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File: ■ Cranberry (*Vaccinium macrocarpon*)
■ Urinary Tract Infection Prevention

HC 121222-471

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RE: 2012 Cochrane Review of Cranberry for the Prevention of Urinary Tract Infections

Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2012;10:CD001321. doi: 10.1002/14651858.CD001321.pub5.

Cranberries (*Vaccinium macrocarpon*) have been widely used for the prevention and treatment of urinary tract infection (UTI). UTIs are one of the most common outpatient conditions, with some subpopulations being especially susceptible, such as pregnant women, the elderly, patients with spinal cord injuries and/or catheters, and diabetics. Infections are the result of the introduction and growth of uropathogenic bacteria in the otherwise sterile urinary tract. The range of symptoms may include dysuria (pain on passing urine), frequent urination, cloudy urine, haematuria (blood in the urine), and pyuria (urine white cell count >10,000/mL). While no definitive mechanism of action has been shown in humans, in vitro work suggests that cranberry prevents *Escherichia coli* bacteria from adhering to the uroepithelium, the critical first step in infection. This action is thought to be due to 2 compounds in the cranberry, fructose and A-type proanthocyanidins (PACs); however, fructose prevents adhesion in vitro, but not in vivo, as it is metabolized prior to reaching the urine.

A commonly recommended therapeutic dose for UTI prevention is 300 mL of cranberry juice containing 36 mg of PACs, consumed once or twice daily. A 2010 randomized, controlled trial (RCT) evaluating cranberry powder found that 36 mg of cranberry PACs/day produced a bacterial anti-adhesion effect, and that 72 mg/day may offer better protection in more persistent cases. It was also found that the anti-adhesion activity of cranberry decreases over time, suggesting that cranberry products may offer more protection if consumed twice a day.[1]

Depending on the methods and materials used to process cranberry into a powder for administration in tablets and capsules, cranberry PACs may be degraded, resulting in many commercial products with little or no PAC content. The results of chemical analyses to determine PAC content may vary widely as not all utilize the same certified reference standards and validated analytical methods.

This paper updates the 2008 Cochrane review of the efficacy of cranberry use in UTI prevention; it includes 14 new studies in the analysis and excludes 11 others. [Note: The efficacy of cranberry in the *treatment* of UTIs is evaluated in another review by the same authors.] Literature searches and evaluations were performed in accordance with Cochrane review protocols.

Inclusion criteria were parallel, crossover, or quasi-randomized (participants randomly assigned by date of birth or case record number) RCTs comparing cranberry use to placebo, no treatment, or another treatment. Acceptable populations were those with a history of recurrent lower UTIs (>2 episodes in the previous 12 months), elderly men and women, those needing intermittent catheterization or with an indwelling catheter, pregnant women, those with a urinary tract abnormality, and children with a first or subsequent UTI. Studies of cranberry's physiological effects and any urinary tract condition not caused by bacterial infection were excluded. Acceptable treatments included cranberry juice and cranberry products (concentrates, extracts, capsules, or tablets) taken for at least 1 month.

The primary outcome assessed was the number or incidence of UTIs confirmed by bacterial culture of urine samples. Secondary outcomes were adherence to therapy and side effects. Risk ratios (RRs) were calculated where appropriate. Trial quality was assessed using the Cochrane risk of bias assessment tool.

In this 2012 Cochrane review, 14 new studies (1 crossover and 13 parallel) were added to the 10 studies previously included in the 2008 review (4 crossover and 6 parallel) for a total of 24 studies. Eleven of these studies (2,249 patients) evaluated a cranberry juice product, 9 studies (1,032 patients) evaluated cranberry tablets/capsules, 2 evaluated a liquid cranberry concentrate/syrup (131 patients), 1 compared cranberry juice and tablets (150 patients), and 1 compared cranberry capsules and tablets (56 patients). These 24 studies compared the effects of cranberry (juice, concentrate, extract, capsules, or tablets) to no treatment, juice placebo, water, methenamine hippurate, and/or antibiotic treatment (6 of these studies included a third-arm comparator).

Seven studies included women with current and recurrent UTIs; 4 evaluated cranberry juice for the prevention of UTIs in elderly populations; 6 assessed cranberry products in patients needing either indwelling catheters or intermittent catheterization; 3 enrolled children at risk of or susceptible to repeat UTIs; 2 studies (659 patients) included pregnant women; 1 assessed patients undergoing radiation treatment for bladder or cervical cancer; and 1 evaluated patients with multiple sclerosis involving catheterization.

