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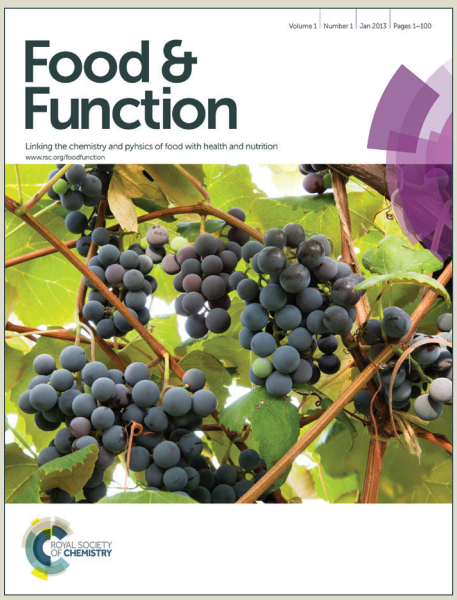

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A randomized, double-blind, placebo-controlled trial to assess the bacterial anti-adhesion effects of cranberry extract beverages

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In this study, we examined the *ex vivo* urinary anti-adhesion activity of low-calorie cranberry extract beverages in both a pilot study (n=10) and a randomized, double-blind, placebo controlled clinical trial (n=59). In the pilot study, subjects consumed a cranberry extract beverage (CEB) or a cranberry extract and juice beverage (CEJB), compared to placebo. Both cranberry beverages utilized a standardized cranberry extract powder at a level with an equivalency to low-calorie cranberry juice cocktail (LCJC) on a PAC content basis. Clean-catch urine samples collected at baseline and post intervention were tested for anti-adhesion activity utilizing a mannose-resistant human red blood cell hemagglutination assay specific for P-fimbriated *E. coli*. Results from the pilot study indicated that *ex vivo* anti-adhesion activity for both cranberry treatments were higher ($p<0.05$) than placebo. In the clinical trial, we compared CEJB to LCJC and a placebo beverage. Post-consumption urine from both cranberry treatment groups showed significantly higher ($p<0.05$) anti-adhesion activity compared to placebo. There were no differences observed in anti-adhesion activity between CJEB and LCJC, indicating similar bioactivity. Therefore, acute beverage consumption of cranberry extract and/or juice provides *ex vivo* anti-adhesion activity, which may help to improve urinary tract health.

Introduction

Urinary tract infections (UTIs) are the second most common bacterial infection in the United States[1] and are becoming progressively harder to treat due to antibiotic resistance. Nutritional approaches to maintaining urinary tract health, such as the American cranberry (*Vaccinium macrocarpon*), continue to be recommended for UTI prophylaxis in women with recurrent UTIs.[2-4] Recently, cranberry efficacy has come under question due to inconsistent clinical trial results.[5] These observed inconsistencies may be due to various factors, such as subject population, high drop-out rates resulting in underpowered studies, treatment compliance, lack of cranberry product standardization of bioactive components, and dosing. Although inconsistencies have been observed in some clinical trial results, mechanistic and clinical research continues to favorably demonstrate cranberry's bioactivity.[6-10]

The health promoting properties of cranberries linked to urinary tract health are thought to be due to their rich content of bioactive polyphenols, specifically A-type proanthocyanidins (PACs). The mechanism by which cranberries are efficacious in preventing UTIs has yielded many hypotheses, including the prevention of bacterial adhesion in the bladder [11] and invasion in the gut.[8]

The initiation of infection in the bladder or gut is mediated by bacterial adhesions, or fimbriae, that enable bacterial attachment to the epithelial cell lining.[12] To date, there is substantial *in vitro* and *ex vivo* evidence indicating cranberry bioactives, including PACs, stimulate an activity that results in the inhibition of bacteria, particularly P-fimbriated *E. coli*, from adhering to the globoseries glycoprotein receptor on epithelial cells or red blood cell analogues.[11, 13-16] By blocking the attachment of *E. coli* to these target cells, infection may be prevented. Recent research has shown that cranberry bioactives may contribute to the anti-adhesion activity mechanism by, not only disrupting pedestal formation in bacteria,[17] but also decreasing bacterial motility,[18] fimbriae number and distribution.[19]

