



Can a concentrated cranberry extract prevent recurrent urinary tract infections in women? A pilot study

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Abstract

Background: Urinary tract infections (UTIs) are extremely prevalent and despite treatment with antibiotics, reoccurrences are common causing frustration in the patient and the potential for developing antibiotic resistance. The use of cranberry products to prevent UTIs has recently become popular and more clinical studies are needed to explore this use.

Objective: This open label pilot study examined the ability of a concentrated cranberry preparation to prevent UTIs in women with a history of recurrent infections.

Subjects: Women between the ages of 25 and 70 years old were included with a history of a minimum of 6 UTIs in the proceeding year.

Intervention: The women took one capsule twice daily for 12 weeks containing 200 mg of a concentrated cranberry extract standardized to 30% phenolics.

Design: A questionnaire was used initially to determine the patient's medical history and they were asked at monthly intervals if any of the information had changed. All of the women in the study had urinalysis within 24 h before starting on the study preparation and once a month after that for 4 months. Subjects were followed-up approximately 2 years later.

Results: All 12 subjects participated in the 12-week study and were available for follow up 2 years later. During the study none of the women had a UTI. No adverse events were reported. Two years later, eight of the women who continue to take cranberry, continue to be free from UTIs.

Conclusion: A cranberry preparation with a high phenolic content may completely prevent UTIs in women who are subject to recurrent infections.

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Introduction

Urinary tract infections (UTIs) are extremely prevalent, especially in women, the elderly and in infants.

UTIs are defined as the presence of a certain threshold number of bacteria in the urine (usually greater than 100,000 per ml). One in four women who develop a UTI will have a recurrence. The risk factors that predispose women to a recurrence include sexual intercourse, the use of contraception, antimicrobials, estrogen, genetics

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and the proximity of the urethra to the anus. UTIs are caused by microorganisms, principally Gram-negative bacteria, notably *Escherichia coli*. They are usually treated with antibiotics but recurrences frustrate the patient and may contribute to bacterial antibiotic resistance. Due to these concerns, research has begun to focus on prevention (Avon et al., 1994; Pelton, 2000; Lowe and Fragolman, 2001; Franco, 2005; Liu et al., 2006).

Cranberries are small, dark red fruits that are widely consumed as juice and sauce. They come from a shrub, *Vaccinium macrocarpon* Aiton [Ericaceae], native to eastern North America (Winston et al., 2002). The use of cranberry preparations to prevent UTIs became popular in the 1920s when American scientists demonstrated that the urine became more acidic after eating large amounts of cranberries (Blatherwick and Long, 1923). Subsequent studies have shown that the effectiveness of cranberry is not due to its ability to acidify the urine (Liu et al., 2006). As the first step in developing infections, bacteria must bind to the host cell and tissues. The *E. coli* strains that cause UTIs have proteinaceous macromolecules (fimbriae) that facilitate the adhesion of bacteria to uroepithelial cells in the urinary tract. *In vitro* and *ex vivo* studies indicate that cranberry products prevent adhesion of bacteria to the cell walls of the urinary tract, thus preventing UTIs (Di Martino et al., 2006; Liu et al., 2006).

Two types of compounds in cranberry have been identified as having anti-adhesion activity: fructose (a sugar) and proanthocyanidins (condensed tannins). Fructose, a common constituent of fruits, has been shown to inhibit adherence of *E. coli* with type I (mannose-sensitive) fimbriae to cells grown in tissue culture (Zafriri et al., 1989). Cranberry proanthocyanidins have been shown to inhibit adherence of *E. coli* with P-type fimbriae (Howell et al., 1998).

Proanthocyanidins are composed of oligomers (small chains) of flavanol units. The procyanidins in cranberry are unique from those in other fruits as the flavanol units are linked (A-type) in a manner that is different from those found in other fruits (B-type). Recent studies have determined that proanthocyanidins with this A-type linkage are more effective than those with B-type linkages in inhibiting the adherence of bacteria to cell surfaces (Howell et al., 2005). Further, biochemical studies have revealed that in addition to causing the fimbriae on the surface of the bacteria to become compressed, reducing their adhesion, the proanthocyanidins in cranberry may change the shape of the bacteria from rods to spheres and cause chemical changes to their surface membranes (Camesano, 2006).

Several clinical studies have been conducted on the use of cranberry preparations to prevent UTIs. A review published in 2004 found seven studies that met the criteria of randomized controlled studies. The effective-

ness of cranberry juice (or cranberry–lingonberry juice) compared to placebo was evaluated in six studies and the effectiveness of cranberry tablets compared to placebo was compared in two studies (one study included both juice and tablets). Only two of the studies were considered good quality. These studies demonstrated that cranberry significantly reduced the incidence of UTIs after twelve months of treatment (RR 0.61; 95% CI: 0.40–0.91) in women compared to placebo. One study used 7.5 g cranberry concentrate in 50 ml. The other used a 1:30 concentrate in 250 ml juice or in tablet form. There was no significant difference between the effects due to the juice and the effects due to the tablets (Jepson et al., 2004). The authors of this review commented that the optimum dosage of cranberry or form of administration (e.g. juice or tablet) is not clear.

