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Cranberries and Urinary Tract Infections

By Lynn Keegan, RN, PhD, AHN-BC, FAAN

Dr. Keegan is Director, Holistic Nursing Consultants, Port Angeles, WA; she reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

URINARY TRACT INFECTION (UTI) IS ONE OF THE MOST COMMON bacterial infections in women and has significant financial implications. About 60% of women experience at least one UTI during their lifetime, and up to 20% will experience recurrence.¹

Various risk factors predispose women of different age groups to recurrence. These factors include sexual intercourse, use of contraception, antimicrobials, estrogen, genetics, and the distance of the urethra from the anus.

Of the different pathogens, *Escherichia coli* is the organism most commonly isolated. Often, recurrent infections stem from a strain or type of bacteria that is different from the infection before it, indicating a separate infection. Even when several UTIs in a row are caused by *E. coli*, slight differences in the bacteria indicate distinct infections.²

A variety of treatment options has been proposed, including long-term or post-intercourse prophylaxis and patient-initiated therapy. Estrogen and cranberry juice have also been used as prophylactic treatment adjuncts. At present, these and other therapeutic and preventive modalities are being investigated, including the development of vaccines to treat those most severely affected.³

Cranberry Use

Until recently, antibiotics have commonly been used to decrease the frequency of acute episodes. Indeed, the majority of women referred to specialists for chronic UTI are prescribed long-term, low-dose antibiotic prophylaxis, but this can be expensive, can have side effects, and may lead to resistance.

Given the magnitude of this problem, it is safe to state that large numbers of women are experimenting with alternative remedies such as drinking cranberry juice or ingesting herbal remedies to

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enhance the immune response.

Food supplements based on cranberries are said to prevent recurrent urinary tract infections.⁴ Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the prevention and treatment of UTIs.⁵ A recent study has shown the juice or extract of cranberry (*Vaccinium macrocarpon*) should be used to prevent and treat UTIs.⁶

Although cranberry juice is the form of cranberries most widely used, other cranberry products include cranberry powder in hard or soft gelatin capsules. For additional information see the National Center for Complementary and Alternative Medicine's web page specifically for information about cranberries (available at: <http://nccam.nih.gov/health/cranberry/>).

Mechanism of Action

Cranberry, which is rich in polyphenols, including anthocyanins and proanthocyanidins, has been found to have various effects beneficial to human health, including prevention of UTIs. These effects have been associated with polyphenols in the fruit.⁷ The cranberry produces antimicrobial compounds as well, such as proanthocyanidins in response to microbial invasion.

In vitro, cranberry is able to prevent growth, adhesion, or biofilm formation of a large number of bacteria; clinically, cranberry juice has been shown to prevent UTI in women.⁸

Cranberry extracts and juices also contain quinic acid, which causes hippuric acid to be excreted in the urine. Because bacteria prefer an alkaline pH for growth, acidification was thought to be the mechanism of action.⁹ Traditionally, the juice was thought to cause acidification of the urine resulting in a bacteriostatic effect. However, more recent data have pointed researchers in a different direction.

It is now understood that the most important steps in the pathogenesis of UTIs are the colonization and adherence of uropathogens. Cranberries interfere with the adherence of uropathogens to uroepithelial cells. Therefore, cranberries are potential alternatives in the prophylaxis of UTIs.¹⁰

Summary of Past Research

Many of the clinical studies reported in the literature, and reported previously in this publication (*see Alternative Therapies in Women's Health April 2003*), have suffered from major limitations, even those included in the Cochrane Library reviews. Many trials have not been controlled or randomized, and randomization procedures have not always been described. Crossover designs used in some studies may not be appropriate for studies of UTI. Other limitations include no blinding or failed blinding, lack of controlled diets or dietary assessment, use of convenience samples, and small number of subjects. Sample sizes have ranged from as few as 10 to as many as 192. Trials have been faulted for the large number of dropouts/withdrawals, which may indicate that cranberry juice is not acceptable over longer periods. Intention-to-treat analyses often were not applied. Most studies have been conducted in older or elderly patients. Very few have been in younger patients, with or without comorbidities. Primary outcomes have differed and often have been urinary pH, rate of bacteriuria, biofilm load, and urinary white and red blood cells, rather than UTI.

The National Center for Complementary and Alternative Medicine (NCCAM) developed a cranberry research initiative in 2003 to encourage quality research, both basic and clinical research, on the role of cranberry in the prevention and treatment of UTIs (*see Table 1 for a summary of ongoing NCCAM-sponsored clinical trials*).

