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Research Communication

Consumption of Cherries Lowers Plasma Urate in Healthy Women[1,2]

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ABSTRACT To assess the physiologic effects of cherry consumption, we measured plasma urate, antioxidant and inflammatory markers in 10 healthy women who consumed Bing sweet cherries. The women, age 22–40 y, consumed two servings (280 g) of cherries after an overnight fast. Blood and urine samples were taken before the cherry dose, and at 1.5, 3 and 5 h postdose. Plasma urate decreased 5 h postdose, mean ± SEM = 183 ± 15 μmol/L compared with predose baseline of 214 ± 13 μmol/L ($P < 0.05$). Urinary urate increased postdose, with peak excretion of 350 ± 33 μmol/mmol creatinine 3 h postdose compared with 202 ± 13 at baseline ($P < 0.01$). Plasma C-reactive protein (CRP) and nitric oxide (NO) concentrations had decreased marginally 3 h postdose ($P < 0.1$), whereas plasma albumin and tumor necrosis factor-α were unchanged. The vitamin C content of the cherries was solely as dehydroascorbic acid, but postdose increases in plasma ascorbic acid indicated that dehydroascorbic acid in fruits is bioavailable as vitamin C. The decrease in plasma urate after cherry consumption supports the reputed anti-gout efficacy of cherries. The trend toward decreased inflammatory indices (CRP and NO) adds to the in vitro evidence that compounds in cherries may inhibit inflammatory pathways. J. Nutr. 133: 1826–1829, 2003.

KEY WORDS: • cherries • gout • humans • anti-inflammatory • fruit

In addition to providing essential vitamins, minerals and dietary fiber, fruits contain phytochemicals that may lower the risk of cancer, heart disease and other chronic diseases. Both sweet and tart cherries are rich in antioxidants, including anthocyanins (responsible for red skin and flesh color), catechins, chlorogenic acid, flavonal glycosides and melatonin. Anthocyanins, cyanidin and hydroxycinnamates isolated from tart or sweet cherries inhibited oxidation of isolated human LDL and model liposomes to an extent comparable to vitamin E and BHT (1–3). Anthocyanins extracted from cherries have also shown anti-inflammatory properties, via inhibition of cyclooxygenase (COX)[4] activities (2,3) and scavenging of the reactive nitric oxide (NO) radical (4). In activated macrophages, anthocyanins and other phenolics inhibit NO production and modulate tumor necrosis factor (TNF)-α secretion (5,6).

Consumption of cherries and cherry products has been reported to be health promoting, particularly to alleviate arthritic pain and gout (7). Clinical case reports of three patients with gout showed that consumption of 227 g of cherry products daily for 3 d to 3 mo reduced plasma urate to normal levels and alleviated attacks of gouty arthritis (7). It is not known what compounds in cherries might be responsible for these alleged actions. Moreover, the putative anti-gout and anti-inflammatory properties of cherries have not been assessed in controlled experimental studies. The present study was conducted to determine the extent of these effects in healthy women consuming an acute dose of Bing sweet cherries.

SUBJECTS AND METHODS

Subjects and study design. The clinical portion of the study was conducted in May 2002, during California's fresh cherry season, at the USDA Western Human Nutrition Research Center (WHNRC), University of California Davis. Candidates recruited from the Davis, CA area were screened for good health by a medical history questionnaire, physical exam and standardized blood and urine tests including a complete blood cell count with leukocyte differential, clinical chemistry panel, urinalysis and tests for infectious disease. Candidates were excluded if they were in poor health, obese (body mass index >30 kg/m^2), regularly used nutritional supplements, medications, alcohol or recreational drugs. The ten women accepted into the study were nonsmokers, age 22–40 y (mean ± SD = 29.9 ± 6.1 y) and primarily Caucasian. The study was approved by the Human Subjects Review Committee of the University of California, Davis. All subjects signed informed consent before entering the study.

To partially standardize and limit intake of antioxidants before the experimental cherry dose, subjects were asked to refrain from consuming fruits and vegetables or their juices, tea or wine for 2 d before the cherry dose. Fresh sweet Bing cherries were obtained from O.G. Packing, Stockton, CA and were stored at 4°C until they were consumed. The subjects consumed 280 g of depitted cherries (about 45 cherries) after an overnight fast and were required to consume all

[1] Supported in part by the United States Department of Agriculture, Agricultural Research Service, and the California Cherry Advisory Board, Lodi, CA.

[2] Reference to a company or product name does not imply approval or recommendation of the product by the U.S. Department of Agriculture to the exclusion of others that may be suitable.