Typical cranberry preparations are dried and ground whole cranberries, or dried cranberry juices. The dried, ground berries commonly contain 0.5% total phenolic compounds, including proanthocyanidins. The dried juice concentrates commonly contain 3–5% total phenolics (private communication, R. Dietz, Eurofins Scientific data, 2006). Through selective extraction of the berries, Phenolics, LLC has produced an extract that contains 30% phenolics (US Patent nos. 6,780,442 and 6,960,360, and European Patent no. 1, 328,282). This extraction process concentrates the phenolic compounds and eliminates other compounds in the fruit such as oxalic acid and other small organic acids, as well as sugars. As this preparation concentrates the active proanthocyanidins, it might be more effective in preventing UTIs. The aim of this study is to test the effects of this concentrated extract on women with recurrent UTIs.

Materials and methods

An open label pilot study of 4 months duration was conducted at Helios Integrated Medicine, PC in Boulder, CO. The study was conducted with women between the ages of 25 and 70 years of age with a history of a minimum of 6 UTIs in the past year. Women who were pregnant, currently using antibiotics, had a major illness or diseases other than UTIs were excluded.

The cranberry product used in this study was manufactured in the US according to the aforementioned-patented processes. It is currently being used by GNC as the ingredient in Cranberry Supreme™. The women took one capsule twice daily for 12 weeks. Each capsule contained 200 mg cranberry extract standardized to 30% total phenols (25% minimum proanthocyanidins). The total cranberry proanthocyanidin intake during the study was approximately 100 mg per day. Total phenols were determined according to the use of Folin–Ciocalteu method (Singleton and Rossi, 1965) as

modified by Slinkard and Singleton (1977) and Cliffe et al. (1994) and reported in milligrams of gallic acid equivalents per gram of extract.

A questionnaire was used initially to determine patient's medical history and they were asked at monthly intervals if any of the information had changed. All of the women in the study had urinalysis within 24 h before starting on the study preparation and once a month after that for 4 months. The urinalysis included a dipstick and microscopy exam on a clean voided midstream first morning urine sample. The dipstick test examined the specimen for red blood cells, nitrates, lymphocytes, protein, glucose, and measured specific gravity. The microscopic exam looked for red blood cells and white blood cells as well as bacteria and casts. Any samples with positive results were to be cultured and sensitivity toward antibiotics determined.

The same patients were followed up approximately 2 years after the study and the same questionnaire used above was reviewed with each patient and any changes noted.

Results-trial

Included in the study were 12 women ranging in age from 25 to 70 years old. The women all had a history of a minimum of 6 UTIs in the preceding year and several had this many infections or more per year for the past several years. Several of the women had been trying to drink cranberry juice on a regular basis or were taking cranberry capsule products from the health food store with varying results. They were told not to take any other berry products during the study. Each of the women was screened prior to administration of the test product and found to be free of a UTI.

All patients were followed for a period of 12 weeks. The study began in May 2004 and concluded in September 2004. There were no dropouts or withdrawals from the study. None of the women developed a UTI during the study, on the basis of symptoms or laboratory results. Based on past history of this patient group, 24 UTI occurrences would have been expected over the 12-week period of the study. None of the subjects reported any adverse effects due to the supplement.

Results-follow-up

Patient follow-up 2 years later revealed that eight of the patients have not had any changes in their health since the study began. They have all continued to take various cranberry supplements prepared by different manufacturers in doses ranging from 150 to 300 mg per day except for occasional days they missed. If they missed taking them for 1–3 days they did not notice any symptoms. Several commented that they took extra

capsules for 1–2 days following more sexual activity than usual, and if they did not do this they could have some UTI symptoms. However, these symptoms did not ever develop into a true UTI and resolved with extra cranberry capsules and an increase in water intake.

Four of the patients stopped taking cranberry supplements for various unrelated medical reasons. One patient remained free of UTIs and two developed symptoms, which resolved upon resumption of cranberry supplementation. One patient developed a UTI confirmed by urinalysis and was treated with antibiotics. She then resumed treatment with cranberry and has not had any further symptoms.

Discussion

This study indicates that women with a history of recurrent UTIs can prevent those infections with daily use of a cranberry extract. The cranberry product used in this study is unique in that it is standardized to 30% phenolics, principally proanthocyanidins. It is much higher in phenolic content than both dried cranberries that contain 0.5% and dried juices that range from 3% to 7%.

