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

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RE: Cranberry Juice Intake Prevented Recurrent Urinary Tract Infections in Women 50 Years of Age and Older

Takahashi S, Hamasuna R, Yasuda M, et al. A randomized clinical trial to evaluate the preventive effect of cranberry juice (UR65) for patients with recurrent urinary tract infection. *J Infect Chemother*. September 8, 2012; [epub ahead of print]. doi: 10.1007/s10156-012-0467-7.

Recurrent cystitis in women is often treated with prophylactic antimicrobial agents. Associated with this treatment are high costs, the potential development of resistant uropathogens, and adverse events. Cranberry (*Vaccinium macrocarpon*) juice is an attractive alternative; it is significantly less expensive, does not induce bacterial resistance, and adverse effects are rare (other than complaints about the taste). However, clinical evaluations of its efficacy in treating recurrent urinary tract infections (UTIs) have produced mixed results. These Japanese authors conducted a randomized, placebo-controlled, double-blinded trial to examine the effect of cranberry juice (UR65) or a placebo beverage on the rate of relapse in patients with UTIs who had suffered multiple relapses.

The 24-week study was conducted at 40 urology clinics in Japan from October 2007 to September 2009. Eligible subjects were outpatients aged 20 to 79 years with exacerbation of acute uncomplicated cystitis or chronic complicated cystitis with a history of multiple UTIs in the past year and in whom the efficacy of antimicrobial agents was confirmed. Exclusion criteria were comorbid urological or systemic disease, severe medical complications, cranberry allergy, and subjects otherwise deemed ineligible by the clinic doctor.

Of the 213 female subjects included in the study, 107 were randomly assigned to Group A to receive cranberry juice (UR65) and 106 to Group P to receive the placebo beverage. The color and taste of the drinks were adjusted to maintain adequate blinding.

UR65 contained more than 40 mg of proanthocyanidins per 125 mL (Kikkoman Food Products and The Nisshin Oillio Group; Tokyo, Japan). Subjects drank 1 bottle (125 mL) of cranberry juice or the placebo beverage once daily at bedtime for 24 weeks. They

visited a clinic every 4 weeks, during which time they were interviewed about their symptoms and any adverse events.

The primary endpoint was a UTI requiring antibiotic treatment. Upon being diagnosed with a relapse, subjects discontinued the study beverage and were withdrawn from the study. Only 1 subject reported an adverse event—a strong burning sensation after drinking the study beverage for the first time. The beverage was discontinued and the symptom was resolved by the next day.

The authors report no significant difference in the UTI relapse rates between the 2 groups. Relapse was observed in 32 of 107 subjects (19.9%) in Group A and 38 of 106 subjects (35.8%) in group P. A subset of 170 subjects with acute uncomplicated cystitis was analyzed separately, but again, no significant difference between the 2 groups was found.

Further analysis of the acute cystitis subset identified 52 subjects <50 years, and 118 subjects aged ≥50 years. No significant difference in relapse rate was seen in the younger group; however, in the older subjects, a significant difference in UTI relapse rates was seen in 16 of 55 subjects (29.1%) in Group A and 31 of 63 subjects (49.2%) in Group P (log-rank test, P=0.0425).

To identify the factors responsible for UTI relapse in the ≥50-year-old subjects, a multivariate analysis using Cox's proportional hazards model was conducted. The results revealed that drinking cranberry juice had a marginally significant effect in the prevention of UTIs (hazard ratio [HR], 0.545); that aging was significantly associated with relapse (HR, 1.037); and that a history of recurrent UTIs during the preceding year was not associated with relapse (HR, 0.909).

The scientific literature contains conflicting reports regarding the efficacy of cranberry products in preventing recurrent UTIs. Its prophylactic effect is supported by experimental evidence. Cranberry inhibits the adherence of *Escherichia coli* to bladder cells,[1] and this effect is proportional to the proanthocyanidin concentration in the juice.[2] The metabolism of the constituent quinic acid produces hippuric acid, which acidifies the urine and exerts a strong bacteriostatic effect. However, evidence that cranberry ingestion results in therapeutic concentrations of these compounds is lacking.

A 2008 Cochrane review[3] concluded that over a 12-month period, cranberry juice may decrease the number of recurrent UTIs, especially in the female sub-population (mostly pre-menopausal or sexually active women). However, a 2011 placebo-controlled study involving 319 college women reported there was no significant difference in relapse rates.[4] A systematic review analyzing 10 clinical trials published prior to November 2011 concluded that cranberry-containing products are associated with a protective effect against UTIs but the reviewers cautioned that this finding should be interpreted in the context of substantial heterogeneity across trials. [5] The results of this Takahashi et al. study support the heterogeneity proviso, as a clinical effect was only seen once the data set was restricted to the more homogeneous acute cystitis sub-population.

A key challenge in prevention studies is statistical power; the lower the recurrence rate of the disorder, the more participants are required to detect a significant difference. The ≥50-year-old group had a higher risk of UTI recurrence (HR, 1.037). Conversely, the <50-year-old cohort was much smaller and had a much lower risk of recurrent UTI (the

relapse rate was only 12% in the placebo group). The authors suggest that the lack of statistical significance in the overall results may be due to those factors (and they may also explain why some previous studies failed to detect any significant differences).

Compliance is also a substantial challenge in prevention trials. This study required participants to drink the beverage every night for 168 nights. The authors state that doctors "strictly confirmed the regular intake of the beverage," but with no other checks in place, protocol compliance must be questioned.

In order to obtain more definitive results, future trials should enroll more homogeneous high-risk subject pools, use more conservative estimates of relapse rates to ensure sufficient statistical power, and employ more robust compliance protocols such as random urine analysis.

—Shari Henson

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