REVIEW

Cranberries and lower urinary tract infection prevention

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Lower urinary tract infections are very common diseases. Recurrent urinary tract infections remain challenging to treat because the main treatment option is long-term antibiotic prophylaxis; however, this poses a risk for the emergence of bacterial resistance. Some options to avoid this risk are available, including the use of cranberry products. This article reviews the key methods in using cranberries as a preventive measure for lower urinary tract infections, including *in vitro* studies and clinical trials.

KEYWORDS: Urinary Tract Infection; Cranberry; Cystitis; Prevention.

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INTRODUCTION

Lower urinary tract infections (UTIs) are very common and have been estimated to occur in at least 60% of women at some stage during their lives (1-3). Because of their high prevalence, UTIs are a public health concern, having an estimated cost of diagnosis and treatment exceeding US $25 billion over a 20-year period (approximately US $2.47 billion in the year 2000) (1,4). UTIs are approximately 50-fold more common in adult females than males because women have shorter urethras that allow bacteria to ascend into the bladder. The first step in an infection is the colonization of the periurethral tissues, followed by the passage of bacteria through the urethra. The second step is the adherence of bacteria to the urethra and bladder walls and proliferation (5,6).

UTIs are caused by microorganisms, mainly Gram-negative bacteria. Indeed, *Escherichia coli* (*E. coli*) account for most cases (2,3,5). Treatment usually involves antibiotics, and recurrence is a major concern (7). The risk factors that predispose women to recurrent UTIs include sexual intercourse, the use of contraception, antimicrobial resistance, menopause, genetics and bacterial virulence (2).

Focusing on UTI prevention became a major goal because of their recurrent nature, increasing antimicrobial resistance and medical costs (8). The current management of recurrent UTIs involves either repeated courses of antibiotics or low-dose, long-term antibiotic prophylaxis (2). Although effective, these treatments have side effects, such as fungal super-infection (oral or vaginal thrush) and gastrointestinal infections, notably *Clostridium difficile* (9).

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CRANBERRIES

Cranberry is a term derived from the contraction of ''crane berry.'' This name is derived from the nickname of the bilberry flower, which, when it withers, is similar in appearance to the head and neck of the sand crane, a bird that often feeds on the berries of this plant (10). The cranberry is part of the Ericaceae family and naturally grows in acidic swamps full of peat moss in humid forests (11).

The American cranberry (*Vaccinium macrocarpon*) was historically used by North American Indians to treat UTIs (10). There are other relatives of the cranberry family (European cranberry – *V. oxycoccus*; lingonberry – *V. vitis-idaea*; blueberry – *V. myrtillus*) that share some of the cranberry's basic components, but research evidence for a role in prevention is limited (12,13).

Cranberries are composed of water (88%), organic acids (including salicylate), fructose, vitamin C (high levels, i.e., 200 mg/kg of fresh berries), flavonoids, anthocyanidins, catechins, and triterpinoids (10). The chemical constituents responsible for their taste are the iridoid glycosides. The anthocyanidins and proanthocyanidins (PAC) are tannins (stable polyphenols) found only in vaccinium berries and function as a natural plant defense system against microbes (10,14).

Common preparations with cranberries include fresh, whole berries, gelatinized products, juices (usually 10-25% pure juice) and capsules (10-16). Pure juice is too acidic (pH<2.5) and unpalatable, even with sweeteners (10). Despite cranberry presentation, it is generally recommended to consume cranberries just prior or two hours after meals; it is also important to drink lots of water, mainly after preparations from dehydrated juices (11). Cranberry juice, predominantly in the form of a juice cocktail drink with approximately 25% cranberry juice, has been the traditional choice of most women seeking to prevent UTIs.