Preparation forms, concentrations, dosages, and dosage schedules varied widely between studies; in most cases, the rationale for their selection was not explained. Only 5 studies reported the amount of PACs in the dosage unit. The amount of juice given ranged from 30 mL/d to 1,000 mL/d for adults and 15 mL/kg/d to 600 mL/d for children. The amount given in capsules or tablets ranged from 400 mg to 2,000 mg/d (concentration or PAC content not specified).

Overall, only 13 studies (n=2,462) had data suitable for meta-analysis, and their combined RR of repeat UTIs was not statistically significant. Twelve studies had data which could not be meta-analyzed. There was moderate overall heterogeneity (I^2=53%), but no significant between-study heterogeneity (I^2=5.2%).

Of the 5 studies that included a placebo group, 4 reported data that could be combined and meta-analyzed. The results indicated a small, non-significant reduction in risk of repeated symptomatic UTI with cranberry supplementation compared to placebo (RR: 0.74, 95% confidence interval [CI]: 0.42 to 1.31). There was significant heterogeneity in these results (I^2=65%), primarily due to a new, large study (the only study adequately powered, but with a lower threshold for defining UTI); omitting this study changed the RR to 0.58 (95% CI: 0.39 to 0.86).

Adverse effects (AEs) were reported in only 7 out of 24 studies; of those, fewer than 10 AEs were reported, and they were mild and similarly distributed across the treatment arms.

Compliance, withdrawal, dropout, and loss to follow-up rates varied considerably between studies due to differences in methodology, protocols, and preparation forms. Sixteen out of 24 studies reported adherence to the treatment; 10 used self-reporting, 5 used pill or bottle counts, and 1 assessed antibiotic activity in urine samples. Five studies reported no dropouts or withdrawals; while dropout/withdrawal rates in other trials ranged from 3-55% (several studies cited unpalatable or intolerable cranberry products as the reason, but supporting data was not given). [Note: In summarizing these results, the authors did not differentiate between cranberry juice and cranberry product studies.]

Cost savings were calculated in 1 study, which reported that the mean annual cost for prevention was $624 CAD for cranberry tablets and $1400 CAD for juice; cranberry prophylaxis was most cost-effective when patients had more than 2 UTIs/year. Tablets were calculated to be twice as cost-effective as organic juice.

The authors deemed that many of the studies had design flaws, the most serious of which was a marked difference in the baseline characteristics between treatment arms in 1 study. Only 6 trials included all patients who had been randomly assigned in the analysis, while the remainder (where it could be determined) excluded 5-50% of patients. Nineteen studies may have been underpowered due to overoptimistic power calculations, resulting in populations that were too small (and made even smaller by high dropout rates) for statistical significance.

The 2008 Cochrane review concluded that there "was some evidence to show that cranberries (juice and capsules) can prevent recurrent infections in women. However, the evidence for elderly men and women was less clear, and there is evidence that (it) is not effective in people who need catheterization." After the addition of 14 studies (and exclusion of 12 others), this 2012 review concludes that, "Cranberry products do not significantly reduce the risk of repeat symptomatic UTI compared to placebo or no treatment in groups of people at risk of repeat UTI (overall RR: 0.86, 95% CI: 0.71 to 1.04) or for any of the subgroups analyzed." [Note: Criticisms of this review were recorded in the press; it is worthwhile to read these discussions to get another perspective, which question the validity of this type of meta-analysis for comparing studies on complex food product formulations, given the heterogeneity and lack of standardization.[1]]

The authors comment that it seems unlikely that cranberry juice would be a sustainable therapy given that it must be drunk twice a day for a year to prevent 1 UTI. Capsules or

tablets may be a more manageable regime, but the studies to date did not provide information on the PAC content, making it difficult to draw strong conclusions. The authors conclude by saying that additional studies are justified for women with recurrent UTIs, but only if the treatment contains the recommended minimum amount of PACs (at least 36 mg/d), quantified by using validated analytical methods and certified reference standards.

—Risa Schulman, PhD

Editor's Note:
Another article summarizing this review and adding perspectives on it was published as a Research Review in *HerbalGram* 97:
http://cms.herbalgram.org/herbalgram/issue97/hg97-resrvw-craberry.html.

Reference

[1]Smith T. Cochrane Collaboration Revises 2008 Conclusions on Cranberry for UTI Prevention. *HerbalEGram*. December 2012;9(12). http://cms.herbalgram.org/heg/volume9/12December/cochranecranberryUTI.html?t=1355348828. Accessed April 18, 2013.

The American Botanical Council has chosen not to reprint the original article.