Due to the challenges described earlier, there is heightened interest in utilizing standardized powders, extracts and beverages in an effort to consistently deliver a specific amount of bioactive compounds to clinical trial subjects, thereby

providing efficacious doses for UTI and anti-adhesion outcomes.[3, 5, 20, 21]

The objective of this study was to compare the anti-adhesion activity of urine from healthy individuals after the consumption of cranberry beverages prepared from different combinations of cranberry juice and a standardized cranberry powder, first in a pilot study, then followed by a clinical trial. We hypothesized that cranberry beverages used in the pilot and clinical trials would provide comparable *ex vivo* anti-adhesion effects in the urine due to their similar PAC content.

Experimental

The pilot study and clinical trial were approved by the Institutional Review Boards at Rutgers University (New Brunswick, NJ) and Quorum Review (Seattle, WA), respectively. All subjects provided written informed consent prior to enrollment.

Study subjects

Healthy male and female subjects were recruited to participate in the pilot study (n=10) and clinical trial (n=60). Both studies excluded subjects with a history of current or recurrent urinary tract infections, urinary disorders, antibiotic use within the last 6 months, or history of adverse reaction to cranberry products. All subjects were asked to refrain from cranberry, blueberry and other *Vaccinium* products 1 week prior to study initiation and throughout its completion.

Study beverages

In order to evaluate the effect of cranberry juice and cranberry extract on anti-adhesion activity, four different beverages were formulated: 1) Cranberry Extract Beverage (CEB), 2) Cranberry Extract and Juice Beverage (CEJB), 3) Low-calorie Cranberry Juice Cocktail (LCJC) and 4) placebo beverage. The cranberry extract is a water-soluble, phenolic-rich extract of cranberry juice utilizing a proprietary resin separation process. The cranberry extract was standardized to 55% PAC content on a dry weight basis as analyzed by the DMAC method. All treatment beverages were designed to be low-calorie and contain similar PAC content (>80 mg PACs) by using cranberry juice, cranberry extract or a combination of both.

Study beverage analytical methods. PAC content was determined by using a modified 4-dimethylaminocinnamaldehyde colorimetric method (OSC-DMAC) using a a cranberry quality control reference.[22] Samples were separated by lipophilic Sephadex LH20 media (Sigma-Aldrich, St. Louis, MO, USA) in a poly prep chromatography column (Bio-Rad, Hercules, CA, USA) and eluted with 70% acetone. DMAC reagent was added to samples and absorbance was measured at 640 nm.

Anthocyanins were analyzed by HPLC (Aligent 1100, Aligent Technologies, Inc., Santa Clara, CA, USA) and eluted through a 2.6 um C18 column (Kinetix XB-C18, Phenomenex, Torrance, CA, USA) under gradient conditions using deionized water, phosphoric acid and acetonitrile. Absorbance was read at 520 nm (diode array detector G1315A, Agilent Technologies, Inc.) and peaks were compared to commercially available cyanidin-3-galactoside, cyanidin-3-glucoside, and peonidin-3-glucoside standards (ChromaDex, Irvine, CA USA).[22]

Vitamin C concentrations were determined by an idiometric titration method[23] and total phenolics were determined by Folin-Ciocalteu colorimetric method.[24]

Pilot study

The acute effect of cranberry beverage consumption on urinary bacterial anti-adhesion activity was initially assessed by a double-blind, randomized, placebo-controlled, cross over pilot study, with a 1-wk washout period between treatments. On the mornings of intervention, subjects reported to the Marucci Center for Blueberry and Cranberry Research at Rutgers University in a fasting state for baseline urine collection (0 h) and were randomly assigned to 1) CEB, 2) CEJB or 3) placebo to take home and consume that evening. Subjects were given a 450 ml beverage to consume between 17:00 and 20:00 h. The next day, subjects returned to the Center in a fasting state and consumed the same beverage administered the previous day. Unpublished studies from our laboratory suggest that two acute doses (evening and morning) result in higher anti-adhesion activity compared to a single, acute dose. Clean-catch urine samples were collected post beverage consumption in the following time intervals: 0-3, 3-6, 6-9 and 24 h.

