Cranberries for preventing urinary tract infections (Review)

Jepson RG, Craig JC

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW . . . 3
SEARCH METHODS FOR IDENTIFICATION OF STUDIES . . . 3
METHODS OF THE REVIEW . . . 4
DESCRIPTION OF STUDIES . . . 5
METHODOLOGICAL QUALITY . . . 6
RESULTS . . . 6
DISCUSSION . . . 8
AUTHORS' CONCLUSIONS . . . 9
POTENTIAL CONFLICT OF INTEREST . . . 9
ACKNOWLEDGEMENTS . . . 9
SOURCES OF SUPPORT . . . 9
REFERENCES . . . 10
TABLES . . . 11
Characteristics of included studies . . . 11
Characteristics of excluded studies . . . 19
ADDITIONAL TABLES . . . 19
Table 01. Characteristics of studies . . . 19
Table 02. Study design and quality of reporting . . . 20
Table 03. Asymptomatic UTIs (bacteraemia) . . . 21
Table 04. Symptomatic UTIs . . . 22
ANALYSES . . . 22
Comparison 01. Cranberry products versus placebo/control . . . 22
INDEX TERMS . . . 22
COVER SHEET . . . 23
GRAPHS AND OTHER TABLES . . . 24
Analysis 01.01. Comparison 01 Cranberry products versus placebo/control, Outcome 01 At least one symptomatic UTI 24

Cranberries for preventing urinary tract infections (Review)

Jepson RG, Craig JC

Status: *Updated*

This record should be cited as:
Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub4.

This version first published online: 23 January 2008 in Issue 1, 2008.
Date of most recent substantive amendment: 10 September 2007

ABSTRACT

Background
Cranberries have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs).

Objectives
To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations.

Search strategy
We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*) and the Internet. We contacted companies involved with the promotion and distribution of cranberry preparations and checked reference lists of review articles and relevant studies.
Date of last search: January 2007.

Selection criteria
All randomised controlled trials (RCTs) or quasi-RCTs of cranberry products for the prevention of UTIs in all populations.

Data collection and analysis
Two authors independently assessed and extracted information. Information was collected on methods, participants, interventions and outcomes (UTIs - symptomatic and asymptomatic, side effects, adherence to therapy). Relative risk (RR) were calculated where appropriate, otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane criteria.

Main results
Ten studies (n = 1049, five cross-over, five parallel group) were included. Cranberry/cranberry-lingonberry juice versus placebo, juice or water was evaluated in seven studies, and cranberries tablets versus placebo in four studies (one study evaluated both juice and tablets). Cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95% CI 0.46 to 0.90) compared with placebo/control. Cranberry products were more effective reducing the incidence of UTIs in women with recurrent UTIs, than elderly men and women or people requiring catheterisation. Six studies were not included in the meta-analyses due to methodological issues or lack of available data. However, only one reported a significant result for the outcome of symptomatic UTIs. Side effects were common in all studies, and dropouts/withdrawals in several of the studies were high.

Authors' conclusions
There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. It's effectiveness for other groups is less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules). Further properly designed studies with relevant outcomes are needed.

PLAIN LANGUAGE SUMMARY

Cranberries for preventing urinary tract infections

Cranberries (usually as cranberry juice) have been used to try and prevent urinary tract infections (UTIs). Cranberries contain a substance that can prevent bacteria from sticking on the walls of the bladder. This may help prevent bladder and other urinary tract infections. This review identified 10 studies (1049 participants) comparing cranberry products with placebo, juice or water. There was some evidence to show that cranberries (juice and capsules) can prevent recurrent infections in women. However, the evidence for elderly men and women was less clear, and there is evidence that is not effective in people who need catheterisation. Many people in the trials stopped drinking the juice, suggesting it may not be a popular intervention. In addition it is not clear how long cranberry juice needs to be taken to be effective or what the required dose might be.

BACKGROUND

The term urinary tract infection (UTI) refers to the presence of a certain threshold number of bacteria in the urine (usually greater than 100,000/mL). It consists of cystitis (bacteria in the bladder), urethral syndrome and pyelonephritis (infection of the kidneys). Lower UTIs involve the bladder, whereas upper UTIs also involve the kidneys (pyelonephritis). Bacterial cystitis (also called acute cystitis) can occur in men and women and the signs and symptoms include dysuria (pain on passing urine), frequency, cloudy urine, occasionally haematuria (blood in the urine), and is often associated with pyuria (urine white cell count greater than 10,000/mL). Urethral syndrome (frequency and dysuria syndrome) is used to describe approximately 50% of women with these complaints who have either no bacterial growth or counts less than 100,000 colony-forming units (cfu)/mL on repeated urine cultures. Pyelonephritis most commonly occurs as a result of cystitis, particularly in the presence of transient (occasional) or persistent backflow of urine from the bladder into the ureters or kidney pelvis (vesicoureteric reflux). Signs and symptoms include flank pain or back pain, fever, chills with shaking, general ill feeling plus those symptoms of a lower UTI. Acute pyelonephritis can be severe in the elderly, in infants, and in people who are immunosuppressed (for example, those with cancer or AIDS). Although most people who present to the doctor or hospital have symptomatic UTIs, some can be asymptomatic and only those who are at high risk of developing further infections (pregnant women and the elderly) may require treatment. Some people also have recurrent UTIs with an average of two to three episodes/year (Roberts 1979; Wong 1984). Children typically present with a high fever and systemic symptoms such as lethargy (tiredness), vomiting and poor feeding.

Specific subpopulations at increased risk of developing a UTI. These groups include infants, pregnant women, the elderly, patients with spinal cord injuries and/or catheters, patients with diabetes or multiple sclerosis, patients with acquired immunodeficiency disease syndrome/human immunodeficiency virus, and patients with underlying urologic abnormalities (Foxman 2002). Although UTIs can occur in both men and women, they are about 50 times more common in adult women than adult men. This may be because women have a shorter urethra that may allow bacteria to ascend more easily into the bladder. Symptomatic infection of the bladder (lower UTI) has been estimated to occur in up to 30% of women at some stage during their lives (Kelly 1977). Most UTIs arise from the 'ascending' route of infection. The first step is colonisation of periurethral tissues with uropathogenic organisms, followed by the passage of bacteria through the urethra. Infection arises from bacterial proliferation (growth) within the otherwise sterile urinary tract. In children, UTI occurs more commonly in boys up to the age of six to 12 months, but overall occurs about three times more often in girls (1% to 3% in boys, 3% to 7% in girls) (Hellstrom 1991; Winberg 1974).

Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the prevention and treatment of UTIs. Cranberries comprise nearly 90% water, but also contain various organic substances such as quinic acid, malic acid and citric acid as well as glucose and fructose. Until recently, it was suggested that the quinic acid caused large amounts of hippuric acid to be excreted in the urine which then acted as an antibacterial agent (Kinney 1979). Several studies, however, have shown no difference in the levels, or only a transient (short lived) effect thus casting some doubt on this theory (Kahn 1967; McLeod 1978). No definite mechanism of action has been established for cranberry in the prevention or treatment of UTIs. However, the main suggestion is that cranberries prevent bacteria (particularly *Escherichia coli*) from adhering (sticking) to uroepithelial cells that line the wall of the bladder (Schmidt 1988; Zafriri 1989). Without adhesion, *E. coli* cannot infect the mucosal surface of the urinary tract. In vitro, this adhesion is mediated by two components of cranberry; fructose, which inhibits adherence of type 1 (mannose specific) fimbriated *E. coli*, (Foo 2000) and substances called proanthocyanidins, which inhibit the adherence of p-fimbriated (a-galactose-(1-4) specific) *E. coli* (Zafriri 1989).

UTIs are one of the most common medical conditions requiring outpatient treatment, and complications resulting from persistent and repeated infections necessitate well over one million hospital admissions annually in the USA (Patton 1991). The aim of this review is to assess the effectiveness of cranberries in the prevention

of UTIs in susceptible populations.

The treatment of UTIs with cranberries is evaluated in another review by the same authors (Jepson 1998b).

OBJECTIVES

We wished to test the following hypotheses:

- Cranberry juice and other cranberry products are more effective than placebo/no treatment in the prevention of UTIs in susceptible populations.
- Cranberry juice and other cranberry products are more effective than any other treatment in the prevention of UTIs in susceptible populations.

An attempt was also made to quantify the side effects of cranberry juice and the findings were taken into account in the discussion to determine the risk-benefit of the treatment.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials (RCTs) of cranberry juice (or derivatives) versus placebo, no treatment or any other treatment. Quasi-RCTs (e.g. those studies which randomised participants by date of birth, or case record number) were included, but the quality of the studies was taken into account during the analysis and discussion. Both parallel group and cross-over design were included.