MECHANISM OF ACTION

One important property of *E. coli* is its adherence to the host tissue. The main protein structure related to this phenomenon is the adhesin protein, and its name is based on its shape: pili or fimbriae (2). Bacterial adhesion is accomplished by the binding of lectins exposed on the cell surfaces of these fimbriae to complementary carbohydrates on the host tissues. Pili are small filaments that enable bacteria to adhere to the host tissue; these proteins can be either mannose-resistant or mannose-sensitive. The mannose-sensitive pili, called type 1 pili, permit bacterial adhesion to the urothelium; the fimbriae are inhibited by fructose (present in grapes, oranges, and cranberries). The more virulent strains of *E. coli*, isolated from patients with pyelonephritis and recurrent UTIs, have other types of fimbriae, notably p-fimbriae (pyelonephritis fimbriae). These fimbriae bind to glycosphingolipids of the lipid double membrane of renal cells, which precedes renal parenchymal invasion (6).

The current hypothesis is that cranberries work principally by preventing the adhesion of type 1 and p-fimbriae strains (particularly from *E. coli*) to the urothelium (17-20). Without adhesion, the bacteria cannot infect the mucosal surface. *In vitro*, this adhesion is mediated by two components of cranberries: fructose, which inhibits the adherence of type 1 fimbriae (18,21), and PAC, which inhibits the adherence of p-fimbriae (22,23). The binding of the proteinaceous bacterial fimbrial tips to mucosal surfaces on the uroepithelium occurs as a specific receptor–ligand association favored by hydrophobic interactions. One possible mechanism is that the cranberry compounds, acting as receptor analogs, competitively inhibit the adhesion of *E. coli* to host cells by binding to the fimbrial tips. The *in vitro* anti-adherence effect of cranberries is dose-dependent (15,19,24,25).

Another mechanism of cranberry activity is the *in vitro* reduction in the expression of p-fimbriae in *E. coli* by changing the conformation of surface molecules (19,26). Lavigne et al. (24) demonstrated that cranberries can decrease the virulence of *E. coli* strains. Furthermore, they described a reduction in adherence activity even in strains with no expression of type 1 fimbriae or p-fimbriae, which adhere via an adhesin, suggesting that cranberry extracts affect a variety of fimbriae. In a recent study, pH-neutralized cranberry juice induced conformational changes in the surface macromolecules of p-fimbriated *E. coli* by specifically reducing fimbrial length and density (26).

Despite data suggesting that PACs are the active moieties in cranberries, there is doubt regarding the route from ingestion through urinary excretion. Some authors believe that intact PACs may not be active *in vivo* because they are too large to be absorbed as intact molecules in the gastrointestinal tract (27,28). However, PAC dimers and trimers are permeable in the Caco-2 human intestinal cell line, suggesting that they could be absorbed intact (29). There are few studies assessing PAC excretion in humans (30,31). Valentova et al. (32) measured low levels of anthocyanins and PAC oligomers in urine after the consumption of 1200 mg of dried cranberry juice. Experimental studies concerning human anthocyanins absorption after cranberry juice consumption demonstrated that only 0.078 to 5% of the anthocyanins are excreted in the urine (31,33). Peak urinary anthocyanidin concentration is observed 3-6 hours after intake, and urinary excretion is nearly complete within the first 12 hours (31). Another possibility is that PAC (or its metabolites) could be active in the colon and the urinary tract (18). They could bind to uropathogenic rectal *E. coli* isolates, thereby rendering them anti-adherent prior to their possible introduction into the urinary tract. Indeed, they could alter the bacterial selection pressure in the colon to favor nonadherent strains (30).

Most studies have focused on uropathogenic *E. coli* type 1 and p-fimbriated *E. coli*, but there are many *in vitro* studies showing an inhibition of adherence for *Proteus spp.*, *P. aeruginosa*, *E. faecalis*, *S. aureus*, *S. typhimurium* and *K. pneumoniae* (10,34,35). Even multi-drug resistant strains of *E.coli* exhibited inhibition of adherence to uroepithelial cells in the presence of proanthocyanidin (36).

There are many *in vitro* studies (15,16,19,24,25,32,35) confirming the anti-adherence activity of cranberries (Table 1). The biosafety of cranberries has been tested, and no biochemical or hematological alterations were identified. Tao et al. (37) demonstrated that cranberry juice could decrease *E. coli* adhesion up to 8 hours after consumption.

