REVIEW ARTICLE

Cranberry-Containing Products for Prevention of Urinary Tract Infections in Susceptible Populations

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Urinary tract infection (UTI) is one of the most commonly acquired bacterial infections. Cranberry-containing products have long been used as a folk remedy to prevent UTIs. The aims of this study were to evaluate cranberry-containing products for the prevention of UTI and to examine the factors influencing their effectiveness.

Methods: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were systemically searched from inception to November 2011 for randomized controlled trials that compared prevention of UTIs in users of cranberry-containing products vs placebo or nonplacebo controls. There were no restrictions for language, population, or publication year.

Results: Thirteen trials, including 1616 subjects, were identified for qualitative synthesis from 414 potentially relevant references; 10 of these trials, including a total of 1494 subjects, were further analyzed in quantitative synthesis. The random-effects pooled risk ratio (RR) for cranberry users vs nonusers was 0.62 (95% CI, 0.49-0.80), with a moderate degree of heterogeneity (I^2=43%) after the exclusion of 1 outlier study. On subgroup analysis, cranberry-containing products seemed to be more effective in several subgroups, including women with recurrent UTIs (RR, 0.53; 95% CI, 0.33-0.83) (I^2=0%), female populations (RR, 0.49; 95% CI, 0.34-0.73) (I^2=34%), children (RR, 0.33; 95% CI, 0.16-0.69) (I^2=0%), cranberry juice drinkers (RR, 0.47; 95% CI, 0.30-0.72) (I^2=2%), and subjects using cranberry-containing products more than twice daily (RR, 0.58; 95% CI, 0.40-0.84) (I^2=18%).

Conclusions: Our findings indicate that cranberry-containing products are associated with protective effect against UTIs. However, this result should be interpreted in the context of substantial heterogeneity across trials.

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URINARY TRACT INFECTION (UTI) is defined by the presence of clinical signs and symptoms arising from the genitourinary tract in the presence of a certain threshold level of bacteria in the urine. It is one of the most commonly acquired bacterial infections in ambulatory and hospitalized populations.[1] It is estimated that UTIs cause approximately 7 000 000 office visits each year in the United States, along with an additional 1 000 000 visits to emergency departments, and result in approximately 100 000 hospitalizations.[1] The estimated annual cost of community-acquired UTIs is $1.6 billion in the United States.[2]

Adult women are particularly susceptible to UTIs. Up to 40% to 50% of women will experience at least 1 episode of UTI during their lifetimes.[2] Approximately 20% to 30% of women who have had an infection will experience a recurrence with concurrent short-term morbidity.[2] Other groups with an increased risk of UTI include pregnant women, elderly patients, and patients with neuropathic bladder.[3]

Cranberry (genus *Vaccinium*, including the species *V oxycoccus*, *V macrocarpon*, *V microcarpum*, and *V erythrocarpum*) has been used as a folk remedy to prevent UTI for many years.[4] In the 1920s, the preventive effect of cranberry was thought to be a result of acidification of the urinary tract, but this was refuted in 1959.[3] In 1984, cranberry was found to interfere with the attachment of bacteria to uroepithelial cells, thereby potentially preventing infection.[3] In 1989, A-type proanthocyanidins (PACs) were identified as compounds with the potential to inhibit the adherence of P-fimbriated *Escherichia coli* to the urogenital mucosa,[5] and there are hundreds of other compounds found in cranberries that have yet to be explored for their potential antiadherence activity.

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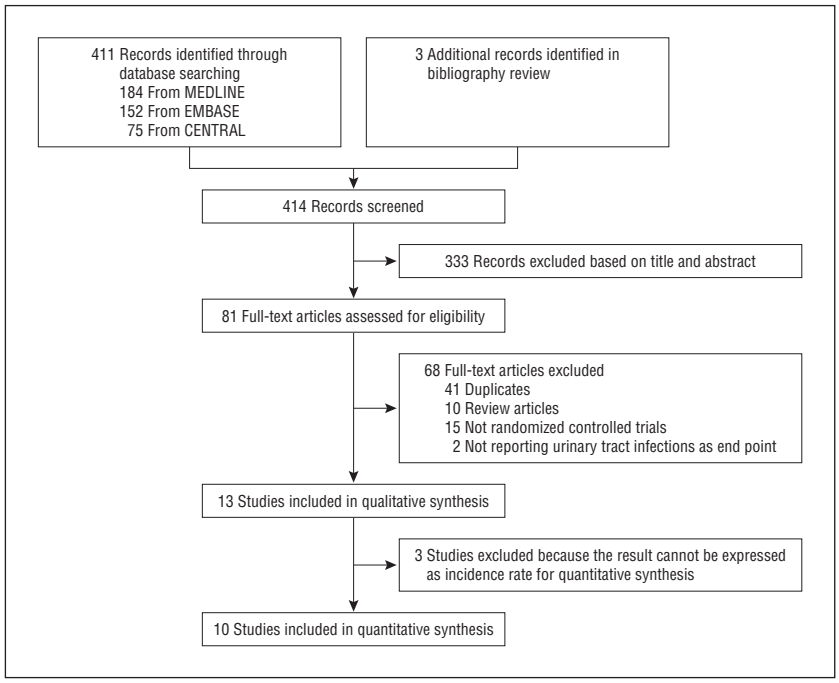

Figure 1. Literature search flow diagram. CENTRAL indicates Cochrane Central Register of Controlled Trials.