Clinical trial

Sixty subjects were recruited to participate in a randomized, double-blind, placebo-controlled, crossover clinical trial in order to confirm anti-adhesion results from the pilot study. A 1-wk washout period was used between treatments. Baseline (0 h) urine samples were collected at each visit prior to beverage consumption. Subjects were then randomly assigned to 1) CEJB, 2) LCJC or 3) placebo, and instructed to consume the beverage that evening at home. The next day, at t=0 h, the same study beverage administered the previous evening was consumed within 30 min. Standardized, low-polyphenol meals were provided and subjects were asked to consume approximately 80-85 mL of water/h, plus an additional 500 mL of water with the lunch meal. Clean-catch urine samples were collected for 6 h post-beverage consumption based on increased anti-adhesion activity of samples collected at those time points from the pilot study. Pooled urine samples (0-6 h) were used to assess anti-adhesion activity.

Hemagglutination assay

Anti-adhesion activity was tested by measuring the ability of urine samples to suppress agglutination of human red blood cells (HRBC; A1, Rh+) following incubation with uropathogenic *E. coli*. The *E. coli* strain used in this assay was isolated from the urine of a patient diagnosed with pyelonephritis and expressed mannose resistant/P agglutinins.[25]

In order to enhance the production of P fimbriae, bacteria was subcultured on colonization factor agar plates, and grown overnight at 37 °C. The bacteria was next harvested by centrifugation, washed once, and then suspended in phosphate-buffered saline solution (PBS; $5x10^8$ bacteria/mL) at pH 7.0. A 30 µL urine sample was incubated with 10 µL of bacterial suspension on a 24-well polystyrene plate and placed on a rotary shaker for 10 min at ambient temperature. HRBCs were diluted in PBS (3% v/v) and 10 µL was added to the urine-bacteria suspensions. The samples were incubated at 21°C for 20 min on a rotary shaker and evaluated microscopically for their ability to prevent agglutination. Results were reported on an ordinal scale with anti-adhesion activity as follows: 0 = 0% adhesion inhibition; 1 = 50% inhibition; and 2 = 100% inhibition. Please note that the low anti-adhesion detection limit does not allow for serial dilutions to be done on the urines, therefore, the percentages are approximate and the results are qualitative, with activity being present or not present. Negative controls included wells containing bacteria + PBS, HRBC + PBS, bacteria + urine, and HRBC + urine. A well containing bacteria + HRBC served as a positive control for agglutination.

Statistical analysis

The Wilcoxon signed rank test was used to compare the mean post consumption responses between treatments in the pilot trial ($p<0.05$). The sample size calculation for the clinical trial was determined by the McNemar Normal Approximation Test. In order to detect a 20% difference between treatments, 45 subjects were needed to complete the study. Significant differences among treatment means (post – pre consumption anti-adhesion activity scores) were analyzed by the non-parametric Friedman test. Pairwise comparisons were made using the Fisher LSD procedure ($p<0.05$). Differences between post treatment responses and subject demographics were analysed using the two-sample Wilcoxon test ($p<0.05$).

Results

No adverse events (AEs) were observed in the pilot study. Two subjects experienced AEs defined as digestive issues in the clinical trial. These reports were categorized as either "unlikely" or "possibly related" to consumption of the study beverages. No changes in protocol treatment were made and both subjects completed the study without further incidence. Compliance was reported at 100% for both studies based on empty bottle return and subject questionnaires regarding beverage consumption.

Study beverage analyticals

Nutritional and analytical data for study beverages are shown in Table 1. All beverages were designed to deliver a similar PAC content per serving size, with the exception of LCJC. In the clinical trial, we chose to replace the CEB with LCJC for the purpose of a positive control, as it reliably indicates urinary anti-adhesion activity. [15, 26] Although the CEB had slightly higher anti-adhesion activity in the pilot trial, the CJEB was administered in the clinical trial so as to determine if it would be at least as bioactive as the positive control (LCJC). The beverage volumes differed based on the recommended serving sizes set forth by the Food and Drug Administration via the nutritional facts panel. The LCJC calorie content was higher as it contained 27% cranberry juice, whereas the CJEB contained a maximum of 7% cranberry juice.

