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Cranberries and Cranberry Products: Powerful in Vitro, ex Vivo, and in Vivo Sources of Antioxidants

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Cranberry products and especially cranberry juice (CJ) have been consumed for health reasons primarily due to their effect on urinary tract infections. We investigated the quantity of both free and total (after hydrolysis) phenolic antioxidants in cranberry products using the Folin assay. The order of amount of total polyphenols in cranberry foods on a fresh weight basis was as follows: dried > frozen > sauce > jellied sauce. On a serving size basis for all cranberry products, the order was as follows: frozen > 100% juice > dried > 27% juice > sauce > jellied sauce. High fructose corn syrup (HFCS) is a major source of sugar consumption in the U.S. and contains both glucose and fructose, potential mediators of oxidative stress. We investigated the effect of the consumption of HFCS and ascorbate with CJ antioxidants or without CJ (control) given to 10 normal individuals after an overnight fast. Plasma antioxidant capacity, glucose, triglycerides, and ascorbate were measured 6 times over 7 h after the consumption of a single 240 mL serving of the two different beverages. The control HFCS caused a slight decrease in plasma antioxidant capacity at all time points and thus an oxidative stress in spite of the presence of ascorbate. CJ produced an increase in plasma antioxidant capacity that was significantly greater than control HFCS at all time points. Postprandial triglycerides, due to fructose in the beverages, were mainly responsible for the oxidative stress and were significantly correlated with the oxidative stress as measured by the antioxidant capacity. Cranberries are an excellent source of high quality antioxidants and should be examined in human supplementation studies.

KEYWORDS: Cranberry; cranberry juice; polyphenols; antioxidant; oxidative stress; high fructose corn syrup; glucose; triglycerides; plasma antioxidant capacity

INTRODUCTION

There are two kinds of cranberry (CB) fruit. The small-fruited or European CB (*Vaccinium oxycoccos*) is found in marshy land in northern North America, northern Asia, and northern and central Europe. The North American CB (*Vaccinium macrocarpon*) is found wild from Newfoundland to the Carolinas. This CB plant grows on vines, which spread across the surface of a bog, and the first commercial bogs were planted in Massachusetts (*1*). The CB has garnered considerable attention due to its possible health benefits. Recently, the French government health agency ruled that the powder and juice of North American CBs can be used to improve urinary tract health (*2*). This is the world's first government-approved use for a fruit to treat a health condition. The decision is based on a number of reports, at first anecdotal and then scientific. CJ and CB powder can prevent urinary tract infections due to the ability of the CB phytochemicals (most notably the high molecular weight proanthocyanidins) to inhibit the adhesion of *Escherichia coli* bacteria that are the cause of the infections. These studies have been currently reviewed (*3, 4*). The possible health benefits of CBs are diverse. For instance, CBs may have anticancer activity as a result of their inhibition of tumor cell growth (*5*) by a mechanism that may include apoptosis and G1 phase arrest (*6*). Another group showed that the phenols from CB extract reportedly acted synergistically in antiproliferative activity against human tumor cell line constituents (*7*). Dental health also may be improved by the antiadhesion mechanism of flavonols and A-type linked proanthocyanidins (*8*).

Our interest in CBs has been due to their function as antioxidants and their possible benefit for heart disease. CB's action against LDL oxidation was first demonstrated by Wilson et al. (*9*). Their use in the prevention of atherosclerosis and the promotion of cardiovascular health has been recently reviewed (*10, 11*). Two groups using two different assay methodologies showed that CBs have the greatest antioxidant content of any fruit by fresh weight (*12, 13*). We thus decided to investigate the antioxidant content and antioxidant quality of different commercial CB products.

High fructose corn syrup (HFCS) is manufactured by enzymatically converting cornstarch to syrup that is almost entirely glucose. The syrup is then enzymatically isomerized

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to a mixture of glucose and fructose, either 42 or 55% fructose. In Europe, HFCS is known as isoglucose and occupies a niche market in soft drinks, canned fruits, condiments, ice cream, and frozen desserts. HFCS represents more than 40% of Americans' added sugar consumption, which was 121 g per person/day in 2005 (*14*). The total caloric intake for U.S. diets has increased over the past two decades largely due to the greater consumption of HFCS soft drinks. HFCS is the sole caloric sweetener in soft drinks in the U.S. The conservative estimated 2003 daily intake of HFCS in the U.S. is 552 kJ, which is the equivalent of 326 mL of an average soft drink (*15*). Consumption of soft drinks is hypothesized to provide a link to obesity in both children and adults (*16*). Obesity is a risk factor for many chronic diseases including diabetes, cardiovascular disease, hypertension, and stroke. Obesity is a growing problem in industrialized nations and represents a significant medical problem and economic burden for society.

