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Cranberry Quercetin-3-Galactoside in Postprandial Human Plasma

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Abstract

Flavonoid glycoside bioavailability may be important for determining the health benefits of cranberry consumption. Human quercetin-3-galactoside bioavailability of raw cranberries (RC; 55g), sweetened dried cranberries (SDC; 40g) and sweetened dried cranberries containing less sugar (SDCLS; 40g) was measured using a liquid chromatography-mass spectrometry system before consumption and for 240 minutes postprandially. Peak plasma concentrations (ng/ml) for RV, SDC and SDCLS were 15.5 ± 3.0, 14.0 ± 2.9, and 9.8 ± 2.9, with observed peak times of 60, 60 and 120 minutes respectively. This study suggests that quercetin-3-galactoside in the blood stream could be used as a phenolic marker of cranberry consumption.

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Introduction

Phenolic compounds unique to cranberry juice[1] and sweetened dried cranberries[2] may be beneficial for reducing urinary tract infections. Cranberries may also reduce cardiovascular disease risk by providing antioxidant protection[3-5], improving the plasma lipid profile[6,7], and promoting vasodilation[8,9]. Our recent metabolic study in mice also suggests that cranberry flavonoids may be responsible for adiponectin-AMPK dependent beneficial health effects[10]. Diabetics tend to have low fruit and vegetable consumption, and interventions that increase fruit consumption may protect tehm from cardiovascular disease risk[11]. Sweetened dried cranberries (SDC) and SDC with less sugar (SDCLS) produced using polydextrose to reduce the sugar and caloric content may have a glycemic profile making them useful for improving fruit consumption by type 2 diabetics[12].

Sweetened dried cranberries, SDCLS, and raw cranberries (RC) have phenolic profiles that are rich in anthocyanidins, A-type PACs (e.g. epicatechin dimers and trimers) and several flavonols especially quercetin-3-galactoside (Q-3-gal) [5,12-14]. However, using an in situ rat perfusion model, Arts et al (2004) conclude that quercetin-3-galactoside is not bioavailable[15], however, Liburt et al (2010) identified quercetin-3-galactoside and other cranberrty flavonol glycosides in plasma and urine in an equine study during a 12 hour period after ingestion[16]. The appearance of plasma phenolic acids, flavonols, anthocyanidins and proanthocyanins following consumption of cranberry juice in plasma and urine has been characterized using LCMSMS[17], although they did not report the presence of Q-3-gal in plasma or urine.

Glycosidic flavonoids such as Q-3-gal could be responsible for cranberry health benefits. The presence of Q-3-gal in human blood could be an excellent marker for validating cranberry consumption. This study represents a follow-up of our previous study of glycemic response in human type 2 diabetics who consumed SDC, low calorie-SDC, raw cranberries or white bread in single-cross-over fashion[12]. The present study determined that following cranberry consumption, Q-3-gal is effectively absorbed into the blood plasma reaching peak concentrations within 90 minutes or less.

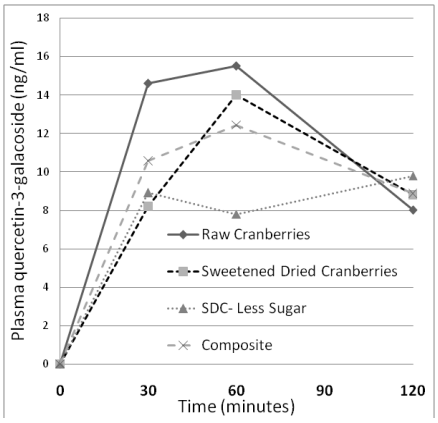

Figure 1: Appearance of quercetin-3-galactoside in the plasma of human diabetics following consumption of raw cranberries (55g; 21 Cal), sweetened dried cranberries (40g, 138 Cal), or low sugar sweetened dried cranberries (40g; 113 Cal).

Methods

Subjects and study design

The subject population and study design has been described in greater detail previously[12]. The Winona State University Institutional Review Board approved the study prior to recruitment of non-insulin dependent type-2 diabetics (six female and seven male), 61.6 ± 2.3 yrs old, with HbA1C values of 6.25 ± 0.16 and a BMI of 33.25 ± 1.22. In single cross-over fashion on alternate weeks subjects received RC (55g; 21 Cal; 1 g fiber) that were stored frozen and thawed just before use; SDC (40g, 138 Cal; 2.1g fiber), SDC with less added sugar (SDC-LS; 40g; 113 Cal; 1.8g fiber + 10g polydextrose) or white bread as a control (57g; 160 Cal; 1 g fiber; Sara Lee Soft & Smooth Classic White, Downers Grove, Illinois, USA) Nutritional qualities of the four treatments are described elsewhere[12] and summarized in Table 1. The cranberry products used in this study were obtained from Ocean Spray Inc. Lakeville-Middleboro, MA, USA.

Prior to laboratory presentation, subjects completed a 10-hour fast from all food and beverages except water prior to each weekly laboratory visit. Upon arrival in the lab subjects sat quietly for 30 minutes prior to study initiation before a baseline-fasting venous blood sample was collected (0-minutes). Treatments were then consumed within five minutes and additional blood collections repeated 30, 60 and 120 minutes. Subjects returned to the laboratory on a weekly basis until each subject had completed each of the four treatments. Subjects agreed to consume no cranberry or blueberry containing products, fruits, onions, or chocolate to reduce the effect of background dietary phenolics during the course of the study.

