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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 have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). This is the third update of our review first published in 1998 and updated in 2004 and 2008.

Objectives

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

Search methods

We searched the Cochrane Renal Group's Specialised Register (4 June 2013) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.We contacted companies involved with the promotion and distribution of cranberry preparations and checked reference lists of review articles and relevant studies.

Date of search: July 2012

Selection criteria

All randomised controlled trials (RCTs) or quasi-RCTs of cranberry products for the prevention of UTIs.

Data collection and analysis

Two authors independently assessed and extracted data. Information was collected on methods, participants, interventions and outcomes (incidence of symptomatic UTIs, positive culture results, side effects, adherence to therapy). Risk ratios (RR) were calculated where appropriate, otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane risk of bias assessment tool.

Main results

This updated review includes a total of 24 studies (six cross-over studies, 11 parallel group studies with two arms; five with three arms, and two studies with a factorial design) with a total of 4473 participants. Ten studies were included in the 2008 update, and 14 studies have been added to this update. Thirteen studies (2380 participants) evaluated cranberry juice/concentrate; nine studies (1032 participants) evaluated cranberry tablets or capsules; one study compared cranberry juice and tablets; and one study compared cranberry capsules and tablets. The comparison/control arms were placebo, no treatment, water, methenamine hippurate, antibiotics,

or lactobacillus. Eleven studies were not included in the meta-analyses because either the design was a cross-over study and data were not reported separately for the first phase, or there was a lack of relevant data. Data included in the meta-analyses showed that, compared with placebo, water or not treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI overall (RR 0.86, 95% CI 0.71 to 1.04) or for any the subgroups: women with recurrent UTIs (RR 0.74, 95% CI 0.42 to 1.31); older people (RR 0.75, 95% CI 0.39 to 1.44); pregnant women (RR 1.04, 95% CI 0.97 to 1.17); children with recurrent UTI (RR 0.48, 95% CI 0.19 to 1.22); cancer patients (RR 1.15 95% CI 0.75 to 1.77); or people with neuropathic bladder or spinal injury (RR 0.95, 95% CI: 0.75 to 1.20). Overall heterogeneity was moderate (I^2 = 55%). The effectiveness of cranberry was not significantly different to antibiotics for women (RR 1.31, 95% CI 0.85, 2.02) and children (RR 0.69 95% CI 0.32 to 1.51). There was no significant difference between gastrointestinal adverse effects from cranberry product compared to those of placebo/no treatment (RR 0.83, 95% CI 0.31 to 2.27). Many studies reported low compliance and high withdrawal/dropout problems which they attributed to palatability/acceptability of the products, primarily the cranberry juice. Most studies of other cranberry products (tablets and capsules) did not report how much of the 'active' ingredient the product contained, and therefore the products may not have had enough potency to be effective.

Authors' conclusions

Prior to the current update it appeared there was some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. The addition of 14 further studies suggests that cranberry juice is less effective than previously indicated. Although some of small studies demonstrated a small benefit for women with recurrent UTIs, there were no statistically significant differences when the results of a much larger study were included. Cranberry products were not significantly different to antibiotics for preventing UTIs in three small studies. Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and the evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs. Other preparations (such as powders) need to be quantified using standardised methods to ensure the potency, and contain enough of the 'active' ingredient, before being evaluated in clinical studies or recommended for use.

PLAIN LANGUAGE SUMMARY

Cranberries for preventing urinary tract infections

Cranberries (usually as cranberry juice) have been used to 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 UTIs. This review identified 24 studies (4473 participants) comparing cranberry products with control or alternative treatments. There was a small trend towards fewer UTIs in people taking cranberry product compared to placebo or no treatment but this was not a significant finding. Many people in the studies stopped drinking the juice, suggesting it may not be an acceptable intervention. Cranberry juice does not appear to have a significant benefit in preventing UTIs and may be unacceptable to consume in the long term. Cranberry products (such as tablets or capsules) were also ineffective (although had the same effect as taking antibiotics), possibly due to lack of potency of the 'active ingredient'.

BACKGROUND

The term urinary tract infection (UTI) refers to the presence of a certain threshold number of bacteria in the urine (usually > 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 is thought to occur as a result of cystitis, particularly in the pres-

ence 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) are considered to need treatment. Some people also have recurrent UTIs with an average of two to three episodes/year (Roberts 1979; Wong 1984). Children often present with a fever and non-specific symptoms such as lethargy (tiredness), vomiting or poor feeding.

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). Specific subpopulations are 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). The annual incidence of acute uncomplicated UTI is 7% for all ages of women peaking at 15-24 years and women older than 65 (Giesen 2010). Up to 25% of women who have a UTI are likely to have a reoccurrence within six months (Epp 2010). UTIs often occur in clusters with long periods (several months) where patients are symptom free (Stapleton 1997).

Most UTIs are thought to 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 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 to prevent and treat 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 effect thus casting some doubt on this theory (Kahn 1967; McLeod 1978). No definitive mechanism of action has been established for cranberry in the prevention or treatment of UTIs. However, research suggests that cranberries prevent bacteria (particularly *Escherichia coli*) from adhering 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; Howell 2007), and substances called proanthocyanidins (PAC), which inhibit the adherence of p-fimbriated (a-galactose-(1-4) specific) *E. coli* (Zafriri 1989). PAC have A- and B- type linkages but It is only the PAC which contain the A-type linkages (found in cranberry juice) which have been associated with preventing adhesion of the *E.coli* to (Howell 2002; Howell 2005). PAC with B-type linkages are found in a number of sources including commercial apple and grape juice, dark chocolate but these do not appear to have any anti-adhesion effects (Howell 2005).

Cranberry products include juice, syrup, capsules and tablets. A commonly recommended amount for UTI prevention is daily consumption of 300 mL of cranberry juice cocktail containing 36 mg PAC (Howell 2010). However, processing of cranberries into various products such as tablets or capsules can impact on the PAC composition (Howell 2010) which may result in products which contain little or no PAC - the 'active' anti-adhesion ingredient. In addition, the complexities of the PAC structures and A-type linkages means that measurement of PAC content can often be erroneous and may not be reproducible (Prior 2010). To ensure potency in cranberry powders, levels of PAC must be quantified properly; and the 4-dimethylaminocinnamaldehyde method is currently the most validated standard method for quantifying PAC in cranberry powders (Prior 2010). A randomised controlled trial (RCT) evaluating the dosage effect of cranberry powder found that to achieve a bacterial anti-adhesion effect in urine, 36 mg of cranberry PAC equivalents/d is effective, but 72 mg may offer better protection in some cases. As the anti-adhesion activity decreases over time, it is recommended that cranberries products should be consumed in the morning and in the evening (Howell 2010).

The aim of this review is to assess the effectiveness of cranberries in the prevention of UTIs in susceptible populations including children, women with recurrent UTIs, people with a neuropathic bladder, and older people.

The treatment of UTIs with cranberries is evaluated in another review by the same authors (New Reference).

OBJECTIVES

We wished to test the following hypotheses:

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

- Cranberry juice/ cranberry products are more effective than any other treatment in the prevention of UTIs in susceptible populations.

- Different cranberry products (juice, capsules, tablets, concentrate) may differ in the effectiveness for preventing 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 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 catheterization
- Pregnant women
- Participants with an in-dwelling catheter
- Participants with an abnormality of the urinary tract
- Children with a first or subsequent UTI.

Exclusion criteria

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

Types of interventions

Cranberry juice or a cranberry product (e.g. cranberry capsules, tablets or extract) taken by participants for at least one month. The amount taken/d, concentration of the juice/cranberry product and length of treatment was also taken into account in subgroup analyses.

Types of outcome measures

Primary outcomes

- Number (incidence) of UTIs in each group (confirmed by a catheter specimen of urine (CSU), midstream 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, with some clinicians also requiring concurrent 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 or fever.
Methods used to diagnose upper and lower UTIs will also be subjected to sensitivity analysis if enough data is available.

Secondary outcomes

- Adherence to therapy.
- Side effects.

Search methods for identification of studies

Review update

We searched the Cochrane Renal Group's Specialised Register (4 June 2013) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

The Cochrane Renal Group's Specialised Register contains studies identified from:

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL;
2. Weekly searches of MEDLINE OVID SP;
3. Handsearching of renal-related journals & the proceedings of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal-journals;
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal & ClinicalTrials.gov.

Studies contained in the Specialised register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the 'Specialised Register' section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review.

Initial search

Relevant studies were obtained from the following sources.

- Registry of randomised studies for the Cochrane Collaboration Field in Complementary Medicine.
- Companies involved with the promotion and distribution of cranberry preparations were approached and asked to provide information on both published and unpublished studies.
- Electronic databases including PsycLit, LILACS, CINAHL, 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

- 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.)

- The Internet was searched using the terms listed.
- Reference lists of review articles and relevant studies were searched.
- 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 for the initial review. Handsearching was then undertaken by the Cochrane Renal Group.
- The National Research Register was searched for studies 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 and for the 2012 update, GW, 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 2012 update included Cochrane risk of bias assessments, these details were recorded by two authors (RJ and GW) and compared for discrepancies. Differences were

resolved through discussion and a third author (JC) when necessary. Summary descriptors are provided in the additional tables (Table 1 - *Characteristics of studies;* Table 2 - *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. All first authors were contacted for more data if necessary. Five authors replied (Kontiokari 2001; NAPRUTI Study 2011 I; Salo 2010; Stothers 2002; Walker 1997) but no additional information was obtained from three of these communications (Walker 1997; NAPRUTI Study 2011 I;Salo 2010). 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 along with the analysed studies (Table 3 - *Positive urine culture (bacteriuria)*; Table 4 - *Symptomatic UTIs*). Risk ratio (RR) was used as the measure of effect for dichotomous outcomes, using a random effects model. Studies were sub-grouped by population type (e.g. older people, women with recurrent UTIs). 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. CSU or MSU specimen of urine), the causative organism (e.g. *E. coli*) and the method of diagnosing upper or lower UTI.

RESULTS

Description of studies

Included studies

Ten studies (1049 participants) were included in the previous version (four cross-over studies and six studies with a parallel design). Of these, two were only published as letters, and no additional data were received from the authors (Haverkorn 1994; Walker 1997). A further 14 studies were added in the current update (one cross-over and 13 parallel design). Across all 24 included studies, 11 studies (2249 participants) evaluated a cranberry juice product (Avorn 1994; Barbosa-Cesnik 2011; Cowan 2012; Essadi 2010; Foda 1995; Haverkorn 1994; Kontiokari 2001; McMurdo 2005; Salo 2010; Schlager 1999; Wing 2008), 10 studies (1032 participants) evaluated cranberry tablets/capsules (Hess 2008; Lee 2007; Linsenmeyer 2004; McGuiness 2002; McMurdo 2009; NAPRUTI Study 2011 I; PACS Study 2008; Sengupta 2011; Waites 2004; Walker 1997), two studies (131 participants) evaluated a liquid cranberry concentrate/syrup (Ferrara 2009; Uberos 2010); one study compared cranberry juice and tablets (Stothers 2002); and one study compared cranberry capsules and tablets (PACS Study 2008). Studies compared cranberry product with a placebo, no treatment, water, Methenamine Hippurate and antibiotic treatment. Six studies included a third arm comparator. Of these, four studies included another cranberry product arm (PACS Study 2008; Sengupta 2011; Stothers 2002; Wing 2008) and one study included a probiotic Lactobacillus GG arm (Ferrara 2009). One study used a four arm factorial design of cranberry, placebo and methenamine hippurate (Lee 2007) .