A Cochrane meta-analysis by Jepson and Craig[6] showed some evidence that cranberry juice decreases the number of symptomatic UTIs, particularly among women with recurrent UTIs. However, because of a limited number of included trials, it did not explore how other factors, such as dose, frequency, or form of cranberry-containing products, influence the effectiveness in prevention of UTI. Furthermore, since its publication, several new studies have been published. The goals of the present review were to reevaluate cranberry-containing products for the prevention of UTI and to examine the factors influencing their effectiveness.

METHODS

DATA SOURCES AND SEARCHES

We performed this meta-analysis in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for systematic reviews.[7] Two authors (C.-H.W. and C.-C.F.) independently searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to November 2011 according to a prespecified protocol. Search terms included *cranberry*, *Vaccinium macrocarpon*, *Vaccinium oxycoccus*, *Vaccinium microcarpum*, *Vaccinium erythrocarpum*, *Vaccinium*, *urinary tract infection*, *pyelonephritis*, *cystitis*, *bacteriuria*, and *pyuria*. No language, population, or publication year restrictions were enforced. The search strategy for MEDLINE is presented as an example in the eAppendix (http://www.archinternmed.com). We did not search abstracts from conferences, proceedings, or clinical trial registries. Instead, we manually checked bibliographies of relevant studies, reviews, and meta-analyses to identify references that may have been missed in our primary search. Authors of included trials were contacted for missing information if necessary.

STUDY SELECTION

Two authors (C.-H.W. and C.-C.F.) independently scanned the titles and abstracts of all retrieved manuscripts to identify those pertinent to this review. The following prespecfied inclusion criteria were used: (1) randomized controlled trials (RCTs); (2) comparison of cranberry-containing products vs placebo or nonplacebo control for prevention of UTI; and (3) outcomes reported as incidence of UTIs. (One trial[8] was included according to this criterion but not pooled in the quantitative analysis because it reported incidence in a manner that we could not pool its with others.)

After retrieving full reports of potentially relevant trials, the same reviewers independently assessed the eligibility of the studies on the basis of the inclusion criteria and settled differences of opinion by consensus or by consultation with a third investigator (C.-C.L.).

DATA EXTRACTION AND QUALITY ASSESSMENT

Four authors (N.-C.C., S.S.-H.L., P.-H.Y., and T.-Y.W.) independently extracted data by a prespecified protocol. Each trial was reviewed independently by any 2 of the 4 authors to ensure the correctness of the extracted data. The information included the following: (1) type of study and study design; (2) characteristics of the study population; (3) types of intervention and controls; (4) definitions of UTI; (5) types of outcomes measured; and (6) number and reasons of participants lost to follow-up. The detailed list of variables is presented in the eAppendix.

The primary outcome was prespecified as the incidence of UTI, which was expressed as either incidence or cumulative incidence rate, depending on the original data. If the outcome data could not be expressed as such, the original data were presented.

The Cochrane risk of bias tool was adopted to assess the risk of bias for each trial, which was scored as "high risk," "low risk," or "unclear" based on methods of random sequence generation, allocation concealment, blinding process, incomplete outcome data, and selective reporting.[9] Discrepancies in assessment were resolved through discussions between the authors (C.-H.W. and C.-C.F.) or consultation with a third investigator (C.-C.L.).

DATA SYNTHESIS AND ANALYSIS

Data synthesis and analysis were performed using the metafor package in the R 2.11.1 statistical software (R Foundation for Statistical Computing). $P \leq .05$ (2-sided) was considered statistically significant. Dichotomous outcomes from individual studies were collected to compute individual-study risk ratios (RRs) with 95% confidence intervals. To deal with studies with multiple intervention arms, all relevant treatment arms were grouped together by adding together the sample sizes and numbers of subjects with events.[10] Heterogeneity was tested using both the I^2 statistic, with I^2 of 50% or greater indicating a substantial level of heterogeneity, and the statistical test of heterogeneity, with $P \leq .05$ indicating heterogeneity.[11,12] Random-effects summary estimates (DerSimonian-Laird method)[13] were reported if the heterogeneity was significant in either test of heterogeneity; otherwise, fixed-

Table 1. Study Design and Quality of Reporting of Included Randomized Controlled Trials Evaluating Cranberry-Containing Products in the Prevention of UTIs

