values for fresh cranberries (0.86 μM), grapes (0.75 μM), and plums (0.70 μM) are much lower than values of their respective dried fruits ($P=0.05$), suggesting that the antioxidants in dried fruits are of higher quality according to Phenol AntiOXidant Index criteria.

Cranberry phenolics, when mixed with plasma or modified serum prior to LDL isolation, remain associated with lipoproteins after their isolation, and subsequently increase the lag time of Cu^{2+}-induced LDL oxidation.[18,69] Porter et al.[69] determined that a cranberry-derived fraction containing proanthocyanidin oligomers with a higher degree of polymerization (pentamer – nonamer) and more than one A-type bond was more effective ($P<0.05$) at increasing the lag time after mixing with serum than fractions containing proanthocyanidins with a lower degree of polymerization (trimer – heptamer), flavonols, anthocyanins, or cinnamic acids.

Cholesterol Processing

In addition to the anti-atherogenic potential of cranberries increasing the resistance of LDL to oxidation, an acetone extract of this fruit has also been shown to increase cholesterol uptake by HepG2 hepatocytes and to elevate the synthesis of LDL receptors. Chu et al.[68] demonstrated that adding a cranberry extract (15 and 30 mg/mL) to HepG2 cells increased LDL receptor expression (230% and 540%, respectively; $P<0.05$) and cholesterol uptake (270% and 280%, respectively; $P<0.05$) compared to controls. The enhanced synthesis of hepatic LDL receptors and influx of LDL cholesterol into hepatocytes are actions suggesting accelerated cholesterol excretion may occur in vivo.

Enzyme Modulation

The antioxidant potential of phenolic compounds is not limited to their direct action in scavenging free radicals. Phenolic compounds may also decrease oxidative stress indirectly by inhibiting endogenous enzymes that generate reactive oxygen species, binding pro-oxidant transition minerals like Cu^{2+} and Fe^{3+} or activating antioxidant enzymes like superoxide dismutase.[70] Xanthine oxidase (XO) converts xanthine to uric acid and generates superoxide and H_2O_2 as byproducts. Dew et al.[71] examined the XO inhibitory activity of several plant foods. In their analysis of fruit juices, only cranberry and purple grape juices were able to inhibit XO with IC_{50} values of 2.4 and 3.5%, respectively, while apple, orange, pineapple, and pink grapefruit juices promoted XO activity.

Treatment with cranberry juice powder stimulated the cellular antioxidant systems involving superoxide dismutase, catalase, and peroxidase in oxidatively stressed porcine muscle tissue according to Vattem et al.[72]

Cranberry components have also been shown to modulate the activity of enzymes produced by periodontal pathogens and cariogenic bacteria. Proteinases produced by *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* participate in the development of periodontis by degrading connective tissue proteins, disrupting host defense mechanisms, and enabling these pathogens to derive energy from protein sources. Bodet et al.[73] demonstrated that high molecular weight non-dialyzable material extracted from cranberry juice concentrate (65.1% proanthocyanidins, 0.35% an-

thocyanins) is able to inhibit proteinases from these periodontopathogens, thereby reducing their pathogenicity. In a study by Duarte et al.,[74] flavonol and proanthocyanidin-rich cranberry fractions inhibited the activites of surface-absorbed glucosyltransferases and F-ATPases produced by the oral bacteria *Streptococcus mutans*. Topical application of these cranberry phenolics significantly affected *S. mutans* biofilm development and acidogenicity ($P<0.05$), which could prevent the development of dental caries. Given the emerging connection between oral health and CVD,[75,76] it is possible that cranberries may play a role in preventing heart disease via this mechanism. However, further research is required before any conclusions about this mechanism can be drawn.

Neuroprotection

In vitro studies simulating stroke in rat brain neurons were reported by Neto et al.[77] They observed that rat brain neurons treated with whole cranberry extracts suffered 43% less necrosis induced by oxidative stress compared to controls, and that necrosis induced by conditions of ischemia declined by 49%.[77] Among the different fractions derived from the cranberry extract, a combination of anthocyanins and flavonols was most effective at reducing cell death (40% at 100 μg/mL).