Types of participants

Inclusion criteria

Studies of susceptible men, women or children as defined below. These categories were analysed separately.

- Participants with a history of recurrent lower UTIs (more than two episodes in the previous 12 months).
- Elderly men and women.
- Participants needing intermittent catheterisation.
- Pregnant women.
- Participants with an in-dwelling catheter.
- Participants with an abnormality of the urinary tract.

Exclusion criteria

- Studies of the treatment of asymptomatic or symptomatic UTI (these are analysed in a separate review by the same authors Jepson 1998b).
- Studies of any urinary tract condition not caused by bacterial infection (e.g. interstitial cystitis - a chronic inflammation of the bladder wall).

Types of intervention

Cranberry juice or a cranberry product (e.g. cranberry capsules) given for at least one month. If further studies become available for review, the amount taken/day, concentration of the juice/cranberry product and length of treatment will be taken into account in subgroup analyses.

Types of outcome measures

Primary outcome measure

- Number of UTIs in each group (confirmed by a catheter specimen of urine, mid stream specimen of urine (MSU) if possible, or a 'clean catch' specimen).

The 'gold standard' bacteriological criteria for diagnosis of UTI includes microbiological confirmation from a MSU (or similar method) with greater than 100,000 bacterial cfu/mL, often associated with pyuria (white cells in the urine). In some situations a bacterial count < 100,000/mL is acceptable. For example, when a supra-pubic bladder tap or a catheter urine specimen is obtained. If further studies become available for review, the method of collecting a specimen of urine, the causative organism (e.g. *E. coli*) and the presence of mixed organisms in the urine (which signifies contamination) will be subject to sensitivity analyses.

If further studies become available for review, this outcome will also be subgrouped into rate of symptomatic lower UTIs, rate of symptomatic upper UTIs (UTI plus fever) and rate of asymptomatic UTIs. Symptomatic is defined as having one or more or the following symptoms: dysuria, frequency, urgency.

Methods used to diagnose upper and lower UTIs will also be subjected to sensitivity analysis if enough data is available.

Secondary outcome measures

- Adherence to therapy.
- Side effects.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Renal Group methods used in reviews.

Initial search

Relevant studies were obtained from the following sources (date of last search January 2007):
1). The search strategy developed by the Cochrane Renal Group.
2). Cochrane Controlled Trials Register (CCTR) and CENTRAL (issue 1, *The Cochrane Library* 2007)
3). Registry of randomised trials for the Cochrane Collaboration Field in Complementary Medicine.

4). Companies involved with the promotion and distribution of cranberry preparations were approached and asked to provide information on both published and unpublished studies.
5). Electronic databases including PsycLit, LILACS, CINAHL, MEDLINE, EMBASE, Biological Abstracts, Current Contents. These databases were searched using the following terms*:

1. (beverages.sh. or cranberr$.ti,ab or fruit adj5 beverage$.ti,ab. or fruit adj5 drink$.ti,ab. or fruit adj5 juice$ or vaccinium macrocarpon.ti,ab. or vaccinium oxycoccus.ti,ab. or vaccinium vitis-idaea.ti,ab.)
2. (UTIs.sh. or cystitis.sh. or bacteriuria.sh. or pyelonephritis.sh. or UTI$.ti,ab. or urinary adj5 infection$.ti,ab. or bacter$.ti,ab. or pyelonephrit$.ti,ab. or cystitis.ti,ab.)
3. 1 and 2

(* this is the MEDLINE search strategy. The EMBASE search expressions are slightly different but the search terms were the same, except that the term urogenital tract infections was also searched on as a subject heading.)

6). The following terms were searched to identify non-English language studies:

- Danish - (Tranebaersaft.ti,ab. or tranebaer.ti,ab. or orkaempetranebaer.ti,ab. or store tranebaer.ti,ab. or cranberry.ti,ab.) and (urinvejsinfektion.ti,ab. or cystitis.ti,ab. or blaerebetaendelse.ti,ab. or pyelonephritis.ti,ab. or pyelonefrit.ti,ab.)
- Dutch - (veenbes.ti,ab. or lepeltjeheide.ti,ab. or lepeltjesheide.ti,ab. or Amerikaanse veenbes.ti,ab. or cranberry.ti,ab.) and (cystitis.ti,ab. or catarrhus.ti,ab. or vesicalis.ti,ab. or blaasontsteking.ti,ab. or urineweginfectie.ti,ab. or pyelonephritis.ti,ab. or nephropyelitis.ti,ab.)
- French - (canneberges ronce d'Amerique.ti,ab. or cranberry.ti,ab. or cranberrie.ti,ab.) and (cystite.ti,ab. or infection urinaire.ti,ab. or pyélonéphrite.ti,ab.)
- German - (moosbeere.ti,ab or kranbeere.ti,ab.) and (zystitis.ti,ab. or cystitis.ti,ab. or harnwegsinfektion.ti,ab. or harninfekt.ti,ab. or pyelonephritis.ti,ab.)
- Italian - (vaccinium oxycoccus.ti,ab. or ossicocco palustro.ti,ab.) and (cistite.ti,ab. or infezione del tratto urinario.ti,ab or infezione urinaria.ti,ab. or infezione delle vie urinarie.ti,ab. or pielonefrite.ti,ab. or nefropielite.ti,ab.)
- Portuguese - (cranberry.ti,ab. or oxicoco$.ti,ab. or vaccinium oxycoccos.ti,ab. or oxycoccus palustris) and (cistite.ti,ab. or pielonefrite.ti,ab.)
- Spanish - (arandano agrio.ti,ab or arandano americano.ti,ab.) and (cistitis.ti,ab. or infección urinaria.ti,ab or pielonefritis.ti,ab.)

7). The Internet was searched using the terms listed in 3) and 4).
8). Reference lists of review articles and relevant studies were searched.
9). Conference abstracts from The Proceedings of the Urological Association (1990-1998), and The Journal of the American Geriatrics Society (1990 -1998) were searched for relevant studies.
10). The National Research Register was searched for studies currently underway.

Review update
For this update the Cochrane Renal Group's specialised register and CENTRAL was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2007). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched.
Date of most recent search: January 2007

METHODS OF THE REVIEW

The search strategy described previously was employed to obtain titles and, where possible, abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened by RJ, who discarded studies that were clearly ineligible but aimed to be overly inclusive rather than risk losing relevant studies. Two authors independently assessed, using full copies of the papers, whether the studies met the inclusion criteria, with disagreements resolved by discussion. Further information was sought from the authors of those papers which contained insufficient information to make a decision about eligibility.

The quality of all studies which were deemed eligible for the review were then assessed independently by two authors, with discrepancies resolved by discussion. The quality of allocation concealment was graded as either (A) adequate, (B) unclear, or (C) inadequate, following the detailed descriptions of these categories provided by the Cochrane Collaboration. It was intended to use this grading in investigation of any heterogeneity and in sensitivity analyses. Other aspects of study quality assessed included the extent of blinding, whether groups were comparable at baseline, the extent of losses to follow-up, non-participation, whether the outcome assessment was standardised, and whether an "intention-to-treat" analysis was undertaken. This information is presented in a table describing the included studies and the section on methodological quality, and provided a context for discussing the reliability of the results. Summary tables are provided in the additional tables (Table 01 - *Characteristics of studies;*Table 02 - *Study design and quality of reporting*).

Two authors independently extracted information using specially designed data extraction forms. For each included study,

information was collected regarding the location of the study, methods of the study (as per quality assessment checklist), the participants (sex, age, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified previously. Where possible, missing data (including side effects) were sought from the authors. Discrepancies in the data extraction were resolved via discussion.

Studies with either parallel group or cross-over design were included in the review. For cross-over studies, only the period before the cross-over is able to be synthesised in RevMan. However, this data were not available for any of the studies, so end of study data were reported descriptively (Table 03 - *Asymptomatic UTIs (bacteraemia)*; Table 04 - *Symptomatic UTIs*). Relative risk (RR) were used as the measure of effect for dichotomous outcomes, using a random effects model. Studies were sub-grouped by population type (e.g. the elderly, young women). If enough data becomes available in the future, heterogeneity in the data will be noted and cautiously explored using previously identified characteristics of the studies, particularly assessments of quality. Sensitivity analyses will be undertaken to examine the stability of the results in relation to a number of factors including study quality, the source of the data (published or unpublished), the method used for confirming the presence of bacteria in the urine (e.g. catheter specimen of urine or midstream specimen of urine), the causative organism (e.g. *E. coli*) and the method of diagnosing upper or lower UTI. Where continuous scales of measurement are used to assess the effects of treatment, these data will be analysed in continuous form using the mean difference (WMD). If different scales are used in different studies the results will be standardised and then combined using the standardised mean difference (SMD).