Concomitant use of cranberries with antibiotics has been tested. Li et al. (38) performed a study on β-lactam antibiotic (i.e., amoxicillin and cefaclor) absorption when administered with cranberry juice and reported a modest delay in absorption; however, total absorption was not affected; this delay was deemed not clinically significant. It is also important to know that the anti-adherence activity associated with cranberry consumption is not related to antibiotic sensitivity or resistance (16).

Despite all of these data, there is still no clear understanding of how cranberry PAC is absorbed, metabolized and excreted in urine to result in the protective action against bacterial adherence.

CLINICAL TRIALS

Cranberries have been tested for their clinical relevance in many different conditions. They have been evaluated in the treatment of UTIs but were deemed ineffective (2,7,14,24). Cranberries were also studied for UTI prophylaxis chiefly in women, but also in children and men; additionally, they have been studied in conditions such as neurogenic bladder and pregnancy, as summarized in Table 2 (12,39-52). Most clinical interest in the use of cranberries is for cystitis prevention. In the 2008 Cochrane Database of Systematic Reviews, there were ten randomized trials regarding UTI prevention on a total of 1,049 patients. They concluded that there is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly, and only, for women with recurrent UTIs (53). Limitations included the dose, type of drug administration (juice or capsules), treatment duration, and type of subjects.

For UTI prevention in young women, there are three randomized studies (cranberry versus placebo) in women with recurrent UTIs. Walker et al. (39) determined incidences of UTIs of 2.4 subjects/year in the cranberry arm and 6.0 subjects/year in the placebo arm ($p<0.0005$). Stothers et al. (40) tested both cranberry juice and tablets versus placebo in women aged 21 to 72 years old and found that 32% of the placebo group contracted a UTI, whereas 20% of the cranberry juice group ($p<0.05$) and 18% of the tablets group ($p<0.05$) contracted UTIs. He also estimated the annual cost of juice and tablets to be US $1,400 and US $624, respectively; the average cost-effectiveness ratios for tablets

Table 1 - *In vitro* activity of cranberries against bacteria.

Study	N	Study design	Cranberry preparation	Micro-organism	Results
Pinzon-Arango et al., 2009	-	*In vitro* bacteria cultured in medium and human uroepithelial cell culture	PAC of 0, 64, 128 and 345.8 μg/ml	*E.coli*	*E. coli* cultured in the presence of PAC inhibited adhesion from 50.2 to 7.9 bacteria/cell ($p<0.01$); dose-dependent effect.
Lee et al., 2010	Phase 1, N = 20 (16 women, 4 men); phase 2 (7 women, 2 men) N = 9.	*In vitro* urine activity after cranberry consumption in volunteers	275 mg of whole, dry cranberries and 25 mg of concentrated, dry cranberries	*E. coli, K. pneumonia and C. albicans*	Phase 1: anti-adhesion activity in 35% (*E. coli*), 65% (*K. pneumoniae*) and 45% (*C. albicans)*. Phase 2: anti-adhesion activity in 23% (*E. coli*), 33% (c. albicans) and 67% (*K. pneumoniae)*.
Lavigne et al., 2007	N = 8 females	*In vitro* urine activity after cranberry consumption in volunteers with crossover	36 mg cranberry capsules of; daily dosage was 36 or 108 mg or placebo	*E. coli*	Dose-dependent effect on anti-adhesion activity ($p<0.001$). Virulence reduction when *E. coli* tested against worms ($p<0.00001$).
Gupta et al., 2007		*In vitro* anti-adhesion activity against bladder and vaginal epithelial cells	Cranberry capsule with 2.7 mg of PAC diluted from 0 to 75 μg/ml	*E. coli*	Dose-dependent effect on anti-adhesion activity of PAC against *E. coli* from 6.9 to 2.2 and 1.6 bacteria/cell following PAC at 0, 25 and 50 μg/ml, respectively ($p<0.001$).
Howell et al., 2010	N = 32 females	Multicentric, randomized, double-blind *in vitro* urine activity after cranberry consumption in volunteers	Cranberry capsule of 0, 18, 36 or 72 mg of PAC	*E. coli*	Dose-dependent effect of anti-adhesion activity increasing with the amount of PAC. Virulence was also reduced with PAC in a dose-dependent fashion.
Valentova et al., 2007	N = 65 females	Double-blind, placebo-controlled *in vitro* urine. Group I (n = 23) placebo; group II (n = 20) 400 mg; group III (n = 22) 1200 mg	400 mg or 1200 mg per day of dried cranberry juice	*S. aureus, E. faecalis, E. coli, P. aeruginosa, E. faecium and K. pneumoniae*	Anti-adhesion activity in a dose-dependent fashion ($p<0.05$); highest activity observed against *P. aeruginosa*.
Di Martino et al., 2006	N = 20 (10 males, 10 females)	Double-blind, randomized, placebo-controlled *in vitro* urine activity after cranberry consumption in volunteers	250 or 750 ml of 27% cranberry juice	*E. coli*	Dose-dependent decreases in bacterial adhesion to human epithelial cell line of 45% and 62% for 250 and 750 ml of cranberry juice, respectively ($p<0.05$), independent of antibiotic resistance.

