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Cranberry Juice for Prevention of Urinary Tract Infection

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Abstract

A urinary tract infection (UTI) is an infection in any part of your urinary system — your kidneys, ureters, bladder and urethra. Lower urinary tract infections are very common diseases. Recurrent urinary tract infections remain challenging to treat because the main treatment option is long-term antibiotic prophylaxis; however, this poses a risk for the emergence of bacterial resistance. Some options to avoid this risk are available, including the use of cranberry products. Approximately 1 dozen clinical trials have been performed testing the effects of cranberries on the urinary tract. However, these trials suffer from a number of limitations. This article reviews the methods in using cranberries as a preventive measure for urinary tract infections, including in vitro studies and clinical trials.

Keywords: Urinary Tract Infection, Cranberry, Mechanism of action, Prevention

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1. Introduction

A urinary tract infection (UTI) is an infection in any part of your urinary system - your kidneys, ureters, bladder and urethra. Most infections involve the lower urinary tract - the bladder and the urethra.[1] Women tend to get more bladder infections than men.[2] This is probably because women have shorter urethras, so it is easier for the germs to move up to their bladders. Having sex can make it easier for germs to get into your urethra. You may be more likely to get an infection if you do not drink enough fluids, you have diabetes, or you are pregnant. The chance that you will get a bladder infection is higher if you have any problem that blocks the flow of urine from your bladder. Examples include having kidney stones or an enlarged prostate gland.[2, 3]

Lower urinary tract infections (cystitis), the lining of the urethra and bladder becomes inflamed and irritated. Dysuria, frequent urination, Hesitancy, Cloudy, bad-smelling, mild fever is sign and symptoms for cystitis.[4, 5] (Table1). Upper urinary tract infection (pyelonephritis): Symptoms develop rapidly and may or may not include the symptoms for a lower urinary tract infection. High fever, shaking chills, nausea, vomiting, and flank pain are sign of pyelonephritis.[5, 6] (Table 2)

Table 1. Treatment Regimens for Uncomplicated Acute Bacterial Cystitis

Antimicrobial Agent	Dose	Adverse Events
Trimethoprim–sulfamethoxazole	One tablet (160 mg trimethoprim–800 mg sulfamethoxazole), twice daily for 3 days	Fever, rash, photosensitivity, neutropenia, thrombocytopenia, anorexia, nausea and vomiting, pruritus, headache, urticaria, Stevens–Johnson syndrome, and toxic epidermal necrosis
Trimethoprim	100 mg, twice daily for 3 days	Rash, pruritus, photosensitivity, exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrosis, and aseptic meningitis
Ciprofloxacin	250 mg, twice daily for 3 days	Rash, confusion, seizures, restlessness, headache, severe hypersensitivity, hypoglycemia, hyperglycemia, and Achilles tendon rupture (in patients older than 60 years)
Levofloxacin	250 mg, once daily for 3 days	Same as for ciprofloxacin
Norfloxacin	400 mg, twice daily for 3 days	Same as for ciprofloxacin
Gatifloxacin	200 mg, once daily for 3 days	Same as for ciprofloxacin
Nitrofurantoin macrocrystals	50 to 100 mg, four times daily for 7 days	Anorexia, nausea, vomiting, hypersensitivity, peripheral neuropathy, hepatitis, hemolytic anemia, and pulmonary reactions
Nitrofurantoin monohydrate crystals	100 mg, twice daily for 7 days	Same as for nitrofurantoin macrocrystals
Fosfomycin tromethamine	3 g dose (powder) single dose	Diarrhea, nausea, vomiting, rash, and hypersensitivity