Types of participants

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

Seven studies included women with current (Barbosa-Cesnik 2011; Kontiokari 2001) and recurrent UTIs (McMurdo 2009; NAPRUTI Study 2011 I; Sengupta 2011; Stothers 2002; Walker 1997). The definition that the studies used for recurrent UTIs varied between two and four UTIs in the past 12 months and in one study (Sengupta 2011) was simply stated as history of recurrent UTI. Of these studies, five compared cranberry product(s) with placebo (Barbosa-Cesnik 2011; Kontiokari 2001; Sengupta 2011; Stothers 2002; Walker 1997) and two compared cranberry products with antibiotics (McMurdo 2009; NAPRUTI Study 2011 I).

Elderly men and women

Four studies evaluated cranberry juice for the prevention of UTIs in elderly populations (Avorn 1994; Haverkorn 1994; McMurdo 2005; PACS Study 2008). The largest and best quality study (McMurdo 2005) included 360 hospital patients aged 60 years or over who 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-randomised, parallel group study of elderly women randomised 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. Haverkorn 1994 used a cross-over design and included 38 men and women randomised to either cranberry juice or water. Only 17 completed treatment and seven were included in the final analysis. The fourth study was a small (59 participants), three-

armed study of a cranberry capsule, cranberry tablet or placebo (PACS Study 2008).

Participants (adults and children) needing catheterisation (intermittent or indwelling)

Six studies evaluated the effect of cranberry products in people needing either indwelling catheters or intermittent catheterisation (Foda 1995; Hess 2008; Lee 2007; Linsenmeyer 2004; Schlager 1999; Waites 2004). Four of the studies evaluated the effectiveness of cranberry capsules/tablets versus placebo in adults with spinal cord injuries (Hess 2008; Lee 2007; Linsenmeyer 2004; Waites 2004) of which two were cross-over studies (Hess 2008; Linsenmeyer 2004), one was a parallel group study (Waites 2004), and one used a four-arm factorial design comparing cranberry product with methenamine hippurate and placebo (Lee 2007). In the other two studies (Foda 1995; Schlager 1999), participants were children who had a paediatric neuropathic bladder and were managed by clean intermittent catheterisation. Both were cross-over studies which compared cranberry juice to placebo/water and included 40 and 15 children respectively.

Pregnant women

Two studies (659 participants) (Essadi 2010; Wing 2008) enrolled pregnant women. Wing 2008 was a three-arm study comparing a single daily dose (240 mL) or two, three daily doses of cranberry juice (640 mL to 720 mL) with a placebo beverage. Essadi 2010 compared four daily doses (totalling 1000 mL) of cranberry juice with the same volume of water.

Children at risk of repeat UTI

Three studies enrolled children at risk of, or susceptible to, repeat UTI (Ferrara 2009; Salo 2010; Uberos 2010). Two studies (Ferrara 2009; Uberos 2010) included children who had experienced more than one UTI with and Salo 2010 enrolled children at their first UTI. All tested the effectiveness of different cranberry products. Salo 2010 compared cranberry juice with placebo; Uberos 2010 compared cranberry syrup versus trimethoprim syrup; and Ferrara 2009 compared cranberry plus lingonberry concentrate with lactobacillus.

Other populations

Cowan 2012 included patients undergoing radiation treatment for bladder or cervical cancer and compared two daily doses of cranberry juice with a placebo beverage. McGuiness 2002 compared cranberry capsules with placebo and included patients with multiple sclerosis, of which 72 voided naturally and 63 used intermittent self catheterisation.

Dosage, concentration and formulation of cranberries

The rationale behind the dosage and concentration of cranberry juice given to participants was not clearly described in any of the studies, and only five studies (Barbosa-Cesnik 2011; McMurdo 2005; NAPRUTI Study 2011 I; Uberos 2010; Wing 2008) described the amount of PAC - the compound considered to be the 'active' ingredient - in the cranberry juice.

Cranberry juice or cranberry concentrate

Of the 14 studies (13 studies of only cranberry juice/concentrate plus one juice and another cranberry product) evaluating the effectiveness of cranberry juice, the comparison group varied. Eight studies used placebo juice for the control arm (Avorn 1994; Barbosa-Cesnik 2011; Cowan 2012; McMurdo 2005; Salo 2010; Schlager 1999; Stothers 2002; Wing 2008), one studies used no intervention (Kontiokari 2001;), three studies used water (Essadi 2010; Foda 1995; Haverkorn 1994), one used lactobacillus as a control (Ferrara 2009) and one used antibiotic treatment (Uberos 2010). For adults, the amount given ranged from 30 mL/d (Haverkorn 1994) to 1000 mL/d (Essadi 2010). In studies including children, Foda 1995 reported using 15 mL/kg; Schlager 1999 used 300 mL/d; Ferrara 2009 stated using 50mL of concentrate; Uberos 2010 used 0.2 mL/kg of cranberry concentrate; and Salo 2010 reported 15 mL/kg to 300 mL once or twice daily.

Cranberry capsules or tablets

Eleven studies evaluating the effectiveness of cranberry capsules or tablets (Hess 2008; Lee 2007; Linsenmeyer 2004; McGuiness 2002; McMurdo 2009; NAPRUTI Study 2011 I; PACS Study 2008; Sengupta 2011; Stothers 2002; Waites 2004; Walker 1997). The total dose/d ranged from 400 mg (Walker 1997) to 2000 mg (Waites 2004). Only one study described the amount of PAC (Sengupta 2011) and others such as McGuiness 2002 stated that, because they did not measure PAC, they may have used a product that contained no PAC.

Outcome measures

In all of the studies, symptomatic UTI and/or positive urine culture were reported as the primary outcome measures. The outcome reported in this review is the number of people experiencing at least one symptomatic UTI at the end of the follow-up period.

Excluded studies

Eight studies were excluded because although they were randomised and compared cranberry juice with placebo in susceptible populations, they did not meet other inclusion criteria (Howell 2010; Jackson 1997; Jass 2009; Lavigne 2008; Schultz 1984; Tempera 2010; Valentova 2007; Vidlar 2010);(see Characteristics of excluded studies for more details).

Risk of bias in included studies

Figure 1 is a risk of bias graph showing the review authors' judgements about each risk of bias item, presented as percentages across all included studies. Figure 2 is a risk of bias summary showing the review authors' judgements about each risk of bias item for each included study.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

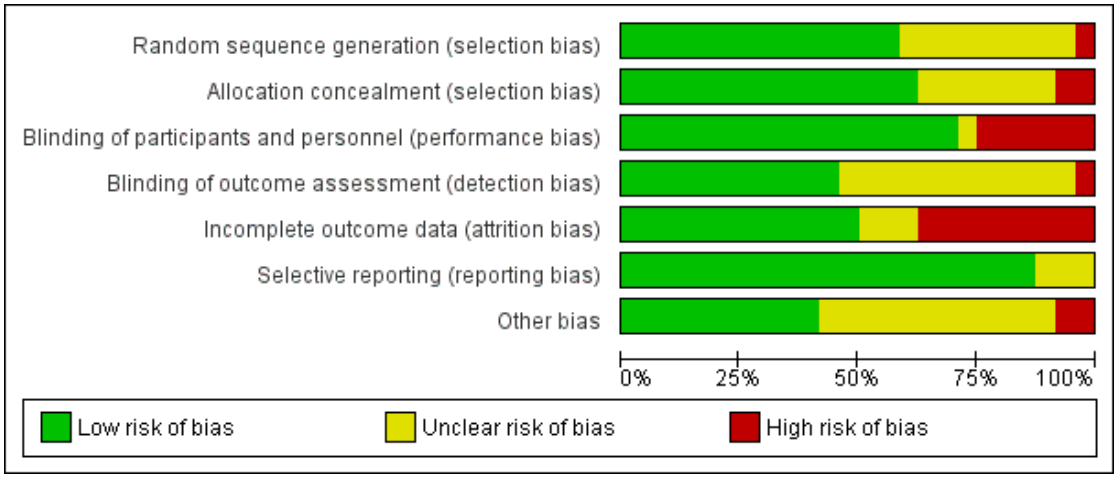

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Random sequence generation

Fourteen studies reported a method of random sequence generation that was judged to be at low risk of introducing bias, in eight studies the issue was unclear and for two studies (Avorn 1994; Haverkorn 1994) the method was considered at high risk of introducing bias (Figure 2)

Allocation concealment

Fifteen studies reported a method of allocation concealment considered to be at low risk of bias, in six studies this issue was unclear and for two studies the method reported was judged as being at high risk of introducing bias (Figure 2).

Blinding

Seventeen of the studies stated that participants and study personnel were blind to treatment allocation, five studies had no blinding, and for one study this issue was unclear (Essadi 2010). In 13 studies the outcome assessor was either stated as blinded (or assumed to be blinded based on study design) and in nine studies it was unclear whether the outcome assessor was blind to treatment allocation.

Incomplete outcome data

Twelve studies reported complete outcome data, eight studies had incomplete outcome data and for four studies this issue was unclear.

Selective reporting

Twenty studies reported the most appropriate outcomes for the study design, repeat symptomatic UTI or positive urine culture, while for three studies selective reporting issues were unclear.

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

The dropout rate varied considerably across the studies, from 0% to 55%. Six studies included all randomised participants in their analysis (Lee 2007; McMurdo 2009; PACS Study 2008; Schlager 1999; Stothers 2002; Wing 2008) whilst the remaining studies - where this was able to be determined - excluded between 5% and 55% of the randomised participants from the outcome analyses. One study (McGuiness 2002) reported that it used an intention-to-treat analysis, but the results do not concur with this assertion. Several studies stated that palatability of the cranberry product (primarily cranberry juice) was assumed to be the reason for participants discontinuing or withdrawing from the study, but none provided actual data about this from participants.

At least one of the studies had serious flaws. 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 but five studies (Barbosa-Cesnik 2011; Essadi 2010; Lee 2007; McMurdo 2005; Uberos 2010) were likely to be underpowered to detect a realistic difference between placebo and cranberry product. The studies stating power calculations made rather optimistic estimates of the benefit of cranberry product (for example a two-fold difference in Barbosa-Cesnik 2011; 1.3 times greater in NAPRUTI Study 2011 I; 20% difference Cowan 2012; 35% difference Hess 2008) and as such the sample size calculations for some studies was small and declined further with the high withdrawal rates.

Effects of interventions

Cranberry product compared with placebo or no treatment

Overall

Across the combined population of patients, 13 studies (2462 participants) had data which were able to be analysed. The combined estimated RR of repeat UTI with cranberry treatment was not statistically significant (Analysis 1.1: RR 0.86, 95% CI 0.71 to 1.04). Twelve studies had data which could not be meta-analysed. Of these, eight studies reported no effect, and two small studies reported a significant effect of cranberries compared to placebo (Hess 2008; Walker 1997). There was moderate overall heterogeneity (I^2 = 53%) but no significant between study heterogeneity (I^2 = 5.2%).

Women with a recurrent UTI

Four of the five studies (594 participants) which included a placebo group provided data that could be combined in a meta-analysis (Kontiokari 2001; Barbosa-Cesnik 2011; Stothers 2002; Sengupta 2011). Results showed a small, non-significant reduction in risk of repeat symptomatic UTI with cranberry treatment compared to

placebo or no treatment (Analysis 1.1.1: RR 0.74, 95% CI 0.42 to 1.31). However there was significant heterogeneity in the results, primarily with the addition of the newest largest study (Barbosa-Cesnik 2011) (I^2 = 65%). When this study was omitted from the meta-analysis, the RR was 0.58 (95% CI 0.39 to 0.86). There may be several reasons why Barbosa-Cesnik 2011 showed different results to the other studies (i.e. no effect of cranberries). As they discuss, theirs was the only study which was powered sufficiently to detect a difference (it had a larger sample size than the other three put together). However, they do use a different (lower) threshold for defining a UTI than the other studies, although measurement of symptoms would have been similar.

