

Cranberry Juice and Urinary Tract Infection

R. Raz,^{1,2} B. Chazan,¹ and M. Dan³

¹Infectious Diseases Unit, Haemek Medical Center, Afula, ²Rappaport School of Medicine, Technion, Haifa, and ³Infectious Diseases Unit, Wolfson Medical Center, Holon, Israel

Cranberries have long been the focus of interest for their beneficial effects in preventing urinary tract infections (UTIs). Cranberries contain 2 compounds with antiadherence properties that prevent fimbriated *Escherichia coli* from adhering to uroepithelial cells in the urinary tract. Approximately 1 dozen clinical trials have been performed testing the effects of cranberries on the urinary tract. However, these trials suffer from a number of limitations. Most importantly, the trials have used a wide variety of cranberry products, such as cranberry juice concentrate, cranberry juice cocktail, and cranberry capsules, and they have used different dosing regimens. Further research is required to clarify unanswered questions regarding the role of cranberries in protecting against UTI in general and in women with anatomical abnormalities in particular.

In women with recurrent urinary tract infections (UTIs), long-term antimicrobial prophylaxis is indicated [1]. This method is effective but can cause adverse reactions and can increase emergence of antimicrobial resistance [2, 3]. Therefore, the need for alternative therapies for UTI prophylaxis is evident. Cranberries are one nonantibiotic alternative.

THE FRUIT

The scientific name for cranberry plant is *Vaccinium macrocarpon* [4]. Cranberries, blueberries, and Concord grapes are the only 3 fruits that are native to the United States and Canada. Most commercial farms today are located in northern United States, Massachusetts, and New Jersey and the Canadian provinces of Quebec and British Columbia [5]. Commercial harvests occur in September and October.

Cranberries contain >80% water and 10% carbohydrates [6]. Among other constituents are flavonoids, anthocyanins, catechin, triterpenoids, organic acids,

and a small amount of ascorbic acid. The major organic acids are citric, malic, and quinic acids, with small amounts of benzoic and glucuronic acids [7]. Anthocyanin pigments obtained from cranberry pulp are used for coloring applications [8]. Cranberries can be processed into fresh fruit, concentrate, sauce products, and juice drinks [5]. The single-strength juice is very acidic (pH, <2.5) and unpalatable. In 1930, cranberry juice cocktail, comprising a mixture of cranberry juice, sweetener, water, and added vitamin C, was introduced. The leading brand of cocktail contains 33% pure cranberry juice. Dried cranberry powder formulated in capsules or tablets is also available.

MECHANISTIC STUDIES: URINE ACIDIFICATION

Native Americans were the first to use cranberries for their medicinal properties [5]. Cranberries were used for a variety of complaints, including blood disorders, stomach ailments, liver problems, and fever. During the 1880s, German physicians observed that urinary excretion of hippuric acid increased after ingestion of cranberries. In 1914, Blatherwick [9] published an article showing that cranberries are rich in benzoic acid, which is then excreted in urine as hippuric acid. Therein followed a long period during which the usefulness of cranberry juice was thought to be based on the urinary excretion of hippuric acid, which is a bacteriostatic

Received 4 November 2003; accepted 12 January 2004; electronically published 26 April 2004.

Reprints or correspondence: Dr. Raul Raz, Infectious Diseases Unit, Haemek Medical Center, Afula, Israel (raz_r@clalit.org.il).

Clinical Infectious Diseases 2004;38:1413-9

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agent and has the potential to acidify urine [10]. In 1923, Blatherwick and Long [11] reported a reduction in urine pH level (6.4–4.5) with a concomitant increase in excretion of hippuric acid (0.77–4.74 g) after subjects ate 350 g of cooked cranberries [12]. In 1933, Fellers et al. [13] published results for 6 men who ingested 100–300 g of cranberries daily. They, too, showed an increase in acidity and excretion of organic acids (including hippuric acid) in urine. However, these authors concluded that an ordinary serving of 22–54 g of cranberries produced only a very slight increase in urine acidity [14].

Kinney and Blount [15] found that certain amounts of cranberry juice (450–720 mL daily) lowered urinary pH. Similarly, Jackson and Hicks [16] showed that 710 mL of cranberry juice (25% pure juice) lowered the urine pH of 21 elderly men. In contrast, Nahata et al. [17] reported that the addition of vitamin C to cranberry cocktail did not change urine pH. Notably, an early study by Bodel et al. [18] in 1959 found that, in 5 healthy subjects, 1200–1400 mL of cranberry juice cocktail slightly acidified urine and increased the amount of hippuric acid excreted in urine to 3–4 g. However, none of the urine samples from these patients was bacteriostatic against *Escherichia coli*. In addition, Bodel et al. [18] demonstrated that hippuric acid was bacteriostatic at a minimum concentration of 0.02 mmol/L at pH 5.0, and the antibiotic activity of hippuric acid decreased ~5-fold as the pH increased to 5.6. Bodel et al. [18] concluded that cranberry juice could not exert a bacteriostatic effect because it was not a rich enough source of hippuric acid, coupled with the fact that it did not lower urine pH sufficiently.