and juice were US $1,890 and US $3,333, respectively, per UTI prevented.

However, Barbosa-Cesnik et al. (41), using a double-blind, placebo-controlled trial, reported a UTI recurrence of 19.3% in individuals consuming 8 oz. of 27% cranberry juice daily versus 14.6% for placebo, with no significant difference between the groups ($p = 0.21$). Kontiokari et al. (12) used a cranberry-lingonberry (CB) juice versus *Lactobacillus GG* versus control (no treatment) and measured a risk reduction of 20% when the CB group was compared to the control group. After 12 months, 24%, 43% and 38%, of the CB, *Lactobacillus GG* and control groups, respectively, had experienced at least 1 UTI.

Elderly men and women have been evaluated for UTI prevention using cranberries in several trials. McMurdo et al. (42) studied 376 hospitalized patients over 60 years old in two groups: cranberry juice versus placebo in a 24-day trial. Of the patients in the placebo group, 7.4% developed symptomatic UTIs, and 3.7% in the cranberry group developed a UTI (p = not significant). In a six month trial, Avorn et al. (43) compared cranberry juice versus placebo and found that there was a 4% bacteriuria and pyuria presence concurrent with UTI symptoms in the cranberry group (n = 473) versus 7% in the placebo group (n = 498) (p = not significant). Therefore, the evidence to recommend cranberries for UTI prevention in the elderly is inconclusive.

To evaluate UTIs and lower urinary tract symptoms in male and female patients undergoing radiotherapy treatment for bladder or cervical cancer, cranberry juice was administered twice daily for six weeks in a randomized, double-blind, placebo-controlled trial. There was no statistical difference between the groups for the incidence of UTIs (44.1% for cranberry and 38.3% for placebo, $p = 0.267$); however, possible explanations for this result could be the small number of patients and poor compliance (54).

Cranberries have been compared with trimethoprim for UTI prevention in a randomized, controlled study in women older than 45 (44). The six-month risk of developing a UTI while consuming cranberries was 60% greater than in women on low-dose trimethoprim; however, this result did not reach statistical significance.

One study evaluated the use of cranberry juice to prevent UTIs during pregnancy (45). Women less than 16 weeks pregnant were randomized into three groups: one consumed cranberries three times daily (n = 58), another consumed cranberries only in the morning and then a placebo (n = 67) and the third group consumed the placebo three times daily (n = 63). There were four UTIs and 23 cases

Table 2 - Clinical trials of cranberry products for UTI prevention in different populations.