A recent study investigated the effect of 75 g of glucose (the usual dose for an oral glucose tolerance test) given to normal subjects. Nitrotyrosine, a marker of oxidative stress, was elevated, and the increase was exacerbated with the addition of a high fat meal (*17*). Postprandial glucose is widely recognized as producing oxidative stress and causing diabetic complications (*18*). A high fat meal given to type 2 diabetics caused an increase in plasma lipid peroxides. The largest decrease in antioxidant capacity occurred in those subjects who experienced the greatest hyperglycemia (*19*). Most recently, type 1 diabetics were studied with the same protocol, and plasma glucose was significantly correlated with protein oxidative stress (nitrotyrosine) and lipid oxidative stress (oxidized LDL). In addition, glucose was inversely correlated to plasma antioxidant capacity. A drug that lowered postprandial glucose was shown to significantly decrease the oxidative stress markers (*20*). Given the knowledge concerning glucose, it is surprising that little is known about the effects of increased consumption of fructose. One telling piece of evidence is an animal study comparing high fructose-fed rats to normal controls. This model mimics metabolic syndrome in humans. Significantly higher reactive oxygen species were produced concurrently with a greater expression of NADPH due to the fructose (*21*). These deleterious effects were attenuated by concurrent consumption of polyphenol-containing extracts. CBs have the highest amount of phenolic antioxidants of any commonly consumed fruit (*12*), but CBs are primarily consumed as juice that contains flavonoids, proanthocyanidins, and phenolic acids (*22*). We thus decided to investigate HFCS in humans for its suspected pro-oxidant nature and to test the antioxidant efficacy of high antioxidant-containing CJ with HFCS.

MATERIALS AND METHODS

Commercially available CB products were obtained from local supermarkets and health food stores. CJ concentrate (50 Brix) and HFCS were donated by Northland Cranberry. 27% CJ prepared from the concentrate was analyzed by HPLC for anthocyanins using cyanidin chloride (Sigma) as a standard, and quercetin, the major flavonol in CJ. The CJ was hydrolyzed with HCl (*23*), and the hydrolyzate containing the aglycones was separated using a Phenomenex 4.6 mm × 150 mm Luna 3 μm C18 column with a 30 min gradient from 100% water containing 4% acetic acid to 100% methanol with a flow rate of 2 mL/min and detection of anthocyanins at 520 nm and flavonols at 360 nm. Frozen CBs from different cultivation areas, different varieties, and different harvesting times were supplied by growers through the Cranberry Institute, which sent them coded. Individual sample data from each state were averaged. The commercially packaged products were analyzed immediately after opening the container. Per capita food consumption (availability) was found from the U.S. Government's Economic Research Service Web site for 2004 (*24*).

Table 1. Free and Total Phenols as Catechin Equivalents in CB Products (Fresh Wt)

CB product	free phenol (mg/g)	total phenol (mg/g)
CB Sauce		
brand A whole berry	1.22	2.70
brand B whole berry	2.03	3.54
brand C whole berry	1.48	1.94
brand D whole berry organic	2.90	3.63
av	1.91 ± 0.75	2.96 ± 0.64
Jellied Sauce		
brand A	1.28	1.60
brand B	1.45	2.64
av	1.36 ± 0.12	2.12 ± 0.73
Frozen CBs		
Massachussetts ($n = 5$)	5.10 ± 0.99	6.15 ± 1.45
New Jersey ($n = 4$)	5.25 ± 1.28	6.35 ± 1.65
Wisconsin ($n = 7$)	5.10 ± 0.70	7.16 ± 1.19
Oregon ($n = 4$)	4.81 ± 0.44	5.68 ± 0.64
av of all samples	5.08 ± 0.81	6.44 ± 1.31
Dried CBs		
brand A	4.26	5.77
brand B	10.2	11.9
brand C	6.00	9.89
brand D	4.96	7.25
brand E	4.32	5.28
av	6.35 ± 7.67	8.73 ± 2.78
CB Powder		
brand A	1.28	1.62
brand B	6.12	13.5
brand C	2.73	3.39
brand D	1.60	20.65
av	6.53 ± 6.61	9.77 ± 8.9

Antioxidant Assays. Fruits and sauces were analyzed by a previously published method in which multiple berries from each frozen sample were pooled, finely ground under liquid nitrogen, and freeze-dried. The solid was dissolved in either methanol/water for the free phenol assay or methanol/water/HCl with heating for total phenols by the Folin−Ciocalteu method using catechin as the standard (*25*). The acid hydrolyzes the ethers of phenols bound to sugar residues. This analysis gives the result of free and bound polyphenols and thus the total phenols present. If the product contained vitamin C, its label concentration was subtracted from the Folin value as it interfered on a mole basis with the assay. The phenol assays were performed in duplicate. Pooled extracts were used for the CB products' quality determination.

