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Cranberries for preventing urinary tract infections (Review)

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[Intervention Review]

Cranberries for preventing urinary tract infections

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ABSTRACT

Background

Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). The aim of this review is to assess the effectiveness of cranberries in preventing such infections.

Objectives

To assess the effectiveness of cranberry juice and other cranberry products in preventing UTIs in susceptible populations.

Search methods

Electronic databases and the Internet were searched using English and non English language terms; companies involved with the promotion and distribution of cranberry preparations were contacted; reference lists of review articles and relevant trials were searched. Cochrane Central Register of Controlled Trials (CENTRAL - the Cochrane Library, issue 1, 2003) was searched in February 2003.

Selection criteria

All randomised or quasi randomised controlled trials of cranberry juice/products for the prevention of urinary tract infections in susceptible populations. Trials of men, women or children were included.

Data collection and analysis

Two reviewers independently assessed and extracted information. Information was collected on methods, participants, interventions and outcomes (urinary tract infections (symptomatic and asymptomatic), side effects and adherence to therapy). RR were calculated where appropriate, otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane criteria.

Main results

Seven trials met the inclusion criteria (four cross-over, three parallel group). The effectiveness of cranberry juice (or cranberry-lingonberry juice) versus placebo juice or water was evaluated in six trials, and the effectiveness of cranberries tablets versus placebo was evaluated in two trials (one study evaluated both juice and tablets). In two good quality RCTs, cranberry products significantly reduced the incidence of UTIs at twelve months (RR 0.61 95% CI:0.40 to 0.91) compared with placebo/control in women. One trial gave 7.5 g cranberry concentrate daily (in 50 ml), the other gave 1:30 concentrate given either in 250 ml juice or in tablet form. There was no significant difference in the incidence of UTIs between cranberry juice versus cranberry capsules (RR 1.11 95% CI:0.49 to 2.50). Five trials were not included in the meta-analyses due to methodological flaws or lack of available data. However, only one reported a significant result for the outcome of symptomatic UTIs. Side effects were common in all trials, and dropouts/withdrawals in several of the trials were high.

Authors' conclusions

There is some evidence from two good quality RCTs that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period in women. If it is effective for other groups such as children and elderly men and women is not clear. The large number of dropouts/ withdrawals from some of the trials indicates that cranberry juice may not be acceptable over long periods of time. In addition it is not clear what is the optimum dosage or method of administration (e.g. juice or tablets). Further properly designed trials with relevant outcomes are needed.

PLAIN LANGUAGE SUMMARY

Some evidence that cranberries can prevent symptomatic urinary tract infections

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. Cranberries (usually as cranberry juice) have been used to try and prevent urinary tract infections, particularly in high risk groups such as older people. The review found that there was some evidence from trials to show cranberries (juice and capsules) can prevent recurrent infections in women. Many people in the trials stopped drinking the juice, suggesting it may not be a popular intervention.

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.

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 6-12 months, but overall occurs about three times more often in girls (1-3% in boys, 3-7% in girls) (Winberg 1974; Hellstrom 1991).

Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the prevention and treatment of UTIs. Cranberries contain 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). More recently, it has been demonstrated that cranberries prevent bacteria (particularly *E. coli*) from adhering (sticking) to uroepithelial cells that line the wall of the bladder (Sobota 1984; Schmidt 1988). Cranberries contain two compounds which inhibit adherence - fructose and a polymeric compound of unknown nature (Zafriri 1989). Although many juices contain fructose, only cranberries and blueberries contain the polymeric compound (Ofek 1991).

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. Although cranberry juice is the form of cranberries most widely used for the prevention of UTIs, other cranberry products include cranberry powder in hard or soft gelatin capsules.

The treatment of UTIs with cranberries is evaluated in another review by the same reviewers.

OBJECTIVES

We wished to test the following hypotheses:
1) Cranberry juice and other cranberry products are more effective than placebo/no treatment in the prevention of UTIs in susceptible populations.
2) 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.