Study	N	Study design	Treatment	Results
Walker et al., 1997	19 young women with recurrent UTIs	Double-blind, randomized, placebo-controlled, crossover trial	400 mg of cranberry capsules	Withdrawal rate of 47.4%. UTI incidences were 2.4/subject-year-cranberry and 6.0/subject-year-placebo ($p<0.005$).
Stothers, 2002	150 women with recurrent UTIs	Double-blind, randomized, placebo-controlled	250 ml pure cranberry juice or concentrated cranberry tablets	UTIs were 72% (placebo), 30% (juice; $p<0.05$) and 39% (tablets; $p<0.05$).
Barbosa-Cesnik, 2010	319 young women with previous UTIs	Double-blind, randomized, placebo-controlled	8 oz. of 27% cranberry juice	Recurrence rates of UTIs were 19.3% for cranberry treatment and 14.6% for placebo ($p=0.21$).
Kontiokari et al., 2001	150 young women with previous UTIs	Double-blind, randomized, placebo-controlled	50 ml of cranberry-lingonberry juice (7.5 g of cranberries); *Lactobacillus GG* 100 ml/day; or controls,	20% reduction in UTIs in cranberry group. Recurrence rate of UTIs lower in cranberry group (at six months, $p=0.014$ and at 12 months, $p=0.052$).
McMurdo et al., 2005	376 hospitalized patients older than 60 years	Double-blind, randomized, placebo-controlled	150 ml of cranberry juice (25%) and placebo	Withdrawal rate of 31%. Symptomatic UTI incidences of 7.4% with placebo and 3.7% with cranberry ($p=$ no significance).
Avorn et al., 1994	153 elderly women	Double-blind, randomized, placebo-controlled	300 ml/day of cranberry juice and placebo	Bacteriuria in 28.1% in placebo group and 15% in cranberry group (no significance). OR of 0.42 for bacteriuria in cranberry.
McMurdo et al., 2009	137 women aged >45 years with recurrent UTIs	Double-blind, randomized controlled trial	500 mg of cranberry extract or 100 mg of trimethoprim	25 UTIs in the cranberry group and 14 in the trimethoprim group; relative risk 1.616, $p=0.084$.
Wing et al., 2008	188 pregnant women; gestation of <16 weeks	Double-blind, randomized, placebo-controlled	240 mg of cranberry juice (27%) 3 times/day (group A) or 240 mg once daily (group B) or placebo (group C)	Withdrawal rate of 38.8% (A 50.7%; B 39.7%; C 55.5%). No significant differences between the groups ($p=0.71$)
Lee et al., 2007	305 patients with neurogenic bladder due to spinal cord injury	Double-blind, randomized, placebo-controlled	Group 1- methenamine hippurate (MH); 2- cranberry 800 mg; 3- MH + cranberry; and 4- placebo	No differences for symptomatic UTIs comparing groups of intervention to placebo.
Mc Guinness et al., 2002	135 patients with neurogenic bladder due to multiple sclerosis	Double-blind, randomized, placebo-controlled	8000 mg of cranberry capsules or placebo	34.6% contracted a UTI on cranberries and 32.4% on placebo ($p=$ no significance). Similar results under intermittent catheterization.
Waites et al., 2004	74 patients with neurogenic bladder due to spinal cord injury	Double-blind, randomized, placebo-controlled	1 g of cranberry capsules or placebo	26 patients withdrew. No differences in bacteriuria, pyuria or symptomatic UTIs.
Linsenmeyer et al., 2004	37 patients with neurogenic bladder due to spinal cord injury	Double-blind, placebo-controlled with crossover	400 mg of cranberry tablets for 4 weeks or placebo	16 patients withdrew. No reductions in bacteriuria or pyuria with cranberry.
Foda et al., 1995	40 neurogenic bladder children under intermittent catheterization	Single-blind, randomized with crossover	Cranberry juice 15 mg/kg/day or water	19 children withdrew. No differences between groups for asymptomatic bacteriuria or UTIs.
Schlager et al., 1999	15 children with myelomeningocele under intermittent catheterization	Double-blind placebo-controlled with crossover	Cranberry juice 60 ml/day or placebo	No significant differences between groups regarding bacteriuria or symptomatic UTI.
Ferrara et al., 2009	84 girls with recurrent UTIs	Randomized controlled	Cranberry-lingonberry juice 50 ml/day (n = 27); *Lactobacillus GG* 100 ml 5 days/month (n = 26); control (n = 27)	UTIs in 18.5% (5/27) of patients in the first group versus 42.3% in the second and 48.1% in the control group ($p<0.05$)