Joseph et al.[78] tested extracts of cranberry, blueberry, grape, boysenberry, black currant, dried plum, and strawberry, for their ability to protect muscarinic receptors in transfected COS-7 cells from oxidative stress. Muscarinic receptors are involved in neuronal and vascular functioning and show differential sensitivity to oxidative stress. Each of the fruit extracts showed some degree of protection with pretreatment. Blueberry, boysenberry, and grape provided the most protection, i.e., they were not significantly different from their respective non-stressed controls, while dried plum and strawberry were the least effective ($P<0.001$ from respective controls). Black currant and cranberry were considered somewhat protective ($P<0.05$ from respective control).

Anti-inflammation

Oxidative stress and inflammation are risk factors for the intiation and pathogenesis of CVD.[79] Cranberry flavonoids have been shown to protect endothelial cells against oxidative stress and inhibit pro-inflammatory responses in vitro.[80,81] For example, Youdim et al.[80] found treatment of human microvascular endothelial cells with either cranberry anthocyanins (0.1 mg/mL) or hydroxycinnamic acids (0.1 mg/mL) reduced ($P<0.05$) intracellular H_2O_2-induced damage and inhibited oxidation of cell membrane fatty acids. The cranberry anthocyanin fraction was also able to suppress the up-regulation of the inflammatory mediators interleukin (IL)-8, intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) in human microvascular endothelial cells following exposure to the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) compared to non-treated control cells ($P<0.001$). In contrast, the hydroxycinnamic acid fraction was not able to suppress MCP-1. Bodet et al.[81] found that treating macrophages with non-dialyzable cranberry material prior to lipopolysaccharide stimulation also reduced ($P<0.05$) the production of pro-inflammatory cytokines and chemokines.

ANIMAL MODELS

Vasodilation/Hypotensive Effect

The in vivo vasodilatory effects of cranberry juice were demonstrated in a rat model by Maher et al.[82] A bolus of either cranberry juice (first press) or saline was administered intravenously to anesthetized rats (N=12) at a dose approximately 1/100 of their blood volume and heart rate and blood pressure measured for 20 min. Although the baseline mean arterial blood pressure (MAP) was 15% higher in the rats treated with cranberry juice (100 vs. 85 mmHg in saline-treated rats), the cranberry treatment decreased MAP to 80 mmHg (16% below baseline). In contrast, the saline treatment increased MAP to 105 mmHg (24% higher than baseline). Interestingly, the heart rate of the cranberry-treated rats increased progressively over the course of the experiment (from 216 to 253 bpm), whereas the heart rate increased only slightly (from 240 to 247 bpm) in saline-treated rats. The cardioacceleratory effect of cranberry juice may be a result of arterial dilation, where reduced vascular resistance requires a compensatory increase in cardiac output.

In an accompanying experiment, cranberry juice was able to vasodilate isolated rat aorta in the presence of a functional endothelium. Intact rings were dilated 56.7% by cranberry juice compared to 8.9% in denuded rings ($P<0.002$). N^{ω}-nitro-L-arginine methyl ester, a competitive inhibitor of nitric oxide synthase, was added to assess whether the effects of cranberry were dependent on nitric oxide formation by the endothelium. N^{ω}-nitro-L-arginine methyl ester reversed cranberry-induced vasorelaxation in intact rings (0.54 g contraction) and slightly increased tension in denuded rings (0.04 g; $P<0.007$). These results indicate that the vasodilatory effects of cranberry juice are dependent on endothelial cell nitric oxide formation. Similar effects have been previously observed with grape juice and wine.[83,84]

Hypercholesterolemic Effects

An atherogenic animal model was also used by Reed[85] to examine the effects of cranberry juice powder on blood cholesterol levels. Normal and familial hypercholesterolemic (FH) swine (N=4/group) were fed a diet supplemented for 2 weeks with 57 g/d fructose and 47 g/d citric acid to simulate the amounts of these ingredients in cranberry juice cocktail. On day 15 the swine were fed cranberry juice powder at 150 g/d for 4 weeks. Total blood cholesterol (TC), LDL and high density lipoprotein (HDL) levels were determined weekly. At baseline, the TC level in FH pigs was 7-times higher than in normal pigs (458 vs. 67 mg/dL, respectively; $P<0.0001$), while LDL levels were 11-times higher (428 vs. 37 mg/dL). By the end of the intervention, TC in FH pigs decreased by 92 mg/dL and LDL decreased by 94 mg/dL. No effects on TC or LDL were observed in normal pigs. The results of this experiment suggest that cranberry juice or powder may have the potential to lower cholesterol in hypercholesterolemic patients.