The quality of the unhydrolyzed antioxidant extracts (free phenols) was determined as IC_{50}, the concentration to inhibit the atherogenic lipoprotein LDL + VLDL oxidation by 50% as compared to a control using a standard methodology (*25*). Another measure of antioxidant quality uses an ex vivo spiking of the free phenol extract in pooled human plasma, isolating LDL + VLDL, and determines the lag time of oxidation (time for rapid oxidation to begin), which is a measure of lipoprotein-bound antioxidant activity (*25, 26*). The phenol concentration to increase the lag time by 50% as compared to the control was determined (*25*). This is reported for both pure compounds in micromolar units and for products in micromolar units of catechin equivalents. Both of the quality assays were performed at several concentrations: 0.1−10 μM for IC_{50} and 50−200 μM for CLT_{50}. CB data in **Tables 1** and **2** were used for these quality assays. Green tea had a concentration of 3.48 mg/mL (12×10^3 μM) catechin and red wine was 2.80 mg/ml (9.6×10^3 μM) (*26*).

In Vivo Study. The study was approved by the Institutional Review Board of the University of Scranton, and all procedures involving human subjects complied with the Declaration of Helsinki, as revised in 2000. An industry standard of 27% CJ was prepared just before use by combining a commercial CJ concentrate and HFCS, containing 21 g of glucose and 17 g of fructose, along with 80 mg of added vitamin C per 240 mL serving. A serving size of this juice contained a total of

Table 2. Free and Total Phenols as Catechin Equivalents in CJ

CB product	free phenol (mg/mL)	total phenol (mg/mL)
100% CJ		
brand A	1.91	2.00
brand B	2.43	2.47
av	2.17 ± 0.37	2.24 ± 0.33
27% CJ Cocktail		
brand A	0.53	0.58
brand B	0.40	0.79
brand C	0.34	0.64
brand D	NA[a]	0.85
brand E	NA	0.66
brand F light	NA	0.86
av	0.47 ± 0.09	0.73 ± 0.12
Mixed Juices		
brand A CB/grape	NA	1.48
brand B CB/grape	NA	0.50
brand C CB/grape	NA	1.08
brand D grape/CB	NA	0.80
brand F CB/grape light	NA	0.78
brand A CB/grape/apple	NA	1.05
brand B CB/grape/apple	NA	0.72
brand C CB/grape/apple	NA	0.73
brand D CB/pear	NA	1.01
brand E CB/raspberry light	NA	0.56
brand F CB/pear/aronia/grape/apple	NA	0.84
brand G CB/raspberry/pear/apple/aronia	NA	0.83
brand H CB/raspberry/grape/apple/pear	NA	0.77
av		0.80 ± 0.25
White CB		
brand A	NA	0.60
brand B white CB/strawberry	NA	0.66
brand C white CB/peach	NA	0.72
brand D white CB/apple	NA	0.47
av		0.61 ± 0.11

[a] NA: not analyzed.

175 mg of catechin equivalents as determined by the Folin assay, 16 mg of cyanidin, 8 mg of peonidin anthocyanins, and 3 mg of quercetin, as determined by HPLC. A control was prepared with the same HFCS and 80 mg of ascorbate. Then, 240 mL of each beverage in a random order was given to 10 volunteers after an overnight fast. The subjects' characteristics were the following: three men and seven women with an average age of 32 (range of 25−38) and an average BMI of 26 (range of 22−33). Blood was sampled periodically for 7 h. A low fat bagel and 240 mL of commercial noncola soft drink (51 g of HFCS) was given for lunch after the 4 h draw. A week later, the subjects repeated the regimen with the other beverage. Plasma glucose and triglycerides were measured by an enzymatic method (Sigma Chemical Company). Ascorbate was analyzed in plasma by HPLC at 265 nm after stabilization with meta-phosphoric acid. Plasma antioxidant capacity was measured as ferric reducing antioxidant power (FRAP) using trolox as a standard. FRAP measures the combined antioxidant defenses (capacity) of nonenzymatic substances in plasma. It is widely used for food, beverage, and plasma assays and has been critically evaluated and was found to be a precise method for measuring antioxidant capacity and oxidative stress (*27*). Results are given as mean values and standard errors of the mean for the 10 subjects. Statistical differences between beverages were evaluated by a paired Student's *t* test using Sigma Stat 3.01 for Windows (Systat, Richmond, CA). $p < 0.05$ was considered significant.

RESULTS

In Vitro and ex Vivo Studies. The Folin assay uses catechin as the standard, and thus, the results are in catechin equivalents. The ascorbic acid Folin equivalent was subtracted from the juice data based on label values. In **Table 1** are displayed the results for the CBs. The order of total polyphenols on a fresh weight basis was as follows: dried CBs > frozen CBs > CB sauce > jellied sauce. CB powder usually is not considered a food, but it had the most polyphenols of the CB products and possessed the most variability. The order for total phenols in CB beverages was as follows: 100% CJ > mixed juices > 27% CJ cocktail > white CJ. The single product with just white CJ was 82% of the value of the CJ cocktail. The fairest means of comparison for CB products is on a serving size basis displayed in **Figure 1**. The frozen CBs, 100% juice, and dried CBs provide the most antioxidants distantly followed by mixed and 27% CJ and the other CB products. CBs are easily the highest source of antioxidants among common fresh fruits on a fresh weight basis (*12*). Dried CBs provide more antioxidants on a fresh weight basis than other commonly consumed dried fruits such as apricots and dried plums (*28*). When the per capita consumption of polyphenol antioxidants is calculated based on the amount of fruit consumed and the level of antioxidants in fruit, then CB is a distant 16th (*12*).