Table 2. Inpatient Treatment for Acute Pyelonephritis

First-line therapy
ciprofloxacin (Cipro) 400 mg IV q12h for 10-14d or levofloxacin (Levaquin) 250 mg IV q24h for 10d or levofloxacin (Levaquin) 750 mg IV q24h for 5d
Second-line therapy
Extended-spectrum cephalosporins or penicillins: ampicillin 500 mg IM/IV q6h or ampicillin-sulbactam (Unasyn) 1.5 g IV q6h or piperacillin-tazobactam (Zosyn) 3.375 g IV q6h or ticarcillin-clavulanate (Timentin) 3.1 g IV 4-6h or cefotaxime (Claforan) 1-2 g IV q8h or ceftriaxone (Rocephin) 1 g IV q24h or ceftazidime (Fortaz, Tazicef) 2 g IV q8h All of the above can be administered with or without an aminoglycoside (except in pregnant patients); see Aminoglycosides, below **Carbapenems:** meropenem (Merrem) 500 mg IV q8h or ertapenem (Invanz) 1 g IV q24h or doripenem (Doribax) 500 mg IV q8h Monobactam (penicillin allergy): aztreonam (Azactam) 1 g IV q8-12h
Alternative therapy
Aminoglycosides: gentamicin 3 mg/kg/day IV/IM in 3 divided doses or 7 mg/kg/day pulsed dosing or tobramycin 3 mg/kg/day IV/IM in 3 divided doses or 7 mg/kg/day pulsed dosing or amikacin 10 mg/kg/day IV/IM in 3 divided doses or 20 mg/kg/day pulsed dosing

2. Description

In newborns, infants, children, and elderly people, the classic symptoms of a urinary tract infection may not be present. A doctor can confirm if you have a urinary tract infection by testing a sample of your urine. For some younger women who are at low risk of complications, the doctor may not order a urine test and may diagnose a urinary tract infection based on the description of symptoms. Antibiotics are used to treat UTIs. Most cases of UTIs clear up after a few days of drug treatment, but more severe cases may require several weeks of treatment. Guidelines recommend using nitrofurantoin or trimethoprin-sulfamethoxazole as first-line antibiotic treatments for UTIs. Fluoroquinolones (such as ciprofloxacin) are now only recommended when other antibiotics are not appropriate.[7, 8]

Prevention of UTI:

A number of measures have not been confirmed to affect UTI frequency including: urinating immediately after intercourse, the type of underwear used, personal hygiene methods used after urinating or defecating, or whether a person typically bathes or showers.[9, 10] There is similarly a lack of evidence surrounding the effect of holding one's urine, tampon use, and douching. [1] Constipation can increase your chances of developing a UTI. Treatments for constipation include: increasing the amount of fibre in your diet (20g to 30g of fibre a day), using a mild laxative on a short-term basis, drinking plenty of fluids.[11] Sexual intercourse is one of the most common risk factors for uncomplicated UTIs in women. In addition to abstaining from sex while you have a UTI, the following may reduce the risks from sexual activity, using a diaphragm for contraception can increase the risk of getting a UTI. This is because the diaphragm may press on your bladder and prevent it from emptying completely when you urinate. If you use a diaphragm and have recurring UTIs, you might want to consider changing to another method of contraception. There are 15 different methods of contraception to choose from.[12, 13] Condom use without spermicide or use of birth control pills does not increase the risk of uncomplicated urinated tract infection. Probiotics are beneficial microorganisms that may protect against infections in the genital and urinary tracts. The best-known probiotics are the lactobacilli strains, such as acidophilus, which is found in yogurt and other fermented milk products (kefir), as well as in dietary supplement capsules. The probiotics bifidobacteria and GG lactobacilli may also be helpful. Other probiotics include the lactobacilli rhamnosus, casel, plantarium, bulgaricus, and salivarius, and also Enterococcus faecium and Streptococcus thermophilus. Not all studies show a benefit for probiotics in preventing urinary tract infections. More research is needed.[14, 15]

Cranberries

Cranberries are a group of evergreen dwarf shrubs or trailing vines in the subgenus Oxycoccus of the genus Vaccinium. In some methods of classification, Oxycoccus is regarded as a genus in its own right.[16] They can be found in acidic bogs throughout the cooler regions of the northern hemisphere. While cranberry has been used safely in research, there has been evidence that it also has side effects. These side effects are yet to be proven scientifically. Hence, these should not be reasons not to take cranberry supplements, at least if they are only taken in small doses, and as long as you don't have other conditions that may be affected by the intake of cranberries. Cranberries are very useful for prevention of UTI although there are disadvantage:

1. Cranberries don't seem to work for everyone. Although they may appear to help prevent symptomatic urinary tract infections in some women who are at risk for them, there's no real evidence that cranberries offer any benefit to other groups of people, such as children or seniors. 2) Cranberries don't prevent bacteria from growing in the urinary tract -- they just make it harder for the bacteria to take hold. Cranberry juice also doesn't treat urinary tract infections once they've started.3) Because of their acidity, cranberries can be hard for some people to take. Up to half of people in studies dropped out because of unpleasant side effects like gastroesophageal reflux disease (GERD), upset stomach, nausea, and diarrhea. Many people in the studies also balked at the tart-sweet taste day after day. People who don't like cranberry juice might find cranberry tablets easier to swallow. 4) In addition to its positive effects, cranberry juice can also have a negative effect on the urinary tract. Cranberry juice is high in salts called oxalates. When people drink a lot of cranberry juice, these salts can crystallize into hard urinary oxalate stones, especially in people who already tend to get these types of stones. 5) People who take the blood-thinning medication warfarin should avoid cranberry products because cranberries can interact with warfarin and cause excess bleeding. 6) Drinking cranberry juice or taking cranberry pills isn't cheap. The cost can add up to $1,400 a year for cranberry juice and $624 a year for pills.

Mechanism of action of cranberries:

Cranberries (Vaccinium macrocarpon or Oxycoccus macrocarpus .It differs from V. oxycoccos in the leaves being larger, 10–20 mm long, and in its slightly apple-like taste), blueberries, and lignonberry, a European relative of the cranberry, are three fruits that appear to have protective properties against urinary tract infections. These fruits contain componds called tannins (or proanthocyanadins). Tannins may prevent E. coli bacteria from adhering to cells in the urinary tract, thereby inhibiting infection. Cranberry juice is the best-studied home remedy for UTIs. Many studies have indicated that cranberry juice may help decrease the number of symptomatic UTIs, especially for women with recurrent urinary tract infections. It is not clear what the optimum dosage is for cranberries, or whether it is best to use juice or tablet form although some studies suggest that drinking juice is more effective than taking tablets. Some research recommends drinking at least 1- 2 cups of cranberry juice daily or taking at least 300 - 400

mg in tablet form twice daily.[17, 18] To date the collective data suggest two possible mechanisms of action in the preventive anti adhesion activity of cranberries: A-type PACs are metabolized relatively intact and collect in the urine to provide protective effects from bacteria that migrate from the perineum and vagina; and/or the PACs eliminated through the colon bind to uropathogenic bacteria thus decreasing the virulence of these microbes if they come in contact with the uroepithelium. Indeed, researchers have found that cranberry PACs are absorbed into the bloodstream, accounting for the former preventive effect.[19] Likewise; the authors of the Finnish trial stated their findings support bacterial selection in the stool because subjects in the ranberry group had no increase in UTI recurrence during the six months after they had stopped thecranberry prophylaxis.[20]

Effect of cranberries against antibiotic resistant E. Coli

Given mounting concern over the increase in antibiotic resistant E. coli bacteria, researchers are focusing more attention on alternative measures for the prevention and alleviation of UTI symptoms[21]. In fact, a recent study found that urine collected from women who drank 250 ml (8.5 fluid ounces) of cranberry juice cocktail prevented the adhesion of 80 percent of 39 P-fimbriated E. coli isolates tested and 79 percent of the 24 antibiotic resistant strains.[22] The antiadhesion activity in the subject's urine was noticeable two hours after cranberry juice consumption and lasted up to 10 hours. Of particular interest, these researchers noted that the mechanism by which cranberry juice prevents bacterial adhesion is not likely to increase selective pressure for antibiotic resistant strains.

Effect of cranberries in lower urinary tract infection:

For UTI prevention in young women, there are three randomized studies (cranberry versus placebo) in women with recurrent UTIs. Walker et al. [23] determined incidences of UTIs of 2.4 subjects/year in the cranberry arm and 6.0 subjects/year in the placebo arm ($p<0.0005$). Stothers et al. [24]tested both cranberry juice and tablets versus placebo in women aged 21 to 72 years old and found that 32% of the placebo group contracted a UTI, whereas 20% of the cranberry juice group ($p<0.05$) and 18% of the tablets group ($p<0.05$) contracted UTIs. He also estimated the annual cost of juice and tablets to be US $1,400 and US $624, respectively; the average cost-effectiveness ratios for tablets and juice were US $1,890 and US $3,333, respectively, per UTI prevented.

