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File: ■ Cranberry (*Vaccinium macrocarpon*)
■ Urinary Tract Infections

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RE: Review of Cranberry Use for the Prevention of Urinary Tract Infections

Hisano M, Bruschini H, Nicodemo AC, Srougi M. Cranberries and lower urinary tract infection prevention. *Clinics (Sao Paulo)*. 2012;67(6):661-667.

At least 60% of women contract lower urinary tract infections (UTIs) at some time in their lives. The prevention of UTIs using non-antibiotic sources is of interest because of the adverse side effects of antibiotics. This paper reviews current methods of use of cranberry (*Vaccinium macrocarpon*) and evidence for its benefits in the prevention of UTIs.

Cranberry juice is too bitter to drink on its own; it is most often consumed in a 25% cranberry juice preparation. It contains organic acids, fructose, vitamin C, flavonoids, anthocyanidins, catechins, and triterpenoids. The active ingredients are thought to be anthocyanidins, proanthocyanidins (PACs), and fructose. These act in the body by preventing the adhesion of bacteria to the urothelial wall by physically blocking the pili (filaments) that attach to the cells, thereby impeding infection. This effect is dose-dependent in vitro. In addition, cranberry may reduce the expression of the pili by causing conformational changes in them, as seen in vitro.

It is unclear whether PACs get into the blood in vivo because their large size makes absorption difficult. Only 0.078-5% of the anthocyanins are found to be excreted in the urine. As a result, a separate theory of the mechanism of action of cranberry has been put forth: the PACs may be active in the colon, rendering the *Escherichia coli* that would be responsible for an infection non-infective, before they get to the urinary tract. Clear data showing how cranberries are metabolized in the body to cause an effect in the urinary tract are not available.

There are numerous studies showing the anti-adherence properties of cranberry against not only *E. coli*, but also *Proteus* spp., *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Salmonella typhimurium*, and *Klebsiella pneumoniae*.

Concomitant administration of cranberry with antibiotics, such as amoxicillin, did not impede the activity of the antibiotic in a clinically significant way.

Clinical trials using cranberry have focused on the prevention of UTIs in women, children, and men, and in individuals with conditions such as neurogenic bladder and pregnancy. Most studies have focused on cranberry use for the prevention of cystitis. A 2008 Cochrane

database review of 10 randomized trials that included 1,049 patients showed that there was some preventative benefit over a 12-month period for women who had recurrent infections only.

There have been 3 randomized studies using cranberry versus placebo for UTI prevention that were conducted in young women; 2 showed a significantly lower incidence of UTIs compared to placebo, while the third did not. Another study conducted in women using a combination of cranberry and lingonberry (*Vaccinium vitis-idaea*) juice found a reduced UTI incidence compared to a *Lactobacillus* GG drink or placebo.

Two studies conducted in elderly men and women were inconclusive; 1 showed no significant difference in UTI incidence between the cranberry and placebo groups, and the second showed no significant difference in bacteriuria between the cranberry and placebo groups. There was also no difference between the cranberry and placebo groups in a double-blind, placebo-controlled trial conducted in women with lower urinary tract symptoms (LUTS) due to radiotherapy; however, the study had a small population and poor compliance. A trial with pregnant women in their first trimester showed no significant difference between cranberry and placebo groups in the number of UTIs; however, compliance in this study was poor because of high rates of withdrawal due to nausea, vomiting, and diarrhea. Trials in patients with neurogenic bladder showed no significant difference in UTI-free periods when using cranberry alone or in combination with methenamine hippurate. Similarly, no significant differences between the cranberry and placebo groups were found in 1 study conducted in patients with multiple sclerosis and in 2 studies conducted in patients with intermittent catheterization because of spinal injuries. One study did find a preventative effect in patients with spinal cord injuries, with a significantly lower likelihood and occurrence of UTIs in the cranberry group versus the placebo group.

Two crossover studies conducted in children did not show a significant difference for the cranberry or placebo groups in UTI incidence or bacteriuria. One study using a cranberry-lingonberry juice combination versus a *Lactobacillus* GG drink or placebo showed a significant difference in UTI incidence in young girls with recurrent UTIs.

Trials suggest that a dose of 240-300 ml of 25% juice can prevent 50% of the recurrences of UTIs in women. Twice daily dosages may be the most effective based on the clearance rate from the body. The recommended dose of dried, concentrated juice extract ranges from 600 to >1,200 mg/day divided into 2 or 3 daily doses.

Compliance to treatment is hampered by a number of factors. Study withdrawals ranged from 0-55% and reasons for dropout included gastrointestinal disturbances, pregnancy, and the need for stronger treatment. Cost, the awkwardness of transporting large amounts of liquid, and caloric load were also obstacles. There were a number of adverse side effects reported, including reflux, mild nausea, frequent bowel movements, headaches, elevation in blood glucose levels, and a cutaneous reaction. There are also some concerns about the potential for cranberry use to cause thrombocytopenia and nephrolithiasis. One report of immune-mediated thrombocytopenia was after the ingestion of an unknown amount of cranberry juice. There are conflicting reports from studies that have evaluated the risk for lithiasis.

Cranberry does have some drug interactions, including lowering the clearance of nifedipine oxidase and a potential interaction with warfarin.

Based on their review, the authors conclude that the use of whole fruit cranberry products for the prevention of UTIs, either juices or dried juice powders, cannot be recommended and that future studies should focus on using high PAC formulations instead.

—Risa Schulman, PhD

Referenced article is available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3370320/pdf/cln-67-06-661.pdf.