Source	Design	Washout Period	Analysis	Study Duration	Loss to Follow-up, No./Total No. (%)
Avorn et al,[8] 1994	Parallel	NA	ITT	6 mo	32/153 (21)
Foda et al,[15] 1995	Crossover	None	PP	12 mo	19/40 (48)
Walker et al,[16] 1997	Crossover	None	PP	6 mo	9/19 (47)
Schlager et al,[17] 1999	Crossover	None	ITT	6 mo	0/15 (0)
Kontiokari et al,[18] 2001	Parallel	NA	ITT	6 mo	9/50 (18)
McGuinness et al,[19] 2002	Parallel	NA	ITT	6 mo	12/135 (9)
Stothers et al,[20] 2002	Parallel	NA	ITT	12 mo	NR
Waites et al,[21] 2004	Parallel	NA	PP	6 mo	26/74 (35)
McMurdo et al,[22] 2005	Parallel	NA	ITT	35 d	115/376 (30.6)
Hess et al,[23] 2008	Crossover	None	PP	12 mo	10/57 (18)
Wing et al,[24] 2008	Parallel	NA	ITT	6 mo[a]	73/188 (39)
Ferrara et al,[25] 2009	Parallel	NA	PP	6 mo	3/57 (5)
Barbosa-Cesnik et al,[26] 2011	Parallel	NA	ITT	6 mo	89/319 (27.9)

	Risk of Bias Assessment				
Source	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting
Avorn et al,[8] 1994	High	High	Low	High	High
Foda et al,[15] 1995	Unclear	Unclear	Low	High	High
Walker et al,[16] 1997	Unclear	Unclear	Low	High	Unclear
Schlager et al,[17] 1999	Unclear	Unclear	Low	Low	High
Kontiokari et al,[18] 2001	Low	Unclear	Low	Low	High
McGuinness et al,[19] 2002	Unclear	Unclear	Low	High	High
Stothers et al,[20] 2002	Unclear	Unclear	Low	High	High
Waites et al,[21] 2004	Unclear	Unclear	Low	High	High
McMurdo et al,[22] 2005	Low	Low	Low	Low	High
Hess et al,[23] 2008	Unclear	Unclear	Low	Unclear	High
Wing et al,[24] 2008	Low	Unclear	Low	High	High
Ferrara et al,[25] 2009	Low	Unclear	Low	Low	Unclear
Barbosa-Cesnik et al,[26] 2011	Unclear	Low	Low	Unclear	Low

Abbreviations: ITT, intention to treat; NA, not applicable; NR, not reported; PP, per protocol.
[a] Pregnant women were followed from prior to week 16 of gestation through delivery.

effect summary estimates (Mantel-Haenszel method) were reported.

We used a Galbraith plot to identify potential sources of heterogeneity and an influential plot to assess the impact on pooled summary estimates when significant heterogeneity was detected.[14] We conducted sensitivity analyses based on risks of bias in the randomization process, study characteristics, and definitions of UTI. We performed subgroup analyses by prespecified covariates, including study population, sex, age, and form, amount, and frequency of cranberry-containing products used, and tested these covariates for significance by meta-regression. We drew a funnel plot to evaluate publication bias.

RESULTS

SEARCH RESULTS AND DESCRIPTION

In this systematic review, we identified 13 RCTs that were eligible for qualitative synthesis (**Figure 1**).[8,15-26] There were 9 parallel-group and 4 crossover trials (**Table 1**). None of these crossover trials had washout periods. Eight trials were conducted according to the intention-to-treat principle, and 5 trials used per-protocol analysis. Most of the trials did not report their randomization processes adequately and suffered from a high proportion of subjects lost to follow-up (0%-48%).

There were 1616 subjects included in the qualitative analysis (**Table 2**). Of the 13 trials, 10 were performed in North America (United States and Canada), and the other 3 were conducted in Europe (United Kingdom, Finland, and Italy). All but 1 of the trials[22] followed subjects living in the community. According to the inclusion and exclusion criteria of each trial, we further categorized each study population into the following subgroups for subgroup analysis: women with recurrent UTIs, elderly patients, patients with neuropathic bladder, pregnant women, and children.

Administration of cranberry-containing products differed significantly in form, daily dosage, PAC content, and dosing frequency (Table 2). Nine trials used cranberry juice, and 4 used cranberry capsules or tablets. Six trials used cranberry-containing products provided by the manufacturer Ocean Spray. Daily cranberry dose ranged from 0.4 to 194.4 g. The daily use of cranberry-containing products was reported in 3 trials without specifying the actual cranberry amount.[8,17,20] Cranberry-containing products were administered for 6 months in most trials.[8,15,18,19,21,23-26]

Of the 3 trials involving pediatric groups,[15,17,25] only Foda et al[15] ad-

Table 2. Characteristics of Study Populations and Interventions in Included Randomized Controlled Trials Evaluating Cranberry-Containing Products in the Prevention of UTIs

Source	No. of Patients	Study Region	Setting	Age, Range (Mean or Median), y	Subgroup	Female, %
Avorn et al,[8] 1994	153	US	Nursing homes	NA (78.6)	Elderly patients	100
Foda et al,[15] 1995	21	Canada	Hospital clinic	1.4-18 (NA)	Patients with neuropathic bladder	43
Walker et al,[16] 1997	10	US	Unclear	28-44 (37)	Women with recurrent UTIs	100
Schlager et al,[17] 1999	15	US	Hospital clinic	2-18 (NA)	Patients with neuropathic bladder	53
Kontiokari et al,[18] 2001	100	Finland	University health service	NA (30.5)	Women with recurrent UTIs	100
McGuinness et al,[19] 2002	135	Canada	Hospital clinic	NA (45.1)	Patients with neuropathic bladder	79
Stothers et al,[20] 2002	150	Canada	Unclear	21-72 (42.3)	Women with recurrent UTIs	100
Waites et al,[21] 2004	48	US	Hospital clinic	20-73 (40.9)	Patients with neuropathic bladder	13
McMurdo et al,[22] 2005	376	UK	Inpatients	>60 (81.4)	Elderly patients	68
Hess et al,[23] 2008	47	US	Hospital clinic	28-79 (53)	Patients with neuropathic bladder	0
Wing et al,[24] 2008	188	US	Hospital clinic	NA (26.4)	Pregnant women	100
Ferrara et al,[25] 2009	54	Italy	Hospital clinic	3-14 (NA)	Children	100
Barbosa-Cesnik et al,[26] 2011	319	US	University health service	18-40 (21.2)	Women with recurrent UTIs	100