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[4] Abbreviations used: AA, ascorbic acid; COX, cyclooxygenase; CRP, C-reactive protein; DHA, dehydroascorbic acid; FRAP, ferric reducing ability of plasma; NO, nitric oxide; ORAC, oxygen radical absorbing capacity; TEAC, Trolox equivalent antioxidant capacity; WHNRC, Western Human Nutrition Research Center.

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of the cherries within 10 min. Blood and urine samples were obtained before the dose, and at 1.5, 3 and 5 h postdose. Subjects emptied their bladder for the predose urine collection, and all urine was collected between each blood draw. Subjects were allowed to leave the clinical unit after the 1.5- and 3-h postdose blood draws but were required to return within 10 min of the next scheduled blood draw, and avoid consumption of any food or drink except from a 237-mL bottle of water given after the 1.5-h draw. The subjects were scheduled over 6 d and a 70-g portion of the cherries available was taken on each of the 6 d and frozen at −70°C until analysis for antioxidant and polyphenol content.

For comparison purposes, plasma urate values from a previous (unpublished) study on antioxidant capacity of fruits are included herein. The study design was similar to the present study, i.e., two servings each of red "crimson seedless" grapes (280 g), "Seascape" strawberries (300 g) and "Hayward" kiwifruit (300 g) were consumed 1 wk apart by seven healthy women, 18–40 y old, and blood samples were drawn over the next 5 h.

Sample collection and laboratory methods. Blood was drawn by venipuncture into evacuated tubes with EDTA and heparin anticoagulants. The blood was immediately processed to separate red cells in a refrigerated centrifuge and aliquots of the plasma were frozen at −70°C for later analysis. An aliquot of EDTA plasma was treated with an equal volume of meta-phosphoric acid (100 g/L) and the protein-free supernatant frozen at −70°C for later determination of ascorbic and uric acids by HPLC with electrochemical detection (8). A portion of the heparinized plasma was treated with an equal volume of 0.5 mol/L perchloric acid and the protein-free supernatant was frozen at −70°C for later determination of antioxidant capacity.

Urine was collected in tared containers and the total weight of the urine collection was recorded. After mixing of the urine, dipstick urinalysis was completed (Ames Diagnostics, Indianapolis IN), and aliquots of the urine were frozen at −20°C for later determination of creatinine and urate.

Urine urate was determined by a colorimetric peroxidase/uricase procedure utilizing a 3,5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system applied to a centrifugal analyzer (9). Plasma and urine creatinine were determined by the Jaffe picric acid spectrophotometric method adapted to the Hitachi 902 automated analyzer (Roche Diagnostic, Indianapolis, IN). Antioxidant capacities were determined in the cherries and blood plasma by the hydrophilic and lipophilic oxygen radical absorbing capacity (ORAC) methods (10,11), the spectrophotometric radical cation decolorization method utilizing 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonate), also known as the Trolox equivalent antioxidant capacity (TEAC) method (12) and the ferric reducing ability of plasma (FRAP) method (13).

Plasma C-reactive protein (CRP), TNF-α and NO were measured as inflammatory markers. CRP was measured by a high sensitivity enzyme immunoassay (Biocheck, Burlingame, CA). Plasma TNF-α was measured using the Quantikine high sensitivity TNF-α colorimetric immunoassay kit, and plasma NO was measured using the Total Nitric Oxide colorimetric assay kit (R&D Systems, Minneapolis MN).

Polyphenols were extracted from 5 g of frozen cherries with 10 mL of water/methanol (2:8) containing 2 mmol/L NaF. After filtration through a 0.45-μm filter, the supernatant was analyzed for polyphenols by HPLC with UV diode-array detection (14). Total phenolics were determined in the polyphenol extract using a modified spectrophotometric Folin-Ciocalteu method (15). Ascorbic and dehydroascorbic acids were extracted from cherries with a citric acid buffer and determined by HPLC with UV diode-array detection (16).

Statistical analysis. Data were analyzed using Instat 3.0 (GraphPad Software, San Diego CA). Descriptive statistics were computed for study measures at baseline (predose) and the three postdose time points. Urinary urate was normalized to creatinine concentrations. Repeated measures ANOVA with Student-Newman-Keuls adjustment for multiple comparisons was used to determine the effect of the cherry dose over the entire study period, from baseline to 5 h postdose. Paired t tests or Wilcoxon signed-ranks tests were used to compare specific postdose values with baseline, including Bonferroni adjustment of probability levels for multiple comparisons. Results are presented as mean ± SEM. Differences were considered significant for the two-tailed P-value < 0.05.

RESULTS

Hydroxycinnamates comprised the largest class of phenolics in the cherries ingested, representing ~42% of the total phenolics of 163 mg/100 g (**Table 1**). The next largest fraction of phenolics was anthocyanins at 23%. Only dehydroascorbic acid (DHA), the oxidized form of vitamin C, was detected in the cherries. No HPLC peaks were detected for the reduced form, ascorbic acid (AA).

