

UCLA
Nutrition Bytes

Title

Cranberry Juice for Prevention of Urinary Tract Infection in Women

Permalink

<https://escholarship.org/uc/item/97q108hd>

Journal

Nutrition Bytes, 8(1)

ISSN

1548-4327

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Publication Date

2002

Peer reviewed

Introduction

Urinary tract infections (UTI) are among the most common bacterial infections in women, and it has been estimated that as many as 60% of women will suffer a UTI at some point in their life (4). Although the incidence rate is similar among males and females during early childhood, adult women are 50 times as likely as adult men to develop a UTI. At least 1/3 of patients suffer recurrences within the first year following an infection, and the risk increases with time (4). A study involving celibate nuns indicated that sexual activity is the greatest risk factor (7), although a substantial proportion of patients may not fall into this category. *Escherichia coli* is the most common cause, accounting for roughly 80% of infections, while another 10% of cases are caused by *Staphylococcus saprophyticus* (7). The remainder is made up by a multitude of pathogenic bacteria, including *Klebsiella*, *Enterobacter*, *Serratia*, and *Staphylococcus aureus*. It has long been known that the major source of pathogenic bacteria is fecal in origin (4).

The standard of treatment for urinary tract infections is antibiotic therapy targeted at the pathogenic bacteria. Additionally, patients may be advised to consume large amounts of water to essentially dilute the urine and flush out the infection (8). Most UTI's respond well to treatment within 3-7 days. Given the high rate of recurrence, especially among women older than 55 years, prophylactic antibiotic therapy is sometimes recommended in high-risk patients. The usual regimen is low dose oral antibiotic therapy using a variety of drugs, including ciprofloxacin, ofloxacin, trimethoprim, and nitrofurantoin (7). Although this treatment virtually eliminates recurrence of UTI, it is not desirable in most patients because of potential side effects, cost, and the development of antibiotic resistance. An alternative that many practitioners turn to is cranberry juice.

The Fruit

The cranberry is a native North American fruit of the *vaccinium* genus. It has always been used as a food, but its potential medical benefits can be traced back to the Penobscot Tribe of Maine, who introduced the fruit to European settlers as a treatment for kidney stones and other urinary problems (1). Cranberries have also been used historically as a remedy for liver ailments, gall bladder disease, vomiting, and scurvy (1). The juice of the ripe fruit is acidic and astringent, making it very difficult to eat or drink alone. During the 1950's, the first cranberry cocktail was made by diluting the juice with water and sweeteners, making it more palatable. Folklore and anecdotal evidence helped spread the belief that cranberry juice helped prevent UTI's, although no significant scientific evidence existed. Still, ripe cranberries were commonly used to treat UTI's before the advent of antibiotics.

Early Evidence

During the 1800's, German physicians discovered that patients who consumed large quantities of cranberries had elevated levels of hippuric acid in their urine, and a resulting decrease in pH (1). The physicians hypothesized that the acidic environment of the urine

provided a bactericidal environment in which pathogens could not thrive. Subsequent research confirmed the increase in levels of hippuric acid and the potential for decreased pH (9), and many researchers used these findings to proclaim the folklore true by scientific means. More contemporary research, however, has found that the change in pH is short-lived and highly transient, and is only significant when unreasonably large amounts of cranberry juice are consumed (greater than 1.5 liters per day) (10, 11). Thus, it is no longer believed that hippuric acid is responsible for any bactericidal activity that may be associated with cranberries.

Cranberry Juice and Bacterial Adhesion

The process of pathogenesis in UTI involves the adhesion of bacterial colonies to the cells of the urinary epithelium (7). *E. coli*, *Proteus*, *Pseudomonas*, and most other pathogenic bacteria possess fimbriae, which are strand-like appendages that attach to the host cells (3, 4). These fimbriae come in several varieties based on chemical composition, however the two most important are type I fimbriae, and type P fimbriae.

After the discovery that fructose interfered with the adhesion of type I fimbriae, it was suggested that this could explain the benefits of cranberry juice. Most researchers do not accept these findings, however, because it is known that most strains of bacteria that rely on type I fimbriae are non-pathogenic, while pathogenic strains usually use the type P fimbriae (3). Type P fimbriae are not affected by fructose.

Anthocyanidins Inhibit Type P Fimbriae Adhesion

Anthocyanidins are a subclass of flavonoids found mainly in cranberries and blue berries. They are polyphenolic phytochemicals that have been shown to possess potent antioxidant activity, as well as the ability to scavenge reactive oxygen and nitrogen species (12). Most importantly, however, anthocyanidins have been shown to inhibit the adherence of uropathogenic bacteria by interfering with type P fimbriae (3, 12). Most of the current research supporting cranberry juice as prophylaxis for UTI site anthocyanidins as the active ingredient.