		Cranberry Group				Control Group
Source	Baseline Bacteriuria Excluded?	Form (Daily Dosage, mL)	Manufacturer	Cranberry Amount (g/d) (PAC Content, mg/d)	Dosing Frequency (Daily)	Formula
Avorn et al,[8] 1994	No	Juice (300)	Ocean Spray	NA	Not specified	Juice[a]
Foda et al,[15] 1995	No	Juice (15 mL/kg)	Ocean Spray	4.5 g/kg/d	3-4	Water
Walker et al,[16] 1997	No	Capsule	Solaray	0.4	Not specified	Dicalcium phosphate
Schlager et al,[17] 1999	No	Juice (60)	Ocean Spray	NA	Not specified	Juice[a]
Kontiokari et al,[18] 2001	Yes	Juice (50)	Marli	7.5	Not specified	No placebo
McGuinness et al,[19] 2002	No	Capsule	NOW Natural Foods	8	1	Beetroot
Stothers et al,[20] 2002	Yes	Tablet/juice (750)	Unclear	NA	2/3	Juice[b]
Waites et al,[21] 2004	No	Capsule	Aim This Way	4	2	Lactose
McMurdo et al,[22] 2005	No	Juice (300)	Ocean Spray	75 (0.838)	2	Juice[c]
Hess et al,[23] 2008	Yes	Tablet	Swiss Herbal	1	2	Rice flour
Wing et al,[24] 2008	Yes	Juice (240-720)	Ocean Spray	64.8-194.4 (80-240)	1-3	Juice[a]
Ferrara et al,[25] 2009	Yes	Juice (50)	Unclear	7.5	Not specified	No placebo
Barbosa-Cesnik et al,[26] 2011	Yes	Juice (480)	Ocean Spray	129.6 (224)	2	Juice[a]

Abbreviations: PAC, A-type proanthocyanidin; UK, United Kingdom; US, United States; UTIs, urinary tract infections.
[a] Specially designed juice to imitate cranberry juice.
[b] Filtered water with food coloring plus 20-mL pineapple juice.
[c] Containing water, sucrose, elderberry extract, quinic acid, citric acid, malic acid, vitamin C, and aspartame.

justed the daily cranberry dosage by body weight. Ten trials used a formulated placebo, 2 trials[18,25] did not use a placebo, and 1 trial[15] used water as the placebo.

The definitions of UTI differed significantly in thresholds for bacteriuria and pyuria (**Table 3**). The presence of UTI symptoms was not required in 2 trials.[8,19] Because there was no reliable bioassay to examine the compliance of subjects, most studies used indirect methods for this purpose. These included periodic interviews, self-reported questionnaires, and pill counting of remaining study medications. In most trials, the occurrence of UTI was expressed as incidence or cumulative incidence rate. In 1 trial,[8] however, the final result included baseline urine culture data, which precluded transformation of the outcome data into incidence or cumulative incidence rate. Cumulative incidence of UTI was reported in 10 trials,[17-26] which were further analyzed in quantitative synthesis.

QUANTITATIVE DATA SYNTHESIS

There were 1494 subjects across the 10 trials[17-26] included in the quantitative data synthesis, with 794 in the cranberry group and 700 in the control group. There was significant heterogeneity among trials (RR, 0.68; 95% CI, 0.47-1.00) (I^2 = 59%). The Galbraith plot indicated that the trials by Ferrara et al[25] and Barbosa-Cesnik et al[26] were potential sources of heterogeneity (**Figure 2**). Influential plot further demonstrated that the trial by Barbosa-Cesnik et al[26] had the most significant impact on the pooled summary estimate (**Figure 3**), justifying its exclusion from the main analysis. After exclusion of this trial, heterogeneity decreased, and cranberry-containing products seemed to be effective in prevention of UTIs (RR, 0.62; 95% CI, 0.49-0.80) (I^2 = 43%) (**Figure 4**).

Sensitivity analysis showed that the pooled summary estimate was stable to risks of bias in random sequence generation, study characteristics, and definitions of UTI. However, the protective effect was much stronger in 2 studies[18,25] without placebo in the control group (pooled RR, 0.36; 95% CI, 0.21-0.62) (**Table 4**).