The other study (Walker 1997) was published as a letter with no comparable data. In this study 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) (see Table 4).

Older men and women

Overall the data from the studies in older men and women suggest that cranberries are not effective in preventing UTIs. Of the four studies evaluating the effectiveness of cranberry product(s) versus placebo in the population group, two studies were of high quality and had data available for analysis (McMurdo 2005; PACS Study 2008) (Analysis 1.1.2 (2 studies, 413 participants): RR 0.75, 95% CI 0.39 to 1.44). The other studies had significant flaws. 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. See Table 4 for more results from these two studies.

Participants (adults and children) needing catheterisation (intermittent or indwelling)

Overall the evidence from six studies suggest there is no benefit of cranberry juice in reducing UTIs in this population group. Only two of these studies had relevant data for a meta-analysis (Lee 2007; Waites 2004). When we combined the results of these studies there was no difference between the cranberry and placebo groups (Analysis 1.1.3 (2 studies, 353 participants): RR 0.95, 95% CI 0.75 to 1.20). The other four studies were cross-over studies. One (Hess 2008) found a significant effect, two reported a non-significant effect (Foda 1995; Schlager 1999) and one only had asymptomatic UTIs as an outcome (Linsenmeyer 2004).

Pregnant women

Overall cranberry juice was found not to be effective in reducing UTIs in pregnant women. The two studies in pregnant women (Essadi 2010; Wing 2008) provided data that could be analysed, but these showed widely different results with combined RR of 1.04 (95% CI 0.93 to 1.16) (Analysis 1.1.4). Both studies evaluated relatively large quantities of cranberry juice (up to 1000 mL/d) and both had a high number of withdrawals (39% and 28% respectively). In one of the studies (Wing 2008), the number of withdrawals was so high that the dose was reduced from 720 mL/d to 540 mL/d.

Children with a susceptibility to UTIs

The overall evidence suggested that cranberry products are not effective for preventing UTIs in children. Two studies (Ferrara 2009; Salo 2010) in children showed a non-significant reduction in risk of repeat symptomatic UTI with cranberry treatment compared to placebo (RR 0.48, 95% CI 0.19 to 1.22) (Analysis 1.1.5). The third study (Uberos 2010) was only published as an abstract and it was not clear whether the results were presented for symptomatic UTIs or just a positive culture.

Other populations

A single study (Cowan 2012) reported data in patients undergoing radiation treatment and showed a non-significant increased risk of repeat UTI with cranberry product (RR 1.15, 95% CI 0.75 to 1.77) (Analysis 1.1.6). Another study of people with multiple sclerosis (either voiding naturally or using intermittent self catheterisation (McGuiness 2002) found no significant difference between the cranberry capsule or control group (34.6% of people versus 32.6%).

Cranberry product compared with antibiotic prophylaxis

Two studies in women with recurrent UTI (McMurdo 2009; NAPRUTI Study 2011 I) and one study in children (Uberos 2010), compared cranberry product with antibiotic prophylaxis. All three studies used either cranberry capsules or syrup, rather than cranberry juice. Analysis of the two studies in women showed that cranberry product compared to antibiotic were equally as effective in reducing the risk of repeat UTI in women (Analysis 2.1.1: RR 1.31, 95% CI 0.85 to 2.02) The study in children also showed that the cranberry product were equally as effective in reducing the risk of repeat symptomatic UTI compared to antibiotics (Analysis 2.1.2: RR 0.69, 95% CI 0.32 to 1.51).

Low (1 dose) versus high (≥ 2 doses) dose cranberry product

Three studies compared high versus low dose cranberry products (PACS Study 2008; Sengupta 2011; Wing 2008). There was no

significant difference between two different doses of cranberry product (Analysis 3.1 (3 studies, 208 participants): RR 1.12, 95% CI 0.75 to 1.68).

High dose cranberry versus placebo

Three studies in different populations - pregnant women (Wing 2008); elderly men and women (PACS Study 2008); and adult women (Sengupta 2011) - compared high dose cranberry product to placebo. There was significant heterogeneity, both overall (I^2 = 55%) and between the subgroups (I^2 = 54.5%) and we therefore did not pool the results. The results ranged from RR 5.42 (95% CI 0.27 to 110.66) in pregnant women (Wing 2008) to RR 0.28 (95% CI 0.06 to 1.34) in adult women (Sengupta 2011) (Analysis 4.1).

Cranberry versus complementary therapies

A single study (Lee 2007) compared cranberry product with methenamine hippurate in patients with spinal injury and showed no difference between the groups (Analysis 5.1: RR 1.02, 95% CI 0.79 to 1.31).

Two studies, one in children (Ferrara 2009) and one in adult women (Kontiokari 2001), compared cranberry with a probiotic treatment and showed a significant reduction in symptomatic UTI with cranberry compared to probiotic (Analysis 6.1 (2 studies, 152 participants): RR 0.42, 95% CI 0.24 to 0.74).

Adverse effects

Across all studies, adverse effects were not well reported with only seven studies stating the number of adverse events within each study arm (McMurdo 2005; McMurdo 2009; NAPRUTI Study 2011 I; PACS Study 2008; Sengupta 2011; Stothers 2002; Wing 2008). There were usually fewer than 10 adverse events (except NAPRUTI Study 2011 I), which were mild and similarly distributed across the treatments arms (Analysis 1.2; Analysis 2.2; Analysis 3.2; Analysis 4.2). Three further studies mentioned adverse events but did not report them by study arm (Barbosa-Cesnik 2011; Cowan 2012; Lee 2007).

Adherence to therapy

Sixteen studies reported measuring compliance. Of these, ten used self reporting and five used a pill or bottle count (Avorn 1994; Hess 2008; McMurdo 2009; Schlager 1999; Stothers 2002). One study measured the presence of antibiotic activity in urine samples (NAPRUTI Study 2011 I). Seven studies did not state that they measured adherence (Essadi 2010; Haverkorn 1994; Lee 2007; Linsenmeyer 2004; PACS Study 2008; Sengupta 2011; Uberos 2010). Results of adherence monitoring were highly variable and several studies reported participants withdrawing because of the unpalatable or intolerable nature of the cranberry product.

Withdrawals and losses to follow-up

The withdrawal/drop-out rate and losses to follow-up varied considerably between the studies. Five studies reported no withdrawals or losses to follow-up (Lee 2007; Schlager 1999; Stothers 2002; Sengupta 2011; Uberos 2010). In the other studies the drop-out, withdrawal or loss to follow-up rates ranged from 3% to 55%. Rates, from low to high, for the individual studies were: 3% (PACS Study 2008), 5%(Ferrara 2009), 8% (Kontiokari 2001; Hess 2008), 10% (Salo 2010), 12% (Cowan 2012; McMurdo 2009), 20% (Avorn 1994), 24% (Barbosa-Cesnik 2011) 30% (McMurdo 2005), 32% (NAPRUTI Study 2011 I) 35% (Waites 2004),39% (Wing 2008) 40% (Essadi 2010) 43% (Linsenmeyer 2004), 47% (Foda 1995; Walker 1997) and 55% (Haverkorn 1994). Only six of the studies used an intention-to-treat analysis (Lee 2007; Kontiokari 2001; McMurdo 2005; McMurdo 2009; PACS Study 2008; Wing 2008).

Cost effectiveness

One study (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. The authors of the study reported that cost effectiveness ratios demonstrated cranberry tablets were twice as cost effective as organic juice for prevention.

DISCUSSION

Summary of main results

In the last update of this review (Jepson 2008) we concluded that *'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.* In this update, with the addition of 14 new studies, it has become more evident that cranberry products do not significantly reduce the risk of repeat symptomatic UTI compared to placebo or no treatment in groups of people at risk of repeat UTI (overall RR 0.86, 95% CI 0.71 to 1.04) or for any of the subgroups analysed. There was however moderate heterogeneity (53%), which is largely unexplained. The two studies in children suggest the greatest effect (RR 0.48, 95% CI 0.19 to 1.22), however this result was not significant, reflecting the small sample size and infrequency of events. In adult women

(RR 0.74, 95% CI 0.42 to 1.31) and the elderly (RR 0.75, 95% CI 0.39 to 1.44) the CIs were wide and do not reach not statistical significance. Studies in pregnant women, patients with spinal injury or neuropathic bladder, people with multiple sclerosis, and people receiving radiation therapy showed no significant benefit to cranberry product with RRs close to 1.

Three studies compared cranberry product with antibiotic treatment, two in adult women and one in children. When pooled, the two studies in women showed no significant difference in terms of risk of repeat UTI for women taking cranberry product while the study in children suggested the lower risk of repeat infection for those taking cranberry products compared with antibiotics.

Overall completeness and applicability of evidence

Several sub-groups of the populations are at increased risk of repeat UTI and the majority of these groups are represented in studies included in this review. Adult women were most frequently studied (seven studies) and the range of other susceptible population groups - children, the elderly, pregnant women, those with a spinal injury, neuropathic bladder, multiple sclerosis or undergoing radiotherapy - were included.

From the evidence it is unlikely that cranberry in its juice form is going to be an acceptable and effective intervention, even if the anti-adhesion can be demonstrated in vitro. Effectiveness of the cranberry juice in non-research populations is likely to be dependant on high adherence to the amount and the timing. To maintain levels of cranberry PAC that are necessary to prevent anti-adhesion, people would have to continuously drink the juice twice a day in serving of 150 mL for an indefinite period of time. If a woman only has two UTIs a year she would have to drink the juice twice a day for a year to potentially have one less UTI. Although for some women this regime may be acceptable (i.e. those who have a high rate of occurrence), others may find that the price, the calories in the juice, and the taste may make it less appealing.

Given the potential drawbacks of drinking cranberry juice for long periods, in recent years there have been an increasing number of studies evaluating the effectiveness of cranberry products such as tablets and capsules (Hess 2008; Lee 2007; Linsenmeyer 2004; McGuiness 2002; McMurdo 2009; NAPRUTI Study 2011 I; PACS Study 2008; Sengupta 2011; Stothers 2002; Waites 2004; Walker 1997). However, processing of cranberry into various products such as tablets or capsules can impact on the PAC composition (Howell 2010). Thus, proper standardization of cranberry products for PAC content, and correlation of the PAC level with anti-adhesion bioactivity, may be important to ensure that particular cranberry products contain PAC that are efficacious(Howell 2010). Howell 2010 suggested that at least 36 mg of cranberry PAC equivalents/d is required to be effective, divided into two doses, one in the morning and one at night. Only three studies measured PAC content in non-juice products (NAPRUTI Study 2011 I; Sengupta 2011; Uberos 2010). The PAC content reported in NAPRUTI Study 2011 I was 9.1 mg/g; 1.5% in Sengupta 2011; and in Uberos 2010 (of children) 5 mL of the syrup contained 36 mg. The other studies of non-juice products did not report the PAC content, and thus it is not possible to ascertain whether the products used contained enough PAC content to be effective. There are currently three studies (Bonetta 2011; NCT00280592; NCT01033383) evaluating cranberry tablets or capsules which have not reported enough data to be included in this review update. More studies of cranberry capsules or tablets containing PAC amounting at least 36 mg/d, quantified using a standard measure, and taken twice daily may be warranted but potentially only for women with recurrent UTIs.