HUMAN STUDIES

Bioavailability

Zhang and Zuo[36] developed a gas chromatography-mass spectrometry method for detecting various cranberry juice phenolic compounds, including benzoic acids and flavonoids, in human plasma. The presence of 16 phenolic compounds was detected in a single subject when this method was applied to cranberry juice cocktail. Prior to the consumption of the cranberry juice, no benzoic, phenolic, or flavonoid compounds were observed in the fasting plasma sample. At 45 min after consumption of 1800 mL juice, benzoic acid, *o*-hydroxybenzoic acid, *p*-hydroxyphenylacetic acid, 2,3-dihydroxybenzoic acid, and 2,4-dihydroxybenzoic acid were detected in plasma. At 270 min after consumption, seven benzoic and phenolic compounds were detected, including the five compounds listed above plus ferulic and sinapic acids. Benzoic acid was the most prevalent aromatic compound present both in the cranberry juice (54 μg/mL) and in plasma after juice consumption (4.40 μg/mL after 40 min; 3.11 μg/mL after 270 min). Many of the phenolic compounds identified in the cranberry juice cocktail were not detected in the plasma samples, although *p*-hydroxyphenylacetic and 2,4-dihydroxybenzoic acid were identified in plasma but not in juice. These compounds are likely metabolites of the cranberry juice phenolics.

In a placebo-controlled study of 22 healthy women (mean age 27.5 years) not taking aspirin or other salicylate drugs, Duthie et al.[86] determined that cranberry juice consumption increased the absorption of dietary salicylic acid. A daily, low-dose (~75 mg) aspirin (acetylsalicylic acid) is an established therapy for patients at risk for CVD.[87] The two groups, matched for age, weight, and height, were randomized to receive either cranberry juice cocktail (consumed in 3 daily servings of 250 mL) or a placebo beverage containing 9% (w/v) of sucrose for 2 weeks. The total salicylate content of the cranberry juice was 7.04 mg/L; none was found in the placebo beverage. Within 1 week, increases in urinary salicylic acid and salicyluric acid were detected in subjects consuming the cranberry juice compared to the placebo subjects ($P<0.001$). After 2 weeks, salicylic acid levels had increased in the plasma of the cranberry juice group ($P<0.05$).

Antioxidant Status and Oxidative Stress

The effects of cranberry juice consumption on plasma antioxidant activity and biomarkers of oxidative stress were examined in 20 healthy young females (age 18–40 years) in a placebo-controlled trial by Duthie et al.[88] Free-living subjects consumed 750 mL/d of either cranberry juice cocktail or a placebo drink containing strawberry-flavored mineral water plus 9 g/100 mL sucrose for 2 weeks. Anthocyanin glycosides were identified in the cranberry juice by tandem mass spectrometry; however, no anthocyanins or catechins were detected in the plasma of subjects following either treatment. The antioxidant capacity of plasma was measured with electron spin resonance spectrometry, the FRAP assay, and changes in the activity of superoxide dismutase, glutathione peroxidase, and catalase. In urine, malondialdehyde, a biomarker of lipid oxidation, and 8-oxo-deoxyguanosine, a biomarker of oxidative DNA damage, were measured. Although plasma levels of the antioxidant vitamin C increased significantly in subjects who consumed the cranberry juice (from 63.0 to 89.6 μM after 1 week; $P<0.01$), no changes in the antioxidant capacity of plasma or oxidative stress biomarkers in urine were detected in either group. Similarly, TC, HDL, LDL, triglyceride, and total homocysteine levels were unchanged. The absence of an increase in the FRAP contrasts with other reports that found an increase in this parameter after comparable changes in plasma vitamin C.[89–91]

Using a Latin square design, Pedersen et al.[92] were able to detect changes in plasma phenols and antioxidant potential in nine healthy women (age 23–41 y) within hours of consuming cranberry juice cocktail. After fasting overnight, each subject consumed 500 mL of either cranberry juice, blueberry juice, or a control beverage containing 9% (w/v) sucrose in water. Each volunteer participated on three occasions separated by 1 week, con-

suming one of the beverages during each visit; blood samples were collected 5 min before and 0.5, 1.0, 2.0, and 4.0 h after consumption. Total phenols in plasma and urine were measured using Folin-Ciocalteu reagent with a modification to remove protein interference in the samples. Consumption of the cranberry juice resulted in a significant increase in total phenols after 1 h compared with the control ($P<0.05$), whereas the blueberry juice did not. Plasma antioxidant potential, measured with electron spin resonance and the FRAP assay, also increased after consumption of the cranberry juice but not the blueberry juice ($P<0.001$). The investigators attributed these changes primarily to the 30% increase ($P<0.001$) in plasma vitamin C concentrations that appeared between 0.5 and 4.0 h following cranberry juice consumption.