Cranberry Juice Ineffective against Cystitis[25,26]: Cranberry extract does not prevent urinary tract infections (UTI) and bladder infections, such as cystitis, while any slight advantage would only be seen in women with recurrent UTIs. This is the conclusion of a new study, published in The Cochrane Library. Cranberries and cranberry juice have long been used to ward off UTIs, however, it is unclear how exactly they prevent infection. One theory, reported at a 2010 meeting of the American Chemical Society, suggests that certain sugars and flavanol compounds, present in cranberries, deter bacteria from sticking to cells that line the urinary tract. For this new study Dr. Ruth Jepson and her team from the University of Stirling examined data from 24 studies that included a total of 4,473 people. The treatment groups were given cranberry juice, capsules or tablets, and those in control groups had placebo cranberry products, methenamine hippurate, antibiotics, lactobacillus, water, or nothing. The authors pointed out that the results show that cranberry juice is significantly less beneficial than previous research has stated. The study suggested that cranberry juice is effective only in women suffering from recurrent infections, and did not prove any more effective in preventing UTIs compared with other methods of treatment.

bacteriuria with pyuria in older women: In the first randomized, double blind, placebo-controlled trial studying the effects of cranberry juice cocktail on 153 elderly women, Harvard Medical School researchers found the cranberry drink reduced the incidence of bacteriuria with pyuria in older women by almost 50 percent. While asymptomatic bacteriuria is common for this age group, women more than 65 years old are more likely to experience atleast one UTI a year. During the six-month study period, urine analysis of study subjects consuming 300 ml (10 fluid ounces) of low-calorie cranberry juice cocktail per day showed a decrease in bacteria in the urine after the first study month compared to those drinking placebo. Subjects drinking cranberry juice also demonstrated reduced incidence of UTI during the course of the study. The researchers suggested more randomized trials with younger populations prone to UTI were necessary to further clarify the role of cranberry beverage in the prevention of this common condition.[27]

Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy:

The study in California suggested there may be a protective effect of cranberry ingestion against asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. A total of 188 women were randomized to cranberry or placebo in 3 treatment arms of A-cranberry 3 times daily, B-cranberry at breakfast then placebo at lunch and dinner, and C-placebo 3 times daily. There were 27 urinary tract infections in 18 subjects in this cohort, with 6 in 4 group A subjects, 10 in 7 group B subjects and 11 in 7 group C subjects ($p = 0.71$). There was a 57% and 41% reduction in the frequency of asymptomatic bacteriuria and all urinary tract infections, respectively, in the multiple daily dosing group. However, this study was not sufficiently powered at the alpha 0.05 level (CI 0.14-1.39 and 0.22-1.60, respectively, incidence rate ratios). Of 188 subjects 73 (38.8%) withdrew, most for gastrointestinal upset.[28]

patients undergoing radiotherapy treatment for bladder or cervical cancer: To evaluate UTIs and lower urinary tract symptoms in male and female patients undergoing radiotherapy treatment for bladder or cervical cancer, cranberry juice was administered twice daily for six weeks in a randomized, double-blind, placebo-controlled trial. There was no statistical difference between the groups for the incidence of UTIs (44.1% for

cranberry and 38.3% for placebo, p = 0.267); however, possible explanations for this result could be the small number of patients and poor compliance.[29]

Cranberry juice for urinary tract infection in children

Some evidence suggests that cranberry juice might be beneficial to prevent recurrence of UTI in children. Further studies with robust methodology are needed. However, palatability of cranberry juice is a challenge in children, and the optimal dose has yet to be determined. In a recent double-blind randomized placebo-controlled trial in 7 Finnish hospitals, 255 children treated for UTI were given cranberry juice or placebo for 6 months. The investigators found no differences in timing between first recurrences of UTI (P = .32), but UTI incidence per person-year at risk was 0.16 episodes lower in the cranberry group (P = .035). The number of days on antibiotic therapy was much lower in children receiving cranberry (−6 days per patient-year; P < .001). This suggests a potential for cranberry juice to reduce recurrent UTIs in children.[30, 31]. Two randomized studies on prophylaxis against bacterial UTI in a pediatric neuropathic bladder population were conducted. In 40 patients, drinking 15 mL/kg of cranberry cocktail daily for 6 months did not have any effect compared with water on preventing UTI.19 In another study, 3-month consumption of cranberry concentrate in 15 children had no effect on bacteriuria in this population.20 In a study from Italy, 84 girls divided into 3 groups were randomized to receive 50 mL of cranberry juice, Lactobacillus GG drink, or placebo; there were 5 of 27 (18.5%), 11 of 26 (42.3%), and 18 of 27 (48.1%) episodes of symptomatic UTI, respectively (P < .05). Withdrawal was minimal in all groups.[30, 32]