Pilot Study

Urinary anti-adhesion activity is shown in Figure 1. No anti-adhesion activity was reported in 0 hour baseline urine samples. The mean anti-adhesion activity was significantly higher ($p<0.05$) in the CEB and CEJB compared to placebo. Both cranberry beverages demonstrated an overall similar effect ($p = 0.63$), with activity peaking between 0-6 hours post consumption and lasting up to 9 hours. Anti-adhesion activity decreased to near baseline values at 24 hours post consumption. No anti-adhesion activity was reported for the placebo beverage at any time post-beverage consumption.

Clinical Trial

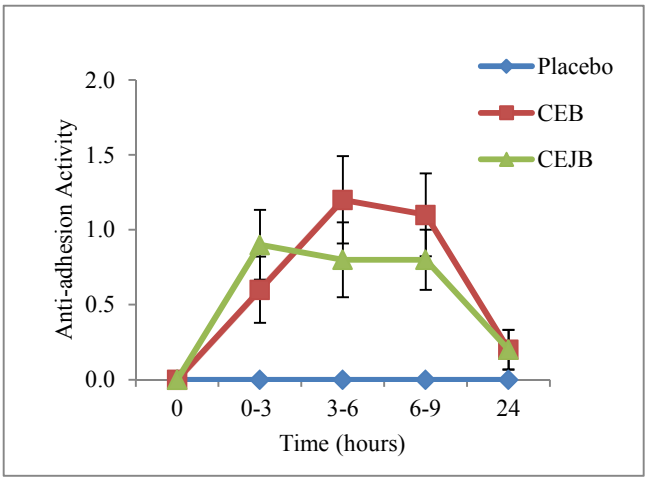
Sixty subjects were initially enrolled and 59 subjects completed the 3 arm cross-over trial. One subject withdrew consent before

Table 1 Analytical characterization of cranberry beverages.

	Pilot study			Clinical trial		
	CEJB	CEB	Placebo	CEJB	LCJC	Placebo
Serving size (mL)	450	450	450	450	240	450
Calories (kcal)	10	10	10	10	40	10
Fat (g)	0	0	0	0	0	0
Carbohydrate (g)	2.5	2.5	2.5	2.5	10	2.5
Protein (g)	0	0	0	0	0	0
Cranberry juice (%)	7	0	0	7	27	0
Cranberry extract	yes	yes	no	yes	no	no
PACs (OSC-DMAC; mg)	86	93	1	117	134	n/d
Total phenolics (mg)	76	72	14	103	215	9
Total anthocyanins (mg)	5.7	4.4	n/d	6.8	4.6	n/d
Vitamin C (mg)	n/d	n/d	n/d	n/d	75	n/d

nt, not tested
n/d, not detected

Fig 1 Pilot study urinary anti-adhesion activity.
Average ± SEM (n=10). The average post consumption anti-adhesion activity for CEB and CEJB was significantly greater ($p<0.05$) compared to placebo.



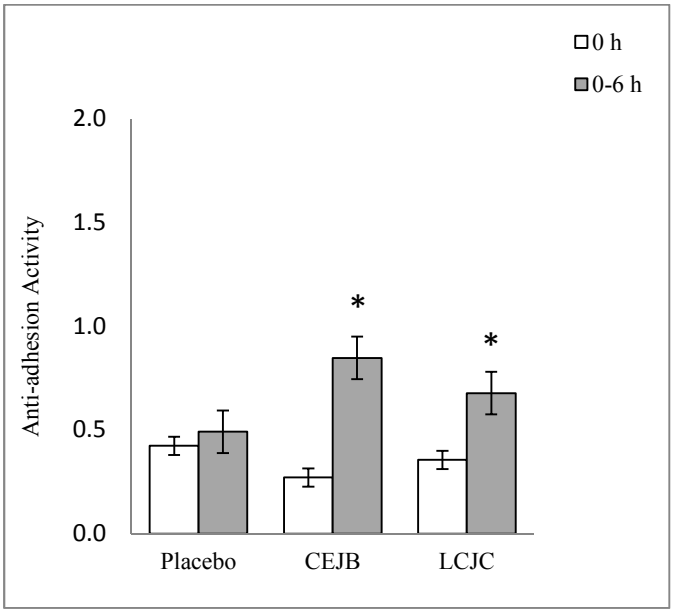
completion of the trial. Subject demographics are displayed in Table 2. The majority of subjects were middle-aged (44.4 ± 11.8 y), white (non-hispanic) females (66.7%), classified as overweight (BMI=27.6 ± 5.2).