The validity of the conclusions of Bodel et al. [18] was subsequently confirmed by others. Today, it is known that the low amount of benzoic acid present in the fruit (<0.1% of weight), coupled with maximum tolerated amounts of cranberry juice (~4 L/d), rarely results in enough hippuric acid excretion necessary to achieve bacteriostatic urinary concentrations [19]. Ingestion of large amounts of cranberry juice is required to slightly reduce pH of urine and modestly increase hippuric acid excretion, changes that do not confer significant antibacterial activity to urine. If cranberry juice is a protective agent for the urinary tract, then another mechanism must be involved.

MECHANISTIC STUDIES: ANTIADHERENT PROPERTIES

Adherence of uropathogens to uroepithelial cells is the initial step in pathogenesis of UTI [20]. In 1984, Sobota [21] was first to suggest that “reported benefits derived from the use of cranberry juice may be related to its ability to inhibit bacterial adherence” (p. 1013). Sobota found that cranberry juice cocktail reduced adherence by >75% in >60% of 77 clinical isolates of *E. coli* recovered from patients with UTI. Fifteen of 22 subjects showed significant antiadherence activity in their urine 1–

3 h after drinking 15 oz (443.6 mL) of cranberry juice cocktail [22].

Since Sobota’s initial report, several studies have confirmed that the presumed efficacy of cranberry in preventing UTI is related to its antiadherent properties. It is now known that *E. coli*, the most common cause of UTI, have hairlike fimbria that protrude from their surface. The fimbriae produce 2 adhesins (mannose sensitive and mannose resistant) that attach to receptors on uroepithelial cells [23].

Zafiriri et al. [24] identified 2 compounds in cranberries that inhibit *E. coli* adhesins. One is fructose, which inhibits the mannose-sensitive fimbrial adhesins; the other is a high-molecular-weight compound that inhibits the mannose-resistant adhesins of uropathogenic *E. coli* [25]. Although all fruit juices contain fructose, only juices from *Vaccinium* berries (i.e., cranberries and blueberries) contain this second unique polymeric compound [26], which was later named “proanthocyanidin.” Interestingly, proanthocyanidin shows a very strong inhibitory activity against mannose-resistant adhesins produced by urinary isolates of *E. coli* [25] but shows only moderate antiadherent activity against fecal *E. coli* isolates [27].

The antiadhesive property of cranberries probably helps to prevent UTI in 2 ways: first, it directly prevents *E. coli* from adhering to uroepithelial cells; and second, it selects for less adherent bacterial strains in the stool. A recent study showed that regular consumption of cranberry juice was also effective in cases in patients with UTI caused by antibiotic-resistant bacteria [28]. Urine samples obtained from healthy volunteers who drank cranberry juice prevented uropathogenic *E. coli* isolates from adhering to isolated uroepithelial cells in bioassays. The antiadherent effect started within 2 h and persisted for up to 10 h after ingestion [29].

CLINICAL STUDIES

UTI prophylaxis. The first clinical study evaluating the effect of cranberry on urinary tract was published in 1966. Papas et al. [30] described the effect of cranberry juice in 60 patients with bacteriuria who received 480 mL of juice daily for 3 weeks. After therapy, 53% had a positive response and an additional 20% had a more modest benefit, but 6 weeks after stopping treatment, bacteriuria reappeared in most of the subjects.

Since the study of Papas et al. [30], about a dozen clinical trials evaluating various cranberry products have been performed. All these subsequent trials have studied the effect of cranberry in *preventing* urinary tract symptoms. In some of them, the primary parameter tested was UTI; in other studies, bacteriuria was the primary end point. These trials have evaluated various patient populations, including sexually active adult women, elderly or pediatric patients, and patients with

different medical conditions. Table 1 summarizes the relevant prospective clinical studies conducted with cranberry products.