METHODS

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 trials which randomised participants by date of birth, or case record number) were included, but the quality of the trials was taken into account during the analysis and discussion. Both parallel group and cross-over design were included.

Types of participants

INCLUSION CRITERIA
Trials of susceptible men, women or children as defined below. These categories were analysed separately.
a) participants with a history of recurrent lower UTIs (more than two episodes in the previous 12 months)
b) elderly men and women
c) participants needing intermittent catheterisation
d) pregnant women
e) participants with an in-dwelling catheter
f) participants with an abnormality of the urinary tract

EXCLUSION CRITERIA
a) Trials of the treatment of asymptomatic or symptomatic UTI (these are analysed in a separate review by the same reviewers).
b) Trials of any urinary tract condition not caused by bacterial infection (e.g. interstitial cystitis, which is a chronic inflammation of the bladder wall).

Types of interventions

Cranberry juice or a cranberry product (e.g. cranberry capsules) given for at least one month. If further trials become available for review, the amount taken per 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 if possible, or a 'clean catch' specimen).

The 'gold standard' bacteriological criteria for diagnosis of UTI includes microbiological confirmation from a mid-stream specimen of urine (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 trials 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 trials 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.

Secondary outcome measures:
a) Adherence to therapy.
b) Side effects.

Search methods for identification of studies

Relevant trials were obtained from the following sources:
1) The search strategy developed by the Cochrane Renal Group.
2) Cochrane Controlled Trials Register (CCTR) and CENTRAL (issue 1 of The Cochrane Library 2003)
3) Registry of randomised trials for the Cochrane Collaboration Field in Complementary Medicine.
3) Companies involved with the promotion and distribution of cranberry preparations were approached and asked to provide information on both published and unpublished trials.
4) 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.)

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

Portugese - (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.)

5) The Internet was searched using the terms listed in 3) and 4).

6) Reference lists of review articles and relevant trials were searched.

7) 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 trials.

8) The National Research Register was searched for trials currently underway.

Data collection and analysis

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. Reviewers RJ and LM independently assessed, using full copies of the papers, whether the studies met the inclusion criteria, with disagreements resolved by discussion and consultation with the third reviewer JC. 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 of the reviewers RJ and LM, with discrepancies resolved by discussion with the third, JC. 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.

RJ then provided LM with the full articles of the included studies and both reviewers independently extracted information using specially designed data extraction forms. For each included trial, 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 was referred to JC for discussion.

Trials with either parallel group or cross-over design were included in the review. It was intended that for cross-over trials, the period before the cross-over would be analysed. However, this data were not available for any of the trials. Relative Risks (RR) were used as the measure of effect for dichotomous outcomes. Where there is sufficient data, a summary statistic for each outcome will be calculated using both a Fixed Effect and a Random Effects model. 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 (i.e., weighted mean difference (WMD)). If different scales are used in different studies, where possible, the results will be standardised and then combined (i.e. standardised mean difference (SMD)).

If further trials 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:
a) dosage (amount and concentration)
b) frequency and duration of treatment
c) in elderly women, number on hormone replacement therapy and/or topical vaginal oestradiol (these have been shown to reduce UTIs)
Where possible, we will be seeking data from within studies where these comparisons have been made, rather than making comparisons across studies.

RESULTS

Description of studies

Seven trials met the inclusion criteria, with a total of 604 participants randomised to treatment or control. Refer to '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). Five out of the seven trials evaluated the effectiveness of cranberry juice/cocktail/versus placebo juice or water (Avorn 1994; Haverkorn 1994; Foda 1995; Schlager 1999), and two compared the effectiveness of cranberry capsules versus placebo (Walker 1997; Stothers 2002). A further two trials had two treatment arms and a control arm. 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. A further trial is currently underway but no data is yet available (McMurdo 2002).

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

The included trials were subgrouped by the types of participants.
a) Participants with a history of recurrent lower UTIs
Three studies included women with recurrent UTIs (Walker 1997; Kontiokari 2001; 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 6 months) because the cranberry juice supplier stopped producing the juice (Kontiokari 2001). The third study was a small cross-over trial 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
Two studies evaluated cranberry juice for the prevention of UTIs in elderly populations. One study of elderly women in America (Avorn 1994) 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 other study, undertaken in The Netherlands (Haverkorn 1994), 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 intermittent catheterisation
Two trials examined 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 trials and included 40 children, and 15 children respectively.