The effects of cranberry beverage consumption on urinary anti-adhesion activity are shown in Figure 2. Baseline anti-adhesion activity ranged from 0.27 (LCJC) to 0.45 (placebo), but were not significantly different. Compared to placebo (0.49), 0-6 h post consumption urines from the CEJB (0.85) and LCJC (0.68) groups had significantly higher anti-adhesion activity ($p<0.05$). Although the CEJB demonstrated a higher anti-adhesion activity post-consumption compared to LCJC, there were no significant differences between these treatments ($p=0.14$) indicating a similar effect. There were no differences observed in anti-adhesion responses among beverages between male and female subjects ($p>0.05$).

Table 2 Clinical trial subject demographics.

Age (y)	44.4 ± 11.8
BMI	27.6 ± 5.2
Sex, Female [n (%)]	40 (66.6)
Male	20 (33.3)
Ethnicity, Non-Hispanic [n (%)]	56 (93.3)
Hispanic	4 (6.7)
Race, White (non-Hispanic) [n (%)]	45 (75)
Black/African American	12 (20)
Asian/Pacific Islander	3 (5)
Current smoker [n (%)]	2 (3.3)
Alcohol consumption [n (%)]	43 (71.7)
Average number drinks/week (drinkers only)	2.0 ± 1.4

Fig 2 Clinical trial urinary anti-adhesion activity.
Average ± SEM (n=59).



* Statistically different at 0-6 h time point compared to placebo beverage ($p<0.05$).

Discussion

This study was designed to investigate the *ex vivo* anti-adhesion effects of cranberry beverages containing different combinations of juice and a standardized extract. The anti-adhesion activity of cranberry beverages used in both trials showed higher activity compared to placebo, indicating that beverages made from cranberry extract and/or juice provide equivalent urinary anti-adhesion properties. Other studies investigating the effect of cranberry juice or extracts on urinary anti-adhesion activity demonstrated similar results.[25, 26]

Interestingly, the cranberry beverages used in the pilot trial demonstrated similar or slightly higher *ex vivo* anti-adhesion activity compared to the clinical trial beverages, although the average PAC content was approximately 30% less. Within each trial, the cranberry beverages were formulated to contain an equivalent amount of PACs. Results suggest that, regardless of the source of PACs (juice or extract) or the PAC content (86-134 mg), the different beverages demonstrated similar anti-adhesion activity. This suggests that 86 mg of cranberry PACs is efficacious for anti-adhesion activity, and that a higher PAC content does not necessarily increase the anti-adhesion response at the concentrations tested in this study.

Based on the OSC-DMAC method, the cranberry extract beverages used in this study were designed to contain a similar amount of PACs as a traditional serving of cranberry juice cocktail (240 mL). At the time the pilot trial was conducted, the BL-DMAC PAC method was not yet published,[27] therefore the pilot trial beverages were not tested using the new methodology. BL-DMAC results for the clinical trial beverages

were inconsistent with published values. These results may, in part, be due to the large inter-lab variation reported (16.9%),[27] or due to the structural heterogeneity of cranberry PACs, resulting in different reaction kinetics compared to the A2 standard.[28] Despite the observed inconsistencies of PAC content as analysed by the BL-DMAC method, the CEJB and LCJC beverages from the clinical trial had similar anti-adhesion bioactivies, indicating that the subjects' PAC dosing was suitable for at least 6 h of anti-adhesion activity. Another notable difference between the CEJB and LCJC was the vitamin C content: LCJC contained vitamin C, but CEJB did not, suggesting that vitamin C does not play a role in urinary tract health as no statistical differences were observed between these beverages.