Although the mechanism of action has not been conclusively elaborated, it has been argued that anthocyanidins somehow prevent type P fimbriae from attaching to uroepithelium (1, 2, 3, 13). Some research suggests that anthocyanidins may reduce the expression of fimbriae at the nuclear level (14). This theory is supported by the observation that anthocyanidins are more effective in preventing adhesion than in dislodging actively bound bacteria (15). At least one study has suggested that cranberry juice may work by selecting for less adhesive bacteria in feces by reducing the expression of type P fimbriae (recall that most uropathogens originate in feces) (4). This theory may also explain why cranberry extract is effective as a preventative measure, but not as a treatment.

Evidence that Cranberry Juice Prevents Recurrence of Urinary Tract Infection

A recent study conducted by Kontiokari et al. showed a significant reduction in the recurrence of UTI in women at a university hospital in Finland (13). Of 50 patients in the control group who consumed no cranberry juice during the study, 18 (36%) had a recurrence of UTI within one year. The experimental group consisted of a similar group of 49 people that were treated with 50 mL of cranberry concentrate per day, diluted to 200 mL with water. Of the experimental group, only 8 (16%) had a recurrence of UTI within one year, resulting in an absolute risk reduction of 20%, and a relative risk reduction of 56%. The validity of this study may be called into question, however, because the sample size was relatively small, the researchers were not blinded as to treatment arm selection, and there was an overall dropout rate of 9%.

In another study, 153 elderly female patients were randomly and blindly assigned to a placebo group and an experimental group that consumed 300 mL of cranberry juice per day (16). The outcome measured was the presence or absence of bacteria (bacteriuria) and white cells (pyuria) in the urine. 15% of the experimental group was found to have bacteriuria and pyuria, while 28% of the placebo group had bacteriuria and pyuria. The difference between treatment arms was not significant until one month into the study, and most patients testing positive were asymptomatic. The major criticism of this study is that the major outcome measured was not UTI, but a condition requiring no treatment. This study was also plagued by a high dropout rate, so its results should be questioned.

Dignam et al. conducted a large study of 538 nursing home residents (17). All residents were treated simultaneously with cranberry extract (in juice or capsule form), and the rate of UTI incidence was compared to historical controls. The study found that the incidence of UTI fell from an average of 27 per month to 20 per month after administering cranberry juice. Significant criticism of this study also hinders its acceptance, however.

Walker et al. conducted a study using cranberry capsules alone (no juice) (18). In this study, a small number of volunteers that were highly prone to UTI recurrence were assigned to a placebo group for 3 months, then to an experimental group for 3 months that was treated with cranberry capsules. Only 10 patients completed the six-month study, and during that time there were 15 UTI's during the placebo phase, and only 6 during the experimental phase. While the difference between the two groups seems large, it is not statistically significant. Given the incredibly small size of the study and the high dropout rate, it is impossible to accept this study as statistically significant.

A multitude of other studies have been conducted, and many make the claim that cranberry juice is effective in preventing urinary tract infection. To date, no evidence exists to suggest that cranberry juice is effective as a treatment, however, and no study has been conducted to compare the effectiveness of antibiotic therapy with cranberry juice as the sole treatment for UTI. Many of the studies currently available produce results that are not statistically significant, and an even greater number produce results that are widely criticized for poor design. A recent publication by Jepson et al. concluded that to date, "there is no good quality evidence to suggest that it [cranberry juice or extract] is effective for the treatment of urinary tract infections" (19).

Conclusion

The use of cranberry juice for the prevention of urinary tract infection has been a home remedy for a long time, and has gained the acceptance of many physicians. Scientific studies have suggested that cranberry juice possesses a bactericidal property that is likely due to the presence of high concentrations of anthocyanidins that prevent bacterial adhesion to uroepithelium. And although several studies have attempted to prove a significant benefit, most have come up short. Most studies are small, often poorly designed, and focused solely on women. To date, there does not exist sufficient evidence to prove definitively that cranberry juice is effective in preventing urinary tract infection. However, there does exist a great amount of data that suggests that cranberry juice may be effective. Given the prevalence of UTI among women, this topic warrants further research. Future studies should assess separately the effects of cranberry juice and other cranberry products in preventing urinary tract infections. The outcomes measured should include reduction in symptoms, recurrence following withdrawal of treatment, side effects, and adherence to therapy. In the mean time, however, current knowledge suggests that consumption of cranberry juice is safe and without major side effects (20), so it would not be inappropriate for physicians to advise patients that cranberry juice may provide some benefit in preventing UTI. Patients and doctors alike eagerly await a final verdict.

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