Of the six trials which evaluated the effectiveness of cranberry juice, three trials used placebo juice in the control group (Avorn 1994; Schlager 1999; Stothers 2002), one trial used no intervention (Kontiokari 2001) and the other two trials used water (Haverkorn

1994; Foda 1995). 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 was ranged from 30 ml/d (Haverkorn 1994) to 300 ml/d (Avorn 1994). 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 these studies. One of the two trials which evaluated the effectiveness of cranberry capsules (Walker 1997) gave participants capsules containing 400 mg of cranberry solids and the other (Stothers 2002) gave participants cranberry tablets containing 1:30 parts of concentrated juice twice a day.

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

Risk of bias in included studies

Allocation concealment

In general, the methodological quality of the trials was good. Three used adequate concealment of allocation (Schlager 1999; Kontiokari 2001; Stothers 2002). Two of the trials did not state the method of randomisation (Foda 1995; Walker 1997) and were graded B (unclear). The other two trials used a quasi-randomised method of allocated and were graded C (inadequate) (Avorn 1994; Haverkorn 1994)

Blinding

Four trials used a cross-over design (Haverkorn 1994; Foda 1995; Walker 1997; Schlager 1999) and three used a parallel group design (Avorn 1994; Kontiokari 2001; Stothers 2002). Four of the trials were double blind (Avorn 1994; Walker 1997; Schlager 1999; Stothers 2002), in one the investigator was blind but not the assessor (Foda 1995) and two trials used no blinding at all (Haverkorn 1994; Kontiokari 2001).

Completeness of follow-up

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

In one trial (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. Three authors replied (Walker 1997; Kontiokari 2001; Stothers 2002) but no additional information was obtained from one of these communications. (Walker 1997).

Effects of interventions

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

In summary, RR were calculated for two trials (Kontiokari 2001; Stothers 2002). When data from cranberry products (capsules and juice) were combined and compared with placebo/control, the RR was 0.61(95% CI:0.40 to 0.91). For the five trials not included in the meta-analyses, only one reported a significant result for the outcome of symptomatic UTIs (Walker 1997) (see additional tables for more information). Four of these trials measured the outcome of asymptomatic UTIs (bacteriuria with or without pyuria), but only one reported a significant result (Avorn 1994). Side effects were common, and dropouts in several of the trials were high.

Participants with a history of recurrent lower UTIs

i) Symptomatic UTIs

Data were available for meta-analyses from two RCTs (Stothers 2002; Kontiokari 2001). One trial 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(95% CI:0.40 to 0.91). The combined RR for both trials for cranberry juice versus placebo/water for a reoccurrence of symptomatic UTIs at 12 months was 0.62 (95% CI:0.40 to 0.97). For cranberry capsules versus placebo (Stothers 2002), the RR was 0.56 (95% CI:0.27 to 1.15). For cranberry juice versus cranberry capsules (Stothers 2002), the RR was 1.11 (95% CI:0.49 to 2.50). This trial also reported that both cranberry juice and cranberry tablets statistically significantly decreased the number of patients experiencing at least 1 symptomatic UTI/year (to 20% and 18% respectively) compared with placebo (to 32%) ($P < 0.05$). 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 trial (Walker 1997), there were 21 incidents of UTIs amongst the 10 people who completed the trial. 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 trials.

iii) Side effects and adherence to therapy

The reason for the nine withdrawals in one trial (Walker 1997) were: pregnancy, unrelated infections requiring antibiotic therapy, and moving from the area; no participants reported side effects. In the second trial (Kontiokari 2001), 13 women dropped out, mainly because of moving away. In the third trial (Stothers 2002) compliance during the 12 months was less for cranberry juice that for the placebo and tablet groups, with compliance dropping below 80% during 5 of the 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). However, participants in the placebo group also complained of headache and mild nausea.