Recent Clinical Trials

Two randomized controlled trials involving a total of about 300 young women showed that daily use of cranberry juice or tablets reduced the relapse rate for acute cystitis: On average, treating 100 women for one year prevented at least one urinary tract infection in 15-33

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Table 1					
Ongoing NCCAM-sponsored clinical trials of cranberry for urinary tract infection					
Principle Investigator	Trial	Purpose	Patients	Intervention	Outcome Measure
Barbosa-Cesnik CT	RCT	Determine effect of cranberry on reducing rate of recurrent UTI and duration of symptoms over antibiotics alone	600 college students presenting to health services with acute UTI	Three arms: 8 ounces twice daily of juice containing 27% cranberry juice, 13.5% cranberry juice, or placebo juice	Change at 3 and 6 months in prevalence of bladder, rectal, vaginal, and peri-urethral colonization with <i>E. coli</i> containing known uropathogenic virulence factors relative to placebo controls
Slothers L	Dose-response trial	Determine: minimum dose to achieve 30% prophylaxis of UTI in women with recurrent UTI; dose-response curve; whether PAC concentration correlates with prophylaxis; relationship between cranberry consumption and urinary PAC levels; efficacy against which strains of <i>E. coli</i> ; benefit to 12 months; adverse effects	250 adult women who have had at least two single-organism UTIs in preceding 12 months but currently UTI-free	One of five dose levels: placebo, very low dose, low dose, medium dose, and high dose	Number of single-organism UTIs in a 12-month period
Gupta K	Two-phase: in vitro and RCT	Phase I to assess urinary anti-adherence activity; Phase II to assess effect of low and high doses of cranberry juice on prevention of UTI	NS	High and low dose not specified	Correlation of clinical outcomes and in vitro measures of activity

Key: RCT = randomized controlled trial; UTI = urinary tract infection; PAC = proanthocyanidin; NS = not specified.

Source: National Center for Complementary and Alternative Medicine. Available at: <http://nccam.nih.gov/research/extramural/awards/2006/>. Accessed Jan. 5, 2007.

women.⁴ The daily doses were 7.5 g of concentrate in 50 mL of water, 750 mL of juice, or two tablets of concentrate. In elderly patients, two trials of cranberry-based products in hospitals or nursing homes showed a small reduction in the frequency of relapses.⁴

A Cochrane database search retrieved all randomized or quasi-randomized controlled trials (RCT) of cranberry juice/products for the prevention of UTI in susceptible populations.⁵ Information was collected on methods, participants, interventions, and outcomes (UTIs, symptomatic and asymptomatic, side effects, and adherence to therapy). Quality was assessed using the Cochrane criteria. Seven trials met the inclusion criteria.

The effectiveness of cranberry juice (or cranberry-lin-gonberry juice) vs. placebo juice or water was evaluated in six trials, and the effectiveness of cranberries tablets vs. placebo was evaluated in two trials (one study evaluated both juice and tablets). In two good quality RCTs, cranberry products significantly reduced the incidence of UTI at 12 months compared with placebo/control in women. One trial gave 7.5 g cranberry concentrate daily (in 50 mL), the other gave 1:30 concentrate in either 250 mL juice or in tablet form. There was no significant difference in the incidence of UTIs between cranberry juice vs. cranberry capsules.

A Japanese team investigated the excretion of anthocyanins in human urine after ingesting cranberry juice to determine how much is absorbed by the body.⁷ Eleven healthy volunteers consumed 200 mL of cranberry juice containing 650.8 µg total anthocyanins. Urine samples were collected within 24 hours before and after consumption. Six of 12 anthocyanins identified in cranberry were quantified in human urine by high-performance liquid chromatography coupled with electrospray ionization and tandem mass spectrometry. Among these, peonidin 3-O-galactoside, the second most plentiful anthocyanin in the juice, was found to be most abundant in urine within 24 hours, corresponding to 41.5 nmol (56.1% of total anthocyanins). The urinary levels of anthocyanins reached a maximum 3-6 hours after ingestion, and the recovery of total anthocyanins in the urine over 24 hours was estimated to be 5.0% of the amount consumed. This study found high absorption and excretion of cranberry anthocyanins in human urine.

In another double-blind, randomized, placebo-controlled, crossover study, each volunteer received at dinner (in addition to normal diet) a single dose of 750 mL of a total drink composed of: 1) 250 mL of the placebo and 500 mL of mineral water, 2) 750 mL of the placebo, 3) 250 mL of the cranberry juice and 500 mL of mineral

Table 2**Conventional steps to avoid a UTI**

- Drink plenty of water every day.
- Urinate when you feel the need; don't resist the urge to urinate.
- Wipe from front to back to prevent bacteria around the anus from entering the vagina or urethra.
- Take showers instead of tub baths.
- Cleanse the genital area before sexual intercourse.
- Avoid using feminine hygiene sprays and scented douches, which may irritate the urethra.
- Drink cranberry juice.