Quality of the evidence

Study design in most studies was relatively robust and free from significant bias. The biggest weakness of the evidence was in attrition bias due to the large number of participants who were randomised but not included in the outcome analysis (intention-to-treat). Not using an intention-to-treat analysis undermines the randomisation process and such an analysis was only undertaken in six studies. A further limitation to the findings is the small size of most studies; most studies lacked power to detect a realistic significant difference between treatment groups and even combining the few studies with similar populations and treatment, did not greatly improve this issue.

Potential biases in the review process

Data extraction was completed independently by two authors without financial interest in the outcome. Data compilation for the new studies in the current update was completed by an author uninvolved in the previous review and without expectations for results. In summary authors believe the review update was an unbiased process limited only by the adequacy of reporting in the included studies.

Agreements and disagreements with other studies or reviews

The most recent and robust systematic review that evaluated cranberry products versus placebo was published in 2012 (Wang 2012). Although the search strategy and inclusion/exclusion criteria were similar, the Wang 2012 only contained 13 studies (1616 participants) compare to this review with 24 studies (4473 participants). The main difference was that the authors did not include studies that compared cranberry products with another intervention (e.g. antibiotics). However, despite this difference, the review did not contain several placebo controlled studies that were included

here (Cowan 2012; Essadi 2010; Lee 2007; Linsenmeyer 2004; NAPRUTI Study 2011 I; PACS Study 2008; Salo 2010; Sengupta 2011; Uberos 2010). Overall Wang 2012 reported similar results to this review. The main difference was their decision to exclude one of the studies with women with recurrent UTIs from their meta-analysis (Barbosa-Cesnik 2011). They excluded the study because there was significant heterogeneity in the results - the Barbosa-Cesnik 2011 study was the only one in the subgroup of women with recurrent UTIs which showed no effect of cranberry on the incidence of UTIs. Wang 2012 hypothesised that one of the reason for the different results in this study could be due to the threshold which Barbosa-Cesnik 2011 used to define a UTI. It was the lowest at 10^3 cfu/mL; most of the other studies used a threshold of 10^5 cfu/mL. However, since this threshold was used to define a UTI in both the control and intervention group in the study, this is unlikely to be the explanation. As the weighted prior probability of UTI varies across diagnostic threshold: 65.1% at $\geq 10^2$ cfu/mL; 55.4% at $\geq 10^3$ cfu/mL; and 44.8% at $\geq 10^5$ cfu/mL (Giesen 2010), you would expect to see more UTIs identified at a lower threshold, but this was not the case in this study. The incidence rate was 16.9%, almost half what would have been expected (27%), based on the literature (Foxman 2000). Therefore the study population may have been women who were less at risk of recurrent UTIs. We decided to include the study in our meta-analysis because it was the largest study, the only one which used blinding, and did a power calculation, and therefore likely to have the most robust results. Wang 2012 also undertook subgroup analysis of cranberry juice versus tablets or capsule and found that juice was more effective but hypothesised that one reason for this could be that the participants who drank the cranberry juice were more hydrated.

AUTHORS' CONCLUSIONS

Implications for practice

The current body of evidence suggest that cranberry products (either in juice or as capsules/tablets) compared to placebo provides no benefits in most populations groups, and the benefit in some subgroups is likely to be very small. The large number of drop-outs/withdrawals from some of the studies indicates that cranberry products, particularly in juice form, may not be acceptable over long periods of time. Cranberry capsules or tablets may overcome some issues with compliance, but from current evidence they do not appear to be any more effective than juice, although they may be as effective as antibiotics. One of the drawbacks of the studies of non-juice products, such as capsules, is few of the triallists reported how much 'active' ingredients (if any) were in the tablets or capsules they used. Until there are more studies of products containing enough of the active ingredient, measured in a standardised way, cranberry products cannot be recommended for preventing UTIs.

Implications for research

A significant number of RCTs have now been conducted to assess the effectiveness of cranberry products for preventing UTIs, particularly in its juice form. Given the majority of studies indicate the benefit is likely to be small at best, and with poor adherence, further studies of cranberry juice are only likely to support this conclusion, and should not be undertaken without strong justification. More studies of cranberry products such as tablets and capsules may be justified, but only for women with recurrent UTIs, and only if they contain the recommended amount of PAC (at least 36 mg/d) which is quantified using standardised and validated measures.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Avorn 1994

Methods	• Study design: quasi-RCT • Power calculation: Yes • Intention-to-treat analysis: No
Participants	Inclusion criteria • Setting: Recruited from a single long-term care facility for the elderly, and 9 housing complexes for the elderly • Country: USA • 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 randomised, 153 analysed • Mean age: 78.5 years Exclusion criteria • Terminal disease or severe dementia; men
Interventions	Treatment group • Cranberry juice cocktail: 300 mL/d (30% cranberry concentrate) • PAC content: NS Control group • Placebo beverage that looked and tasted similar but contained no cranberry juice Treatment duration: 6 months
Outcomes	• Presence of bacteriuria (bacteria in the urine $\geq$ 100,000/mL) with the presence of pyuria (white cells in the urine) • Presence of bacteriuria • Presence of bacteriuria with the presence of pyuria plus symptoms of a UTI
Notes	• 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 $\geq$ 100,000/mL regardless of organism • Definition of pyuria: NS • Exclusions post randomisation: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Odd versus even numbers in institutional identification number or telephone number (quasi-RCT)

Avorn 1994 (*Continued*)

Allocation concealment (selection bias)	High risk	Inadequate, could subvert system by excluding people with certain number, or include more of those with a certain number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	High risk	Absolute numbers not always provided; 39 patients lost to follow-up/withdrawn
Selective reporting (reporting bias)	Low risk	Primary outcome is reasonable though symptomatic would be better
Other bias	High risk	Source of funding: Research grant from Ocean Spray Cranberries, Inc

Barbosa-Cesnik 2011

Methods	• Study design: parallel RCT • Power calculation: yes • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: Women presenting to a health service with symptoms of UTI • Country: USA • Women 18-40 years, with UTI symptoms, residing in Ann Arbor next 6 months • Number: 419 randomised; 319 analysed • Average age: 21 years • Previous UTIs: 3-4 previously; 1 in previous year Exclusion criteria • Antibiotics in past 48 hours; hospitalisation or catheterisation within past 2 weeks; kidney stones; diabetes; pregnancy; cranberry allergy; negative urine culture
Interventions	Treatment group • Low calorie cranberry cocktail: 240 mL (8 oz) twice a day • Mean PAC: 112 mg/240 mL Control group • Placebo drink: same volume matched for flavour and colour Treatment duration: 6 months
Outcomes	• Primary outcome: UTI ($\geq 10^3$ cfu/L of known pathogen) • Secondary outcome: urinary symptoms and vaginal symptoms at day 3, 1-2 weeks, and $\geq$ 1 month

Barbosa-Cesnik 2011 (*Continued*)

Notes	• Compliance measured by direct questioning	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	External, web based allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo drink matched, participants and clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	High risk	100 participants randomised but no outcomes reported for them, they were actually not eligible to be randomised since they were culture negative
Selective reporting (reporting bias)	Low risk	UTI is most appropriate outcome
Other bias	High risk	Selection bias, representative nature of consenters is questionable Source of funding: National centre for alternative medicine at NIH

Cowan 2012

Methods	• Study design: parallel design • Power calculation: provided, assumed 20% reduction in bladder problems • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: radiotherapy booking system used to identify patients, patients had cervical cancer or bladder cancer at 1 centre • Country: UK • Adults > 18 years with cervical or bladder cancer requiring radiation therapy • Number: 128 randomised; 113 analysed (7 in placebo arm, 8 in cranberry arm) Exclusion criteria: NS
Interventions	Treatment group • Cranberry juice twice/d; volume (NS); PAC (NS) Control group

Cowan 2012 (*Continued*)

	• Matched placebo juice twice/d; volume (NS)
Outcomes	• Urinary symptoms
Notes	• Exclusions post randomisation: 0

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based deterministic minimisation algorithm, externally allocated
Allocation concealment (selection bias)	Low risk	Computer algorithm generated a blinded juice pack
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding stated, patients blinded to treatment arm, clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	For UTI outcome probably low risk, microbiology results independent
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very little missing data
Selective reporting (reporting bias)	Low risk	Urinary symptoms and UTI
Other bias	Low risk	Source of funding: west Research Endowment fund, NHS greater Glasgow and Clyde, Juice and placebo supplied by Ocean Spray

Essadi 2010

Methods	• Study design: parallel RCT • Power calculation: no • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: Pregnant women attending an antenatal clinic between October 2008 and October 2009 • Country: NS • Number: 760 randomised; 544 analysed • Age: NS Exclusion criteria: NS

Essadi 2010 (*Continued*)

Interventions	Treatment group • Cranberry juice: 250 mL 4 times/d Control group • Water: 250 mL 4 times/d
Outcomes	• Primary outcome: UTI • Secondary: premature delivery
Notes	• Abstract only, few details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No, participants could tell difference between treatment and drinking water
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up excluded and no best-worst case scenario analysis Losses to follow-up/withdrawals/exclusions post randomisation: 216
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Unclear risk	Too few details to know Source of funding: NS

Ferrara 2009

Methods	• Study design: parallel 3 arm RCT • Power calculation: no • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: ambulatory paediatric nephrology clinic; single centre • Country: Italy • Girls 3-14 years attending an ambulatory paediatric nephrology clinic; more than 1 UTI in previous 12 months

	• Number: 84 randomised; 80 analysed • Mean age: 7.5 years Exclusion criteria • Structural abnormalities; deformities of the urinary tract; impaired kidney function
Interventions	Treatment group • Cranberry-lignoberry concentrate ○ Cranberry concentrate: 50 mL/d for 6 months (97.5 g cranberry concentrate) ○ Ligonberry concentrate: 1.7 g in 50 mL water ○ No sugar additives • Lactobacillus GG drink: 100 mL on 5 days each month for 6 months (contains 4 x 10^7 cfu/100 mL) Control group • No treatment
Outcomes	• Symptomatic UTI (symptoms being frequency, dysuria, urgency, haematuria, nocturia, fever, back or hip pain and $\geq 10^8$ cfu/L
Notes	• Exclusions post randomisation: 0

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	No details on how well allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No, girls knew what treatment they were taking
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Those lost to follow-up were excluded, no analysis of best and worst case scenarios Losses to follow-up/withdrawals: 4
Selective reporting (reporting bias)	Low risk	Appropriate outcome
Other bias	Unclear risk	Details on patients are limited, selection bias may be present Source of funding: NS

Foda 1995

Methods	• Design: Cross-over RCT • Power calculation: No • Intention-to-treat analysis: No
Participants	Inclusion criteria • Setting: Outpatients' residence at a distance not exceeding 150 km from the Children's Hospital of Eastern Ontario • Country: Canada • Children with neuropathic bladder and managed by clean intermittent catheterisation • Number: 40 randomised; 21 analysed • Age range (mean): 1.4 to 18 years (9.35 years) Exclusion criteria: NS
Interventions	Treatment group • Cranberry cocktail: 15 mL/kg/d (30% cranberry concentrate) Control group • Water Duration of treatment: 6 months
Outcomes	• Number of months of positive cultures plus a symptomatic UTI • Number of months of positive cultures plus an asymptomatic UTI • Side effects and compliance
Notes	• Exclusions post randomisation: none • Method of collection urine ○ Sterile catheter urine samples • Definition of bacteriuria ○ ≥ 100,000 cfu/L of a pathogenic organism after 24 hours incubation ○ Any growth in a symptomatic patient was considered significant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind participants; blinding of physician only
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up/withdrawals: 19

Foda 1995 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Not enough detail
Other bias	Unclear risk	Not enough detail Source of funding: NS