Elderly men and women

i) Symptomatic UTIs

In the USA trial (Avorn 1994), it was reported that 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). The trial in The Netherlands (Haverkorn 1994) gave no details about symptomatic UTIs.

ii) Asymptomatic UTIs (bacteruria)
From the 1993 abstract of the USA trial (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 trial in The Netherlands (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 trial only analysed the data from those participants who had a new UTI (7/17 who completed the trial).

iii) Side effects and adherence to therapy
No data on side effects, or adherence to therapy were reported in either trial apart from the number of withdrawals/dropouts. In the American trial, 20% (39/193) of the participants withdrew from the study without providing any urine samples after baseline (Avorn 1994). 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) of participants receiving cranberry juice, and 25% (20/81) of participants receiving placebo. Thus, out of 192 randomised, 37% (72) did not finish the study. In the other trial (Haverkorn 1994), 55% (21/38) of those randomised did not complete the study.

Participants needing intermittent catheterisation
i) Symptomatic UTIs
In both trials of children managed by clean intermittent catheterisation (Foda 1995; Schlager 1999), there was no clinical nor statistical difference in the number of symptomatic UTIs observed in either the cranberry or placebo groups.

ii) Asymptomatic UTIs (bacteruria)
In one trial (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 the other trial (Schlager 1999), The percentage of urine cultures in both the treatment and control group were identical (75%).

iii) Side effects and adherence to therapy
In one trial (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 the other trial (Schlager 1999).

Cost effectiveness

One trial reported on the cost effectiveness of the intervention (Stothers 2002). The mean annual cost of prophylaxis was $624 and $1400 for cranberry tablets and juice respectively. Cost savings were greatest when patients experienced >2 symptomatic UTI's per year (assuming three days of antibiotic coverage) and had > 2 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 no more evidence form the trials that cranberry juice and derivatives might be effective in preventing the reoccurrence of UTIs. However, the two trials which did find an effect were both in women, and this effect has not been shown in any of the other subgroups (e.g. men and children).

The four cross-over trials (Haverkorn 1994; Foda 1995; Walker 1997; Schlager 1999) were very small, and the number of dropouts in three of them was 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 trials was the bacteriological (not clinical) diagnosis of UTI (Avorn 1994; Haverkorn 1994). In the largest trial (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 trials 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 trials described the amount in millilitres, without stating the concentration. Participants in one trial (Avorn 1994) received 10 times more cranberry juice than those in one of the other trials (300 ml versus 30 ml) (Haverkorn 1994). The concentration of cranberries in the Avorn 1994 was 30% but the concentration of the juice used in the Haverkorn 1994 trial was not stated. In could be possible that the concentration of cranberries was the same in both trials, but the amount of juice given differed. Furthermore, none of the trials justified the duration of the study. UTIs often occur in clusters with long periods (several months) when patients are symptom free (Stapleton 1997). Thus trials may need to cover much longer study periods to take into account the natural course of the illness.

The number of withdrawals in some of the trials was high (20-55%). 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 trials of cranberry extract (Walker 1997) and cranberry capsules (Stothers 2002) may have overcome some of these issues of compliance and cost.

Two trials of cranberry juice for UTIs were excluded from this review. One of these trials (Jackson 1997) was excluded because the main outcome of interest was urinary pH. Outcomes relevant to this review were not evaluated. The other trial (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.

AUTHORS' CONCLUSIONS

Implications for practice

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 large number of dropouts/withdrawals from some of the trials, however, 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 treatment to be most effective.

Implications for research

Large, properly randomised, parallel group, placebo controlled, double blind trials 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 trials included in this review indicates that drinking considerable amounts of cranberry juice over a long period may not be acceptable. Further trials of cranberry capsules/tablets or other cranberry products, therefore, are also needed.

ACKNOWLEDGEMENTS

Ruth Jepson would like to thank the Nuffield Trust for giving her a short term fellowship for this review.