If further studies become available for inclusion in the review, the groups of susceptible populations described previously (see under types of participants) will be analysed separately with the following subgroups:

- Dosage (amount and concentration).
- Frequency and duration of treatment..
- In elderly women, number on hormone replacement therapy and/or topical vaginal oestradiol (these have been shown to reduce UTIs).

Where possible, we sought data from within studies where these comparisons have been made, rather than making comparisons across studies.

DESCRIPTION OF STUDIES

Ten studies (1049 participants) were included (see *Table of included studies* for more details). Of these, two were only published as letters, and no additional data were received from the authors (Haverkorn 1994; Walker 1997). Eight studies had one intervention arm and one control arm, and evaluated the effectiveness of either cranberry juice/cocktail (Avorn 1994; Foda 1995; Haverkorn 1994; McMurdo 2005; Schlager 1999) or cranberry capsules (Linsenmeyer 2004; Waites 2004; Walker 1997). A further two studies had two intervention arms and a control arm (Kontiokari 2001; Stothers 2002). Kontiokari 2001 randomised participants to either cranberry-lingonberry juice, lactobacillus GG drink or no intervention. Stothers 2002 randomised participants to cranberry juice, cranberry tablets or placebo juice.

Two studies were excluded because although they were randomised and compared cranberry juice with placebo in susceptible populations, they did not meet other inclusion criteria (Jackson 1997; Schultz 1984) (see *Table of excluded studies* for more details).

Types of participants

a) Participants with a history of recurrent lower UTIs or young women with an uncomplicated UTI

Two studies included women with recurrent UTIs (Stothers 2002; Walker 1997) and one study recruited women with a current UTI (Kontiokari 2001). The definition that the studies used for recurrent UTIs were either four UTIs during the past year or at least one during the previous three months (Walker 1997) or two symptomatic, single-organism, culture positive UTIs in the previous calendar year (Stothers 2002). Two were parallel group RCTs which were undertaken in Finland (Kontiokari 2001) and Canada (Stothers 2002). One of these studies had to be stopped prematurely (after six months) because the cranberry juice supplier stopped producing the juice (Kontiokari 2001). The third study was a small cross-over study undertaken in America (Walker 1997). Nineteen women were randomised to either cranberry capsules or placebo, but only 10 completed the study and were included in the final analysis.

b) Elderly men and women

Three studies evaluated cranberry juice for the prevention of UTIs in elderly populations (Avorn 1994; Haverkorn 1994; McMurdo 2005). The largest and best quality study was a study undertaken in Scotland (McMurdo 2005). Three hundred and sixty hospital patients aged 60 years or over were randomised to daily ingestion of 300 mL of cranberry juice or matching placebo beverage using a parallel group design. Avorn 1994 was a quasi-RCT of elderly women in America and this study used a parallel group design and randomised participants to either cranberry juice or placebo juice. Although 192 women were initially randomised to treatment, only 153 provided enough data to be included in the final analysis. The third study was undertaken in The Netherlands (Haverkorn 1994) and used a cross-over design and included both men and women. Thirty eight people were randomised to either cranberry juice or water, but only 17 completed treatment and only seven were included in the final analysis.

c) Participants needing catheterisation (intermittent or indwelling)

Four studies evaluated the effect of cranberry products in people needing either indwelling catheters or intermittent catheterisation. All the participants in the studies had neuropathic bladders. Two studies evaluated the effectiveness of cranberry juice in children who had a paediatric neuropathic bladder and were managed by clean intermittent catheterisation (Foda 1995; Schlager 1999). Both were cross-over studies and included 40 children, and 15 children respectively.

A further two studies evaluated the effectiveness of cranberry capsules/tablets versus placebo in people who had spinal cord injuries (Linsenmeyer 2004; Waites 2004). Linsenmeyer 2004 was a cross-over study which randomised 37 patients and analysed results from 21. Waites 2004 was a parallel group study which randomised 74 patients and analysed results from 48.

Dosage, concentration and duration of the cranberry intervention

Of the seven studies which evaluated the effectiveness of cranberry juice, four studies used placebo juice in the control arm (Avorn 1994; McMurdo 2005; Schlager 1999; Stothers 2002), one study used no intervention (Kontiokari 2001) and the other two studies used water (Foda 1995; Haverkorn 1994). One study made the participants buy their own cranberry juice (Foda 1995) and the others provided it free of charge. For adults, the amount given ranged from 30 mL/d (Haverkorn 1994) to 300 mL/d (Avorn 1994; McMurdo 2005). In children it was 15 mL/kg (Foda 1995) and 300 mL/d (Schlager 1999). The rationale behind the amount and concentrate of cranberry juice given to participants was not mentioned in any of the studies, and only McMurdo 2005 detailed the amount of active component (a proanthocyanidin concentration of 11.175 µg/g - dry solids basis). Of the four studies which evaluated the effectiveness of cranberry capsules, two gave participants capsules containing 400 mg of cranberry solids (Linsenmeyer 2004; Walker 1997), Waites 2004 gave capsules containing 2 g concentrated cranberry juice and Stothers 2002 gave participants cranberry tablets containing 1:30 parts of concentrated juice twice/day.

Outcomes

In all of the studies, either symptomatic or asymptomatic UTI was one of the outcome measures.

METHODOLOGICAL QUALITY

Allocation concealment

In general, the methodological quality of the studies was good. Four used adequate concealment of allocation (Kontiokari 2001; McMurdo 2005; Schlager 1999; Stothers 2002). Four did not state the method of randomisation (Foda 1995; Linsenmeyer 2004; Waites 2004; Walker 1997) and were graded B (unclear). Avorn 1994 and Haverkorn 1994 used a quasi-randomised method of allocated and were graded C (inadequate).

Blinding and study design

Five studies used a cross-over design (Foda 1995; Haverkorn 1994; Linsenmeyer 2004; Schlager 1999; Walker 1997) and five used a parallel group design (Avorn 1994; Kontiokari 2001; McMurdo 2005; Stothers 2002; Waites 2004). Seven of the studies were double-blind (Avorn 1994; Linsenmeyer 2004; McMurdo 2005; Schlager 1999; Stothers 2002; Waites 2004; Walker 1997), in Foda 1995 the investigator was blind but not the assessor and there was no blinding at all in Haverkorn 1994 and Kontiokari 2001.

Withdrawals, losses to follow-up and intention-to-treat

The dropout rate in all studies varied considerably. Two studies reported no drop-outs (Schlager 1999; Stothers 2002), however adherence with treatment was reported as being less than 80% in 5/12 months in Stothers 2002. In the other studies the drop-out or withdrawal rates were 8% (Kontiokari 2001), 20% (Avorn 1994), 30% (McMurdo 2005), 35% (Waites 2004), 43% (Linsenmeyer 2004), 47% (Foda 1995; Walker 1997) and 55% (Haverkorn 1994). Only two of the studies used an intention-to-treat analysis (Kontiokari 2001; McMurdo 2005).

In Avorn 1994 some of the baseline characteristics of the participants were markedly different in the cranberry and the placebo group. In particular, the rate of UTIs in the previous six months in the placebo group was over three times that of the cranberry juice group, and double for over 12 months. Two letters, published in JAMA, commented on these differences and inferred that the randomisation and/or blinding scheme had failed (Hopkins 1994; Katz 1994).

All first authors were contacted for more data if necessary. Three authors replied (Kontiokari 2001; Stothers 2002; Walker 1997) but no additional information was obtained from one of these communications (Walker 1997).

RESULTS

Meta-analysis was performed using the data from four studies (Kontiokari 2001; McMurdo 2005; Stothers 2002; Waites 2004). Data from the cross-over studies were not available from the pre-crossover period (Haverkorn 1994; Foda 1995; Haverkorn 1994; Linsenmeyer 2004; Schlager 1999; Walker 1997), and data were unclear in the quasi-RCT (Avorn 1994). The results from the cross-over studies and the quasi-RCT are reported in the additional tables, and also descriptively in the text.

In summary, meta-analysis of the results of the four RCTs found that cranberry products significantly reduced the incidence of UTIs at twelve months (*analysis 01.01:* RR 0.66, 95% CI 0.47 to 0.92) compared with placebo/control. Within these studies, cranberry products were more effective reducing the incidence of UTIs in women with recurrent UTIs, than elderly men and women or people requiring catheterisation (although no direct comparison was made). For the five studies not included in the meta-analyses,

only Walker 1997 reported a significant result for the outcome of symptomatic UTIs (see additional Table 03 and Table 04 for more information). Four of these studies measured the outcome of asymptomatic UTIs (bacteriuria with or without pyuria), but only Avorn 1994 reported a significant result. Side effects were common in all studies, and the number of dropouts/withdrawals in several studies was high.