Effect of cranberry juice in prevention of recurrent UTI

Recurrent urinary tract infections, presenting as dysuria or irritative voiding symptoms, are most commonly caused by reinfection with the original bacterial isolate in young, otherwise healthy women with no anatomic or functional abnormalities of the urinary tract. Frequency of sexual intercourse is the strongest predictor of recurrent urinary tract infections in patients presenting with recurrent dysuria.[33] One study showed that of college women with a first UTI, 27 percent had at least one culture confirmed recurrence within the following six months, and 2.7 percent experienced a second recurrence over the same period[34]. In a primary care setting, 53 percent of women older than 55 years and 36 percent of younger women had a recurrence within one year[35].

Cranberry Juice Fails to Prevent Recurrent Urinary Tract Infection: a group of researcher in Michigan conducted a double-blind, placebo-controlled trial of the effects of cranberry on risk of recurring uti among 319 college women presenting with an acute UTI. Overall, the recurrence rate was 16.9% (95% confidence interval, 12.8%–21.0%), and the distribution of the recurrences was similar between study groups, with the active cranberry group presenting a slightly higher recurrence rate (20.0% vs 14.0%). The presence of urinary symptoms at 3 days, 1–2 weeks, and at ≥1 month was similar between study groups, with overall no marked differences. Among otherwise healthy college women with an acute UTI, those drinking 8 oz of 27% cranberry juice twice daily did not experience a decrease in the 6-month incidence of a second UTI, compared with those drinking a placebo.[36]

In other study researcher in University of Washington conducted a randomizes control trial in which they compare the time to urinary tract infection (UTI) and the rates of asymptomatic bacteriuria and urinary P-fimbriated Escherichia coli during a 6-month period in women ingesting cranberry vs placebo juice daily. A total of 176 participants were randomized (120 to cranberry juice and 56 to placebo) and followed up for a median of 168 days. The cumulative rate of UTI was 0.29 in the cranberry juice group and 0.37 in the placebo group (P=.82). The adjusted hazard ratio for UTI in the cranberry juice group vs the placebo group was 0.68 (95% confidence interval, 0.33-1.39; P=.29). The proportion of women with P-fimbriated urinary E coli isolates during the intervention phase was 10 of 23 (43.5%) in the cranberry juice group and 8 of 10 (80.0%) in the placebo group (P=.07). The mean dose adherence was 91.8% and 90.3% in the cranberry juice group vs the placebo group. Minor adverse effects were reported by 24.2% of those in the cranberry juice group and 12.5% in the placebo group (P=.07). At the end they conclude that Cranberry juice did not significantly reduce UTI risk compared with placebo. The potential protective effect we observed is consistent with previous studies and warrants confirmation in larger, well-powered studies of women with recurrent UTI. The concurrent reduction in urinary P-fimbriated E coli strains supports the biological plausibility of cranberry activity.[37]

3. Conclusion

Studies done since 2008 on the cranberry juice / UTI question, a person had a lower risk of UTI if taking cranberry products compared to no treatment or a placebo. However, the researchers pointed out that this was not a very significant difference and could simply have just been chance. They went on to say that numerous people dropped out of several studies because it was too difficult to drink the necessary amount of cranberry juice on a daily bases. cranberry products cannot be recommended for the prophylaxis of recurrent UTIs at this time however it has potential to reduce recurrent UTIs in children. In the population that benefits most from the prophylactic effect of cranberry intake (sexually active women with recurrent UTI), trial results repeatedly show an ~50% reduction in disease morbidity. From a clinical point of view, this is quite a modest benefit, considering the accompanying burden of long-term daily intake of the compound.

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