Kontiokari et al. [32], Stothers [31], and Walker et al. [35] published randomized studies that examined adult women. In the study by Kontiokari et al. [32], which was an open, randomized, controlled trial, 150 women were divided into 3 groups: one group drank 50 mL a day of cranberry-lingonberry juice concentrate containing 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate (lingonberry is another fruit of the *Vaccinium* genus); another group drank 100 mL of a lactobacillus drink; and a third group received no intervention. After 6 months' treatment, 16% of the cranberry group, 39% of the lactobacillus group, and 36% of the control group had experienced ≥ 1 recurrence of UTI. This translates to a 20% reduction in absolute risk for the cranberry group. Interestingly, even though the cranberry group stopped their treatment after 6 months (because the manufacturer stopped producing the juice), the percentage of women who experienced recurrence at 12 months was still significantly lower in the cranberry group, implying a residual effect supporting the hypothesis that cranberry selects for less adherent bacterial strains.

Stothers [31] performed a randomized, placebo-controlled, double-blind study. A total of 150 women with previous UTI were divided into 3 groups: persons who received placebo juice and placebo tablets, persons who received cranberry juice and placebo tablets, and persons who received placebo juice and cranberry tablets. Juice was 250 mL of pure unsweetened cranberry juice taken 3 times daily, and tablets contained 1:30 parts concentrated juice taken twice daily. After 1 year, results showed that 32% of placebo recipients had experienced ≥ 1 UTI during the year, compared with 20% in the cranberry juice group and 18% in the cranberry tablet group. The absolute risk reduction for cranberry products was 12%–14%, similar to the findings of Kontiokari et al. [32].

A smaller study by Walker et al. [35] adds further support to the above findings. In this study, which followed a double-blind crossover design, 19 women with recurrent UTI were provided either cranberry capsule (with 400 mg cranberry solids) or a placebo capsule for 3 months. Patients then switched to an alternative therapy for the next 3 months. Although only 10 patients finished the entire course of treatment, results favored the use of cranberry. Of 21 episodes of UTI, 6 occurred in the cranberry group and 15 occurred in the placebo group.

Overall, these 3 studies show that use of cranberry is effective, at least statistically, for prophylaxis of UTI in adult women with recurrent UTI. It should be noted, however, that none of these 3 studies used the popular commercial brand of cranberry juice cocktail.

Of interest too is an epidemiological study [40] that evaluated the relationship between health/sexual behavior and first-time UTI in sexually active women. The study found that regular

drinking of cranberry juice was associated with decreased risk of UTI. Although this study was retrospective and examined first-time UTI and not recurrent UTI, it adds to the notion that young, sexually active women constitute a population that may benefit from cranberry products.

Two studies have evaluated the use of cranberries in elderly women, but unlike the above 3 prospective studies, these trials chose bacteriuria as their primary parameter. Avorn et al. [38] conducted a large randomized, double-blind study in which 153 asymptomatic elderly women received 300 mL per day of cranberry juice cocktail or placebo. Urine samples were obtained at baseline and at 1-month intervals for 6 months, and tested for bacteriuria and pyuria. At baseline, bacteriuria and pyuria were present in $\sim 20\%$ of samples in both the cranberry group and the placebo group. At the 1-month mark, there was no difference in the percentage of urine samples with bacteriuria and pyuria in the 2 groups ($\sim 25\%$). However, from the 2-month mark on, there was a statistically significant difference between groups favoring the cranberry group. At the end of the 6-month study, bacteriuria and pyuria were present in 28% of urine samples from the cranberry group. The chances of having bacteriuria with pyuria were 42% less in the cranberry group than in the control group. These authors concluded that ingesting cranberry beverages reduced the frequency of bacteriuria with pyuria in older women, although they noted that, in elderly women, asymptomatic bacteriuria does not usually require treatment. Nevertheless, in their study, there were 16 instances of antibiotic use for UTI in the control group versus 8 in the cranberry group.

Haverkorn and Mandigers [39] also evaluated the use of cranberry by elderly patients, but they used a nonblinded crossover design. Men and women in a nursing department of a general hospital were provided 15 mL cranberry juice (type not detailed) mixed with water twice daily or the same amount of water daily. After 4 weeks, the regimens were reversed. Only 17 patients stayed in the department long enough to complete both 4-week periods. Bacteriuria was observed in 3 patients during the entire time course and in neither period in 7 patients. In the additional 7 patients, there were fewer instances of bacteriuria during the cranberry period than during the control period, supporting a moderately preventive role for cranberry juice.

Two additional but not randomized trials involving elderly patients were conducted. In a Danish trial [33], the incidence of UTI was compared in 2 geriatric departments. Patients were offered cranberry juice in one department and the usual mixed berry juice in the other. The results showed that cranberry juice did not influence incidence of UTI. In another study, 538 nursing home residents were provided either 220 mL of cranberry juice or 6 capsules containing cranberry extract daily [36]. Compared with historical controls, the incidence of UTI was

Table 1. Summary of prospective studies evaluating prophylaxis of urinary tract infection (UTI) on bacteriuria.