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Dr Lyn Stothers (Stothers 2002)
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Dr Ed Walker (Walker 1997)
Dr RJ Woodward (Larkhill Green Farm - cranberry tablets)

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

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Ongoing study Starting date of trial not provided. Contact author for more information.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Avorn 1994

Methods	Method of randomisation/allocation: institutional ID number or telephone number (quasi randomised) 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	192 elderly women (mean 78.5 years) Source of participants: recruited from a long term care facility for the elderly, and 9 housing complexes for the elderly. 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. Exclusion criteria: terminal disease or severe dementia; only women were studied. Location: United States of America
Interventions	Intervention: 300 ml cranberry juice cocktail per day (30% cranberry concentrate) Control: placebo beverage that looked and tasted similar but contained no cranberry juice. Duration of study: 6 months
Outcomes	1. Presence of bacteriuria (bacteria in the urine greater or equal to 100 000 per 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 Method of obtaining urine sample: mid-stream clean-voided

Avorn 1994 *(Continued)*

	Definition of bacteriuria: organisms numbering greater or equal to 100 000 per ml, regardless of organism. Definition of pyuria: none given
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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Foda 1995

Methods	Method of randomisation/allocation: not stated Blinding: single blind (physician) Number of centres: one 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: not stated
Participants	40 children, aged 1.4 to 18 years (mean 9.35 years) with a neuropathic bladder and managed by clean intermittent catheterisation. Source of patients: clinic Inclusion criteria: outpatients' residence at a distance not exceeding 150 km from the Children's Hospital of Eastern Ontario; no significant medical conditions. Exclusion criteria: none stated Location: Canada
Interventions	Intervention: cranberry cocktail 15 ml/kg/daily (30% cranberry concentrate) Control: water 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 Method of collecting urine: sterile catheter urine samples. Criteria for assessing bacteriuria: greater than or equal to 100 000 colony-forming units per litre of a pathogenic organism after 24 hours incubation. Any growth in a symptomatic patient was considered significant.

Foda 1995 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Haverkorn 1994

Methods	Method of allocation/randomisation: date of birth (quasi randomised) Blinding: no blinding 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: not stated
Participants	38 participants (9 men, 29 women) with a mean age of 81 years. Source of participants: hospital Inclusion criteria: none stated Exclusion criteria: none stated Location: The Netherlands
Interventions	Intervention: 30 ml cranberry juice per day mixed with water. Concentration not specified. Control: water (same volume) Duration: 4 weeks active treatment (8 weeks total)
Outcomes	1. Bacteriuria Method of obtaining urine sample: not stated Definition of bacteriuria: 100 000 or more colony-forming units of one of the Enterobacteriaceae per millilitre of urine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Kontiokari 2001

Methods	Method of allocation/randomisation: random number tables and sealed opaque envelopes (see footnote 1) Blinding: no blinding 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	150 women of all ages (mean age in the three groups was 29-32 years) Source of participants: Finnish student health service Inclusion criteria: Women who had a urinary tract infection caused by Escherichia coli (105 colony forming units/ml in clean voided midstream urine) and were not taking antimicrobial prophylaxis Exclusion criteria: none stated Location: Finland
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 urinary tract infection, defined as bacterial growth 105 colony forming units/ml Method of collecting urine: clean voided midstream urine specimen.
Notes	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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Schlager 1999

Methods	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

Schlager 1999 *(Continued)*

	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	15 children, aged 2-18 years with a neuropathic bladder and managed by clean intermittent catheterisation. Source of patients: not stated Inclusion criteria: lived at home, had normal findings on renal ultrasonography and voided cystourethrogram, and lived within a 1 hour drive of the hospital. Exclusion criteria: none stated Location: United States of America
Interventions	Intervention: 300 ml cranberry juice cocktail per 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 (bacteria in the urine greater or equal to 100 000 per ml) 2. Symptomatic urinary tract infection. Defined as bacteriuria with fever, abdominal pain, change in continence pattern, or change in colour or odour of urine. 3. Symptomatic urinary tract infection.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Stothers 2002

Methods	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: not stated
Participants	150 sexually active women aged 21 through 72 years who had had at least two symptomatic, single-organism, culture positive UTIs in the previous calendar year, but were currently free of UTI on urinalysis and culture. Exclusion criteria were neurogenic bladder dysfunction, insulin-dependent diabetes, immunosuppressive disease, steroid use, or intermittent or indwelling catheterisation.