Plasma urate decreased significantly over the 5-h period after cherry consumption (ANOVA), and the concentration at 5 h postdose was significantly lower than at baseline (**Table 2**). Urinary urate, expressed per mmol creatinine, increased over the 5 h postdose and at each postdose sampling time compared with baseline. After similar doses of grapes, strawberries or kiwifruit, plasma urate concentrations did not change over time, nor were any postdose concentrations significantly lower than those at baseline.

Among inflammatory biomarkers, plasma TNF-α did not change after cherry consumption. Plasma CRP and NO did not decrease over the entire 5-h period (ANOVA), but both were marginally decreased ($P < 0.1$) at 3 h postdose compared with baseline, by Wilcoxon's signed-ranks test (CRP) and paired t test (NO) (Table 2). The plasma CRP data were not normally distributed because values for one subject were well above the normal range of 0.1–8.2 mg/L (17). The subject's baseline value of 22.9 mg/L was 2.7 SD above the mean and declined 44% to 12.9 mg/L at 3 h postdose.

Among antioxidant capacity measures, the hydrophilic ORAC and TEAC measures did not differ after cherry consumption, lipophilic ORAC increased and FRAP decreased at all postdose sampling times. Plasma ascorbic acid increased significantly at 1.5 and 3 h postdose. Plasma creatinine decreased significantly at 1.5 and 5 h postdose, and marginally ($P = 0.07$) at 3 h postdose. Plasma albumin was unchanged throughout.

DISCUSSION

Fruits contain a wide variety of phytochemicals that are known or suspected to provide health benefits, yet most phytochemicals in fruits have not been studied for their effect on

TABLE 1

Concentrations of antioxidant substances in Bing sweet cherries[1,2]

Substance measured	Concentration
	mg/100 g fresh weight
Hydroxycinnamates	67.9 ± 4.0
Procyanidins	21.7 ± 2.5
Flavanols	34.8 ± 3.9
Anthocyanins	38.0 ± 3.6
Total phenolics	163 ± 9
Vitamin C[3]	18.4 ± 2.3
Antioxidant capacity (TEAC), *µmol TE/100 g*	211 ± 8
Antioxidant capacity (FRAP), *µmol/100 g*	170 ± 2

[1] Values are mean ± SEM, $n = 5$ batches of cherries.
[2] TEAC, Trolox equivalent antioxidant capacity; FRAP, ferric reducing ability of plasma.
[3] As dehydroascorbic acid.

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TABLE 2

Plasma and urine biomarkers in healthy women before and after cherry consumption[1,2,3]

Biomarker	Baseline	1.5 h	3 h	5 h
Plasma urate, *μmol/L*				
Cherries†	214 ± 13	221 ± 22	203 ± 13	183 ± 15*
Grapes	278 ± 25	263 ± 26	257 ± 23	260 ± 21
Strawberries	286 ± 25	280 ± 20	277 ± 25	262 ± 29
Kiwifruit	285 ± 28	256 ± 21	257 ± 23	281 ± 19
Urinary urate, *μmol/mmol creatinine*	202 ± 13	278 ± 29*	350 ± 33*	260 ± 17*
Plasma				
C-reactive protein, *mg/L*	4.29 ± 2.18	ND	3.07 ± 1.26	3.59 ± 1.59
Nitric oxide, *μmol/L*	37.4 ± 5.2	ND	31.1 ± 2.9	31.6 ± 2.1
ORAC (lipophilic),[4] *μmol TE/L*	531 ± 37	628 ± 37*	681 ± 24*	711 ± 27*
FRAP, *μmol/L*	454 ± 23	432 ± 21*	403 ± 14*	414 ± 21*
Ascorbic acid, *μmol/L*	65.4 ± 5.6	74.5 ± 5.6*	71.8 ± 6.0*	68.2 ± 5.2

[1] Values are means ± SEM, $n = 10$. * Different from baseline, $P < 0.05$. † Significant decrease over time, $P < 0.05$.
[2] Plasma urate concentrations of grapes, strawberries, and kiwifruit are for seven women in a separate but similar study (unpublished data) with the last time point at 4.5 h.
[3] Abbreviations: ND, no data; ORAC, oxygen radical absorbing capacity; FRAP, ferric reducing ability of plasma.
[4] Units are μmol Trolox equivalents/L.