Haverkorn 1994

Methods	• Design: cross-over RCT • Power calculation: no • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: Single hospital • Country: The Netherlands • Number: 38 randomised; 7 analysed • Mean age: 81 years • Sex (M/F): 9//29 Exclusion criteria: NS
Interventions	Treatment group • Cranberry juice: 30 mL/d mixed with water • PAC: NS Control group • Water: same volume as intervention Duration of treatment: 4 weeks active treatment (8 weeks total)
Outcomes	• Bacteriuria
Notes	• Exclusions post randomisation: none • Method of obtaining urine sample: NS • Definition of bacteriuria ○ ≥ 100,000 cfu of one of the Enterobacteriaceae/mL of urine • Report is a letter only, so very few methodological details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Date of birth (odd versus even numbers)
Allocation concealment (selection bias)	High risk	Inadequate, able to subvert system by not enrolling some if they were to start on water only
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing stated and no placebo

Haverkorn 1994 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up/withdrawals: 22
Selective reporting (reporting bias)	Unclear risk	Few details, can't be certain all outcomes collected are reported
Other bias	Unclear risk	Insufficient detail to be certain of study design Source of funding: NS

Hess 2008

Methods	• Study design: cross-over RCT • Power calculation: yes • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: spinal cord injury service in Veterans Admin Hospital; single centre • Country: USA • Number: 57 randomised; 47 analysed • Median age: 53 years • Sex (M/F): all men Exclusion criteria • Spinal cord injury duration < 12 mo; GFR < 30 mL/min; immunosuppression; current malignancy
Interventions	Treatment group • Cranberry tablet: 500 mg twice daily Control group • Placebo tablet: rice flour, matched to cranberry tablet
Outcomes	• Primary outcome: symptomatic UTI • Secondary outcome: significant bacteriuria; at least 1 UTI over 6 months; rate of UTI/person-years
Notes	• Cross-over design without data on 1st phase being separate, not analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No method reported

Hess 2008 (*Continued*)

Allocation concealment (selection bias)	Low risk	Concealed, managed by the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unsure if outcome assessors blind, but all others were and outcome is objectively measured
Incomplete outcome data (attrition bias) All outcomes	High risk	10 patients lost to follow-up and no details provided
Selective reporting (reporting bias)	Low risk	Appropriate outcome
Other bias	Low risk	No apparent additional bias Source of funding: NS

Kontiokari 2001

Methods	• Study design: parallel 3-arm RCT • Power calculation: yes, but recruitment stopped before appropriate number recruited • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: Finnish student health service; single centre • Country: Finland • Women who had a UTI caused by E. coli (10^5 cfu/mL in clean voided MSU) and were not taking antimicrobial prophylaxis. • Number: 150 randomised/analysed • Mean age: 29-32 years Exclusion criteria: NS
Interventions	Treatment group 1 • Cranberry-lingonberry juice concentrate (Maija, Marli, Finland): 50 mL/d ◦ Cranberry concentrate: 7.5 g ◦ Lingonberry concentrate: 1.7 g ◦ Water: 50 mL with no added sugars Treatment group 2 • Lactobacillus GG drink (Gefilus, Valio, Finland): 100 mL for five days a week Control group • No intervention Duration of treatment: 6 months cranberry-lingonberry concentrate; 12 months lactobacillus
Outcomes	• First recurrence of symptomatic UTI

Kontiokari 2001 (*Continued*)

Notes	• Method of obtaining urine sample: clean voided MSU 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. • Exclusions post randomisation: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Tables of random numbers and block technique with block size of 6
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes (additional information provided by authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and physicians not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lab staff blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up/withdrawals: 13. Analysed drop outs and withdrawals
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Unclear risk	Uncertain about selection bias, few details Source of funding: Emil Aaltonen, Juho Vainio, and Alma and K A Snellman Foundations

Lee 2007

Methods	• Study design: 4 group factorial design, parallel RCT • Power calculation: yes • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: spinal cord injuries database, predominantly community dwelling patients • Country: Australia • Spnal cord injured people with neurogenic bladder, bladder management with

	either indwelling urethral or suprapubic catheter, intermittent catheterization, or reflex voiding with or without a condom drainage divide, absence of complex urological or serious renal or hepatic pathology, not being prescribed antibiotics at the time of enrolment and absence of symptoms of a UTI at enrolment. Had to be willing to stop any intercurrent urinary antiseptics before entering the study, • Number: 305 randomised/analysed • Mean age: 43.5 years • Sex: 253 males Exclusion criteria • Previous allergy to any of the test interventions
Interventions	Treatment group 1 • Methenamine hippurate: 2 g • Cranberry: 1600 mg Treatment group 2 • Methenamine hippurate: 2 g • Cranberry placebo Treatment group 3 • Cranberry: 1600 mg • Methenamine hippurate placebo Control group • Methenamine hippurate placebo • Cranberry placebo
Outcomes	• Symptomatic UTI: current criteria for treating patients in the spinal injured population
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Dynamically balanced, centralized randomisation performed externally
Allocation concealment (selection bias)	Low risk	External trial centre controlled, sent to pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States all staff and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States all staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for in results

Lee 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	Well described
Other bias	Low risk	No other bias apparent, well reported study Source of funding: Motor accidents authority and Brucia Pharmaceuticals

Linsenmeyer 2004

Methods	• Design: Cross-over RCT • Power calculation: NS • ITT analysis: no
Participants	Inclusion criteria • Setting: patients presenting to outpatient urology rehabilitation clinic; single centre • Country: USA • Patients with neurogenic bladders secondary to spinal cord injury • Number: 37 randomised; 21 analysed Exclusion criteria: NS
Interventions	Treatment group • Cranberry tablets: 400 mg standardised tablets Control group • Placebo Duration of treatment: 9 weeks (4 weeks on each, plus one week wash out)
Outcomes	• Urinary bacterial counts and WBC counts and the combination of bacterial and WBC counts
Notes	Exclusions post randomisation: none Method of obtaining urine sample • CSU or MSU Definition of bacteriuria • MSU: ≥ 10,000/mL • CSU: > 100 cfu/mL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States participants and researchers blinded

Linsenmeyer 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	States researchers are blinded, assume outcomes assessors included
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in results and analysis; losses to follow-up/withdrawals: 16
Selective reporting (reporting bias)	Low risk	Primary outcome is appropriate
Other bias	Unclear risk	Some methods are vague, not a well reported study Source of funding: Eastern Paralyzed Veterans Association

McGuiness 2002

Methods	• Study design: parallel RCT • Power calculation: not mentioned in methods but mentioned in discussion • ITT analysis: yes ((although percentages in results do not make sense)
Participants	Inclusion criteria • Setting: outpatient clinic for Multiple sclerosis patients; single centre • Country: Canada • Multiple sclerosis diagnosis (Poser criteria), Expanded Disability Status Scale 0 - 8; consented; refrain from cranberries during study; no indwelling or condom catheter, if intermittent catheterisation, no more that 6 times daily; symptoms of neurogenic bladder; no current UTI • Number: 135 randomised; 106 analysed • Mean age: treatment group (44.8 years); control group (45.4 years) Exclusion criteria: NS
Interventions	Treatment group • Cranberry containing tablet product (NOW Natural Foods): 8000 mg tablet, one tablet/d Control group • Beetroot powder placebo tablet, identical appearance to cranberry, one tablet/d Duration of treatment: 6 months
Outcomes	• Diagnosed UTI
Notes	• Results reported separately for patients with intermittent catheterisation and normal voiding, but study did not mention if it was stratified for this and numbers of each in the 2 treatment groups are not provided • Very poorly reported study and percentages reported for incidence of UTIs do not make sense
Risk of bias	

McGuiness 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of randomisation method were stated
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment methods were stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Title states the study was double blinded, assume this refers to participants and heath care providers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of microbiologists is assumed so culture result is likely to be unbiased. Less certain about how objectively measured the other criteria were
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 participants withdrew or were lost to follow-up but the numbers in each treatment arm were not provided
Selective reporting (reporting bias)	Low risk	UTI was appropriate outcomes and definition was provided
Other bias	Unclear risk	No details provided on how participants were selected and from how large the group, possible selection bias Source of funding: Alberta Association of Registered Nurses, American Asssociation of Neuroscience Nurses

McMurdo 2005

Methods	• Study design: parallel group • Power calculation: yes • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: single centre • Country: UK (Scotland) • 60 years or over admitted to either acute medicine for the elderly assessment or rehabilitation units for elderly people • Number: 376 randomised and analysed Exclusion criteria • Mental State Questionnaire (MSQ) score < 5/10; dysphagia; symptoms of a UTI; antibiotic treatment; anticipated length of stay < 1 week; regular drinkers of cranberry juice; presence of an in-dwelling catheter; 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	Treatment group • Cranberry juice: 300 mL Control group • Matching placebo beverage Duration of treatment: 6 months
Outcomes	• Time to onset of first symptomatic UTI: defined as a culture positive urine growing a single organism of > 10^4 cfu/mL urine specimen • Adherence to beverage drinking, courses of antibiotics prescribed, and organisms responsible for UTIs
Notes	• Exclusions post randomisation: none • Method of obtaining urine sample: clean catch • Definition of bacteriuria ○ Only pure growths of $\geq 10^4$ cfu/mL were reported with an antibiotic sensitivity

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified by gender and computer generated
Allocation concealment (selection bias)	Low risk	Held by pharmacy, sealed numbered enveloped
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed and reported; Losses to follow-up/withdrawals: 115
Selective reporting (reporting bias)	Low risk	Appropriate clinical outcomes
Other bias	Low risk	No other bias apparent, well reported study 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

McMurdo 2009

Methods	• Study design: parallel RCT • Power calculation: yes • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: single centre • Country: UK (Scotland) • Community dwelling women ≥ 45 years with at least 2 antibiotic treated UTIs in previous 12 months confirmed by GP, but not necessarily culture proven. Predominanty through primary care services but also from newspaper ads • Number: 137 randomised and analysed Exclusion criteria: NS
Interventions	Treatment group • Cranberry tablet: 500 mg Control group • TMP tablet: 100 mg Matched tablets with over-coating
Outcomes	• Symptomatic UTI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Off site by DHP Pharma in Powys,UK, blocks of 4 using Prisym PFW clin software to generate random numbers
Allocation concealment (selection bias)	Low risk	Externally managed, not able to be influenced
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for; losses to follow-up/withdrawals: 17
Selective reporting (reporting bias)	Low risk	Symptomatic UTI is most appropriate

Other bias	Low risk	Well reported, no other bias apparent Source of funding: Moulton charitable foundation

NAPRUTI Study 2011 I

Methods	• Study design: parallel RCT • Power calculation: yes • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: 10 centres • Country: The Netherlands • Premenopausal women > 18 years with at least 3 symptomatic UTIs in the year prior to enrolment, self reported. Recruited through direct advertising and primary care facilities as well as secondary and tertiary level hospital referrals • Number: 221 randomised; 200 analysed (for repeat symptomatic UTI) Exclusion criteria • Symptoms of UTI at inclusion, use of antibiotics or cranberry in previous 2 weeks, relevant interaction with other medications or contraindications for TMP-SMX or cranberries, pregnancy, breastfeeding or renal transplantation
Interventions	Treatment group • Cranberry extract: 500 mg twice daily (9.1 mg/g type A PAC) • Placebo tablet: 1 tablet at night Control group • TMP-SMX: 480 mg at night • Placebo tablet: 1 tablet twice daily Placebo and active tablets were identical Duration of treatment: 12 months
Outcomes	• Primary outcome: mean number of clinically defined UTIs over 12 months • Secondary outcome: proportion of patients with at least 1 symptomatic UTI, median time to symptomatic UTI, bacterial resistance to active treatment
Notes	• Email correspondence from Marielle Beerepoot on 5 June 2012 provided the actual numbers of participants in each arm who experienced a UTI • Exclusions post randomisation: 14