Source: National Kidney and Urologic Diseases Information Clearinghouse. Available at: <http://kidney.niddk.nih.gov/kudiseases/pubs/utiadult/>. Accessed Dec. 27, 2006.

water, or 4) 750 mL of the cranberry juice.¹¹ Each volunteer took the four regimens successively in random order, with a washout period of at least six days between each change in regimen. The first urine of the morning following cranberry or placebo consumption was collected and used to support bacterial growth. Six uropathogenic *E. coli* strains, previously isolated from patients with symptomatic urinary tract infections, were grown in urine samples and tested for their ability to adhere to the T24 bladder cell line in vitro. There were no significant differences in the pH or specific gravity between the urine samples collected after cranberry or placebo consumption; however, the investigators reported a dose-dependent significant decrease in bacterial adherence associated with cranberry consumption. The investigators concluded that cranberry juice consumption provides significant anti-adherence activity against different *E. coli* uropathogenic strains in the urine compared with placebo.

The aim of another study was to determine whether consumption of sweetened dried cranberries elicits urinary anti-adherence properties against *E. coli*, as previously demonstrated with cranberry juice and/or sweetened cranberry juice cocktail, compared to unsweetened raisins.¹² Uropathogenic *E. coli* isolates were obtained from five women with culture-confirmed UTIs. Four urine samples were collected from each subject. The first urine sample was collected before any study intervention. The second urine sample was collected 2-5 hours after consumption of one box (42.5 g) of raisins. The third urine sample was collected 5-7 days later. The final urine sample was collected 2-5 hours after consumption of approximately 42.5 g of dried cranberries.

Of the urine samples collected after dried cranberry consumption, one demonstrated 50% anti-adherence activity, two demonstrated 25% activity, and two did not show any increased activity. None of the control urine samples and none of the post-raisin consumption samples demonstrated any inhibitory activity. Data from this pilot study of only five subjects suggest that consumption of a single serving of sweetened dried cranberries may elicit bacterial anti-adhesion activity in human urine, whereas consumption of a single serving of raisins does not.

Adverse Effects

Adverse effects appear to be negligible. However, several case reports of interactions with warfarin have been published, including one involving severe bleeding. Patients on vitamin K antagonists must be warned about this risk of interactions so that they avoid consuming cranberry-based products without medical supervision.⁴

Conclusion and Recommendations

Randomized studies have confirmed that the proanthocyanidin contained in cranberries can inhibit *E. coli* adhesion to the urothelium and could be useful to treat urinary infections. Clinical studies have shown that the incidence of acute cystitis decreased when treated with cranberries, confirming the probable benefit of this fruit as a prophylactic treatment for female cystitis. Cranberry juice and extract have biologic effects against bacterial adhesion in the bladder. Prescription modalities remain to be defined.⁶

Case reports of bleeding with concomitant warfarin use are the only significant adverse effects noted with this long-used folk remedy. (See Table 2 for practical tips patients can take to avoid a UTI). For those concerned about the high sugar content of cranberry juice, oral capsule extracts are an available option.

This area is ripe for more investigation. Studies could relate to dose intake, use of cranberry products in control and experimental groups combined with antibiotics, or comparing the effects of cranberry in children, adults, and the elderly. ❖

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Green Tea Reduces Mortality Due to Cardiovascular Disease—Most Notable in Women

By Donald Brown, ND

Dr. Brown is Founder and Director, Natural Product Research Consultants, Inc.; serves on the Advisory Board of the American Botanical Council and the President's Advisory Board, Bastyr University, Seattle, WA; and is an Advisor to the Office of Dietary Supplements at the National Institutes of Health; he is a consultant for Nature's Way, Inc.

Source: Kuriyama S, et al. Green tea consumption and mortality due

to cardiovascular disease, cancer, and all causes in Japan: The Ohsaki study. *JAMA* 2006;296:1255-1265.

Abstract: In a population-based, prospective study (The Ohsaki National Health Insurance Cohort Study), Japanese adults were studied for a possible association between green tea consumption and all-cause and cause-specific mortality. The study included 40,530 Japanese adults (aged 40-79 years) with no history of stroke, coronary heart disease, or cancer at baseline. Participants were followed for up to 11 years (1995-2005) for all-cause mortality and for up to seven years (1995-2001) for cause-specific mortality (e.g., cardiovascular disease, cancer). The primary outcome measures were mortality due to cardiovascular disease, cancer, and all causes. A self-administered questionnaire included items on dietary intake (a 40-item food frequency questionnaire). Among the items was frequency of recent average consumption of four beverages (green tea, oolong tea, black tea, and coffee). The frequency of green tea consumption was divided into five categories: never, occasional, 1-2 cups/d, 3-4 cups/d, and 5 or more cups/d. Within the study region, the volume of a typical cup of green tea is 100 mL.