Stothers 2002 *(Continued)*

	Source of participants: not stated Location: Canada
Interventions	Intervention 1: placebo juice + cranberry tablets (1:30 parts concentrated juice, two times per day) Intervention 2: versus cranberry juice 250 ml three times daily + placebo tablets Control: placebo juice (filtered water with food colouring plus 20 ml pineapple juice) + placebo tablets Duration: one year
Outcomes	1. A >50% decrease in symptomatic UTI's per year (symptoms + >/= 100 000 single organisms/ml) 2. A >50% decrease in annual antibiotic consumption. 3. Costs effectiveness of treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Walker 1997

Methods	Method of randomisation/allocation: not stated 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: not stated, but capsules provided by Solaray, Inc
Participants	19 married, sexually active women aged 28-44 years (median 37) Source of participants: not stated Inclusion criteria: Non pregnant, sexually active women between the ages of 18 and 45 years with a re-current UTI (4 UTIs during the past year or at least one during the previous 3 months). Exclusion criteria: none stated Location: United States of America
Interventions	Intervention: cranberry capsules containing 400 mg of cranberry solids (number per day not stated). Control: placebo capsule Duration: each patient had 3 months of active treatment and 3 months placebo
Outcomes	1. Symptomatic urinary tract infection Definition of symptomatic UTI: Women notified the physician and then submitted a urine sample (method not stated).

Walker 1997 *(Continued)*

Notes	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

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Footnote 1. Additional information provided by author(s).

Characteristics of excluded studies *[ordered by study ID]*

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

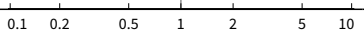
DATA AND ANALYSES

Comparison 1. cranberry juice versus placebo/control

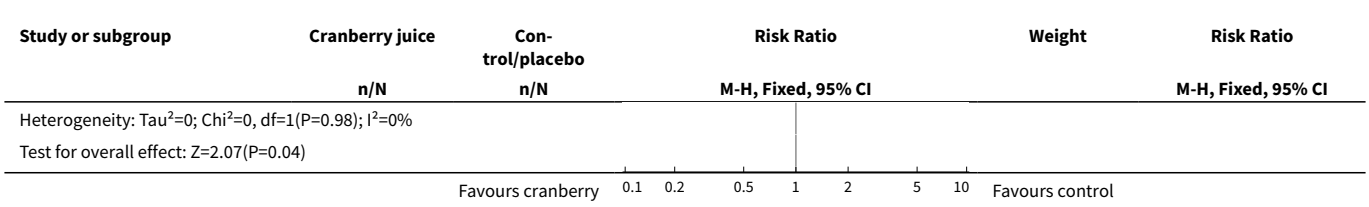
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 at least one symptomatic urinary tract infection	2	191	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.40, 0.97]

Analysis 1.1. Comparison 1 cranberry juice versus placebo/control, Outcome 1 at least one symptomatic urinary tract infection.

Study or subgroup	Cranberry juice n/N	Control/placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kontiokari 2001	12/46	19/45		54.56%	0.62[0.34,1.12]
Stothers 2002	10/50	16/50		45.44%	0.63[0.31,1.24]
Total (95% CI)	**96**	**95**		**100%**	**0.62[0.4,0.97]**
Total events: 22 (Cranberry juice), 35 (Control/placebo)					