Among CB products, frozen CBs have the lowest IC_{50} (i.e., best quality as seen in **Figure 2**). The quality of phenolic antioxidants in frozen CBs and dried CBs is superior to the vitamin antioxidants. Frozen CBs are equivalent in quality to red wine. 100% CJ is equivalent in quality to vitamin E. The second measure of quality is lipoprotein-bound antioxidant activity, which is the reciprocal of concentration to increase the lag time of the lipoproteins LDL + VLDL isolated after plasma spiking and oxidation with cupric ion ($1/CLT_{50}$). In this ex vivo study, the lower the CLT_{50} value indicates a higher quality, which is the result of phenolics binding and acting as antioxidants. An example of the dose−response effect of CJ antioxidants on the LDL + VLDL oxidation time curve is shown in **Figure 3**. The lag times are 86 min for the control (blank), 203 min for 100 μM, and 286 min for 200 μM. CJ has a very similar lipoprotein-bound antioxidant activity to red wine (*26*). At the highest concentration of CJ polyphenols (200 μM), not only is the lag time the longest but the amount of oxidation as exemplified in the change in absorbance from the baseline is considerably lower than the control and 100 μM. In **Figure 4** is seen a comparison of 27% CJ with other beverages and polyphenol compounds. CJ was the second best source of quality antioxidants in this ex vivo assay (i.e., had the second highest $1/CLT_{50}$ value).

In Vivo Human Study. Baseline values for plasma antioxidant capacity, triglycerides, glucose, and ascorbate were 628 ± 22.2 μM, 1.04 ± 0.18 mM, 0.86 ± 0.03 mM, and 31.1 ± 1.9 μM, respectively. The control HFCS plus vitamin C was a pro-oxidant and decreased antioxidant capacity at all time points as compared to the baseline (**Figure 5**). There was an added increase in the pro-oxidant activity several hours after the bagel and soft drink consumption at 4 h. When the subjects were given the CJ plus vitamin C with HFCS, the plasma antioxidant capacity increased at all time points. There also was a significant difference between the CJ and the control HFCS plus ascorbate at all time points. There was no difference between the two beverages with respect to plasma ascorbate (results not shown).

CJ blunted the plasma glucose increase due to HFCS, although the difference between control HFCS and CJ was not significant (**Figure 6**) due to large subject variations (not shown for clarity purposes). The areas under the curves were 4.81 mM h for the control and 0.87 mM h for CJ. The initial very rapid increase in plasma glucose after consuming glucose usually occurred within 30 min and was missed in this study. Changes in plasma triglycerides also are shown in **Figure 6**. Although there were no significant changes due to the large subject variations, CJ completely blocked triglyceride formation during

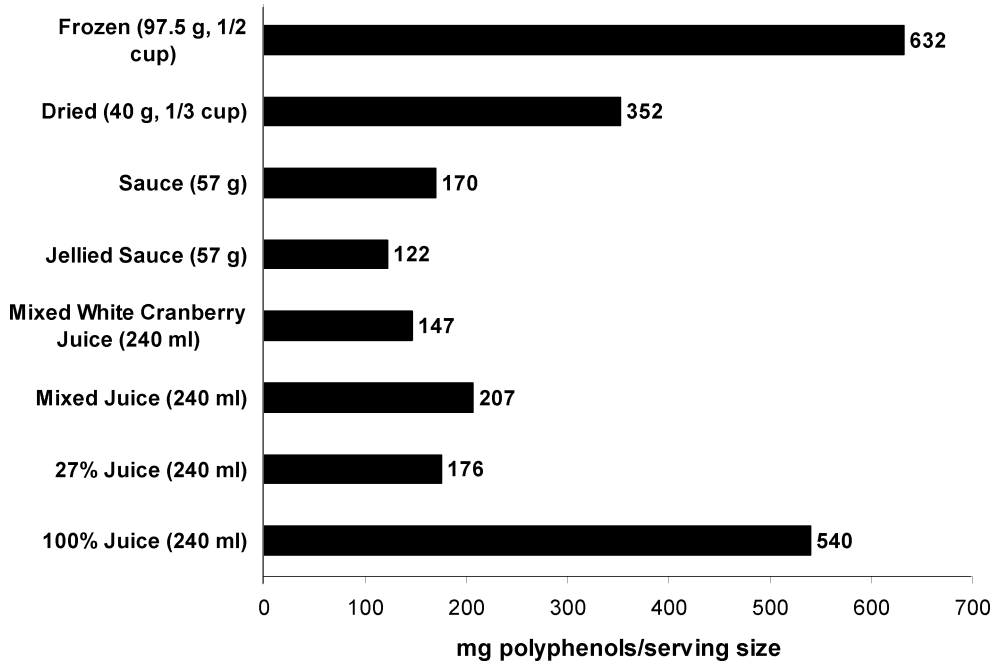

Figure 1. Polyphenols in different CB products based on serving size (mg of total polyphenols as catechin/serving size).