Participants with a history of recurrent lower UTIs or women with a UTI

i) Symptomatic UTIs

Data were available for meta-analyses from two RCTs (Kontiokari 2001; Stothers 2002). One gave 7.5 g cranberry concentrate daily (in 50 mL) (Kontiokari 2001), the other gave 1:30 concentrate given either in 250 mL juice or in tablet form (Stothers 2002). When data from cranberry products (capsules and juice) were combined and compared with placebo/control, the RR was 0.61 (*analysis 01.01.01:* 95% CI:0.40 to 0.91).

Kontiokari 2001 reported that at six months, eight (16%) women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had at least one recurrence. In the third study (Walker 1997), there were 21 incidents of UTIs amongst the 10 people who completed the study. Six were in the treatment group, and 15 were in the placebo group (P < 0.005).

ii) Asymptomatic UTIs (bacteruria)

This was not reported as an outcome in any of the three studies.

iii) Side effects and adherence to therapy

The reason for the nine withdrawals in Walker 1997 were: pregnancy, unrelated infections requiring antibiotic therapy, and moving from the area. No participants reported side effects. In Kontiokari 2001, 13 women dropped out, mainly because of moving away. In Stothers 2002 compliance during the 12 months was less for cranberry juice than for the placebo and tablet groups, with compliance dropping below 80% during 5/12 months. Two participants in the cranberry juice group dropped out due to symptoms of reflux and other problems reported included mild nausea and frequency of bowel movements (in the tablet group). Participants in the placebo group also complained of headache and mild nausea.

Elderly men and women

i) Symptomatic UTIs

In McMurdo 2005 21/376 (5.6%) participants developed a symptomatic UTI, 14/189 in the placebo group and 7/187 in the cranberry juice group. These between-group differences were not significant (*analysis 01.01.02:* RR 0.51, 95% CI 0.21 to 1.22). There were significantly fewer infections with *E. coli* in the cranberry group (13 versus 4) with the authors suggesting that the result should be interpreted with caution as it was a secondary outcome. Avorn 1994 reported 4% (20/473) of the urine samples in the treatment group and 7% (37/498) in the placebo group had bacteriuria and pyuria concurrent with the subjects reporting urinary tract symptoms (P = not significant). These figures, however, appear to include the baseline urine samples (i.e. before the participants began drinking either cranberry juice or placebo juice). Haverkorn 1994 gave no details about symptomatic UTIs.

ii) Asymptomatic UTIs (bacteruria)

From the 1993 abstract of Avorn 1994 subjects randomised to the cranberry juice were 58% (author's OR, 0.42) less likely than controls to have bacteriuria with pyuria (P = 0.004) using 971 samples. These results reappeared in the 1994 report but readers are led to believe that the results are based upon 818 urine samples. It was unclear whether the denominator was 971 urine samples (which would appear to include baseline measurements prior to being given either cranberry juice or placebo juice) or 818 urine samples. Of the 17 people who completed the study by Haverkorn 1994, three had a UTI for the whole study period, seven had no UTI during the study period and seven had one or more episodes. In these seven, there were fewer occurrences of UTI when cranberry juice was being taken. The data from 17 people were not analysed together and no further data has been provided. The study only analysed the data from those participants who had a new UTI (7/17 who completed the study).

iii) Side effects and adherence to therapy

In McMurdo 2005 the median [IQR] adherence from a maximum of 300 mL/day was good at 300 [44] mL for the placebo beverage and 300 [28] mL for the cranberry juice (P = 0.208). Only 13 adverse events occurred and all resulted in withdrawal from the study. The six in the placebo group comprised two deaths and four episodes of gastrointestinal upset. The seven in the cranberry group comprised three deaths, two episodes of gastrointestinal upset, one episode of skin redness and itching, and one elevated blood glucose level in a known diabetic patient. Adherence data were missing for 11/376 (2.9%) participants, five from the placebo group and six from the cranberry juice group.

No data on side effects, or adherence to therapy were reported in other two studies apart from the number of withdrawals/dropouts. In Avorn 1994, 20% (39/193) of the participants withdrew from the study without providing any urine samples after baseline. No reasons for withdrawal were reported. Of the 153 who were included in the analysis, 21% (32) did not complete the full six months; 17% (12/72) received cranberry juice, and 25% (20/81) received placebo. Thus, out of 192 randomised, 37% (72) did not finish the study. In Haverkorn 1994, 55% (21/38) of those randomised did not complete the study.

iv) Antibiotic use

In McMurdo 2005, a total of 35/189 (19%) of participants in the placebo group were prescribed antibiotics for any indication during the period of observation, compared to 32/187 (17%) of the cranberry juice group (P = 0.721). The median (range) duration of antibiotic treatment was 7 (1-19) days and 7 (1-15) days respectively.

Participants needing catheterisation (intermittent or indwelling)

i) Symptomatic UTIs

There was no clinical nor statistical difference in the number of symptomatic UTIs observed in either the cranberry or placebo groups (Foda 1995; Linsenmeyer 2004; Schlager 1999; Waites 2004). Relative risks were only able to be calculated for Waites 2004, and this was not significant (*analysis 01.01.03:* RR 1.06, 95% CI 0.51 to 2.21).

ii) Asymptomatic UTIs (bacteruria)

In Foda 1995, the percentage of months with a positive culture and no UTI symptoms was 24.1% (27/112) in the cranberry group and 17.1% (20/117) in the water group (P = not significant). In Schlager 1999, the percentage of urine cultures in both the treatment and control group were identical (75%). In the other three studies, no statistical differences were found between the intervention and control group.

iii) Side effects and adherence to therapy

In Foda 1995, there were 19 withdrawals/dropouts from the study, 89% (17/19) whilst on cranberry. Of these 17 withdrawals, the reasons 12 gave were directly due to cranberry. The reasons given were taste (9), caloric load (2) and cost (1). The other five dropouts were too busy (2), no reason (2) and non-urologic death (1). In the water group there were two dropouts, but neither gave a reason. No drop-outs or side effects were reported in Schlager 1999.

Cost effectiveness

Stothers 2002 reported on the cost effectiveness of the intervention. The mean annual cost of prophylaxis was CAD$624 and CAD$1400 for cranberry tablets and juice respectively. Cost savings were greatest when patients experienced more than two symptomatic UTIs/year (assuming three days of antibiotic coverage) and had more than two days of missed work or required protective undergarments for urgency incontinence. Total antibiotic consumption was less annually in both treatment groups compared with placebo. Cost effectiveness ratios demonstrated cranberry tablets were twice as cost effective as organic juice for prevention.

DISCUSSION

There is some evidence from the studies that cranberry juice and derivatives might be effective in preventing the re-occurrence of UTIs. Post-hoc analysis of the data (both in the meta-analysis and the study data) suggest that cranberry products may be effective in women with recurrent UTIs and the elderly, but do not appear to be effective in people with neuropathic bladders. For example, the two good quality RCTs which did find an effect were both in women with recurrent UTIs. The largest RCT to have examined the effect of cranberry juice ingestion on symptomatic UTI rates (and the only one to have participants of both sexes) had an observed symptomatic infection rate which was considerably lower than anticipated. This resulted in the study being accordingly underpowered (McMurdo 2005).

The five cross-over studies (Foda 1995; Haverkorn 1994; Linsenmeyer 2004; Schlager 1999; Walker 1997) were very small, and the number of dropouts in three were high. Furthermore, it is debatable whether the data from the quasi-RCT (Avorn 1994), which reported that cranberry juice was effective in reducing the number of asymptomatic UTIs, were reliable on two main counts. Firstly, only a quasi-randomisation method was used and the differences in the baseline characteristics between the two groups suggests that the randomisation and/or blinding scheme failed. Secondly it is possible that the analyses reported included the baseline measurements in the denominator (i.e. before the participants started on either the cranberry juice or the placebo juice).

What is of most interest to the clinician and consumer is whether cranberry juice is effective in preventing symptomatic UTIs. However, the main outcome in two of the studies was the bacteriological (not clinical) diagnosis of UTI (Avorn 1994; Haverkorn 1994). In the largest study (Avorn 1994), the introduction stated that, 'much bacteriuria in this age group (elderly) is asymptomatic and does not require treatment...' Thus, even if cranberry juice is effective in preventing asymptomatic UTIs, it is a condition which does not normally need treating in certain populations.