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generation of the allocation list was computer-aided block randomisation with stratification by centre and presence of complicating host factors. Prepared in advance by coordinating centre, unlikely to

NAPRUTI Study 2011 I (*Continued*)

		be influenced by clinicians/researchers on site
Allocation concealment (selection bias)	Low risk	External to clinical site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched drug and dose regimen
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Considerable loss to follow up, no best and worst case scenario analysis Losses to follow-up/withdrawals: 70 without follow-up at 12 months
Selective reporting (reporting bias)	Low risk	Many outcomes reported, clinically appropriate
Other bias	Low risk	Appears to be a representative sample Source of funding: Netherland Organisation for health research and development

PACS Study 2008

Methods	• Study design: 3-arm parallel RCT • Power calculation: no • Intention-to-treat analysis: appears all were included
Participants	• Setting: 4 dementia units • Country: USA • Elderly mean and women > 60 years of age with dementia and a resident of a nursing home or assisted living facility for > 30 days • Number: 56 randomised and analysed
Interventions	Treatment group 1 • Cranberry capsule: 1 x 650 mg once daily Treatment group 2 • Cranberry capsule: 1 x 650 mg twice daily Control group • No treatment
Outcomes	• Number of urine cultures collected • Number of participants with E.coli isolated from urine culture • Number of participants with > 100,000 cfu/mL if any organism

PACS Study 2008 (*Continued*)

Notes	• Details from clinical trials register, not from a published paper • Designed as a feasibility pilot for a larger study, wanted to determine if collecting urine was feasible

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on this aspect
Allocation concealment (selection bias)	Unclear risk	Open label study, could be possible to subvert randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Expected number of urine samples was less than expected. Losses to follow-up/withdrawals: 2 lost and 28 did not complete treatment
Selective reporting (reporting bias)	Unclear risk	Outcomes are about feasibility not efficacy
Other bias	Unclear risk	Many details missing or poorly detailed Source of funding: NS

Salo 2010

Methods	• Study design: parallel RCT • Power calculation: provided, justified, although highly optimistic • Intention-to-treat analysis: no, 8 excluded
Participants	Inclusion criteria • Setting: 7 centres, (4 university paediatric departments, 3 centralised hospitals) • Country: Finland • Children referred to paediatric departments of 4 university hospitals or 3 centra hospitals for verified UTI in previous 2 months, 2001-2008 • Number: 263 randomised; 255 analysed Exclusion criteria • Children with grade III-V VUR or severe genitourethral malformations

Salo 2010 (*Continued*)

Interventions	Cranberry juice 5mL/kg up to 300mL 1-2 doses daily for 6 months or Placebo juice same volume and dose per day as cranberry	
Outcomes	Repeat UTI	
Notes	Details are from the trial registration, Salo abstract and journal article	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block size 4, externally managed
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, states clinician and parents blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specifically stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few missing data Losses to follow-up/withdrawals: 27 drop outs (16 in cranberry arm, 11 in placebo group) Exclusions post randomisation: 8
Selective reporting (reporting bias)	Low risk	Most appropriate outcome used
Other bias	Low risk	Well reported study Source of funding: Paivikki and Sakari Sohlberg Foundation, Foundation for Paediatric research, Paulo Foundation, Ocena Spray

Schlager 1999

Methods	• Study design: cross-over RCT • Power calculation: no • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: single centre • Country: USA

Schlager 1999 (*Continued*)

	• 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 randomised and analysed • Age range: 2-18 years Exclusion criteria: NS
Interventions	Treatment group • Cranberry juice cocktail: 300 mL/d (30% cranberry concentrate) Control group • Placebo beverage: looked and tasted similar but contained no cranberry juice Duration of treatment: 3 months cranberry juice; 3 months placebo
Outcomes	• Presence of bacteriuria • Symptomatic UTI
Notes	• Method of obtaining urine sample ○ CSU • Definition of symptomatic bacteriuria ○ Defined as bacteriuria with fever, abdominal pain, change in continence pattern, or change in colour or odour of urine • Definition of bacteriuria ○ ≥ 100,000/mL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided, states only "randomly assigned"
Allocation concealment (selection bias)	Low risk	Adequate, randomly assigned by research pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Culture results not available to investigators during the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All children and results accounted for
Selective reporting (reporting bias)	Low risk	Symptomatic UTI reported as appropriate

Schlager 1999 (*Continued*)

Other bias	Low risk	Nothing apparent Source of funding: Grants from Spinal Cord Research Foundation and the Pendleton Pediatric Infectious Disease Research Laboratory

Sengupta 2011

Methods	• Study design: 3-arm parallel RCT • Power calculation: no • Intention-to-treat analysis: no, 3 post randomisation drop outs were not analysed
Participants	Inclusion criteria • Setting: uncertain, possibly single centre • Country: India • Females with a history of recurrent UTIs, with dysuria, frequency, blood in urine or pain in suprapubic region and negative pregnancy test • Number: 60 randomised and analysed Exclusion criteria • Antibiotics in past 48 hours; catheterized within last 2 weeks; diabetes; cardiovascular disease; pyelonephritis; kidney stones
Interventions	Treatment group 1 • Cranberry: 500 mg/d Treatment group 2 • Cranberry: 1000 mg/d Control group • No treatment 1.5% PAC, Decas Botanical Synergies
Outcomes	• Symptomatic UTI with > 10^4 cfu/mL E.coli pure growth
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Externally managed, sealed envelopes opened in order; completed by independent person
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded

Sengupta 2011 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Uncertain if researchers or assessors were blind to allocated treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nothing apparent but unclear in the report Exclusions post randomisation: 3
Selective reporting (reporting bias)	Low risk	Symptomatic culture proven UTI is most appropriate outcome
Other bias	Unclear risk	Unclear how the 225 patients were recruited, may be some selection bias Source of funding: NS

Stothers 2002

Methods	• Study design: parallel RCT • Power calculations: no • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: single centre • Country: Canada • At least two symptomatic, single-organism, culture positive UTIs in the previous calendar year, but were currently free of UTI on urinalysis and culture; sexually active women • Number: 150 randomised and analysed • Age range: 21-72 years Exclusion criteria • Neurogenic bladder dysfunction; insulin-dependent diabetes; immunosuppressive disease; steroid use; intermittent or indwelling catheterisation
Interventions	Treatment group 1 • Placebo juice + cranberry tablets: 1:30 parts concentrated juice, two times/d Treatment group 2 • Cranberry juice: 250 mL three times/d • Placebo tablets Control group • Placebo juice: filtered water with food colouring + 20 mL pineapple juice • Placebo tablets Duration of treatment: one year
Outcomes	• > 50% decrease in symptomatic UTI/y (symptoms + ≥ 100,000 single organisms/mL) • > 50% decrease in annual antibiotic consumption • Costs effectiveness of treatment

Stothers 2002 (*Continued*)

Notes	• Method of obtaining urine sample
	  ○ CSU
	• Definition of bacteriuria
	  ○ Bacteria in the urine ≥ 100,000/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of 10 to one arm of the study, computer generated (additional information provided by authors)
Allocation concealment (selection bias)	Low risk	Adequate, pharmacist dispensed allocated treatment packages
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers blind and microbiology laboratory probably blind when interpreting plated results
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for in results Losses to follow-up/withdrawals: 2 patients in the cranberry juice arm dropped out
Selective reporting (reporting bias)	Low risk	UTI appropriate outcome
Other bias	Low risk	None apparent Source of funding: NS

Uberos 2010

Methods	• Study design: parallel RCT • Power calculation: no • Intention-to-treat analysis: yes, and also survival analysis in which appearance of the event (UTI) was sufficient cause for ending the follow-up period
Participants	Inclusion criteria • Setting: paediatric nephrology and urology departments; single centre • Country: Spain • Children aged from 1 month to 13 years, with recurrent UTI (2 or more infections in 6 months), vesicoureteric reflux of any degree, pyelic ectasia or hydronephrosis or anatomical kidney disorder • Number: 198 randomised; 192 analysed

Uberos 2010 (*Continued*)

Interventions	Treatment group • Cranberry syrup: 0.2 mL/kg (Urell, Pharmatoka) Control group • TMP: 8 mg/kg
Outcomes	• UTI
Notes	• Published first as an abstract, more recently as a full report

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer and ID card
Allocation concealment (selection bias)	Low risk	Method stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Possibly, uncertain who double blind refers to
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up/withdrawals: 3 in each group (six in total)
Selective reporting (reporting bias)	Low risk	Symptomatic UTI is most appropriate
Other bias	Unclear risk	Due to problems during the randomisation process, 75 patients were assigned to receive cranberry syrup and 117 to receive TMP. However, blinding to treatment was maintained Source of funding: Carlos III Institute of Health for Clinical Research, Madrid, Spain

Waites 2004

Methods	• Study design: parallel RCT • Power calculations: no • Intention-to-treat analysis: no

Participants	Inclusion criteria • Setting: single centre • Country: USA • Community residing men and women 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 study. Baseline urine culture demonstrating at least 10^5 cfu/mL • Number: 74 randomised; 48 analysed
Interventions	Treatment group • Concentrated cranberry extract: 2 g in capsule form Control group • Placebo capsule Duration of treatment: 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 ○ $\geq$ 100,000/mL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details about random sequence methods were reported
Allocation concealment (selection bias)	Unclear risk	Uncertain of the process of treatment allocation, no details were reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and clinicians were blind to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Probably likely that microbiology staff assessing culture results were blind to treatment, but this wasn't stated
Incomplete outcome data (attrition bias) All outcomes	High risk	26 withdrawals out of 74 participants had no data on outcomes

Waites 2004 (*Continued*)

Selective reporting (reporting bias)	Low risk	The primary outcome was symptomatic UTI which is appropriate
Other bias	Unclear risk	Few details on how patients were identified, possible selection bias Source of funding: NS, but Cranberry capsules were provided by Aim This Way, Cambridge, Massachusetts

Walker 1997

Methods	• Study design: cross-over RCT • Power calculation: no • Intention-to-treat analysis: no
Participants	Inclusion criteria • Setting: single centre • Country: USA • 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); sexually active women • Number: 19 randomised; 10 analysed • Age range (median): 28-44 years (37) Exclusion criteria: NS
Interventions	Treatment group • Cranberry capsules: 400 mg of cranberry solids (number/d NS) Control group • Placebo capsule Duration of treatment: each patient had 3 months of active treatment and 3 months placebo
Outcomes	• Symptomatic UTI
Notes	• Method of obtaining urine sample: NS • Dedfinition 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS

Walker 1997 (*Continued*)

Allocation concealment (selection bias)	Low risk	States clinicians unaware of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinding and opaque matching bottles
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States double blind, likely that culture results read without knowledge of treatment arm
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear reporting of results, culture appears the units rather than patients Losses to follow-up/withdrawals: 9
Selective reporting (reporting bias)	Low risk	Symptomatic UTI most appropriate outcome
Other bias	Unclear risk	Not well reported, difficult to assess Source of funding: NS (capsules provided by Solaray, Inc)