Collected plasma samples were frozen at -80°C until analysis in single blind fashion on a single day using freshly thawed samples. Separation and quantification of flavonols were performed on a Dionex UltiMate® 3000 LC system coupled with an Applied Biosystems API 3000TM triple quad LC-MS/MS mass spectrometer under following conditions. Ion source: ESI in negative and positive ion mode; m/z range: 50 to 1200; source temperature: 350°C. Mobile phase: Eluent A: 90 % water + 10 % methanol + 0.001 % formic acid; Eluent B: 20 % water + 20 % methanol + 60 % ACN + 0.001 % formic acid. Flow rate: 0.25 ml min^{-1} and injection volume: 5µl for LC-MS-MS. Column: Pursuit C18 (3 µm particle size; 150 mm length x 3.0 mm ID; *Varian*). LC-MS-MS in MRM mode were used to identify and quantify the plasma flavonols.

Statistical analysis

Data was analyzed using the SASS program (SAS Inst. Inc., Cary, N.C., U.S.A): Plasma Q-3-gal (ng/ml) is expressed as least squared means ± standard error. Predicted peak plasma Q-3-gal times for each subject and the trapezoidal method was used to calculate area under the curve (AUC) values. A repeated measures analysis of variance was used to identify significant differences among treatments, among time points, and the interaction between treatment and time. Significant differences among least squares means ($P<0.05$) were determined using the Tukey-Kramer adjustment.

Results and Discussion

Cranberry Q-3-gal was absorbed from the gut and appeared in blood plasma 30 minute post-prandially in all subjects with a calculated plasma peak occurring at one hour for raw cranberries and SDCs and at one and half hours for SDCs containing less sugar (Table 2). Peak plasma concentrations of Q-3-gal were 15.5 ± 3.0, 14.0 ± 2.9, and 9.8 ± 2.9 ng/ml for raw cranberries, SDC and SDC-LS. Plasma Q-3-gal was statistically higher than baseline at 30, 60 and 120 minutes, butno statistically significant differences between the three cranberry treatments were observed at 30, 60 or 120 minutes. The Q-3-gal AUC for SDC-LS was less than that of raw cranberries or SDC, although the difference was not statically significant. SDC actually contained less G-3-gal than SDC-LS (Wilson et al 2010)[12], this

Table 1: Nutritional content of glycemic challenges

	White Bread	Raw Cranberry	Sweetened Dried Cranberry	SDC-Less Sugar
Serving Size	57g	55g	40g	40g
Total (Cal)	160.0	21.0	138.0	113.2
Protein (Cal)	20.0	0.6	0.4	0.6
Fat (Cal)	20.0	0.4	2.7	2.5
Carbohydrates (Cal)	120.0	20.0	134.9	100.0
Polydextrose (g or Cal)	0	0	0	10.1
Total Dietary Fiber (g)	1.0	1.2	2.2	11.3

Table 2: Pharmacokinetics of cranberry plasma quercetin-3-galactosidefollowing consumption by human type 2 diabetics(Least Mean Squares ± Standard Error).

	Plasma Quercetin-3-Galactoside (ng/ml)				Calculated Peak Time	Area Under Curve
Treatment	0- minutes	30- minutes	60- minutes	120- minutes	minutes	
Raw Cranberries	0.0 ± 3.0	14.6 ± 3.0*	15.5 ± 3.0*	8.0 ± 3.1*	57 ± 13	1388 ± 280
Sweetened Dried Cranberries	0.0 ± 2.9	8.2 ± 3.1*	14.0 ± 2.9*	8.8 ± 2.9*	60 ± 13	1254 ± 280
SDC-less sugar	0 ± 2.8	8.9 ± 3.0*	7.8 ± 2.8*	9.8 ± 2.9*	88 ± 12	792 ± 281
White Bread	0	0	0	0	0	0
*Statistically significant vs 0-minutes within group ($P<0.05$).						

difference was not statistically significant. SDC-LS contained polydextrose fiber which could have slowed gastric emptying and contributed to the slight difference[18].

Quercetin and its glycosides can reach the blood stream following absorption in the intestine[19]. The low levels of appearance may be due to the fact that quercetin glucosides are largely hydrolyzed prior to absorption in the intestine[20] and/or their bioavailability is low[15]. However, the presence of Q-3-gal in plasma in this study suggests there is some level and mechanism for intestinal absorption. Even low levels of absorption could contribute to the beneficial health effects of cranberry consumption. In the present study the peak plasma Q-3-gal concentration of 8.2 to 15.5 ng/ml were comparable with that associated with robust in vitro protection of LDL from oxidation in our previous study of cranberry products[5]. We have also observed that Q-3-gal accumulates in mouse tissues at levels far higher than that observe in the plasma[10] .

Conclusions

This pilot study is the first human metabolic study to demonstrate that cranberry Q-3-gal can be absorbed from the human gut with a peak plasma concentration reached in 30 to 60 minutes postprandially. Because CBJ remains the more popular form of cranberry consumption, future studies are needed to characterize cranberry juice Q-3-gal pharmacokinetics to better understand how this glycosidic flavonoid may be responsible for the human health benefits of cranberry product consumption.

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