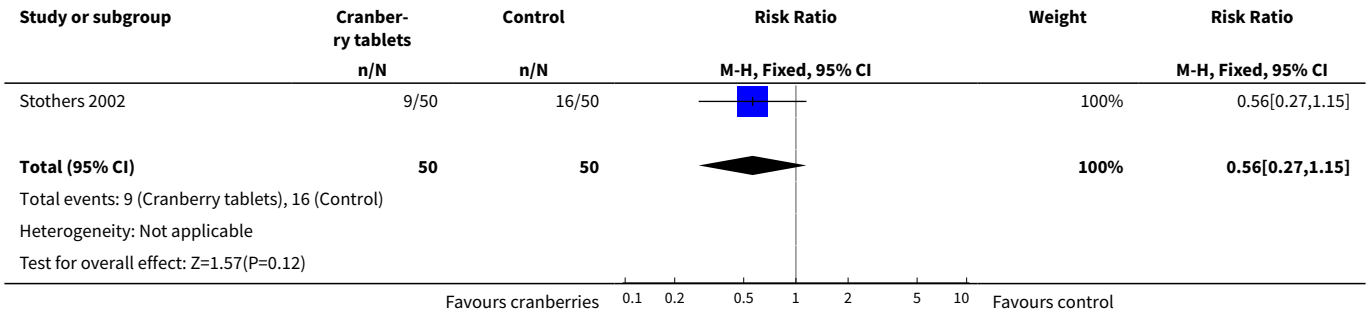
Favours cranberry — Favours control



Comparison 2. cranberry capsules versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Symptomatic urinary tract infections	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.15]

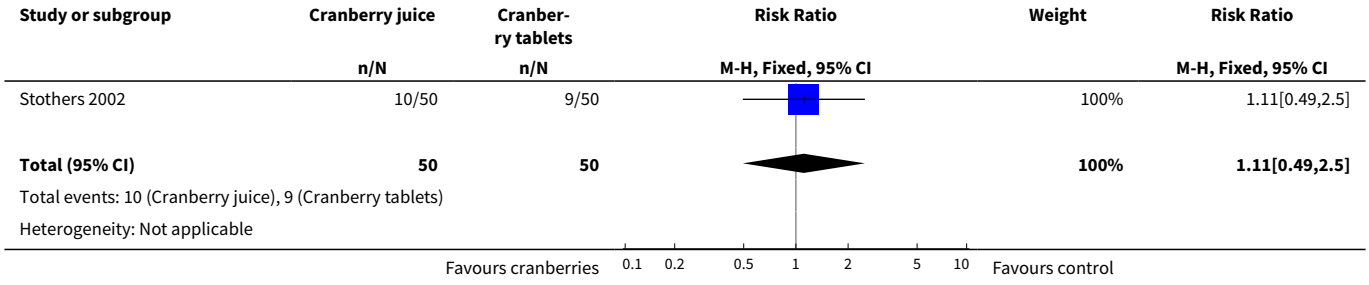
Analysis 2.2. Comparison 2 cranberry capsules versus placebo, Outcome 2 Symptomatic urinary tract infections.

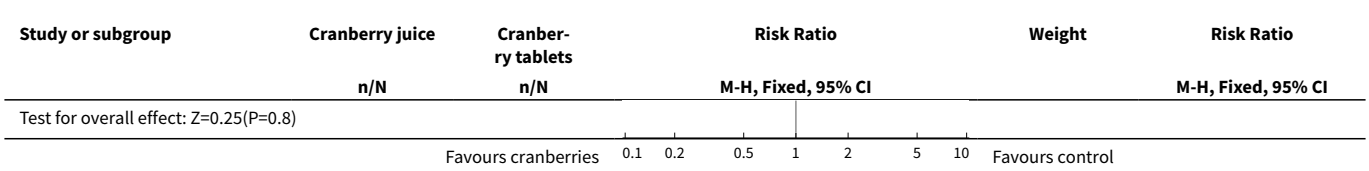


Comparison 3. cranberry juice versus cranberry tablets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic urinary tract infections	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.49, 2.50]

Analysis 3.1. Comparison 3 cranberry juice versus cranberry tablets, Outcome 1 Symptomatic urinary tract infections.