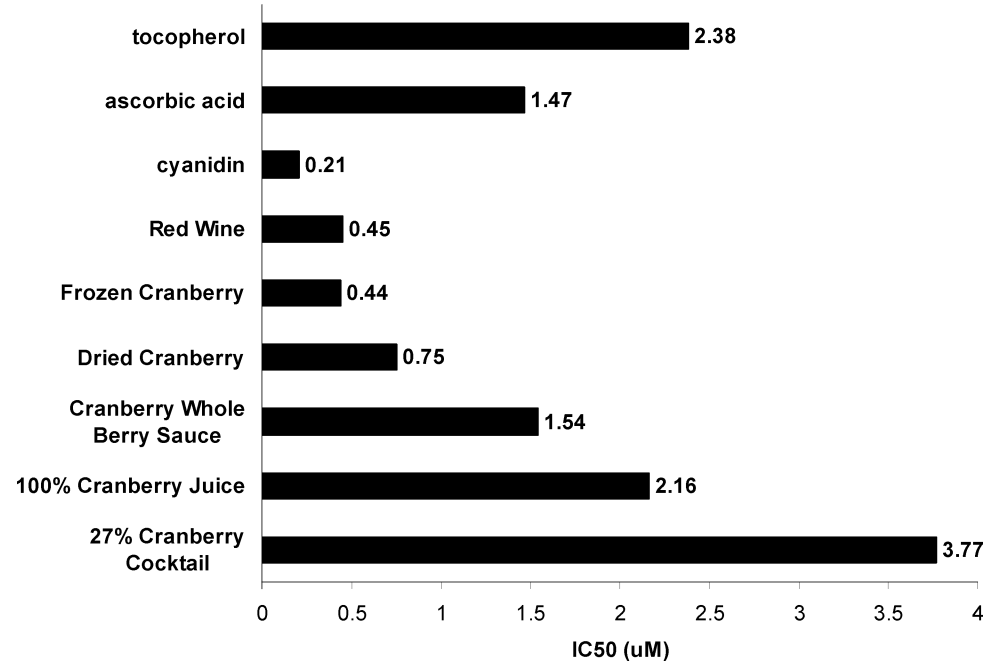

Figure 2. Comparison of quality (IC_{50}) of antioxidants in CB products, red wine, and antioxidant compounds.

the first 4 h. The average areas under the curve were 1.86 and −0.13 mM h for the control and CJ, respectively.

DISCUSSION

Among the frozen CBs, dried CBs, and CB sauce, the total polyphenols were significantly higher than the free level, $p < 0.03$ (**Table 1**). Thus, for analyses without hydrolysis, which is the usual methodology for food extracts, the analyst would miss some of the antioxidants that are present in CBs. CB sauces averaged 65% free polyphenols, jellied sauces 64%, dried CBs 73%, and frozen CBs 79%. The percent of free polyphenols decreased with processing as the sauces had the least percent. Apparently, processing hydrolyzes some of the ether links of sugar molecules attached to the phenolic group. There was little difference between the four CB-producing states as the results are an average of different harvest times and different varieties of CBs. There is a large difference in water content among the different products, ranging from 2−10% for dried CBs to 84−86% for the frozen variety and the sauces ranging widely from 45 to 62%. On a dry weight basis, frozen CBs have an average of 46.1 mg/g and dried CBs 8.9 mg/g. Dried fruits lose a considerable amount of phenolic antioxidants during the drying process: 80% for CBs. All fruits we examined shared this property (*28*). Half of the individually analyzed phenols in plums were lost during drying, as discussed in another published study (*29*). These losses may be due to polyphenol oxidase activation during the drying process.