Over the 11 years of follow-up (follow-up rate, 86.1%), 4,209 participants died. Over the seven years of follow-up (follow-up rate of 89.6%), 892 participants died of cardiovascular disease and 1,134 participants died of cancer. Green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease. The inverse correlation for all-cause mortality was greater in women ($P = 0.03$ for interaction with sex). In men, the multivariate hazard ratios of mortality due to all causes associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/d, 0.93 (95% confidence interval [CI] 0.83-1.05) for 1-2 cups/day, 0.95 (95% CI 0.85-1.06) for 3-4 cups/d, and 0.88 (95% CI 0.79-0.98) for 5 or more cups/d ($P = 0.03$ for trend). The data for women were 1.00, 0.98 (95% CI 0.84-1.15), 0.82 (95% CI 0.70-0.95), and 0.77 (95% CI 0.67-0.89), respectively ($P < 0.001$ for trend).

The inverse correlation was greater for cardiovascular disease mortality than all-cause mortality and this was most notable in women. In women the multivariate hazard ratios of cardiovascular disease mortality across increasing green tea consumption were 1.00, 0.84 (95% CI 0.63-1.12), 0.69 (95% CI 0.52-0.93), and 0.69 (95% CI 0.53-0.90), respectively ($P = 0.004$ for trend). Among the types of cardiovascular disease mortality, the greatest inverse correlation was noted for stroke mortality. The hazard ratios of cancer mortality were not significantly different from 1.00 in all green tea categories compared with the lowest-consumption category and did not differ by sex.

Comments

As opposed to our coffee-fueled culture (broadcasting here from the home of Starbucks), tea is the most consumed beverage in the world aside from water with 3 billion kg of tea produced each year worldwide. This fascinating population-based, prospective study suggests

that the more green tea consumed daily, the greater your chances of staying alive—especially if you're a woman. Compared with participants who consumed less than 1 cup of green tea per day, those who consumed 5 or more cups per day had a risk of all-cause and cardiovascular disease mortality that was 16% lower (during 11 years of follow-up) and 26% lower (during seven years of follow-up), respectively. It should be noted that smoking was greater among males in this study and may explain some of the decreased significance in green tea protection when compared to females. This is the largest study to date to show this remarkable correlation with decreased risk of cardiovascular disease and the results support those found in earlier population studies.^{1,2} However, one earlier population trial found an inverse correlation between green tea and cancer mortality when considering both men and women;² this study failed to show a correlation.

When considering studies that have focused only on women, the news of the chemopreventive effects of tea is far more compelling. A 2006 study published in *Archives of Internal Medicine* reported an inverse correlation between green tea consumption and risk of ovarian cancer in 61,057 Swedish women followed for up to 17 years.³ As was the case with the *JAMA* study reviewed above, this effect was dose-dependent with those women consuming two or more cups of green tea per day having the lowest incidence of ovarian cancer. Another study found that increased consumption of green tea post-diagnosis improved the survival of Chinese women with epithelial ovarian cancer.⁴

The data on protection against breast cancer and breast cancer recurrence are equally impressive. In a case-control study in Los Angeles County focused on Asian-American women, an inverse correlation was found between green tea consumption and risk of breast cancer.⁵ Another study found that consumption of 5 or more cups of green tea per day prior to cancer diagnosis was associated with a decreased risk of recurrence in Japanese women with stage I and II breast cancer.⁶ No improvement in prognosis was noted for women with stage III breast cancer.

Conclusion: It may be safe to assume that we should be telling our female patients to switch out a few of those lattes for green tea. Large population studies suggest that risk of cardiovascular disease, ovarian cancer, and breast cancer in women are all reduced with increased intake of green tea. Caffeine-free versions are widely available for those persons sensitive to caffeine. Finally, it's important to remember that these studies were conducted with populations consuming green tea as a beverage and not in capsules. Recent case studies

suggesting a possible link between encapsulated green tea extracts and hepatotoxicity suggest more careful analysis of these products before recommending them as a tea substitute.⁷ ❖

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Many U.S. Women Use CAM, but Not Specifically to Help with Menopause

CAM use among midlife U.S. women is high, although CAM is not used specifically for menopausal concerns, a study says.