Subgroup analysis demonstrated that cranberry-containing

Table 3. Definitions and Outcomes From the 13 Included Randomized Controlled Trials Evaluating Cranberry-Containing Products in the Prevention of UTIs

Source	Outcome Assessment			UTI Cumulative Incidence Rate, No./No. (%)[a]		UTI Incidence Rate (Episodes/ Patient-year)[b]		
	Threshold of Bacteriuria (CFU/mL)	Pyuria Required in Definition of UTI	Symptoms Required in Definition of UTI	Cranberry	Control	Cranberry	Control	Intervention Duration[c]
Avorn et al,[8] 1994	100 000	Yes (undefined)	No	15%[f]	28.1%[f]	NA	NA	6 mo
Foda et al,[15] 1995	100 000	No	Yes (undefined)[d]	NA	NA	1.8	1.9	6 mo[c]
Walker et al,[16] 1997	Undefined	No	Yes (undefined)	NA	NA	2.4	6.0	3 mo[c]
Schlager et al,[17] 1999	10 000	No	Yes (defined)	2/15 (13)	3/15 (20)	0.8	0.8	3 mo[c]
Kontiokari et al,[18] 2001	100 000	No	Yes (defined)	8/50 (16)	18/50 (36)	NA	NA	6 mo
McGuinness et al,[19] 2002	1 000 000	Yes (undefined)	No	21/62 (34)	24/73 (33)	NA	NA	6 mo
Stothers et al,[20] 2002	100 000	No	Yes (undefined)	19/100 (19)	16/50 (32)	0.4	0.7	12 mo
Waites et al,[21] 2004	10 000	No	Yes (defined)	10/26 (34)	8/22 (36)	1.2	1.3	6 mo
McMurdo et al,[22] 2005	10 000	No	Yes (defined)[e]	7/187 (4)	14/189 (7)	NA	NA	35 d
Hess et al,[23] 2008	10 000	Yes (defined)	Yes (defined)	6/47 (13)	16/47 (34)	0.3	0.9	6 mo[c]
Wing et al,[24] 2008	100 000	Yes (defined)	Yes (defined)	4/125 (3)	0/63 (0)	NA	NA	6 mo[c]
Ferrara et al,[25] 2009	100 000	Yes (defined)	Yes (defined)	5/27 (19)	18/27 (67)	NA	NA	6 mo
Barbosa-Cesnik et al,[26] 2011	1000	Yes (defined)	Yes (defined)	31/155 (20)	23/164 (14)	NA	NA	6 mo

Abbreviations: CFU, colony-forming unit; NA, not available; UTIs, urinary tract infections.
[a] Cumulative incidence rate: number of patients who experienced at least 1 episode of UTI/number of patients at risk during the intervention period.
[b] Incidence rate: number of total episodes of UTIs during the intervention period/number of person-years at risk during the intervention period.
[c] Intervention duration: In crossover trials, intervention duration of each intervention was half of the study duration.
[d] Definition of UTI: bacteriuria or any growth in a symptomatic patient or any growth of *Proteus* or *Pseudomonas* species.
[e] Definition of UTI: bacteriuria in a symptomatic patient and presence of leukocyte esterase and nitrite.
[f] This percentage represented urine samples of bacteriuria with pyuria in all screened urine samples. The odds ratio was 0.42 (95% CI, 0.23-0.76) for bacteriuria with pyuria in cranberry relative to the control group ($P = .004$).

products seemed to be more effective in women with recurrent UTIs (RR, 0.53; 95% CI, 0.33-0.83) ($I^2 = 0\%$), female populations (RR, 0.49; 95% CI, 0.34-0.73) ($I^2 = 34\%$), children (RR, 0.33; 95% CI, 0.16-0.69) ($I^2 = 0\%$), cranberry juice users (RR, 0.47; 95% CI, 0.30-0.72) ($I^2 = 2\%$), and people using cranberry-containing products more than twice daily (RR, 0.58; 95% CI, 0.40-0.84) ($I^2 = 18\%$), although the *P* values were not significant in meta-regression (**Table 5**). The funnel plot did not indicate significant publication bias (**Figure 5**).

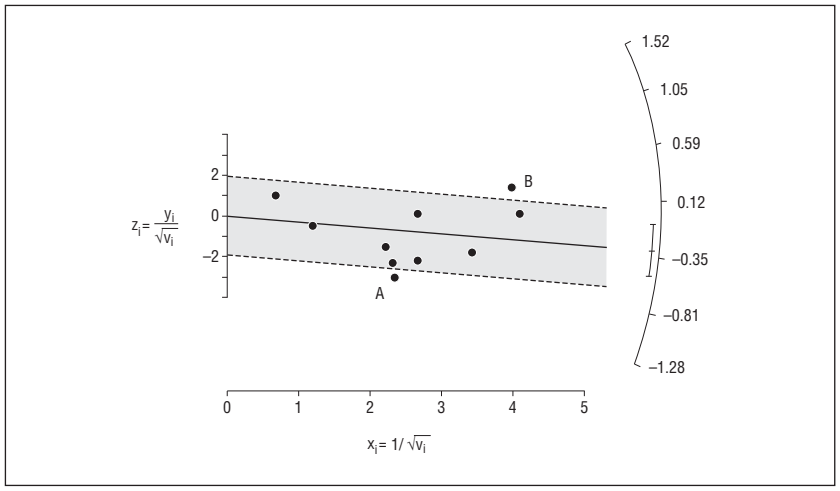

Figure 2. Galbraith plot. There are 2 statistical outliers, A and B, which represent the trials by Ferrara et al[25] and Barbosa-Cesnik et al,[26] respectively.