Among juices in **Table 2**, as expected, the 100% juices (with

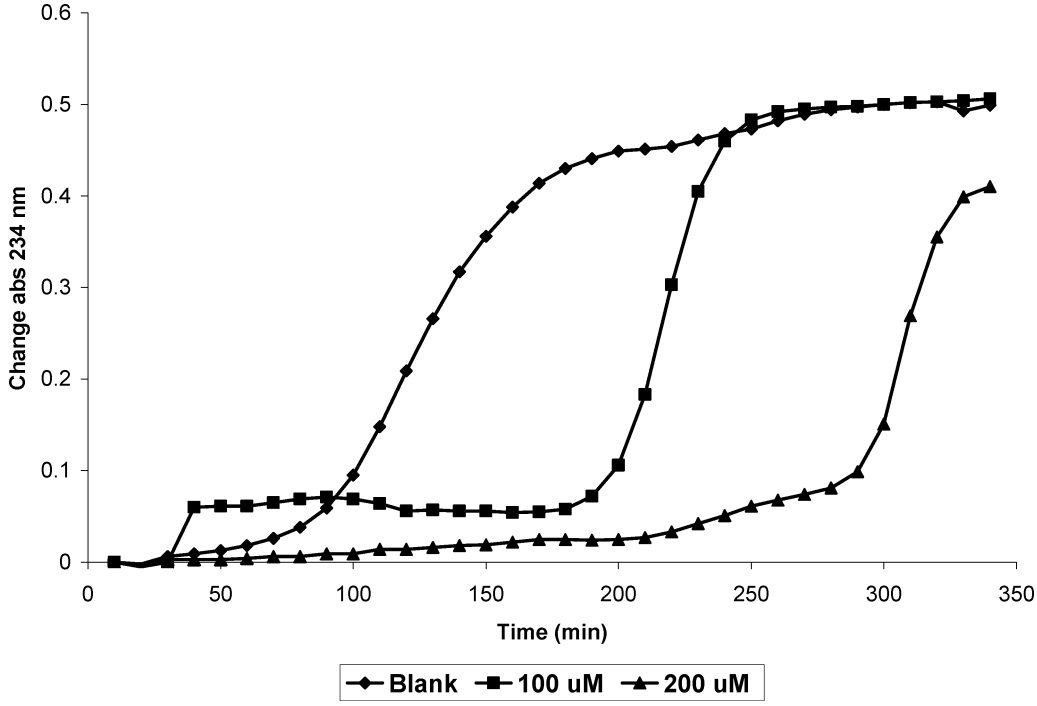

Figure 3. Dose−response effect of CJ polyphenols on lower density lipoprotein (LDL + VLDL) oxidation kinetics.

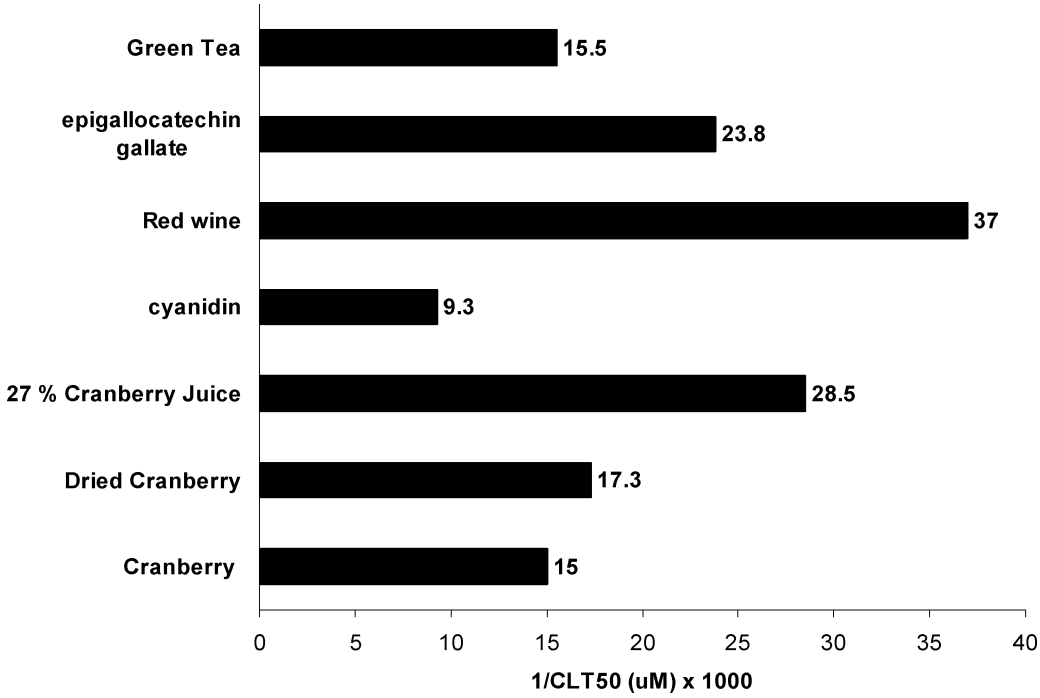

Figure 4. Comparison of quality of antioxidants as the reciprocal of lipoprotein-bound antioxidant capacity ($1/CLT_{50}$) in CB products, red wines, green teas, and polyphenols.

no added sugar) contained the most antioxidants. Red CJ cocktail contained more antioxidants than the white juices, presumably as a result of less anthocyanin content in the white CB. Mixed CJ averaged slightly higher levels of phenols (17%) than 27% CJ probably as a result of grape juice addition since Concord grape juice has about 2 times more polyphenols than 27% CJ (*30*). However, 27% CJ has more phenols per 240 mL serving (176 mg) than the common breakfast fruit juices such as orange juice (53 mg), apple juice (61 mg), and pineapple juice (97 mg) (*31*). CB powder, on average, had only slightly more phenolics than dried CBs, perhaps indicative of increased processing for the powders that destroyed some of the phenols.