Study	Year of study	Method	Population	Intervention	Outcome
Stothers et al. [31]	2002	Randomized, placebo-controlled, double-blind	150 women with previous UTI	Placebo juice/tablets vs. placebo juice/cranberry tablets vs. cranberry juice/placebo tablets; tablets were given b.i.d., and juice was given as 250 mL pure unsweetened product, t.i.d.; 1 year trial	A significant reduction in UTI: 18% for cranberry tablets vs. 20% for cranberry juice vs. 32% for placebo
Kontokari et al. [32]	2001	Open, randomized	150 women with previous UTI	50 mL cranberry-lingonberry concentrate vs. 100 mL lactobacillus drink vs. no intervention for 6 months	A significant reduction in UTI: 16% for cranberry vs. 39% for lactobacillus and 36% for no intervention
Kirchhoff et al. [33]	2001	Nonrandomized, controlled	2 geriatric units	Cranberry juice vs. usual mixed berry juice; mean stay, 4 weeks	No effect on UTI
Schlager [34]	1999	Randomized, double-blind, cross-over	15 children with neurogenic bladder	300 mL cranberry concentrate vs. placebo, each for 3 months	No benefit in preventing UTI or bacteriuria
Walker et al. [35]	1997	Randomized, double blind, cross-over	19 women with recurrent UTI (10 finished the study)	Cranberry capsule with 400 mg of cranberry solids vs. placebo, each for 3 months	Cranberry effective in preventing UTI: of 21 UTIs, 6 UTIs were in the cranberry group and 15 were in the placebo group
Dignam et al. [36]	1997	Nonrandomized, historical controls	538 nursing home residents	220 mL of cranberry juice or 6 capsules with cranberry extract per day	Compared with historical controls, incidence of UTI significantly reduced, from 27 cases per month to 20 cases per month
Foda [37]	1995	Randomized, single-blind, cross-over	40 children with neurogenic bladder (21 finished)	Cranberry cocktail, 15 mL/kg/d, vs. water, each for 6 months	No benefit in preventing UTI or bacteriuria
Avorn [38]	1994	Quasi randomized placebo-controlled, double-blind	153 elderly women	300 mL of cranberry juice cocktail vs. placebo for 6 months	Bacteriuria and pyuria were significantly reduced: 28% of samples from placebo recipients vs. 15% of samples from cranberry patients
Haverkorn and Mandigers [39]	1994	Quasi randomized cross-over	38 elderly men and women (17 finished the study)	15 mL of cranberry juice mixed with water b.i.d. vs. water, each for 4 weeks	7 of 17 patients had reduction of bacteriuria during cranberry period
Papas et al. [30]	1966	Nonrandomized	60 patients (73% women) with bacteriuria	480 mL of cranberry juice for 21 days	Positive response in 53% of cases and modest response in 20%

significantly reduced, from 27 cases a month to 20 cases a month.

Two studies have evaluated the potential of cranberry in pediatric patients with medical conditions predisposing them to UTI. These trials did not show any benefit of cranberry for prevention of UTI or bacteriuria. In the crossover, placebo-controlled, double-blind study of Schlager et al. [34], 300 mL of cranberry concentrate provided for 3 months did not have any benefit when provided to 15 children with neurogenic bladder receiving intermittent catheterization. Frequency of bacteriuria was 75% during both placebo and cranberry periods, and the number of UTIs was not significantly different either. In a similar patient population, Foda et al. [37] administered water or cranberry cocktail (15 mL/kg/d) to 40 children for 6 months, and the reverse for an additional 6 months. Only 21 patients finished the study. Cranberry had no effect on the frequency of UTI or bacteriuria. Two additional studies were performed in adult patients, but neither study evaluated clinical outcomes. In 8 adult patients with multiple sclerosis randomized to receive 20 days' therapy, cranberry increased acidity of urine, and in 15 patients with spinal cord injury, cranberry reduced bacterial biofilm load in the bladder [41, 42].