In an uncontrolled study of 21 healthy men (mean age 38 years), Ruel et al.[93] assessed the antioxidant capacity of plasma following the daily consumption of light cranberry juice cocktail at 7 mL/kg for 14 days. An increase in the plasma total antioxidant capacity, measured with the 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) radical cation (+0.11 μmol/L; $P<0.05$), and a reduction in plasma oxidized LDL concentration, measured with an enzyme-linked immunoabsorbent assay kit (–6.0 U/L; $P<0.05$), from baseline to the end of the intervention were observed. No changes were observed in the lipoprotein-lipid profile of subjects, including LDL peak particle sizing, after the intervention.

Ruel et al.[94] also examined total antioxidant capacity and oxidative stress levels following the consumption of increasing doses of light cranberry juice cocktail (125, 250, and 500 mL) over a 3-month period. In this uncontrolled study of 31 men with mildly elevated LDL (3.4–5.0 mmol/L) and increased waist circumference (≥90 cm), the antioxidant capacity of plasma, measured with a commercial kit (ImAnOx; ALPCO Diagnostics, Windham, NH, USA) significantly changed over the course of the intervention ($P<0.006$). After an intial increase (from 244.8 to 256.9 μmol/L) following the 125 mL dose of cranberry juice, plasma antioxidant capacity declined after the 250 mL (250.3 μmol/L) and 500 mL doses (241.5 μmol/L) to a level below baseline. However, oxidative stress, measured as nitrite/nitrate (NO_x) concentrations, significantly decreased following the 500 mL dose compared to baseline (–7.4%, $P<0.05$). Interestingly the change in NO_x was correlated with increased apo A-I concentrations over the course of the intervention ($R=-4.5$, $P<0.013$).

Lipid Profile Effects

The effects of cranberry juice consumption on lipid profile changes have been investigated in preliminary studies by Caron et al.,[95] Ruel et al. (unpublished), and Vinson et al.[96] Caron et al.[95] reported the effect of consuming either low-calorie cranberry juice (4.3 mL/kg) or an isocaloric placebo twice daily for 28 days. Subjects who consumed the cranberry juice had significantly reduced TC ($P<0.026$) and LDL ($P<0.014$) compared to the placebo control subjects. No statistically significant differences were observed for HDL or triglyceride concentrations.

Ruel et al. (unpublished) and Vinson et al.[96] each reported the results of uncontrolled studies examining the effects of cranberry juice consumption over 3 months in subjects with hypercholesterolemia. Ruel et al. had 14 men (mean age 48 years) consume 125 mL/d of juice for 4 weeks, then 250 mL/d for the next 4 weeks, followed by 500 mL/d for the last 4-week period. At the end of their experiment, HDL concentrations were increased compared to baseline (6.4% or 0.12 mmol/L; $P<0.05$). With 19 subjects (11 females) and a similarly designed intervention, Vinson et al.[96] observed significantly improved HDL concentrations with either 2 or 3 servings of cranberry juice daily. In this experiment, 2 daily servings of cranberry juice also decreased LDL, though no effect on TC was observed. As anticipated, triglycerides were elevated in the subjects who consumed 3 servings/d of cranberry juice cocktail due to the 9% (w/v) sugar, but not in those who consumed the cranberry juice cocktail containing artificial sweetener.