COMMENT

In a 2008 Cochrane review, Jepson et al[6] reported a favorable effect of cranberry juice in the prevention of symptomatic UTIs (RR, 0.66; 95% CI, 0.47-0.92 [4 trials]), especially in women with recurrent UTIs (RR, 0.61; 95% CI, 0.40-0.91 [2 trials]). In light of newly available studies, the present review has reevaluated the effectiveness of cranberry-containing products in the prevention of UTI and factors influencing their effectiveness. Our result was high in heterogeneity but included a greater number of available trials in analysis and showed a similar but nonsignificant pooled result (RR, 0.68; 95% CI, 0.47-1.00) ($I^2 = 59\%$). After exclusion of a potential outlier by Barbosa-Cesnik et al,[26] our results were more similar to those of Jepson and Craig[6] (RR, 0.62; 95% CI, 0.49-0.80) ($I^2 = 43\%$).

The trial by Barbosa-Cesnik et al[26] showed that cranberry juice gave no protection against the risk of recurring UTI among college-aged women (RR, 1.43; 95% CI, 0.87-2.33), which made it an outlier among the trials. There are 2 possible reasons for this deviation. First, Barbosa-Cesnik et al[26] used the lowest bacteriuria threshold (1000 colony-forming units [CFU]/mL) among all included trials to define UTI. Kontiokari et al,[18] who used 10 000 CFU/mL as the threshold, showed a protective effect for recurrent UTI (RR, 0.44; 95% CI, 0.21-0.93) in a similar population. Second,

the incidence rate of UTIs observed in the control group in the trial by Barbosa-Cesnik et al[26] was almost half that in the trial by Kontiokari et al.[18] Barbosa-Cesnik et al[26] suggested that this was because of the inadvertent addition of ascorbic acid, which may also prevent UTI, to the placebo, along with better hydration in their control group. Whether the population studied in the trial by Barbosa-Cesnik et al[26] was significantly different in other aspects from the populations in other trials could not be determined in the present meta-analysis.

Our sensitivity analyses showed that the protective effect of cranberry-containing products was stronger in nonplacebo-controlled trials, which suggest that expectations of efficacy may have played a role. The 2 trials without placebos were relatively small, and the pooled effect estimate did not change significantly after removal of these 2 trials (RR, 0.73; 95% CI, 0.55-0.97) (I^2 = 25%).

By including a greater number of available studies than were available for the review by Jepson and Craig,[6] other factors potentially influencing the effect of cranberry were available for subgroup analysis. The results revealed that subgroups of younger age, female sex, individuals with recurrent UTI history, and using cranberry juice rather than capsules or tablets might benefit more from cranberry-containing products than others, although the difference was not statistically significant.

Cranberry-containing products were more effective in women with recurrent UTIs than others (RR, 0.61; 95% CI, 0.40-0.91) (I^2 = 0%), which was similar to the result of the review by Jepson and Craig.[6] Furthermore, when results for girls[25] and pregnant women[24] were pooled together with those for women with recurrent UTIs,[18,20] the summary estimate for this group composed of 100% female participants also demonstrated a preventive effect of cranberry-containing products (RR, 0.49; 95% CI, 0.34-0.73) (I^2 = 34%).

Cranberry juice was noted to be more effective than cranberry capsules or tablets in subgroup analysis. Since the volume of cranberry juice may influence the incidence of UTI,[27] this result might be because subjects drinking cranberry juice were better hydrated than those taking cranberry capsules or tablets. Alternatively, because the mechanism of the protective effect of cranberries against UTIs has not yet been elucidated, the better preventive effect of cranberry in juice form might come from the additive or synergistic effect of other unknown substances in the juice, which are devoid in cranberry capsules and tablets. However, ingesting a large volume of cranberry juice with high sugar content might raise concerns about sugar control in diabetic patients, and it may cause severe gastrointestinal upset or other adverse effects, as observed by Wing et al,[24] who had to change their protocol to allow less frequent dosing to maintain compliance and avoid withdrawal of participants. Nonetheless, although these adverse effects are a concern, until the protective mechanism is clearly understood, use of cranberry in juice form might be favorable to cranberry in capsules or tablets.

A better preventive effect from cranberry-containing products was noted with dosing frequency more than twice daily. Because in vitro data have suggested that the antiadhesion activity of cranberry juice on fimbriated *E coli* lasts for approximately 8 hours after ingestion,[3] dosing more frequently than twice daily may be a reasonable choice.

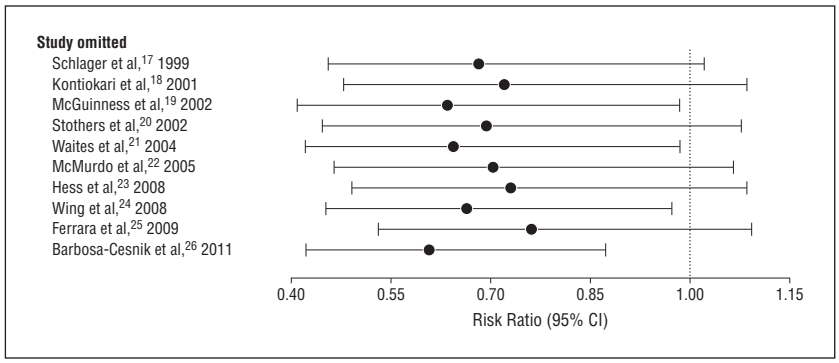

Figure 3. Influential plot: pooled summary effect estimates with each study omitted at one time.