Wing 2008

Methods	• Study design: 3-arm RCT • Power calculation: no, feasibility pilot • Intention-to-treat analysis: yes
Participants	Inclusion criteria • Setting: 2 centres • Country: USA • Women < 16 weeks gestation presenting for prenatal care at 1 of 2 centres • Number: 188 randomised and analysed Exclusion criteria • Underlying medical conditions (e.g. diabetes mellitus, kidney failure, sickle cell disease, chronic hypertension, chronic kidney disease) previous or current antimicrobial therapy; known urological abnormalities
Interventions	Treatment group 1 • Cranberry juice: 240 mL at breakfast, placebo juice at other meals Treatment group 2 • Cranberry drink: 240 mL, 3 times/d, reducing to twice/d after 52 enrolments because not well tolerated Control group • Placebo: 3 daily doses of matched juice product
Outcomes	• Primary outcome: asymptomatic bacteriuria, > 10^8 cfu of a single organism and no symptoms • Secondary outcomes

	○ Symptomatic bacteriuria, > 10^8 cfu of single organism and dysuria or frequency or urgency ○ Pyelonephritis, culture as above, + flak pain, fever > 100.4°F, chills nausea, vomiting ○ At least 1 UTI, UTI due to enteric bacteria, ○ Pregnancy outcomes: preterm delivery, spontaneous vaginal delivery, instrumental vaginal delivery, caesarean/caesarean hysterectomy, mean birth weight, low birth weight, 1 min Apgar < 7, 5 min Apgar < 9, admission to NICU, tolerability and compliance
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation table, stratified by site
Allocation concealment (selection bias)	Low risk	Treatment options were not known to researchers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States all were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clearly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data are well reported for completeness Losses to follow-up/withdrawals: 73 withdrawals
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Low risk	Details suggest free of bias, although selection methods a little unclear Source of funding: NS

cfu - colony forming units; CSU - catheter specimen of urine; GFR - glomerular filtration rate; ITT - intention-to-treat; MSU - midstream urine; NS - not stated; PAC - proanthocyanidin; SMP - sulfamethoxazole; TMP - trimethoprim; WBC - white blood cell

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

Study	Reason for exclusion
Howell 2010	No clinically relevant outcomes, only laboratory measures
Jackson 1997	RCT of elderly people looking at the effect of cranberry juice on urinary acidity. No relevant outcomes reported.
Jass 2009	No clinically relevant outcomes, laboratory measures of urine chemistry
Lavigne 2008	No clinically relevant outcomes, only laboratory measures of urine kinetics
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
Tempera 2010	No clinically relevant outcomes, only laboratory measures of adhesion
Valentova 2007	No clinically relevant outcomes, only laboratory measures of urine biochemistry
Vidlar 2010	No clinically relevant outcomes, only laboratory measures of urine biochemistry

RCT - randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Afshar 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Bonetta 2011

Methods	Not clear
Participants	Men with prostate cancer undergoing radiotherapy
Interventions	Cranberry extract

Bonetta 2011 (*Continued*)

Outcomes	UTIs
Notes	Abstract only

NCT01079169

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Stapleton 2012

Methods	RCT
Participants	Women who have had a UTI within the past year
Interventions	Cranberry juice cocktail
Outcomes	Rate of UTIs
Notes	Study completed in 2009: no publications

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

NCT00100061

Trial name or title	Dose response to cranberry of women with recurrent UTIs
Methods	RCT
Participants	Women with recurrent UTIs
Interventions	Cranberry juice
Outcomes	UTIs
Starting date	May 2007
Contact information	Principal investigator: Lynn Stothers Bladder Care Centre, University of British Columbia

NCT00100061 (*Continued*)

Notes	Although due to finish in 2011, the website states 'This study is ongoing, but not recruiting participants'

NCT00280592

Trial name or title	Prospective, randomized, double-blind, placebo-controlled study on parallel groups evaluating the efficacy and safety of cranberry (Vaccinium macrocarpon) in prevention of urinary tract infections in multiple sclerosis patients
Methods	RCT
Participants	Patients with multiple sclerosis
Interventions	Dry essence of cranberry presented as 18 mg of PAC sachets of powdered cranberry. Cranberry juice is administered twice a day (in the morning and in the evening)
Outcomes	Time to onset of a first UTI within one year of treatment
Starting date	2006
Contact information	Philippe Gallien, http://clinicaltrials.gov/ct2/show/NCT00280592
Notes	Study completed February 2008: no publications

NCT01033383

Trial name or title	Pilot study: Dosing study of cranberry capsules for the prevention of bacteriuria in nursing home residents
Methods	RCT
Participants	Females at least 65 years of age or older who live in a nursing home and who have a history of UTIs
Interventions	Different doses of cranberry capsules
Outcomes	Time to onset of first UTI
Starting date	2009
Contact information	http://clinicaltrials.gov/ct2/show/NCT01033383
Notes	Should completed December 2010: no publications

PAC - proanthocyanidin; RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. Cranberry products versus placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with one or more UTIs at follow-up	13	2462	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.04]
1.1 Women with recurrent UTIs	4	594	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.42, 1.31]
1.2 Elderly men and women	2	413	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.44]
1.3 People with neuropathic bladder/spinal injuries	2	353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.20]
1.4 Pregnant women	2	674	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.17]
1.5 Children	2	309	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.19, 1.22]
1.6 Radiotherapy patients	1	119	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.75, 1.77]
2 Adverse effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Stomach burn and general weakness	1	34	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.46]
2.2 Vomitting	1	37	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.33, 108.56]
2.3 Nausea	2	187	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.23, 3.94]
2.4 Diarrhoea	1	37	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.06, 12.59]
2.5 Gastroenteritis	2	413	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.10, 1.96]
2.6 Any gastrointestinal effect	4	597	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.31, 2.27]

Comparison 2. Cranberry products versus antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Repeat symptomatic UTI	3	536	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.79, 1.73]
1.1 Adult women	2	344	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.85, 2.02]
1.2 Children	1	192	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.32, 1.51]
2 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Gastrointestinal	2	344	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.42, 1.42]
2.2 Rash or urticaria	1	207	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.25, 1.18]
2.3 Vaginal	1	207	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.40, 1.40]
2.4 Allergic reaction	1	207	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.28]

Comparison 3. Cranberry dose: 2 or more/day versus 1 dose/day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic UTI	3	208	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.75, 1.68]
1.1 Pregnant women	1	125	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.17, 7.94]
1.2 Adult women	1	44	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.14, 5.92]
1.3 Elderly men and women	1	39	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.75, 1.72]
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Weakness and abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Mild fever	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Heart burn	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Stomach burn and general weakness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Cranberry (dose: ≥ 2/day) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic UTI	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Pregnant women	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Elderly men and women	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Adult women	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Vomitting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Gastroenteritis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Stomach burn and general weakness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Cranberry products versus methenamine hippurate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Spinal injured neuropathic bladder participants	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Cranberry versus probiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic UTI	2	152	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.74]
1.1 Children with previous UTI	1	53	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.18, 1.09]
1.2 Adult women	1	99	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.20, 0.85]

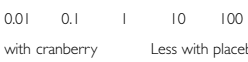
Analysis 1.1. Comparison 1 Cranberry products versus placebo/control, Outcome 1 Participants with one or more UTIs at follow-up.

Review: Cranberries for preventing urinary tract infections

Comparison: 1 Cranberry products versus placebo/control

Outcome: 1 Participants with one or more UTIs at follow-up

Study or subgroup	Cranberry product n/N	Placebo/control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Women with recurrent UTIs					
Barbosa-Cesnik 2011	31/155	23/164		8.7 %	1.43 [0.87, 2.33]
Kontiokari 2001	12/46	19/45		7.0 %	0.62 [0.34, 1.12]
Sengupta 2011	2/21	4/13		1.5 %	0.31 [0.07, 1.46]
Stothers 2002	19/100	16/50		7.3 %	0.59 [0.34, 1.05]
Subtotal (95% CI)	**322**	**272**		**24.5 %**	**0.74 [0.42, 1.31]**
Total events: 64 (Cranberry product), 62 (Placebo/control)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 8.50, df = 3 (P = 0.04); I^2 =65%					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 Elderly men and women					
McMurdo 2005	7/187	14/189		3.9 %	0.51 [0.21, 1.22]
PACS Study 2008	13/20	12/17		9.8 %	0.92 [0.59, 1.44]
Subtotal (95% CI)	**207**	**206**		**13.7 %**	**0.75 [0.39, 1.44]**
Total events: 20 (Cranberry product), 26 (Placebo/control)					
Heterogeneity: Tau^2 = 0.12; Chi^2 = 1.92, df = 1 (P = 0.17); I^2 =48%					
Test for overall effect: Z = 0.87 (P = 0.38)					
3 People with neuropathic bladder/spinal injuries					
Lee 2007	67/153	71/152		15.1 %	0.94 [0.73, 1.20]
Waites 2004	10/26	8/22		5.2 %	1.06 [0.51, 2.21]



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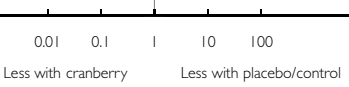
Study or subgroup	Cranberry product n/N	Placebo/control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**179**	**174**		**20.2 %**	**0.95 [0.75, 1.20]**
Total events: 77 (Cranberry product), 79 (Placebo/control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
4 Pregnant women					
Essadi 2010	182/258	194/286		18.7 %	1.04 [0.93, 1.16]
Wing 2008	2/67	0/63		0.4 %	4.71 [0.23, 96.15]
Subtotal (95% CI)	**325**	**349**		**19.1 %**	**1.04 [0.93, 1.17]**
Total events: 184 (Cranberry product), 194 (Placebo/control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.98, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 0.72 (P = 0.47)					
5 Children					
Ferrara 2009	5/27	18/27		4.3 %	0.28 [0.12, 0.64]
Salo 2010	20/126	28/129		8.2 %	0.73 [0.44, 1.23]
Subtotal (95% CI)	**153**	**156**		**12.5 %**	**0.48 [0.19, 1.22]**
Total events: 25 (Cranberry product), 46 (Placebo/control)					
Heterogeneity: Tau^2 = 0.34; Chi^2 = 3.73, df = 1 (P = 0.05); I^2 =73%					
Test for overall effect: Z = 1.54 (P = 0.12)					
6 Radiotherapy patients					
Cowan 2012	26/59	23/60		10.1 %	1.15 [0.75, 1.77]
Subtotal (95% CI)	**59**	**60**		**10.1 %**	**1.15 [0.75, 1.77]**
Total events: 26 (Cranberry product), 23 (Placebo/control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
Total (95% CI)	**1245**	**1217**		**100.0 %**	**0.86 [0.71, 1.04]**
Total events: 396 (Cranberry product), 430 (Placebo/control)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 25.64, df = 12 (P = 0.01); I^2 =53%					
Test for overall effect: Z = 1.53 (P = 0.13)					
Test for subgroup differences: Chi^2 = 5.27, df = 5 (P = 0.38), I^2 =5%					