As mentioned previously, *in vitro* studies indicate that proanthocyanidins are the active components of cranberry. Bioavailability studies indicate that these compounds are absorbed. A mouse study demonstrated that the urine of the animals had anti-adherence activity (Howell et al., 2001). A human study found that 5% of the total amount of anthocyanins secreted in the urine over 24 h following consumption of 200 ml of cranberry juice (Ohnishi et al., 2006). Another human study reported that the urine of those that ingested 250 or 750 ml cranberry juice demonstrated anti-adherence properties. Uropathogenic *E. coli* strains were grown in the urine of those who consumed either placebo or cranberry juice and then tested for adherence to bladder cells in an *in vitro* assay. The urine from those that drank cranberry juice prevented the bacteria from adhering in a dose-related manner (Di Martino et al., 2006).

Three previous clinical studies that have been conducted on women with a history of recurrent UTIs have reported positive results. However neither the phenolic content nor the proanthocyanidin content of the cranberry products used in these studies have been described. Therefore, we are not able to make any firm judgments regarding the amount of phenolic compounds delivered in these studies.

Unique to this study is that not one of the women developed a UTI during the 12 weeks of treatment. This is in contrast with their history of an infection every 2 months. Further, those women who continued to take a cranberry product remained free from infections 2 years later. Although this is just a pilot study and the results

preliminary, it is a remarkable finding. The three previous clinical studies have published promising results in which the women did not develop as many infections, but none were completely free of them.

A small crossover trial studied 10 sexually active women who had a history of UTIs (four UTIs during the previous year or at least one UTI within the previous 3 months). The subjects were given either 400 mg cranberry extract or placebo, daily for three months before switching treatments. As a result, cranberry concentrate was found to be more effective than placebo in reducing the occurrence of UTI ($p < 0.005$). Nineteen women entered the study; while 10 completed the study and were included in the analysis. While taking cranberry 7 of the 10 subjects exhibited fewer UTIs, 2 subjects exhibited the same number, and 1 subject experienced one more UTI. Of the total 21 incidents of UTIs recorded among the participants during the 6 months, 6 UTIs occurred during the time they were taking cranberry (2.6 per subject year). In contrast, a total of 15 UTIs occurred while on placebo (6.0 per subject year) (Walker et al., 1997). We estimate that at a maximum expected concentration of 5% total phenolics, the subjects might have received 20 mg daily total phenolics. The proanthocyanidin content provided might be 15 mg per day. This amount is approximately one-sixth the 100 mg provided in the preparation used in the current study. The fact that not all infections were prevented in the Walker study indicates that there might be a dose-response effect.

Two parallel group studies were also conducted on women with a history of recurrent UTIs. The first study was a parallel group, placebo controlled study that used a cranberry–lingonberry juice concentrate, described as 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate in 50 ml water. The preparation was compared to a drink containing lactobacillus and no treatment. The study included 150 women (mean age approximately 30 years) from the student health services who currently had a UTI (105 cfu *E. coli* per ml). The outcome measure was the first recurrence of symptomatic UTI as defined above. After 6 months, 16% (8) of the women in the cranberry group, 39% (19) in the lactobacillus group and 36% (18) in the control group had had at least one infection. Thus cranberry reduced the risk of infection by 20% (95% CI, $p = 0.023$) (Kontiokari et al., 2001). We estimate that the amount of proanthocyanidins provided might be 35–40 mg per day. If this is so, this amount would be just over one-third that provided by the preparation used in the current study.

The second study included 150 sexually active women aged 21–72 years that had had at least two symptomatic, single organism, culture positive UTIs in the previous year but currently did not have an infection. The subjects were given either cranberry juice (250 ml three times daily), cranberry tablets (1:30 juice concentrate

twice daily) or placebo using a double dummy method. In the year of treatment, 32% (16) of the placebo group, 20% (10) in the juice group and 18% (9) in the tablet group had at least one infection. The mean number of UTIs was 0.72 in the placebo group, 0.30 in the juice group and 0.39 in the tablet group (Strothers, 2002). This paper did not sufficient information for us to estimate the amount of phenolics or proanthocyanidins given in this study.

Conclusions

The current pilot study adds evidence to three previous studies that indicate that cranberry products are effective in preventing recurrent UTIs in women. *In vitro* and *ex vivo* evidence indicates that the active ingredients in cranberry products are proanthocyanidin compounds that are unique to cranberry. The current study was conducted with a unique cranberry ingredient standardized to 30% phenolics. The results of this preliminary study are unique in that none of the women in the study had a recurrent infection. Further studies are required that include a control group. However, comparison of this study with earlier reports suggests that there is a correlation between the amount of phenolic compounds ingested and prevention of recurrent infections. Additional studies are needed to determine the optimal dose and to compare this product with cranberry juice and other cranberry products containing low concentrations of proanthocyanidins.

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