of asymptomatic bacteriuria, but there was no significant difference with regard to the numbers of UTIs between the groups. Compliance and tolerability were considerable obstacles in this study. Of the 188 subjects, 38.8% did not complete the study and withdrew, most because of gastrointestinal upset, including nausea, vomiting, diarrhea, and bad taste.

There are several trials for patients with neurogenic bladder and under intermittent catheterization (IC). The study with the largest number of participants (n = 305) is made up of four different treatment groups (1- methenamine hippurate (MH); 2-cranberries 800 mg; 3-MH + cranberries; and 4-placebo). The follow-up at six months did not determine a significantly longer UTI-free period in any of the regimens (46). McGuiness et al. (47) studied 135 patients with multiple sclerosis and found that 34.6% of the patients receiving less than 8000 mg of cranberries and 32.4% of the patients receiving placebo developed a UTI ($p=$ not significant). One study by Hess et al. (55) reported a preventative effect for cranberries in UTIs. They randomized patients with spinal cord injuries into two groups (i.e., 500 mg of cranberries or placebo). After six months, the patients alternated groups for six more months. They observed a reduction in the likelihood of UTIs for all patients receiving cranberries ($p<0.05$) and determined that fewer subjects developed UTIs during the cranberry phase (13%) compared with the placebo phase (34%, $p=0.03$).

For patients with IC, two randomized trials have been published, both in adults with spinal cord injuries. One study had 74 participants divided in two groups receiving

either 2 g of cranberries or placebo. No differences were observed in pyuria, bacteriuria, or episodes of symptomatic UTIs (48). The other study had 21 patients randomly assigned to 1,200 mg/day of cranberry tablets or placebo for four weeks and then patients crossed over to the other group after a washout period. No statistically significant protective effect was observed for cranberry consumption in this population (49).

In pediatric populations, there are two studies concerning children with neurogenic bladder under IC. Foda et al. (50) studied 40 children; however, only 21 completed the study. They randomized two groups receiving 15 ml/kg/day of cranberry juice and water for six months and then crossed over to placebo with no washout period. No statistical difference was observed. In another study, 15 children were randomized into two groups that received either cranberries or placebo for three months and then crossed over. No statistical differences were observed for bacteriuria or UTIs (51). Ferrara et al. (52) performed a study involving young girls ranging from 3 to 14 years old with recurrent UTIs. They conducted a six-month, randomized trial comparing a 50 ml daily cranberry-lingonberry juice to 100 ml, five days per month of *Lactobacillus GG* drink containing 4×10^7 colony-forming units or placebo. Over this time period, they observed UTIs in 18.5%, 42.3%, and 48.1% of the children in each group, respectively ($p<0.05$).

The recommended doses of cranberry products for the prevention of UTIs have been poorly defined, and beverage formulations vary widely. The most highly studied formulation has 25% pure juice (13). Clinical research suggests that daily dosages of 240–300 ml of cranberry juice cocktail can prevent 50% of the recurrences of UTIs and can reduce bacteriuria (11,15,16,30). An *ex vivo* study examining human urine following cranberry juice cocktail consumption suggests that twice-daily dosages of cranberries (36 mg of PAC) might offer additional protection during a 24 h period (25,28). Recommended doses of dried, concentrated juice extract range from 600 to >1,200 mg/day (56) divided into two or three daily doses. It is important to consider that dried cranberry extract can be broken down by exposure to light, heat or cold. However, the addition of vitamins C and E exert a stabilizing influence (57).

ADHERENCE TO TREATMENT

The number of patient withdrawals in most studies varied considerably, ranging from 0 to 55%. Additionally, adherence to treatment was not high; some trials observed less than 80% adherence (13,53). Reasons for dropout included: pregnancy, unrelated infections requiring antibiotic therapy, moving from the area, and gastrointestinal symptoms. In children in particular, taste was the main reason for stopping therapy (50).