None of the studies of cranberry juice justified the dosage of cranberries given to participants. In addition, there was no standardisation of the description of the dosage (i.e. concentration) given which made comparison difficult. For example, some studies described the amount in millilitres, without stating the concentration. Participants in Avorn 1994 received 10 times more cranberry juice than Haverkorn 1994 (300 mL versus 30 mL). The concentration of cranberries in the Avorn 1994 was 30% but the concentration of the juice used in Haverkorn 1994 was not stated. It could be possible that the concentration of cranberries was the same in both studies, however the amount of juice given differed. Generally the chemical composition of available cranberry products is not standardised, and the bioequivalence between the juice and capsules/tablets is not clear. Furthermore, none of the studies justified their duration. UTIs often occur in clusters with long periods (several months) where patients are symptom free (Stapleton 1997). Thus studies may need to cover much longer time periods to take into account the natural course of the illness.

The number of withdrawals in some of the studies was high (20% to 55%). This could indicate that cranberry juice is not an acceptable therapy taken over a long period of time. Children in particular cited taste as the main reason for withdrawal (Foda 1995). Furthermore, the cost of consuming large amounts of cranberry juice may limit acceptance in the general population. The studies of cranberry extract (Walker 1997) and cranberry capsules (Stothers 2002) may have overcome some of these issues of com-

pliance and cost. Withdrawals from the two studies of cranberry capsules/tablets in people with neuropathic bladders (Linsenmeyer 2004; Waites 2004) were high (> 40%), but reasons for the withdrawals were not related to taste.

Two studies of cranberry juice for UTIs were excluded from this review. Jackson 1997 was excluded because the main outcome of interest was urinary pH. Outcomes relevant to this review were not evaluated. Schultz 1984 was excluded because people were only randomised to 20 days of treatment. The inclusion criteria for this review was a minimum length of treatment of one month. Furthermore, number of UTIs was not a primary outcome and only descriptively reported.

No published studies have been undertaken that compare cranberry with established interventions (e.g. antibacterials) for preventing UTIs. Theoretically, using cranberry instead of antibacterials might reduce the risk for the development of antibacterial-resistant organisms (Howell 2002) but there is currently no evidence to confirm this.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, the evidence from four RCTs indicates that cranberry products can be effective in reducing UTIs. However, it may only be effective in certain sub-populations. From the results of two well conducted RCTs there is some evidence to recommend cranberry juice for the prevention of UTIs in women with symptomatic UTIs. The evidence is inconclusive as to whether it is effective in older people (both men and women), and current evidence suggest that it is not effective in people with a neuropathic bladder. In addition, the large number of dropouts/withdrawals from some of the studies, indicates that cranberry juice may not be acceptable over long periods of time. Furthermore, there is no clear evidence as to the amount and concentration that needs to be consumed, and the length of time for the intervention to be most effective.

Implications for research

Large, properly randomised, parallel group, placebo controlled, double blind studies are needed to determine the effectiveness of cranberries for the prevention of UTIs in susceptible populations. The study period needs to be longer than six months to take into account the natural course of the illness, since UTIs often occur in clusters with long periods (several months) during which patients are symptom free. Furthermore, the dosage and concentration of the cranberry juice/product to be given should be determined scientifically. Outcomes should include the number of symptomatic and asymptomatic UTIs, side effects and adherence to therapy. The large number of dropouts/withdrawals in the cranberry juice studies included in this review indicates that drinking considerable amounts of cranberry juice over a long period may not be acceptable. Further studies of cranberry capsules/tablets or other cranberry products, therefore, are also needed.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

Ruth Jepson would like to thank the Nuffield Trust for giving her a short term fellowship for this review.
The authors are grateful to Dr Lara Mihaljevic who contributed to the original iteration of this review (Jepson 1998a; Jepson 2004), contributing to the study selection, quality assessment and data extraction.
The authors would also like to thank the following people for replying to correspondence:
Dr Lyn Stothers (Stothers 2002)
Prof Tero Kontikari (Kontiokari 2001)
Dr Ed Walker (Walker 1997)
Dr RJ Woodward (Larkhill Green Farm - cranberry tablets)
Professor Marion McMurdo (McMurdo 2005)

We would also like to thank Narelle Willis (Review group Co-ordinator, Renal Group) for her input into the review.

SOURCES OF SUPPORT

External sources of support

- Nuffield Trust UK

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

Avorn 1994 *{published data only}*

Avorn J, Monane M, Gurwitz J, Glynn R. Reduction of bacteriuria and pyuria with cranberry beverage: a randomized trial [abstract]. *Journal of the American Geriatrics Society* 1993;**41**(10 Suppl):SA13.

Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994;**271**(10):751–4. [MEDLINE: 8093138].

Foda 1995 *{published data only}*

Foda MM, Middlebrook PF, Gatfield CT, Potvin G, Wells G, Schillinger JF. Efficacy of cranberry in prevention of urinary tract infection in a susceptible pediatric population. *Canadian Journal of Urology* 1995;**2**(1):98–102.

Haverkorn 1994 *{published data only}*

Haverkorn MJ, Mandigers J. Reduction of bacteriuria and pyuria using cranberry juice [letter]. *JAMA* 1994;**272**(8):590. [MEDLINE: 8057506].

Kontiokari 2001 *{published data only}*

Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ* 2001;**322**(7302):1571–3. [MEDLINE: 11431298].

Linsenmeyer 2004 *{published data only}*

* Linsenmeyer TA, Harrison B, Oakley A, Kirshblum S, Stock JA, Millis SR. Evaluation of cranberry supplement for reduction of urinary tract infections in individuals with neurogenic bladders secondary to spinal cord injury. A prospective, double-blinded, placebo-controlled, crossover study. *Journal of Spinal Cord Medicine* 2004;**27**(1):29–34. [MEDLINE: 15156934].

McMurdo 2005 *{published data only}*

* McMurdo ME, Bissett LY, Price RJ, Phillips G, Crombie IK. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. *Age & Ageing* 2005;**34**(3):256–61. [MEDLINE: 15863410].

Schlager 1999 *{published data only}*

Schlager TA, Anderson S, Trudell J, Hendley JO. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. *Journal of Pediatrics* 1999;**135**(6):698–702. [MEDLINE: 10586171].

Stothers 2002 *{published data only}*

* Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Canadian Journal of Urology* 2002;**9**(3):1558–62. [MEDLINE: 12121581].

Waites 2004 *{published data only}*

* Waites KB, Canupp KC, Armstrong S, DeVivo MJ. Effect of cranberry extract on bacteriuria and pyuria in persons with neurogenic bladder secondary to spinal cord injury. *Journal of Spinal Cord Medicine* 2004;**27**(1):35–40. [MEDLINE: 15156935].

Walker 1997 *{published data only}*

Walker EB, Barney DP, Mickelsen JN, Walton RJ, Mickelsen RA Jr. Cranberry concentrate: UTI prophylaxis [letter]. *Journal of Family Practice* 1997;**45**(2):167–8. [MEDLINE: 9267377].

References to studies excluded from this review

Jackson 1997

Jackson B, Hicks LE. Effect of cranberry juice on urinary pH in older adults. *Home Healthcare Nurse* 1997;**15**(3):199–202. [MEDLINE: 9110682].

Schultz 1984

Schultz A. Efficacy of cranberry juice and ascorbic acid in acidifying the urine in multiple sclerosis subjects. *Journal of Community Health Nursing* 1984;**1**(3):159–69. [MEDLINE: 6569071].

Additional references

Foo 2000

Foo LY, Lu Y, Howell AB, Vorsa N. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated Escherichia coli in vitro. *Phytochemistry* 2000;**54**(2):173–81. [MEDLINE: 10872208].

Foxman 2002

Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *American Journal of Medicine* 2002;**8**(113 Suppl 1A):5S–13S. [MEDLINE: 12113866].

Hellstrom 1991

Hellstrom A, Hanson E, Hansson S, Hjalmas K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. *Archives of Disease in Childhood* 1991;**66**(2):232–4. [MEDLINE: 2001110].

Hopkins 1994

Hopkins WJ, Heisley DM, Jonler M, Uehling DT. Reduction of bacteriuria and pyuria using cranberry juice. *JAMA* 1994;**272**(8):588–9. [MEDLINE: 8057504].

Howell 2002

Howell AB, Foxman B. Cranberry juice and adhesion of antibiotic-resistant uropathogens. *JAMA* 2002;**287**(23):3082–3. [MEDLINE: 12069670].

Jepson 1998b

Jepson RG, Mihaljevic L, Craig JC. Cranberries for treating urinary tract infections. *Cochrane Database of Systematic Reviews* 1998, Issue 4. Art. No.: CD001322. DOI:10.1002/14651858.CD001322.

Kahn 1967

Kahn HD, Panariello VA, Saeli J, Sampson JR, Schwartz E. Effect of cranberry juice on urine. *Journal of the American Dietetic Association* 1967;**51**(3):251–4. [MEDLINE: 6035629].