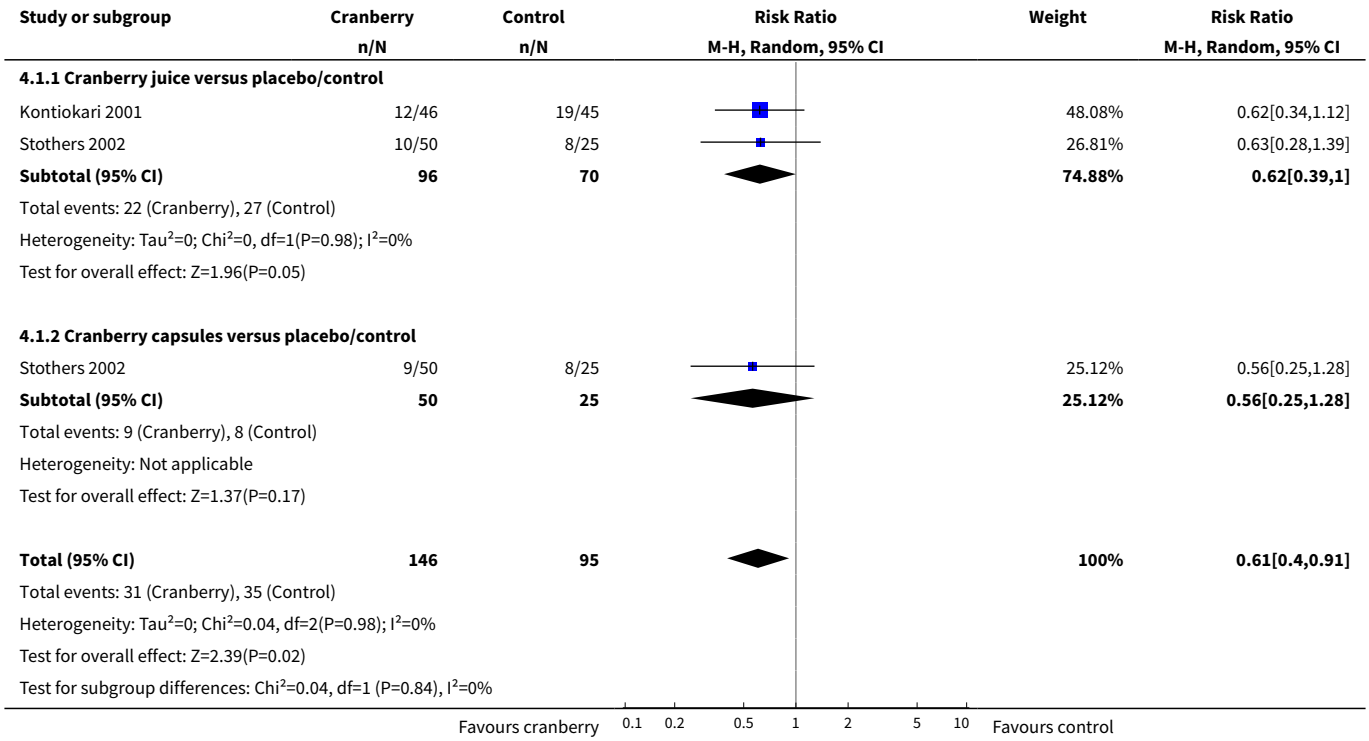




Comparison 4. Cranberry products versus placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At leat one symptomatic UTI	2	241	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.40, 0.91]
1.1 Cranberry juice versus placebo/control	2	166	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.39, 1.00]
1.2 Cranberry capsules versus placebo/control	1	75	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.25, 1.28]

Analysis 4.1. Comparison 4 Cranberry products versus placebo/control, Outcome 1 At leat one symptomatic UTI.



WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

Review first published: Issue 2, 1998

Date	Event	Description
27 March 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

RJ - study design, search strategy, trial selection, quality assessment, data extraction, data analysis, writing of review, updating of review.
LM - trial selection, quality assessment, data extraction
JCC - study design, writing of review, updating review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nuffield Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Beverages; *Vaccinium macrocarpon; Capsules; Cross-Over Studies; Phytotherapy [*methods]; Plant Preparations [*therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Sex Factors; Tablets; Urinary Tract Infections [*prevention & control]

MeSH check words

Female; Humans; Male