Other important issues are the cost and the necessity to carry large amounts of cranberry juice that may limit acceptance in general population. Cranberry products at high doses can be expensive (over US $1,000 annually) (10). In Brazil, the usual dose intake would cost between US $1,000 to $1,200 annually. Caloric load in some formulations was also the cause of some withdrawals. This could indicate that cranberry juice is not an acceptable therapy over a long time period.

Side effects commonly reported include the following: reflux, mild nausea, frequent bowel movements, headaches, elevation in blood glucose levels, and a cutaneous reaction. There are some concerns about the potential for cranberries to cause thrombocytopenia and nephrolithiasis (58,59). There is one report of immune-mediated thrombocytopenia after the ingestion of an unknown amount of cranberry juice. Four studies evaluated the potential risk for lithiasis (60-63); however, none have shown an increased risk, though some reported elevated oxalate in the urine that could potentially enhance the risk for oxalate stones. Nonetheless, another study described a protective effect after cranberry usage, an increase in citrate excretion and a reduction in oxalate excretion.

DRUG INTERACTIONS

Flavonoids, the major constituent of cranberries, have an established effect on the cytochrome P450 (CYP) drug-metabolizing enzyme. Flavonoids are also aromatase inhibitors, which are crucial enzymes in estrogen biosynthesis. Cranberry juice also confers a significant reduction in the activity of nifedipine oxidase (CYP3A4), thus reducing oral clearance by 39% and increasing the serum concentration/time curve (64).

There are some reports of interactions between cranberry juice and warfarin (65,66). Increases in the international normalized ratio (INR) of prothrombin time values were reported in these patients; one patient died as a result of gastrointestinal and pericardial hemorrhage (67). Potential mechanisms of this interaction have included the salicylate content of the juice (68) and the presence of CYP enzyme-inhibiting flavonoids. There are other studies suggesting that the potential interaction is low; however, the dosage was low (250 ml of juice daily). The effect of more than 1,000 ml/day has not been evaluated. A placebo-controlled study using volunteers found that cranberries increased sensitivity to the dynamic effects of warfarin. However, a systematic evaluation of *in vitro* and *in vivo* interactions determined that cranberries could inhibit warfarin hydroxylation *in vitro*, but cranberry juice had no effect on warfarin clearance *in vivo*. This lack of concordance reflects the fact that the site of warfarin metabolism (liver) is different from the site of exposure to the inhibitory components in the cranberry juice (intestine) (69). Aside from these data, the effect of purified PAC on drug metabolism is unknown. There are many discrepancies in the published data that make comparisons difficult, including the type of cranberry product used, the amount of cranberry ingested, the type of subjects and comorbidities. *In vitro* studies suggest a possible effect of PAC, the active compound in cranberries that inhibits the adhesion of p-fimbriated bacteria, mainly *E. coli*, to the urothelium. Similar effects on activity *in vivo* are not found in the literature.

In 2008, the Cochrane review supported cranberry potential use only in recurrent UTI prophylaxis for young women. Even for this indication, further clinical trials (double-blinded, randomized, placebo-controlled) displayed no differences between cranberry consumption and controls. The efficacies in other groups of subjects, such as the elderly or pediatric populations with neurogenic bladder, are even more questionable.

Patient withdrawal rates in studies are high due to cost, taste and gastrointestinal intolerance. However, patients should be aware of drug interactions (mainly warfarin) that may even have potentially fatal consequences. Using the

current available data, the use of cranberries cannot be scientifically promoted for UTI prevention. Future studies should focus on PAC, the active compound in cranberries, instead of the whole fruit.

AUTHOR CONTRIBUTIONS

Hisano M, Bruschini H and Nicodemo AC wrote the manuscript. Bruschini H, Nicodemo AC and Srougi M provided revisions, additional aspects and details for the subject that were not present in the initial manuscript, along with contributions and article selection for table design.

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