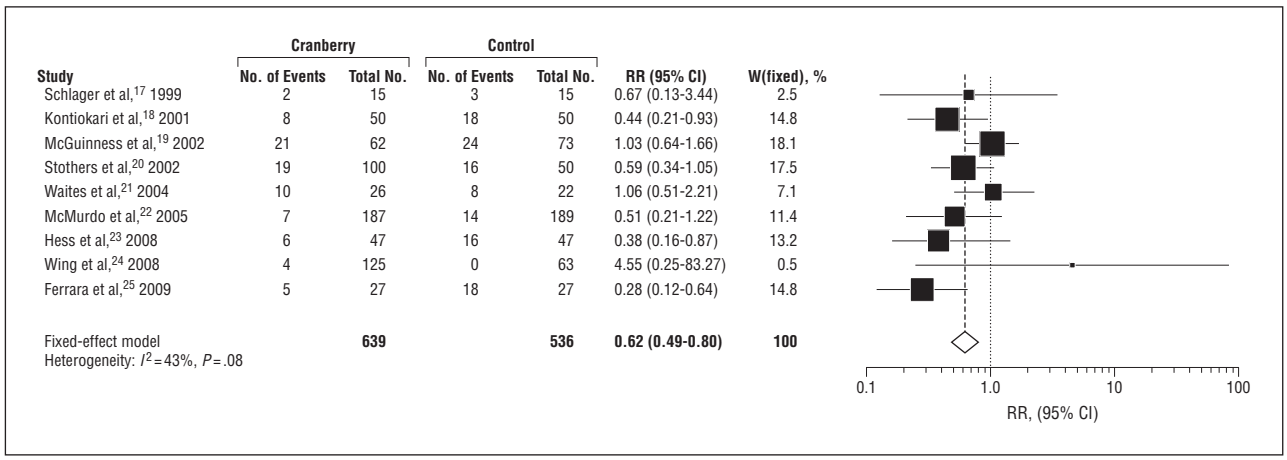

Figure 4. Forest plot: summary effect of cranberry in prevention of urinary tract infection, expressed as risk ratio (RR). W(fixed) indicates weights in fixed-effect Mantel-Haenszel model.

Table 4. Summary Results of Sensitivity Analyses From the Included Randomized Controlled Trials Evaluating Cranberry-Containing Products in the Prevention of UTIs

Sensitivity Analysis According to:	No. of Trials	Pooled Cumulative Incidence Rate of UTI, No./No.[a]		Heterogeneity I^2, % (*P* Value)	Risk Ratio (95% CI)	*P* Value in Meta-regression
		Cranberry	Control			
Study design						
Parallel	7	74/577	98/474	51 (.05)	0.64 (0.42-0.97)	.45
Crossover	2	8/62	19/62	0 (.54)	0.42 (0.20-0.89)	
Study analysis						
ITT	6	61/539	75/440	22 (.27)	0.70 (0.52-0.95)	.44
PP	3	21/100	42/96	69 (.04)	0.49 (0.21-1.13)	
Risk of random sequence generation						
Low risk	4	24/389	50/329	22 (.28)	0.46 (0.29-0.71)	.08
Unclear	5	58/250	67/207	31 (.21)	0.74 (0.55-1.00)	
Treatment in control group						
Placebo	7	69/562	81/459	25 (.23)	0.73 (0.55-0.97)	.05
No placebo	2	13/77	36/77	0 (.41)	0.36 (0.21-0.62)	
Incidence rate in control group						
≥30%	6	69/312	100/269	59 (.03)	0.59 (0.38-0.91)	.81
<30%	3	13/327	17/267	5 (.35)	0.69 (0.33-1.41)	
Bacteriuria threshold in definition of UTI						
10 000 CFU/mL	4	25/275	41/273	19 (.30)	0.58 (0.37-0.91)	.46
100 000 CFU/mL	4	36/302	52/190	34 (.21)	0.49 (0.34-0.73)	
Pyuria requirement in definition of UTI						
Pyuria unrequired	5	46/378	59/326	0 (.54)	0.60 (0.42-0.85)	.88
Pyuria required	4	36/261	58/210	72 (.01)	0.59 (0.25-1.40)	

Abbreviations: ITT, intention to treat; PP, per protocol; UTIs, urinary tract infections.
[a]Pooled incidence rate: number of patients who experienced at least 1 episode of UTI/number of patients at risk during the intervention period.