Ruel et al.[94] later reported additional findings from their completed experimental cohort of 31 men (mean age 51 years). At baseline, subjects had mildly elevated fasting LDL (3.4–5.0 mmol/L) and an initial waist circumference of ≥90 cm. Prior to the 3-month intervention with progressively increased doses of low-calorie, sugar-free cranberry juice cocktail (described above), subjects consumed 500 mL/d of a placebo juice for a 4-week run-in period. HDL levels in the complete cohort increased significantly over the course of the intervention ($P<0.001$). Compared to values after the run-in period, HDL concentration increased by 8.6% ($P<0.05$) after the consumption of 250 mL/d, and plateaued after 500 mL/d was consumed (8.1% increase, $P<0.001$). Increases in HDL were correlated with changes in body weight ($r=-0.37$, $P<0.04$), BMI ($r=-0.42$, $P<0.02$), apo A-I concentration ($r=0.62$, $P<0.00$), and triglycerides ($r=-0.39$, $P<0.03$). In a multivariate regression analysis, only the changes in plasma apo A-I ($R^2=48\%$, $P<0.00$) and triglycerides ($R^2=16\%$, $P<0.001$) were related to the increase in HDL. Increased production of apo A-I has been observed following the consumption of wine,[97] although this mechanism has not been examined with cranberry consumption. It is also possible that the cranberry juice protected apo A-I from oxidation, though this parameter was not measured. While it appears that

changes in HDL may occur only with increased dosage and duration of cranberry juice consumption, it is not clear why changes in LDL or TC do not.

Platelet Aggregation

A preliminary investigation by Wilson et al.[98] evaluated the ability of cranberry juice to inhibit platelet aggregation in vivo. After 4 days of consuming cranberry juice four times daily, platelet-rich plasma aggregation values, in response to adenosine diphosphate and collagen, declined significantly compared to baseline values. These aggregation reponses returned to near baseline levels 4 days after cessation of cranberry juice consumption. Attempts to recreate the inhibition of adenosine diphosphate- and collagen-induced aggregation in vitro by adding cranberry juice to platelet-rich plasma from subjects who did not consume cranberry juice were not successful.

Control of Blood Glucose

Diabetic patients are at increased risk of developing CVD. In a placebo-controlled study of 27 adults diagnosed with type 2 diabetes within the previous 4–6 years, Chambers et al.[99] examined the effect of cranberry juice concentrate powder on measures of glucose control. Subjects in the treatment group (N=14, mean age 57.9 years) consumed six capsules of cranberry powder (equivalent to a 240 mL serving of cranberry juice cocktail) daily for 12 weeks. Control subjects (N=13, mean age 52.6 years) received capsules containing a placebo powder. At baseline, >50% of subjects were reported to have good control of their blood glucose levels (<7.0 mmol/L). After 6 and 12 weeks, no differences were observed between groups in fasting glucose, glycosylated hemoglobin (HbA_{1c}), fructosamine, triglyceride, HDL, or LDL concentration. However, at week 12, cranberry-supplemented subjects had lower ($P<0.05$) insulin levels (86 pmol/L) than placebo subjects (160 pmol/L).

SAFETY

Anecdotal case reports implying an interaction between the anticoagulant drug warfarin and the consumption of cranberry products are present in the literature.[100,101] The theoretical basis for this potential interaction involves the ability of cranberry flavonoids to inhibit cytochrome P450 enzymes and the metabolism of warfarin by CYP2C9 (S-warfarin), CYP3A and CYP1A2 (R-warfarin). However, in vivo clinical studies by Greenblatt et al.[102] and Grenier et al.[103] refute the possibility of this interaction. The nonsteroidal anti-inflammatory drug flurbiprofen is metabolized almost exclusively by CYP2C9 in humans. According to Greenblatt et al.,[102] the administration of 8 oz cranberry juice, grape juice, or tea did not alter the CYP2C9-mediated clearance of flurbiprofen in 14 healthy volunteers, although grape juice and tea did impair this activity in vitro. Grenier et al.[103] found that 240 mL cranberry juice had no significant effect on the overall disposition of cyclosporine (200 mg), a substrate for CYP3A, when administered together, although 240 mL of pomelo juice did when compared to water as the control ($P<0.00$, N=12).

CONCLUSION

A growing body of literature indicates polyphenolics, including those found in cranberries, may contribute to reducing the risk of CVD by increasing the resistance of LDL to oxidation, inhibiting platelet aggregation, reducing blood pressure, and via other anti-thrombotic and anti-inflammatory mechanisms.[26,104] While most of this evidence is derived from in vitro studies and animal models, a limited number of human studies indicate these phytochemicals are bioavailable and bioactive. More information is required on the bioavailability and metabolism of cranberry polyphenolics as well as on the relationship between cranberry dose and duration of use to better understand their impact on risk factors for CVD, particularly clinically meaningful parameters such as inflammation, insulin resistance, vascular reactivity, and vascular remodeling.

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