Katz 1994

Katz LM. Reduction of bacteriuria and pyuria using cranberry juice. *JAMA* 1994;**272**(8):589. [MEDLINE: 8057505].

Kelly 1977

Kelly J. Clinical syndromes of urinary tract infection. *Current Therapeutics* 1977;**38**(7):15–21.

Kinney 1979

Kinney AB, Blount M. Effect of cranberry juice on urinary pH. *Nursing Research* 1979;**28**(5):287–90. [MEDLINE: 38439].

Master List 2007

United States Cochrane Center. Master list of journals being searched. http://apps1.jhsph.edu/cochrane/masterlist.asp (accessed May 2007).

McLeod 1978
McLeod DC, Nahata MC. Methenamine therapy and urine acidification with ascorbic acid and cranberry juice. *American Journal of Hospital Pharmacy* 1978;**35**(6):654. [MEDLINE: 27096].

Patton 1991
Patton JP, Nash DB, Abrutyn E. Urinary tract infection: economic considerations. *Medical Clinics of North America* 1991;**75**(2):495–513. [MEDLINE: 1996046].

Roberts 1979
Roberts AP, Phillips R. Bacteria causing symptomatic urinary tract infection or asymptomatic bacteriuria. *Journal of Clinical Pathology* 1979;**32**(5):492–6. [MEDLINE: 381327].

Schmidt 1988
Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios* 1988;**55**(224-225):173–81. [MEDLINE: 3063927].

Stapleton 1997
Stapleton A, Stamm WE. Prevention of urinary tract infection. *Infectious Disease Clinics of North America* 1997;**11**(3):719–33. [MEDLINE: 9378932].

Winberg 1974
Winberg J, Andersen HJ, Bergstrom T, Jacobsson B, Larson H, Lincoln K. Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatrica Scandinavica - Supplement* 1974, (252):1–20. [MEDLINE: 4618418].

Wong 1984
Wong ES, Fennell Cl, Stamm WE. Urinary tract infection among women attending a clinic for sexually transmitted diseases. *Sexually Transmitted Diseases* 1984;**11**(1):18–23. [MEDLINE: 6546811].

Zafriri 1989
Zafriri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated Escherichia coli to eucaryotic cells. *Antimicrobial Agents & Chemotherapy* 1989;**33**(1):92–8. [MEDLINE: 2653218].

References to other published versions of this review

Jepson 1998a
Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 1998, Issue 2. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub4.

Jepson 2004
Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub3.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Avorn 1994
Methods	Country: USA Method of randomisation/allocation: Institutional ID number or telephone number (quasi randomised). Recruitment: Recruited from a long-term care facility for the elderly, and 9 housing complexes for the elderly. Blinding: Double blind (participants and investigators). Number of centres: One Design: Placebo controlled, parallel group Power calculation: Yes Number of patients randomised: 192 Number of patients analysed: 153 Losses to follow-up/withdrawals: 39 Exclusions post randomisation: None Intention-to-treat analysis: No Source of funding: Research grant from Ocean Spray Cranberries, Inc.
Participants	INCLUSION CRITERIA Not clearly stated, but participants had to be willing to ingest at least 300 mL of cranberry juice daily for a 6 month period. Number: 192 elderly women Age: mean 78.5 years

Characteristics of included studies (*Continued*)

	EXCLUSION CRITERIA Terminal disease or severe dementia; only women were studied.
Interventions	INTERVENTION 300 mL cranberry juice cocktail/day (30% cranberry concentrate). CONTROL Placebo beverage that looked and tasted similar but contained no cranberry juice. DURATION: 6 months
Outcomes	1. Presence of bacteriuria (bacteria in the urine greater or equal to 100,000/mL) with the presence of pyuria (white cells in the urine). 2. Presence of bacteriuria. 3. Presence of bacteriuria with the presence of pyuria plus symptoms of a UTI.
Notes	A total of 192 subjects were enrolled in the study. Data were presented for 153 subjects who provided a baseline urine sample and at least one additional sample after randomisation. METHOD OF OBTAINING URINE SAMPLE Mid-stream clean-voided. DEFINITION OF BACTERIURIA Organisms numbering greater or equal to 100,000/mL regardless of organism. DEFINITION OF PYURIA: NS
Allocation concealment	C – Inadequate

Study	**Foda 1995**
Methods	Country: Canada Method of randomisation/allocation: NS Blinding: Single blind (physician) Number of centres: One Source of patients: Clinic Design: Cross-over Power calculation: No Number of patients randomised: 40 Number of patients analysed: 21 Losses to follow-up/withdrawals: 19 Exclusions post randomisation: None Intention-to-treat analysis: No Source of funding: NS
Participants	INCLUSION CRITERIA Neuropathic bladder and managed by clean intermittent catheterisation. Outpatients' residence at a distance not exceeding 150 km from the Children's Hospital of Eastern Ontario. No significant medical conditions. Number: 40 children Age: 1.4 to 18 years (mean 9.35) . EXCLUSION CRITERIA: NS
Interventions	INTERVENTION Cranberry cocktail 15 mL/kg/d (30% cranberry concentrate) CONTROL Water

Characteristics of included studies (*Continued*)

	DURATION: 6 months cranberry juice, 6 months water
Outcomes	1. Number of months of positive cultures plus a symptomatic UTI. 2. Number of months of positive cultures plus an asymptomatic UTI. 3. Side effects and compliance.
Notes	METHOD OF COLLECTING URINE Sterile catheter urine samples. DEFINITION OF BACTERIURIA Greater than or equal to 100,000 cfu/L of a pathogenic organism after 24 hours incubation. Any growth in a symptomatic patient was considered significant.
Allocation concealment	B – Unclear

Study	**Haverkorn 1994**
Methods	Country: The Netherlands Source of participants: Hospital Method of allocation/randomisation: Date of birth (quasi randomised) Blinding: No Number of centres: One Design: Cross-over Power calculation: No Number of patients randomised: 38 Number of patients analysed: 7 Losses to follow-up/withdrawals: 22 Exclusions post randomisation: None Intention-to-treat analysis: No Source of funding: NS
Participants	INCLUSION CRITERIA: NS Number: 38 participants Age: mean 81 years Sex (M/F): 9//29 EXCLUSION CRITERIA: NS
Interventions	INTERVENTION 30 mL cranberry juice/day mixed with water. Concentration: NS. CONTROL Water (same volume as intervention). DURATION 4 weeks active treatment (8 weeks total).
Outcomes	1. Bacteriuria.
Notes	Method of obtaining urine sample: NS DEFINITION OF BACTERIURIA >/= 100,000 cfu of one of the Enterobacteriaceae/mL of urine.
Allocation concealment	C – Inadequate

Study	**Kontiokari 2001**
Methods	Country: Finland Source of participants: Finnish student health service

Characteristics of included studies (*Continued*)

	Method of allocation/randomisation: Random number tables and sealed opaque envelopes (see footnote 1). Blinding: No Number of centres: One Design: Parallel group Power calculation: Yes, but recruitment stopped before appropriate number recruited. Number of patients randomised: 150 Number of patients analysed: 150 Losses to follow-up/withdrawals: 13 Exclusions post randomisation: None Intention-to-treat analysis: Yes Source of funding: Emil Aaltonen, Juho Vainio, and Alma and K A Snellman Foundations
Participants	INCLUSION CRITERIA Women who had a UTI caused by E. coli (105 cfu/mL in clean voided midstream urine) and were not taking antimicrobial prophylaxis. Number: 150 women Age: mean age in the three groups was 29-32 years EXCLUSION CRITERIA: NS
Interventions	INTERVENTION 50 mL of cranberry-lingonberry juice concentrate (Maija, Marli, Finland) a day. The cranberry-lingonberry juice contained 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate in 50 mL of water with no added sugars OR 100 mL of Lactobacillus GG drink (Gefilus, Valio, Finland) five days a week. CONTROL No intervention DURATION 6 months cranberry juice, 12 months lactobacillus.
Outcomes	1. First recurrence of symptomatic UTI.
Notes	METHOD OF COLLECTION URINE Clean voided midstream urine specimen. DEFINITION OF BACTERIURIA Bacterial growth 10(5) cfu/mL. Recruitment had to be stopped prematurely because the cranberry juice supplier stopped producing the juice. A total of 150 women gave their informed consent and were randomly allocated into three groups, 50 in each. One subject in the lactobacillus group who was taking post coital antimicrobials was excluded from the analysis.
Allocation concealment	A – Adequate

Study	**Linsenmeyer 2004**
Methods	Country: USA Source of participants: Patients presenting to outpatient urology rehabilitation clinic. Method of allocation/randomisation: NS Blinding: Double blind Number of centres: One Design: Cross-over Power calculation: NS Number of patients randomised: 37 Number of patients analysed: 21 Losses to follow-up/withdrawals: 16

