

Overview on Cranberry and Urinary Tract Infections in Females

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Abstract: Cranberry (*Vaccinium macrocarpon*) has been used for decades to prevent urinary tract infections (UTIs) that are among the most common bacterial infections in women. As to the traditional use of cranberry and its A-type proanthocyanidins' ability to inhibit adherence of the bacterial *P* fimbriae in a dose-dependent manner, clinical trials have been conducted on different subpopulations. A Cochrane meta-analysis in 244 females with symptomatic UTI suggests that the effect was more pronounced in women with recurrent UTIs than elderly males and females or people requiring catheterization. A first head-to-head trial in older females has been published comparing effectiveness of a low-dose antibiotic versus cranberry in which investigators suggest that cranberry products may have a role in older females with recurrent UTI. Still with regard to antibiotic treatment in women, a recently published study investigated also the potential cranberry juice interaction with β -lactam antibiotics supporting the hypothesis that cranberry juice in usual quantities as prophylaxis for UTI is not likely to alter the pharmacokinetics of these oral antibiotics. In addition, the effects of cranberry in pregnant female patients have been investigated. A first pilot trial has been published in which, while a possible protective effect was shown, more than one third of the females withdrew mainly for gastrointestinal upset.

Key Words: cranberry, UTIs in women, UTIs prevention

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Urinary tract infections (UTI) in females are among the most common bacterial infections with almost half of the total females expected to experience 1 UTI during their lifetime. The estimated cost of community-acquired UTI in USA is about 1.6 billion dollar per annum.¹ Cystitis accounts for about 95% of all symptomatic UTIs, whereas 70% to 95% of all uncomplicated UTIs is caused by uropathogenic *Escherichia coli* whose virulence factors, such as fimbriae adhesins, confer the ability to adhere to the host uroepithelium, which is the first step in the colonization and subsequent growth with infection.² Cranberry (*Vaccinium macrocarpon*) has been used for decades to prevent UTIs. It is rich in vitamin C, saccharides, flavonoids (flavonols, anthocyanidins, and proanthocyanidins-tannins acting as natural defense against microbes), gallic, benzoic, citric, and oxalic acids. Originally, cranberry's antimicrobial effect was ascribed to its potential ability to acidify urine, although it seems that at tolerable quantities there is little or no acidification.³ Antimicrobial activity was then ascribed to the ability of

cranberry fructose to inhibit adherence of type 1 fimbriated *E. coli* and of A type proanthocyanidins trimers to inhibit adherence of the *P* fimbriae,^{4,5} which works in a dose-dependent manner.⁶ The antiadherence effect of urine on uropathogenic *E. coli* strains after consumption of cranberry, and its efficacy in preventing bacterial adhesion to uroepithelial cells of the bladder has been shown in several in-vitro and in-vivo studies.⁷

Owing to these properties and traditional use, clinical trials have been conducted and are ongoing in different subpopulations. From the Cochrane database, critical appraisals of these studies show that in regard of treatment no good quality evidence was found to suggest that cranberry is effective.⁸ Regarding prevention, 10 RCTs were considered⁹; a meta-analysis done by using data from 665 patients from 4 of these studies^{10–13} revealed that cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.66, 95% CI: 0.47-0.92, $P=0.01$) compared with placebo/control. In particular, the data available from the meta analysis of 2 studies for symptomatic UTI in 244 females—mean age 32 and 42 years, treated for 6/12 months^{10,11} show a risk ratio of 0.61 (CI: 0.40-0.91), suggesting that the effect was more pronounced in females with recurrent UTIs than in elderly males and females or people requiring catheterization (NNT 7 vs. 16 of the 4 studies combined). The results of the meta-analysis show that in females with recurrent UTIs daily intake of cranberry products can reduce the incidence of symptomatic UTI.^{9,14,15} Although tolerability has been reported as generally good, the overall drop-out/withdrawal rates varied up to 55%, maybe, also implying that drinking large amounts of cranberry juice is not acceptable over a long period of time. Moreover, despite the generally good methodology of these studies, only two out of 10 used an intention-to-treat analysis,^{11,12} the duration of the studies is not justified, and the variety of cranberry dosage regimens and formulations in these studies is high and without a clear rationale, also considering the chemical composition of the generally not standardized cranberry products.⁹ On the basis of their analysis, the investigators' implications for research are that properly designed double-blind studies longer than 6 months are needed to determine the effectiveness of cranberries in the prevention of UTIs in susceptible populations without using large amounts of juice over a long period as to avoid compliance issues. They also underlined the lack of published studies comparing cranberry with antibacterials for preventing UTIs, as theoretically, cranberry may reduce the risk of the development of antibacterial-resistant organisms. This is increasingly important in very frequent infections with a low risk of severe complications, such as uncomplicated cystitis in which a remarkable increase of antibiotic resistance is seen.¹⁶

In fact, a first head-to-head trial in older females comparing the effectiveness of a low-dose antibiotic versus

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cranberry has then been published. In a 6-month, double-blind study, 137 older females (at least 45 y old, mean age 63) with recurrent UTI were given either 1 capsule of 500 mg of cranberry extract or 100 mg trimethoprim daily. The relative risk of having a symptomatic antibiotic-treated UTI was 1.616 in the cranberry group (95% CI: 0.93, 2.79; $P=0.084$); median time of recurrence was not significantly different, whereas withdrawal occurred in 9% of cranberry versus 16% of trimethoprim-treated patients ($P=0.205$). Investigators conclude that, although less effective than low-dose antibiotics, cranberry products may still have a role in older people with recurrent UTI.¹⁷

Still with regard to antibiotic treatment, a recently published study also investigated the potential interaction of cranberry juice with β -lactam antibiotics after oral administration. In a cross-over trial, 18 healthy females received a single oral dose of amoxicillin 500 mg and 2 g with or without 8 oz of cranberry cocktail containing 27% juice. In parallel, 18 healthy females received cefaclor 500 mg with or without 12 oz of the same cocktail. No significant effect on oral absorption or renal clearance were observed, nor were observed any clinically significant delays in antibiotics absorption supporting the hypothesis that cranberry juice taken at the usual quantities as prophylaxis for UTI is not likely to alter the pharmacokinetics of these oral antibiotics.¹⁸

In addition, the first pilot trial in pregnant female patients has been published, in which 188 pregnant women at less than 16 weeks of gestation were given single or 3 daily doses of cranberry juice (240 mL bottle of 27% juice with a mean proanthocyanidin concentration of 80 mg) or placebo until delivery. Although a possible protective effect was shown (57% and 41% reduction in the frequency of asymptomatic bacteriuria and all urinary tract infection, respectively, in the group receiving the multiple daily dosing), 38.8% of the female patients withdrew, mainly for gastrointestinal upset, which led to alteration of the treatment regimen after about one third of the patients were randomized.¹⁹ Even if there is no direct evidence of safety or harm to the mother or fetus as a result of consuming common dosages of cranberry during pregnancy, caution is warranted in case of predisposition to nephrolithiasis in the consumption of foods containing high amounts of oxalic acid, including cranberry.^{7,20} Caution is also recommended in associating cranberry with warfarin, as possible interactions have been reported.²¹

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