Although anti-adhesion is widely described in the literature as the mechanism of action for urinary tract health, based mainly on *in vitro* studies investigating type A PACs,[29] relatively few double-blind, placebo-controlled, *ex vivo* studies investigating anti-adhesion activity have been published.[25, 26, 30] Di Martino[26] studied the effects of cranberry juice consumption on bacterial adherence to T24 uroepithelial cells and found that urine from cranberry juice consumers inhibited the adhesion of *E. coli* with either type 1 or P-fimbriated strains. Interestingly, cranberry has typically been reported to help prevent adhesion of P-fimbriated *E. coli*, which is associated with pyelonephritis, a more severe form of UTI that progresses to the kidneys. The reported significant increase in anti-adhesion activity in type 1 *E. coli* strains from the cranberry group does not appear to be associated with fructose, a known inhibitor of type 1 fimbriae,[14] since both placebo and cranberry beverages contained similar amounts of fructose. Additionally, fructose metabolism occurs in the liver, where it is mostly metabolized into glucose, lactate or lipids,[31] resulting in little to no urinary fructose. Taken together, cranberry compounds or metabolites may be able to inhibit type 1 fimbriae *in vivo*. This finding may be of significance because the majority of symptomatic UTIs are caused by *E. coli* with type 1 fimbriae.[32] Current research indicates type 1 fimbriaed *E. coli* have a high binding affinity for certain carbohydrates,[33] and they may help to prevent bacterial invasion.[34] In this study, we did not investigate the effect of cranberry consumption on type 1 fimbrial adhesion.

Another study investigated the anti-adhesion properties from subjects who consumed cranberry extract capsules (1 or 2 servings of reconstituted cranberry extract), or mineral water by using the hemaggutination assay or a T24 human bladder epithelial cell binding assay.[35] No significant differences were observed in urinary anti-adhesion as assessed by the hemagglutination assay, but the binding assay revealed a reduction in bacterial adhesion in the cranberry groups. P-fimbriated *E. coli*, with the PapGII adhesion, tended to demonstrate more anti-adhesion activity compared to other phenotypes, including the P-fimbriated PapGI adhesin. This indicates that cranberry's activity against bacterial adhesion may depend on the expressed fimbrial allele. Additionally, no PAC or other analytical details regarding the cranberry drink or capsules were reported, making it hard to draw conclusions based on the purported active compound concentrations.

Other investigations are contributing to elucidate the optimal cranberry PAC dosing for urinary tract health benefits. Howell[25] found dose-dependent anti-adhesion activity in subjects supplemented with 18, 36 and 72 mg PACs from cranberry extract (analyzed by BL-DMAC). The 72 mg dose was considered to be optimal because the effects lasted for up to 24 hours post-consumption, whereas the 18 and 36 mg doses provided significantly less activity at that time point. Our pilot trial did not show activity at the 24 h time point, perhaps indicating that the PAC dosage was too low to achieve sustained activity. Alternatively, the 18 and 36 mg PAC doses may help prevent bacterial adhesion, especially if consumed twice per day.

A-type PACs have recently been reported in the urine of healthy older adults after cranberry juice consumption.[36] The authors reported a urinary T_{max} of 11 h and C_{max} of 24 ng/mg creatinine for A2 PACs. Our pilot trial showed that maximal anti-adhesion activity was reached between 0-6 h, which corresponded to the T_{max} for phenolic acids and anthocyanins. Further work is necessary in order to determine the function of A2 PACs in the urine. Meanwhile, hypothesis are being generated regarding how cranberry may work in the gut to prevent bacterial invasion[8] or stimulate an immune activity/compound that could lead to anti-adhesion activity in the bladder.[37]

PACs continue to be a major cranberry bioactive for urinary tract health, but only recently have concentrations in test products been reported in the literature for clinical trials. The lack of PAC dosing information from former trials makes it challenging to compare results and draw valid conclusions. Future research with cranberry products should include a detailed analytical description of the test beverages, powders or extracts. The utilization of a standardized cranberry extract will help provide a consistent dose of bioactive cranberry compounds.

Conclusions

Cranberry extract beverages and low calorie cranberry juice cocktail provide *ex vivo* urinary anti-adhesion activity for up to 6 h post consumption, indicating that daily cranberry intake may help deliver urinary tract health benefits.

Notes and references

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Consumption of cranberry extract and/or juice beverages provides *ex vivo* bacterial anti-adhesion.