On a serving size basis, there was a wide variation in polyphenol levels with the frozen CBs first among the CB food products and followed by 100% juice. On the basis of serving size, 100% CJ had more polyphenols (587 mg) than Concord grape juice (356 mg) and more than red wine (400 mg). A single serving of 100% CJ or dried or frozen CBs provides more phenolic antioxidants than the total per capita consumption of antioxidants from all fruits, which was 255 mg in 1997 (*12*) and calculated to be 267 mg per day in 2004. CBs are highest in antioxidant content among fruits, yet are underconsumed, ranking 16th. In fact, the tiny 2 mg/day from CBs (less than

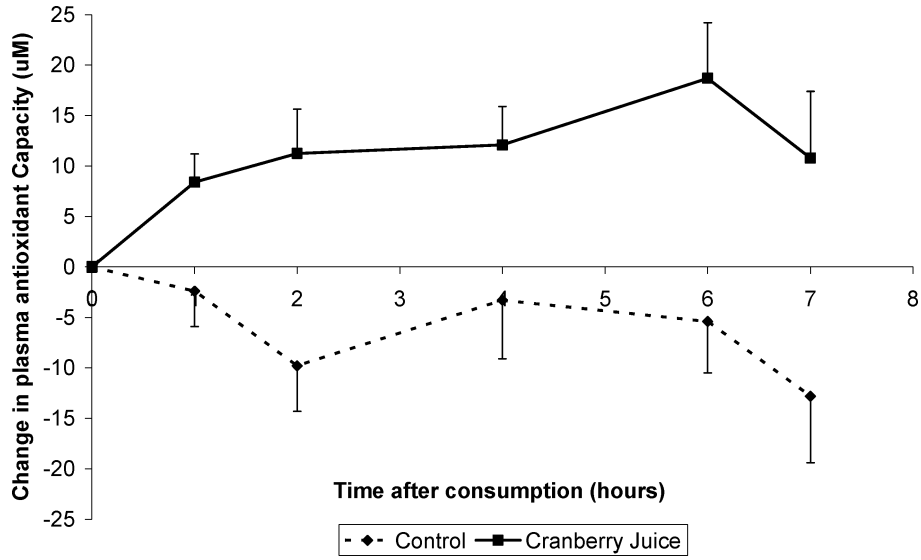

Figure 5. Effect of CJ and HFCS plus vitamin C consumption on the change in plasma antioxidant capacity (FRAP): mean ± SE.

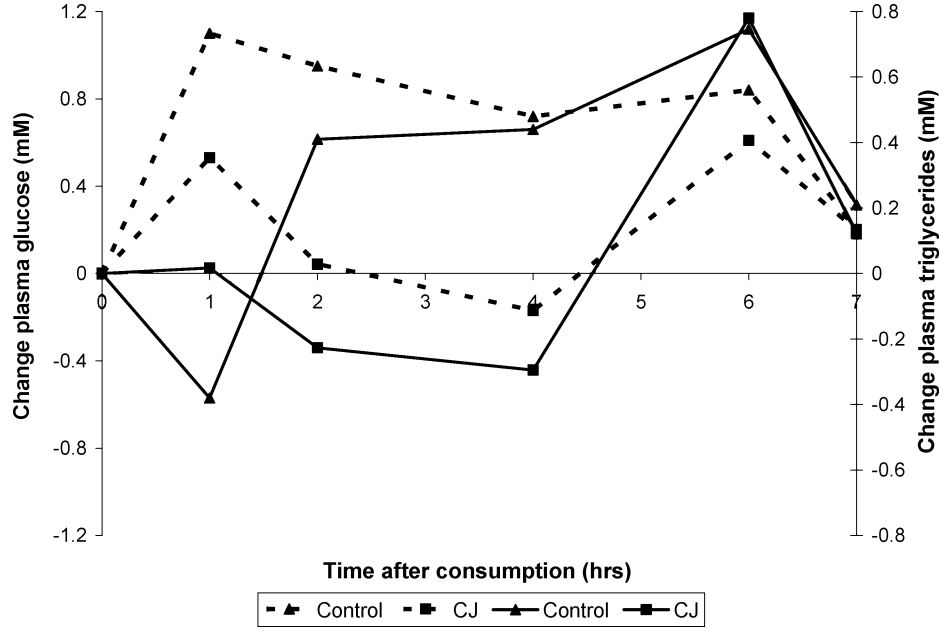

Figure 6. Effect of CJ and HFCS plus vitamin C consumption on the change in plasma glucose and triglycerides.

1% of the total from all fruits) is the result of including juice consumption since only 5% of CB consumption is from the fruit (*24*).

The quality of antioxidants in a food or beverage is the result of the chemical composition and is independent of the quantity of antioxidants present. Of special interest for the polyphenol antioxidant field is the quality of the antioxidants as shown in **Figure 2**. This is due to the fact that polyphenols in plasma circulation are seldom found at concentrations greater than several micromolar (*32*). IC_{50} values are the result of determining the inhibition of LDL + VLDL oxidation at several concentrations and calculating the percent inhibition (i.e., a dose−response study). Dried CBs and frozen CBs are better antioxidants (i.e., have a much lower IC_{50} value than the vitamins ascorbic acid and tocopherol). The concentrations used for quality assays for CB products are all physiologically possible (0.44−3.77 μM), although metabolites are more likely to be present in plasma than the original phenols in CBs. Comparing the different CB products, it appears that processing seems to decrease the quality, most likely by changing the polyphenols' composition.