human health. Polyphenolic flavonoids have been shown to provide antioxidant, anti-inflammatory, antithrombotic, and anticarcinogenic actions, which may reduce the risk of chronic diseases (18). Deeply colored cherries and berries contain a large amount of phenolic compounds, ~9 times the amount of vitamin C for the Bing sweet cherries ingested in the present study (Table 1). Cherries have a unique reputation for providing anti-gout and anti-inflammatory benefits; this is largely anecdotal and has not been confirmed in controlled nutrition studies. The present results support an anti-gout effect of cherries because the cherries provoked a significant decrease in plasma urate over 5 h postdose, whereas the other fruits produced no change (Table 2). Although the observed mean decrease (214 to 183 μmol/L or 14.5%) is within the lower range of normal (155–357 μmol/L) (17), it supports the claim that consumption of cherry products may benefit individuals who suffer from high levels of plasma urate and arthritic gout. By comparison, acute ingestion of milk proteins also lowered serum urate (19), whereas purine-rich foods (beef liver, haddock, soybeans) increased serum urate at 2–4 h postdose (20).

Data from the present study cannot definitively establish the mechanism whereby cherry consumption lowers plasma urate. Plasma urate is largely reabsorbed in the renal tubules after glomerular filtration, whereas plasma creatinine is cleared without reabsorption. The observed postdose increase in urinary urate per unit creatinine excretion and the decrease in plasma creatinine suggest that cherries may exert their urate-lowering effect by increasing the rate of renal glomerular filtration and/or reducing tubular reabsorption.

Biomarkers of the inflammatory response, plasma CRP, NO and TNF-α, were measured in the present study because of reports that consumption of cherries relieved the arthritic joint pain of gout (7), that anthocyanins and other phenolics inhibit NO and alter TNF-α production in activated macrophages (5,6), and that anthocyanins isolated from cherries inhibit the activity of the proinflammatory enzyme COX II in vitro (2,3). The trend toward decreased plasma CRP and NO 3 h after cherry consumption is consistent with previous in vitro evidence (2–5) and suggests that compounds in cherries may inhibit inflammatory pathways in vivo. Decreased in vivo NO production may reduce the progression of inflammatory arthritis because increased 3-nitrotyrosine concentrations found in rheumatoid arthritis patients have been cited as evidence that the NO radical plays a role in arthritic joint damage (21).

The constancy of plasma albumin values throughout indicates that postdose changes in urate and inflammatory markers were not due to changes in hemodilution or hydration status. That measures of plasma water-soluble antioxidant capacity were unchanged (hydrophilic ORAC and TEAC) or decreased (FRAP) after cherry consumption is not surprising because urate is the largest single contributor to plasma hydrophilic antioxidant capacity (22), and its concentration decreased after cherry consumption. The finding that lipophilic ORAC increased substantially is unexpected because most antioxidant compounds in cherries, e.g., phenolic glycosides and vitamin C are water-soluble compounds. However, reports that cherry and berry phenolics show strong antioxidant activity in phospholipid liposomes (1,2,23) indicate that these compounds are active in lipophilic as well as hydrophilic systems. Support for this includes findings that the less polar anthocyanin aglycone, cyanidin, has stronger antioxidant activity than its glycosides (2), and that flavonoids alter membrane fluidity by partitioning into the lipophilic core of model membranes (24). Melatonin may have contributed to the increase in lipophilic ORAC because it is more active than vitamin E as a lipophilic antioxidant (25) and occurs in "Balaton" and "Montmorency" cherries in amounts of 0.2 and 1.3 mg/100 g, respectively (26).

The finding that the cherries ingested contained only the oxidized form of vitamin C, dehydroascorbic acid (DHA), and not the reduced form, ascorbic acid (AA), is unusual among fruits. The average DHA content of 12 fresh fruits as a percentage of total vitamin C (AA + DHA) was 15.2%, with a range of 6–48% (27). Because care was taken to keep the cherries frozen until analysis, and acidic extraction buffers were used to preserve any AA, it is not likely that the DHA finding is due to artifactual oxidation of the vitamin C. Indeed, a small amount of AA standard added to a cherry homogenate was converted to DHA. This is likely due to oxidation of the AA in the cherries by phenoxyl semiquinone radicals and/or *o*-quinone metabolites formed from the reaction of polyphenols with polyphenol oxidases (28). That plasma AA increased significantly after consumption of cherries that contain only DHA (Table 2) argues against recent claims that DHA in fruits is poorly available as vitamin C (29,30) and is consistent

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with evidence that DHA is absorbed in the small intestine and recycled into AA in vivo (31).

In conclusion, the decrease in plasma urate after cherry consumption supports the anti-gout reputation of cherries. The trend toward decreased plasma concentrations of the inflammatory markers CRP and NO adds to the in vitro evidence that compounds in cherries may inhibit inflammatory pathways. Further research is required to determine the potential of cherry and polyphenol consumption for inhibiting the inflammatory cascade and for improving the condition of individuals who are at risk or suffer from gout and arthritis.

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