Jepson et al. [43] reviewed in the Cochrane Library all randomized or quasi-randomized controlled studies for the prevention of UTI with cranberry juice. Until 2000, only 5 trials met all the criteria adopted for evaluation. (These 5 trials are discussed above.) The conclusion of the review was that because of the small number and poor quality of trials, there is insufficient evidence to show the effectiveness of cranberry juice for prevention of UTI. However, the Cochrane reviewer did not include the latest 2 studies by Stothers [31] and Kontiokari et al. [32]. Both studies were randomized and large, and they found that women with previous UTIs who took cranberry products as prophylaxis experienced fewer recurrent UTI. On the basis of these 2 trials, a recent evidence-based answer published in the *Journal of Family Practice* [44] suggested that a trial of cranberry juice (3 glasses daily) was reasonable for women with recurrent UTI who are being considered for antibiotic prophylaxis. The author of the "answer" also noted that "no national practice guidelines have recommended cranberry juice as a preventive strategy for recurrent UTI" [44, p. 155]. However, educational brochures published by the National Kidney Foundation contain statements supporting the possible use of cranberry juice in helping to prevent the development of UTI [45].

Evidence regarding the role of cranberries for treating, rather than preventing, UTI is almost nonexistent. The same Cochrane reviewer who evaluated UTI prevention also systematically reviewed the literature for trials that evaluated use of cranberries for treating UTI [46]. As mentioned above, Papas et al. [30] studied patients with bacteriuria, but this was not a randomized

trial. Another nonrandomized study [47] found decreased leukocyte counts in urine samples obtained from handicapped children (most with indwelling catheters) who drank cranberry juice. This, too, was not a randomized trial.

UTI treatment. The Cochrane reviewers concluded that randomized studies assessing effectiveness of cranberry juice for treatment of UTI have not yet been conducted. Therefore, at present, there is no evidence to suggest that cranberry juice or other cranberry products are effective for treatment of UTI.

The safety of cranberries is considered to be excellent. Some patients may experience a slight laxative effect, depending on the amount ingested [9, 15, 16]. Nevertheless, at least one author has warned that ingesting a large amount of cranberries over a long duration may increase risk of some types of urinary stones in high-risk patients because of the increased urinary excretion of oxalate and slight urinary acidification [48].

CONCLUSION AND DIRECTIONS FOR THE FUTURE

Results of clinical studies suggest a possible clinical benefit of cranberry juice in preventing UTI in some populations. The strongest evidence available is for sexually active adult women with previous UTI. In this population, cranberry appears to be effective in the prophylaxis of recurrent UTI, although standard juice cocktail was not specifically tested. In elderly patients, cranberry consumption reduces the incidence of bacteriuria, although this is often not treated with antibiotics. In contrast, none of the randomized clinical studies that evaluated patients at high risk of UTI—for example, those with neurogenic bladder—found cranberries to have a beneficial effect.

In the population that benefits most from the prophylactic effect of cranberry intake (sexually active women with recurrent UTI), trial results repeatedly show an ~50% reduction in disease morbidity. From a clinical point of view, this is quite a modest benefit, considering the accompanying burden of long-term daily intake of the compound. Not less significant is the inconvenience associated with the amount of juice required to assure continuous availability and the need to carry a daily supply if twice- or thrice-daily dosing is needed to work, business, or vacation travel. If one considers the understandably high rate of dropouts, the 50% efficacy rate may drop to a remarkably lower effectiveness.

Furthermore, results of the reviewed studies should not be viewed as conclusive because many of the trials suffer from various limitations, including lack of randomization, no or improper blinding, small number of subjects, short trial duration, large number of dropouts, and no reported intent-to-treat analysis [43]. Perhaps the single most consistent limitation of these trials is the lack of uniformity regarding the intervention, including the particular cranberry product evaluated (juice,

sweetened cocktail, or capsules/tablets), concentration, dosing regimen, and duration of the intervention, which greatly differed from study to study [43, 49]. Further properly designed trials addressing these issues are needed [38].

Future trials should also assess patient acceptability of treatment. Some studies have indicated that the taste and caloric load of cranberry juice cocktail is unacceptable to many patients, especially over the long term [15, 40, 44]. Capsules of cranberry concentrate could be a better-tolerated alternative [31]. Cost is another issue that affects patient uptake of treatment, because cranberry products are not currently covered by health insurance [44, 49]. In the single trial that evaluated the issue of cost, Stothers [31] found that cranberry tablets are more cost-effective than organic cranberry juice.

Therefore, the potential of cranberry products to act as a nonantibiotic alternative for preventing UTI, thereby reducing the total amount of antibiotics prescribed for UTI, could have great public health significance. In November 2002, the National Center for Complementary and Alternative Medicine, a branch of the US National Institutes of Health, announced an initiative to fund research on the role of cranberry in promoting urinary tract health [50]. As antimicrobial resistance continues to climb, the time is ripe to recognize the importance of further cranberry research.

Acknowledgments

We thank Frances Nachmani, Hana Edelstein, and Miriam Ben-Yashar for their assistance in data collection and processing.

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