Table 5. Summary Results of Subgroup Analyses From the Included Randomized Controlled Trials Evaluating Cranberry-Containing Products in the Prevention of UTIs

Subgroup Analysis According to:	No. of Trials	Pooled Cumulative Incidence Rate of UTI, No./No.[a]		Heterogeneity I^2, % (*P* Value)	Risk Ratio (95% CI)	*P* Value in Meta-regression
		Cranberry	Control			
Population type						
Women with recurrent UTIs	2	27/150	34/100	0 (.54)	0.53 (0.33-0.83)	NA
Neuropathic bladder	4	39/150	51/157	37 (.19)	0.80 (0.57-1.14)	
Children	1	5/27	18/27	NA	0.28 (0.12-0.64)	
Elderly patients	1	7/187	14/189	NA	0.51 (0.21-1.22)	
Pregnant patients	1	4/125	0/63	NA	4.57 (0.25-83.60)	
Age						
<18 y	2	7/42	21/42	0 (.35)	0.33 (0.16-0.69)	.15
≥18 y	7	75/597	96/494	39 (.14)	0.68 (0.52-0.89)	
Sex						
Female	4	36/302	52/190	34 (.21)	0.49 (0.34-0.73)	.17
Form of cranberry-containing products						
Cranberry juice	5	26/404	53/344	2 (.39)	0.47 (0.30-0.72)	.07
Capsule or tablet	3	37/135	48/142	57 (.10)	0.79 (0.44-1.44)	
Dose frequency						
More than twice daily	4	42/360	54/308	18 (.30)	0.58 (0.40-0.84)	.12
Once daily	1	21/62	24/73	NA	1.03 (0.64-1.66)	

Abbreviations: NA, not available; UTIs, urinary tract infections.
[a]Pooled incidence rate: number of patients who experienced at least 1 episode of UTI/number of patients at risk during the intervention period.

Among all included studies, only Wing et al[24] attempted a dose-response study to determine the optimal dose.[24] The results showed a trend toward fewer UTIs in women given higher doses of cranberry juice vs those who received placebo. Our study did not have the power to examine differences in incidence of UTI by cranberry dose. Most researchers for the trials included in the present review did not state their rationale in selecting a cranberry dose, except for McGuinness et al,[19] who mentioned that the they chose the highest available cranberry dose for their study. More dose-response studies are needed to find the

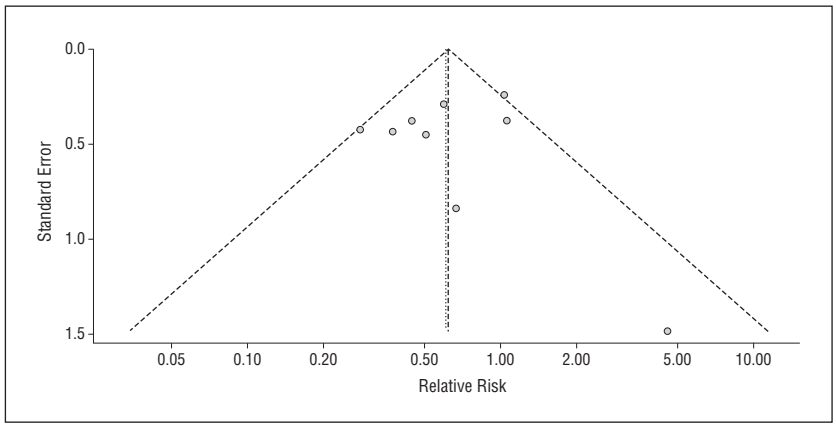

Figure 5. Funnel plot to evaluate publication bias.

optimal in vivo dosage of cranberry; an ongoing study to determine dose is currently under way (clinicaltrials.gov Identifier: NCT00100061).

In trials using daily cranberry amounts greater than 10 g, a huge range of PAC contents, from 0.838 mg to 224 mg per day, was reported. In contrast, those using daily cranberry amounts of less than 10 g did not include information about PAC content. Only recently have PACs been recognized as potential antiadhesion constituents of cranberry.[5] Quantification and standardization of PAC content was available in only 3 of the 13 trials included, and it is difficult to effectively compare outcomes among the trials without this information. The results of 1 in vitro study have suggested that daily intake of 72 mg of PACs may protect against bacterial adhesion in the urinary tract after cranberry consumption.[28] However, in 2 trials included in the present review, using daily PAC amounts above 72 mg did not show a protective effect.[24,26]

Theories about the role of cranberry in the prevention of UTIs have gradually evolved and in part have only recently been formulated. The PAC content should be specified in future trials to allow differentiation of the effects of PACs on clinical response. Also, consumers of cranberry-containing products should have access to this information when they buy products touted for prevention of UTI.

Regarding study limitations, we did not search abstracts from conferences, proceedings, or clinical trial registries, which may cause incomplete literature search. We tried to compensate for this by manually checking bibliographies of relevant studies, reviews, or meta-analyses. Also, we were unable to reach several authors for missing data necessary for synthesis.[8,15,16] We checked relevant meta-analyses and systemic reviews and confirmed that no such data were available.

In conclusion, the results of the present meta-analysis support that consumption of cranberry-containing products may protect against UTIs in certain populations. However, because of the substantial heterogeneity across trials, this conclusion should be interpreted with great caution. Cranberry-containing products tend to be more effective in women with recurrent UTIs, female populations, children, cranberry juice drinkers, and people using cranberry-containing products more than twice daily.

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