	Exclusions post randomisation: None Intention to treat analysis: No Source of funding: Eastern Paralyzed Veterans Association.
Participants	INCLUSION AND EXCLUSION CRITERIA: NS. 21 individuals with neurogenic bladders secondary to spinal cord injury.
Interventions	INTERVENTION standardised 400 mg cranberry tablets. CONTROL Placebo DURATION 9 weeks (4 weeks on each, plus one week wash out).
Outcomes	1. Urinary bacterial counts and white blood cell (WBC) counts and the combination of bacterial and WBC counts.
Notes	METHOD OF COLLECTING URINE SAMPLE CSU or MSU DEFINITION OF BACTERIURIA >/= 10,000/mL for a MSU; > 100 cfu/mL for a CSU
Allocation concealment	B – Unclear

Study	**McMurdo 2005**
Methods	Country: Scotland Method of allocation/randomisation: Computer-generated random numbers program. Allocation by sealed envelopes in numbered sequence Blinding: Double blind Number of centres: One Design: Parallel group Power calculation: Yes Number of patients randomised: 376 Number of patients analysed: 376 Losses to follow-up/withdrawals: 115 Exclusions post randomisation: None Intention-to-treat analysis: Yes Source of funding: Chief Scientist Office at the Scottish Executive Department of Health. The cranberry juice and matching placebo were supplied by Ocean Spray Cranberries, Inc.
Participants	Number: 376 older patients in hospital. Age: 60 years or over admitted to either acute medicine for the elderly assessment or rehabilitation units for elderly people. EXCLUSION CRITERIA Mental State Questionnaire (MSQ) score <5/10; dysphagia; symptoms of a UTI; antibiotic treatment; anticipated length of stay less than 1 week; regular drinkers of cranberry juice; presence of an in-dwelling catheter; and terminal illness. In light of a UK Committee on Safety of Medicines alert about a potential interaction between cranberry juice and warfarin which emerged during the final 8 weeks of recruitment, warfarin was added as an exclusion for that period only.
Interventions	INTERVENTION 300 mL of cranberry juice. CONTROL

Characteristics of included studies (*Continued*)

	Matching placebo beverage. DURATION 6 months
Outcomes	1. Time to onset of first symptomatic UTI. This was defined as a culture positive urine growing a single organism of > 10(4) cfu/mL urine specimen. 2. Adherence to beverage drinking, courses of antibiotics prescribed, and organisms responsible for UTIs.
Notes	METHOD OF OBTAINING URINE SAMPLES Clean catch. DEFINITION OF BACTERIURIA Only pure growths of >/= 10(4) cfu/mL were reported with an antibiotic sensitivity.
Allocation concealment	A – Adequate

Study	**Schlager 1999**
Methods	Country: USA Source of patients: NS Method of allocation/randomisation: Pharmacy Blinding: Double blind (participants and investigators) Number of centres: One Design: Cross-over Power calculation: No Number of patients randomised: 15 Number of patients analysed: 15 Losses to follow-up/withdrawals: None Exclusions post randomisation: None Intention-to-treat analysis: Yes Source of funding: Grants from Spinal Cord Research Foundation and the Pendleton Pediatric Infectious Disease Research Laboratory.
Participants	INCLUSION CRITERIA Neuropathic bladder and managed by clean intermittent catheterisation. Lived at home, had normal findings on renal ultrasonography and voided cystourethrogram, and lived within a 1 hour drive of the hospital. Number: 15 children Age: 2-18 years EXCLUSION CRITERIA: NS
Interventions	INTERVENTION 300 mL cranberry juice cocktail/day (30% cranberry concentrate). CONTROL Placebo beverage that looked and tasted similar but contained no cranberry juice. DURATION 3 months cranberry juice, 3 months placebo.
Outcomes	1. Presence of bacteriuria. 2. Symptomatic UTI.
Notes	METHOD OF OBTAINING URINE SAMPLE CSU DEFINITION OF SYMPTOMATIC UTI Defined as bacteriuria with fever, abdominal pain, change in continence pattern, or change in colour or odour of urine.

Characteristics of included studies (*Continued*)

	DEFINITION OF BACTERIURIA >/= 100,000/mL
Allocation concealment	A – Adequate

Study	**Stothers 2002**
Methods	Country: Canada Source of participants: NS Method of randomisation/allocation: Computer and sealed envelopes (see footnote 1). Blinding: Double blind (participants and investigators) Number of centres: One Design: Placebo controlled Power calculations: No Number of patients randomised: 150 Number of patients analysed: 150 Losses to follow-up/withdrawals: 2 patients in the cranberry juice arm dropped out. Exclusions post randomisation: None Intention-to-treat analysis: yes (see footnote 1). Source of funding: NS
Participants	INCLUSION CRITERIA At least two symptomatic, single-organism, culture positive UTIs in the previous calendar year, but were currently free of UTI on urinalysis and culture. Number: 150 sexually active women. Age: 21-72 years EXCLUSION CRITERIA Neurogenic bladder dysfunction, insulin-dependent diabetes, immunosuppressive disease, steroid use, or intermittent or indwelling catheterisation.
Interventions	INTERVENTION 1 Placebo juice + cranberry tablets (1:30 parts concentrated juice, two times/day). INTERVENTION 2 Cranberry juice 250 mL three times daily + placebo tablets. CONTROL Placebo juice (filtered water with food colouring + 20 mL pineapple juice) + placebo tablets. DURATION One year.
Outcomes	1. > 50% decrease in symptomatic UTI's/year (symptoms + >/= 100,000 single organisms/mL). 2. > 50% decrease in annual antibiotic consumption. 3. Costs effectiveness of treatment.
Notes	METHOD OF COLLECTING URINE SAMPLE CSU DEFINITION OF BACTERIURIA Bacteria in the urine greater or equal to 100,000/mL.
Allocation concealment	A – Adequate

Study	**Waites 2004**
Methods	Country: USA Source of participants: Community residing men and women.

	Method of allocation/randomisation: NS Blinding: Double blind Number of centres: One Design: Parallel group Power calculations: No Number of patients randomised: 74 Number of patients analysed: 48 Losses to follow-up/withdrawals: 26 Exclusions post randomisation: None Intention-to-treat analysis: No Source of funding: NS, but CranBerry capsules were provided by Aim This Way, Cambridge, Massachusetts.
Participants	INCLUSION CRITERIA At least one year post spinal cord injury, age 16 years or older, neurogenic bladder managed by clean intermittent catheterization or external collection device, no systemic antimicrobials or urinary acidifying agents taken within 7 days, no current fever and chills suggestive of acute symptomatic UTI, and agreement not to ingest and cranberry-containing products whilst participation in the clinical trial. Baseline urine culture demonstrating at least 10(5) cfu/mL. Number: 48 people.
Interventions	INTERVENTION 2 g of concentrated cranberry juice in capsule form. CONTROL Placebo capsule. DURATION 6 months.
Outcomes	Baseline urinalysis and cultures were performed at the time of the initial clinic visit and monthly for 6 months.
Notes	Microbiologic data were evaluated using analysis of variance with repeated measures. METHOD OF OBTAINING URINE SAMPLE CSU or clean catch. DEFINITION OF BACTERIURIA >/= 100,000/mL
Allocation concealment	B – Unclear

Study	**Walker 1997**
Methods	Country: USA Source of participants: NS Method of randomisation/allocation: NS Blinding: Double blind (participants and doctors) Number of centres: One Design: Placebo controlled, cross-over Power calculation: No Number of patients randomised: 19 Number of patients analysed: 10 Losses to follow-up/withdrawals: 9 Exclusions post randomisation: None Intention-to-treat analysis: No Source of funding: NS, but capsules provided by Solaray, Inc
Participants	INCLUSION CRITERIA

	Non pregnant, sexually active women between the ages of 18 and 45 years with a recurrent UTI (4 UTIs during the past year or at least one during the previous 3 months). Number: 9 married, sexually active women. Age: 28-44 years (median 37) EXCLUSION CRITERIA: NS
Interventions	INTERVENTION Cranberry capsules containing 400 mg of cranberry solids (number/day not stated). CONTROL Placebo capsule. DURATION Each patient had 3 months of active treatment and 3 months placebo.
Outcomes	1. Symptomatic UTI.
Notes	METHOD OF OBTAINING URINE SAMPLE: NS DEFINITION OF SYMPTOMATIC UTI Women notified the physician and then submitted a urine sample (method: NS). To ensure a consistent entry point into the study, each participant was held in a queue until suffering a symptomatic UTI. Each subsequent UTI episode was treated with antibiotics.
Allocation concealment	B – Unclear

cfu - colony forming units; NS - not stated
Footnote 1. Additional information provided by author(s).