Researchers in the study wanted to obtain national estimates of CAM use for U.S. midlife women. To do this, the researchers looked at data from the 2002 National Health Interview Survey. The survey, which had a 74% response rate, included a CAM supplementary questionnaire. The analysis looked at the more than 3,600 female respondents between 45 and 57 years of age who had answered all of the relevant questions.

The researchers found that 45% of women 45-57 years of age had used some form of CAM within the last 12 months. Approximately 25% used biologics (e.g., herbs) or mind-body (e.g., biofeedback) modalities, whereas only 15% used body work (massage and chiropractic medicine). Use did not vary by age, but white

race, higher education, and residence in the West were associated with increased use. Only 45% of CAM users mentioned its use to a medical provider. The most cited reason for using CAM involved treatment of pain, with only 3% mentioning menopause. However, the odds for use of CAM were almost twice as high for women with menopausal symptoms in the past year compared with women with no symptoms.

The results were published ahead of print in the online version of the journal *Menopause* in November.

Diabetes Not an Independent Predictor of CAM Use, Study Finds

A new study has found a dramatic increase in overall use of CAM in adults with diabetes, although diabetes was not an independent predictor of overall use of CAM.

To determine national patterns and correlates of CAM use among adults with diabetes, researchers

CME Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a credit letter. Upon receipt of your evaluation, a credit letter will be mailed.

CME Questions

4. Which of the following factors predispose women to recurrence of urinary tract infection?
 - a. Sexual intercourse
 - b. Use of contraception
 - c. Antimicrobial use
 - d. Distance of the urethra from the anus
 - e. All of the above
5. Which of the following pathogens is most commonly implicated in urinary tract infection?
 - a. *Haemophilus influenzae*
 - b. *Escherichia coli*
 - c. *Proteus mirabilis*
 - d. *Pseudomonas aeruginosa*
6. Several case reports have been published of interactions between cranberry and warfarin.
 - a. True
 - b. False
7. In large population studies which of the following is reduced with increased intake of green tea?
 - a. Cardiovascular disease
 - b. Ovarian cancer
 - c. Breast cancer
 - d. All of the above

Answers: 4. e, 5. b, 6. a, 7. d.

compared CAM use in 2,474 adults with diabetes to 28,625 adults without diabetes. These adults had participated in the 2002 National Health Interview Survey on CAM use.

Eight CAM use categories were created, including dietary, herbal, chiropractic, yoga, relaxation, vitamin, prayer, and other (acupuncture, Ayurveda, biofeedback, chelation, energy healing or Reiki therapy, hypnosis, massage, naturopathy, and homeopathy), according to the study abstract, published in the November issue of the *Journal of Alternative and Complementary Medicine*. An overall CAM use category also was created that excluded vitamins and prayer.

Patterns of use were compared with chi-square and independent correlates of CAM use with multiple logistic regression controlling for relevant covariates. STATA was used for analysis.

The researchers found that prevalence of overall use of CAM did not differ significantly by diabetes status. Diabetes was not an independent predictor of overall use of CAM. However, persons with diabetes were more likely to use prayer, but less likely to use herbs, yoga, or vitamins than people without diabetes after controlling for relevant covariates. Independent correlates of overall use of CAM differed by age, income, employment, comorbidity, and health status between people with and without diabetes.

Many Physicians Not Comfortable Counseling Patients about CAM Treatments

A recent study found that many internists aren't comfortable counseling patients about complementary and alternative medicine (CAM) treatments or referring them to a CAM practitioner.

To evaluate the attitudes of physicians at an academic medical center toward CAM therapies and the physicians' knowledge base regarding common CAM therapies, researchers e-mailed 660 internists at Mayo Clinic in Rochester, MN, and sent them a link to a web-based survey.

According to the results, published in the December 2006 issue of *Evidence-based Complementary and*

Alternative Medicine, 76% of the 233 physicians who responded to the survey had never referred a patient to a CAM practitioner. However, 44% stated that they would refer a patient if a CAM practitioner were available at their institution.

Fifty-seven percent of physicians thought that incorporating CAM therapies would have a positive effect on patient satisfaction, and 48% believed that offering CAM would attract more patients. Most physicians agreed that some CAM therapies hold promise for the treatment of symptoms or diseases, but most of them were not comfortable counseling their patients about most CAM treatments. Prospective, randomized controlled trials were considered the level of evidence required for most physicians to consider incorporating a CAM therapy into their practice.

Although many physicians are interested in helping their patients make informed decisions, most do not feel qualified to do so, the researchers say. "The study highlights the need for educational interventions and the importance of providing physicians access to evidence-based information regarding CAM." ❖

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