Looking at **Figure 4**, CJ had twice the lipoprotein-bound antioxidant activity of green tea and was slightly better (higher $1/CLT_{50}$ value) than the main antioxidant in green tea, epigallocatechin gallate (*30*). All three CB products were superior to the anthocyanin cyanidin. Thus, CB antioxidants have the ability to bind to lower density lipoproteins and to protect them from oxidation. This is one mechanism by which CB products can protect against heart disease.

It is clear from **Figure 5** that HFCS is a pro-oxidant after consumption and that CJ is an antioxidant. There was a significant negative correlation between changes in triglycerides and changes in antioxidant capacity: Pearson coefficient −0.746 and $p < 0.02$. The increase in triglycerides after HFCS consumption is almost completely due to fructose rather than glucose (*33*). Postprandial triglycerides are known to produce oxidative stress (*34*) and are a major source of oxidative stress in the present study as determined by the correlation calculation.

CJ inhibits the absorption of glucose and the in vivo formation of triglycerides from fructose and thus decreases the oxidative stress.

Plasma urate was not measured in this protocol due to the lack of sample. Fructose in consumed apples recently was shown to elevate plasma urate, and this correlated with the plasma antioxidant activity (FRAP) increase (*35*). This human study also showed that doses of fructose >0.5 g/kg body weight caused an increase in urate. Our dose was <0.3 g/kg body weight, and thus, urate should not increase from consumption of HFCS or CJ. Another difference between the apple study and the CJ experiment is the greater glucose/fructose ratio in HFCS, 1.23, versus that in apples, 0.41 (*24*). This would indicate that glucose, in addition to fructose, also may be responsible for decreasing the plasma antioxidant capacity. Confirming our results, 75 g of glucose produced a slight decrease in plasma FRAP antioxidant capacity in fasting normal subjects (*36*). Thus, it appears that both fructose and glucose are pro-oxidants in HFCS. We also reported a decrease in antioxidant capacity (oxidative stress) after subjects consumed the same brand of HFCS soft drink we gave in the present study, and a different measure of antioxidant capacity was used for the analysis (*28*).

The results indicate that drinking a HFCS beverage, even with the recommended daily intake of vitamin C but containing no additional antioxidants, is deleterious due to a decrease in antioxidant capacity of the plasma from the baseline (i.e., oxidative stress). All soft drinks, and many fruit drinks and cocktails containing added HFCS and none or very low levels of fruit juice, would probably fall into this category of oxidative stressors.

A previous human single dose study with CJ sweetened with sucrose resulted in an increase in plasma FRAP, but it was attributed to ascorbate, although no ascorbate was used in the sucrose control (*37*). Polyphenol antioxidants have previously been found in human plasma after drinking CJ and reached a maximum of ~10 μM (*38*). These authors did not hydrolyze the plasma extracts and thus may have underestimated the phenol concentration. The phenolic compounds may be responsible for the in vivo effect of CJ in this study (i.e., an increase in FRAP of ~15 μM).

Tea polyphenols have been shown in humans to decrease postprandial triglycerides after a meal (*39*). Grape polyphenols were shown to lower triglycerides and oxidative stress in a human supplementation study (*40*). The cardioprotective effect of dietary polyphenols has recently been reviewed and indicates that multiple mechanisms may operate (*40*). Polyphenols can decrease glucose by decreasing glucose uptake in the intestine (*41*) and by improving insulin sensitivity (*42*). Thus, the ingredients in CJ block and even overcome the oxidative stress of HFCS, most probably by an indirect effect of decreasing postprandial glucose and triglycerides, which are responsible for inducing oxidative stress as well as a direct in vivo antioxidant mechanism.

The moderate intake of red wine is known to lower the risk of heart disease. It has been shown that 375 mL of red wine improved plasma antioxidant capacity, increased HDL levels, and decreased markers of oxidative stress in humans (*43*). A recent 2 week human supplementation with low calorie CJ found an increase in plasma antioxidant capacity and a decrease in oxidized LDL (*44*). This Canadian group also found that low calorie CJ increased HDL in obese men (*45*). It is thus possible that chronic CJ supplementation can have the same antioxidant and beneficial HDL-raising effects as red wine without consuming alcohol. We are currently investigating this hypothesis in hypercholesterolemic subjects.

ABBREVIATIONS USED

CB, cranberry; CJ, cranberry juice; IC_{50}, concentration to inhibit the oxidation of LDL + VLDL by 50%; CLT_{50}, concentration to increase the lag time of LDL + VLDL by 50%; FRAP, ferric reducing ability of plasma; HFCS, high fructose corn syrup.

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