Characteristics of excluded studies

Study	Reason for exclusion
Jackson 1997	RCT of elderly people looking at the effect of cranberry juice on urinary acidity. No relevant outcomes reported.
Schultz 1984	RCT, (placebo controlled) of eight subjects with multiple sclerosis. Only randomised to 20 days of treatment. The inclusion criteria for this review was a minimum length of treatment of one month. Furthermore, number of UTIs was not a primary outcome and only descriptively reported.

ADDITIONAL TABLES

Table 01. Characteristics of studies

Author	Year	N	Country	Setting	Participants	Intervention
Avorn	1994	192	USA	Nursing homes	Elderly women, mean age 78.5 years	300 mL cranberry juice cocktail/day (30% cranberry concentrate)
Haverkorn	1994	38	Netherlands	Hospital	Elderly men (9) and women (29), mean age 81 years	30 mL cranberry juice/day (concentration not specified)
Foda	1995	40	Canada	Hospital clinic	Children with neuropathic	15 mL/kg cranberry

Table 01. Characteristics of studies (*Continued*)

Author	Year	N	Country	Setting	Participants	Intervention
					bladder requiring clean intermittent catheterisation, mean age 9.35 years	juice cocktail/day (30% cranberry concentrate)
Walker	1997	19	USA	Family practice	Young women with recurrent UTI, median age 37 years	Cranberry capsules (400 mg of cranberry solids)
Schlager	1999	15	USA	Hospital clinic	Children with neuropathic bladder requiring clean intermittent catheterisation, aged 2-18 years	300 mL cranberry juice cocktail/day (30% cranberry concentrate)
Kontiokari	2001	150	Finland	Student health service	Young women (mean age 29-32 years) with previous UTI	50 mL cranberry-lingonberry juice five days/week (7.5 g cranberry concentrate)
Stothers	2002	150	Canada	Unclear	Women with recurrent UTI (aged 21-72 years)	Cranberry juice (250 mL three times/day) or one concentrated cranberry juice tablet twice daily
Linsenmeyer	2004	21	USA	Urology rehabilitation clinic	Spinal cord injury patients with neuropathic bladders	Cranberry tablets (400 mg)
Waites	2004	48	USA	Hospital clinic	Spinal cord injury with neuropathic bladder	Cranberry juice concentrate (2 g)
McMurdo	2005	376	Scotland	Hospital	Elderly inpatients	300 mL cranberry juice

Table 02. Study design and quality of reporting

Author	Design	Study duration	Urine collection	Threshold	Other definitions	Allocation	Loss to follow-up	Blinding	Intention-to-treat
Avorn 1994	Parallel	6 months	Voided	= 10(8)/L	Pyuria (not defined)	No (quasi-RCT - assigned by ID or phone number)	71/192 (36.9%) Participants, investigators Unclear		
Haverkorn 1994	Crossover	4 weeks	Not stated	= 10(8)/L		No (quasi-RCT by date of birth)	22/38 (57.9%)	Unclear	Unclear
Foda 1995	Crossover	6 months	Catheter	= 10(8)/L		Unclear	19/40 (47.5%)	Investigators	Unclear
Walker	Crossover	3 months	Not stated	Not stated	Symptoms	Unclear	9/19	Partici-	Unclear

Table 02. Study design and quality of reporting (*Continued*)

Author	Design	Study duration	Urine collection	Threshold	Other definitions	Allocation	Loss to follow-up	Blinding	Intention-to-treat
1997					present (not defined)		(47.4%)	pants, investigators	
Schlager 1999	Crossover	3 months	Catheter	= 10(7)/L	Symptoms present (defined)	Yes, pharmacy	0/15 (0%)	Participants, investigators	Yes
Kontiokari 2001	Parallel	6 months	Voided	= 10(8)/L	Symptoms present (defined)	Yes, sealed opaque envelopes	13/150 (8.7%)	Unclear	Yes
Stothers 2002	Parallel	12 months	Voided	= 10(8)/L	Symptoms present (undefined)	Yes, sealed envelopes	2/150 (1.3%)	Participants, investigators	Yes
Linsenmeyer 2004	Crossover	9 weeks	Catheter or voided	= 10(8)/L	White blood cell count	Unclear		Participants, investigators	
Waites 2004	Parallel	6 months	Catheter or voided	= 10(8)/L		Unclear		Participants, investigators	No
McMurdo 2005	Parallel	6 months	Voided	= 10(4)/L	Symptoms present (not defined)	Yes, sealed envelopes		Participants, investigators	Yes

Table 03. Asymptomatic UTIs (bacteraemia)

Study	Pre crossover	P value	End of of study data	P value	Notes
Schlager 1999	Cranberries: 85/97; placebo 33/55	Not stated	Cranberries: 120/160 (75%); placebo 114/151 (75%)	Not stated	
Havercorn 1994	Not stated	Not stated	Not stated	p = 0.004	Actual number of people in each group not stated.
Avorn 1994	N/A	N/A	Cranberries: 20/473 (4%) of the urine samples; placebo		
Foda 1995	Not stated	Not stated	Cranberry: 27/112 months (24.1%); placebo: 34/117 months (29%)	Not stated	Months with positive/significant culture but no UTI symptoms
Linsenmeyer 2003	Not stated	Not stated	Not stated	Not stated	The authors report that, 'We failed to find a statistically significant treatment effect for

Table 03. Asymptomatic UTIs (bacteraemia) (*Continued*)

Study	Pre crossover	P value	End of of study data	P value	Notes
					the cranberry tablets beyond the placebo effect when evaluating urinary bacterial count (t20=-0.05,p=0.96), urinary WBC (t20= 1.14, p=0.27), or urinary bacterial and WBC in combination (t20=1.14,p=0.27

Table 04. Symptomatic UTIs

Study	Pre-crossover	P value	End of trial data	P value	Notes
Schlager 1999	Not stated	Not stated	Cranberry: 3 UTIs in 2 children; placebo: 3 UTIs in 3 children	Not stated	
Avorn 1994	Not applicable	Not applicable	Cranberry: 20/473 (4%); placebo: 37/498 (7%)	Not significant (p value not stated)	Denominator unclear
Walker 1997	Not stated	Not stated	Cranberry: 6 UTIs; placebo: 15 UTIs	$p < 0.05$	Whilst taking cranberry capsules as opposed to placebo, 7 of the 10 subjects exhibited fewer UTIs, two subjects exhibited the same number of UTIs, and one subject experienced one more UTI.
Foda 1995	Not stated	Not stated	Cranberry: 19/112 months (17%); placebo: 20/117 months (17.1%)	Not stated	Months with positive/significant culture and UTI symptoms
Havercorn 1994	Not stated				No details provided

ANALYSES

Comparison 01. Cranberry products versus placebo/control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 At least one symptomatic UTI	4	665	Relative Risk (Random) 95% CI	0.66 [0.47, 0.92]

INDEX TERMS

Medical Subject Headings (MeSH)

*Beverages; Cross-Over Studies; *Phytotherapy; Randomized Controlled Trials; Sex Factors; Urinary Tract Infections [*prevention & control]; *Vaccinium macrocarpon

MeSH check words

Humans

COVER SHEET

Title	Cranberries for preventing urinary tract infections
Authors	Jepson RG, Craig JC
Contribution of author(s)	RJ - study design, search strategy, trial selection, quality assessment, data extraction, data analysis, writing of review, updating of review. JCC - study design, writing of review, updating review
Issue protocol first published	1998/2
Review first published	1998/2
Date of most recent amendment	15 November 2007
Date of most recent SUBSTANTIVE amendment	10 September 2007
What's New	A search was performed in January 2007, and three new trials were identified. None of these trials found a significant effect of cranberry on either people with a neurogenic bladder (2 studies) or elderly men and women (one study).
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	16 February 2007
Date authors' conclusions section amended	16 February 2007
Contact address	Ms Ruth Jepson Senior Research Fellow Cancer Care Research Centre University of Stirling Unit 1, Scion House Innovation Park Stirling FK9 4LA UK E-mail: ruth.jepson@stir.ac.uk Tel: +44 1786 849260 Fax: +44 1786 460060
DOI	10.1002/14651858.CD001321.pub4
Cochrane Library number	CD001321
Editorial group	Cochrane Renal Group
Editorial group code	HM-RENAL

Analysis 01.01. Comparison 01 Cranberry products versus placebo/control, Outcome 01 At least one symptomatic UTI

Review: Cranberries for preventing urinary tract infections

Comparison: 01 Cranberry products versus placebo/control

Outcome: 01 At least one symptomatic UTI