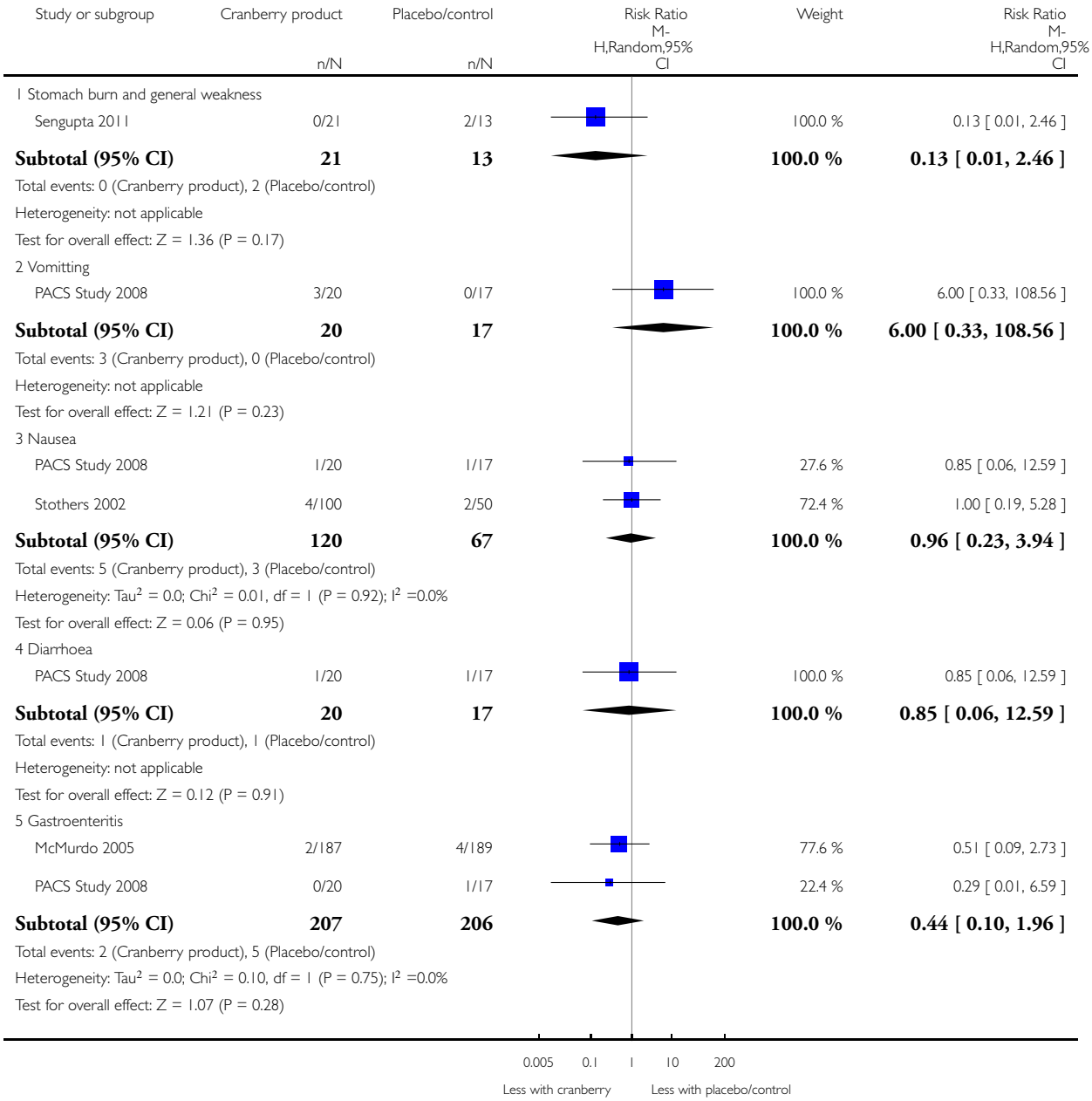


Analysis 1.2. Comparison 1 Cranberry products versus placebo/control, Outcome 2 Adverse effects.

Review: Cranberries for preventing urinary tract infections

Comparison: 1 Cranberry products versus placebo/control

Outcome: 2 Adverse effects



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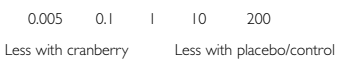
Study or subgroup	Cranberry product n/N	Placebo/control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
6 Any gastrointestinal effect					
McMurdo 2005	2/187	4/189		32.7 %	0.51 [0.09, 2.73]
PACS Study 2008	3/20	1/17		20.3 %	2.55 [0.29, 22.31]
Sengupta 2011	0/21	2/13		11.1 %	0.13 [0.01, 2.46]
Stothers 2002	5/100	2/50		35.8 %	1.25 [0.25, 6.22]
Subtotal (95% CI)	**328**	**269**		**100.0 %**	**0.83 [0.31, 2.27]**
Total events: 10 (Cranberry product), 9 (Placebo/control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 3.17$, df = 3 (P = 0.37); I^2 =5%					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: $Chi^2 = 3.99$, df = 5 (P = 0.55), I^2 =0.0%					

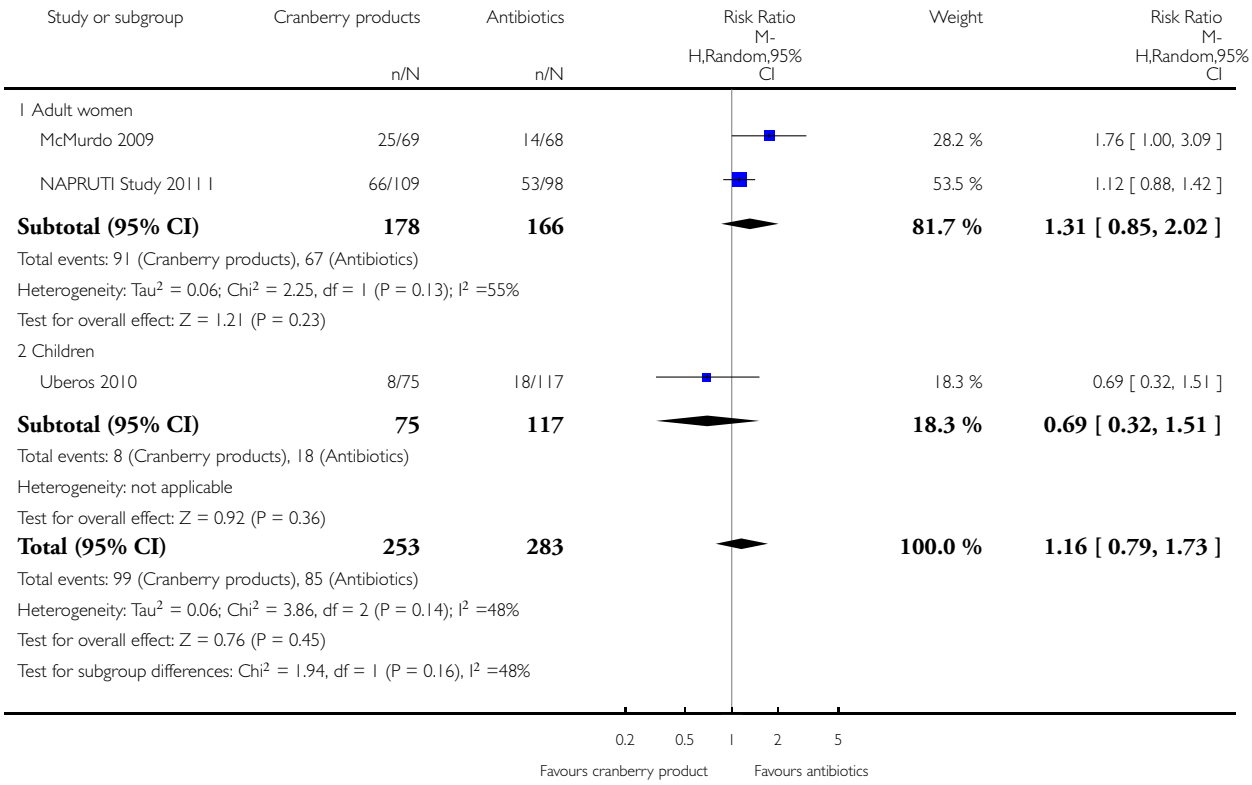


Analysis 2.1. Comparison 2 Cranberry products versus antibiotics, Outcome 1 Repeat symptomatic UTI.

Review: Cranberries for preventing urinary tract infections

Comparison: 2 Cranberry products versus antibiotics

Outcome: 1 Repeat symptomatic UTI

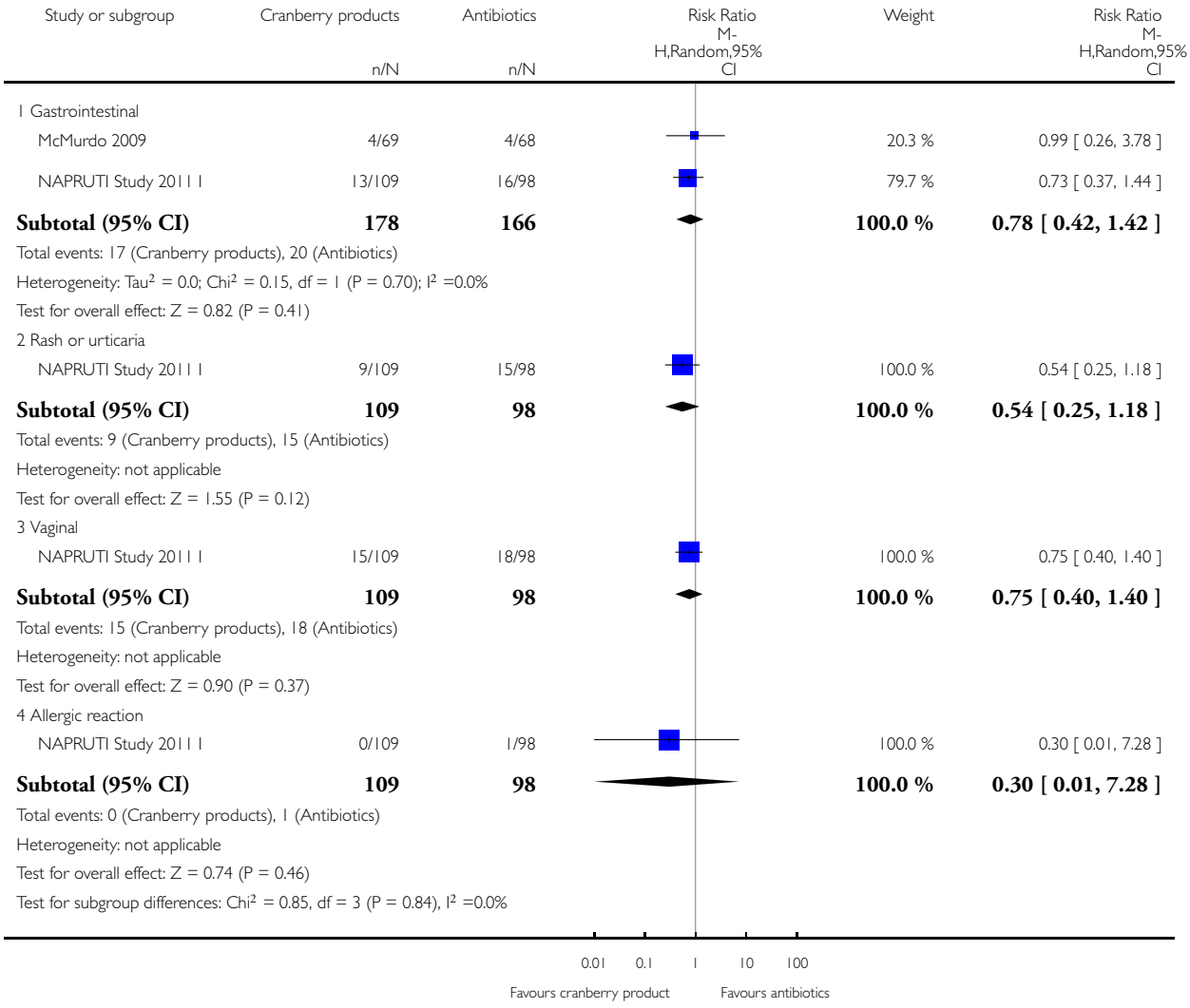


Analysis 2.2. Comparison 2 Cranberry products versus antibiotics, Outcome 2 Adverse effects.

Review: Cranberries for preventing urinary tract infections

Comparison: 2 Cranberry products versus antibiotics

Outcome: 2 Adverse effects

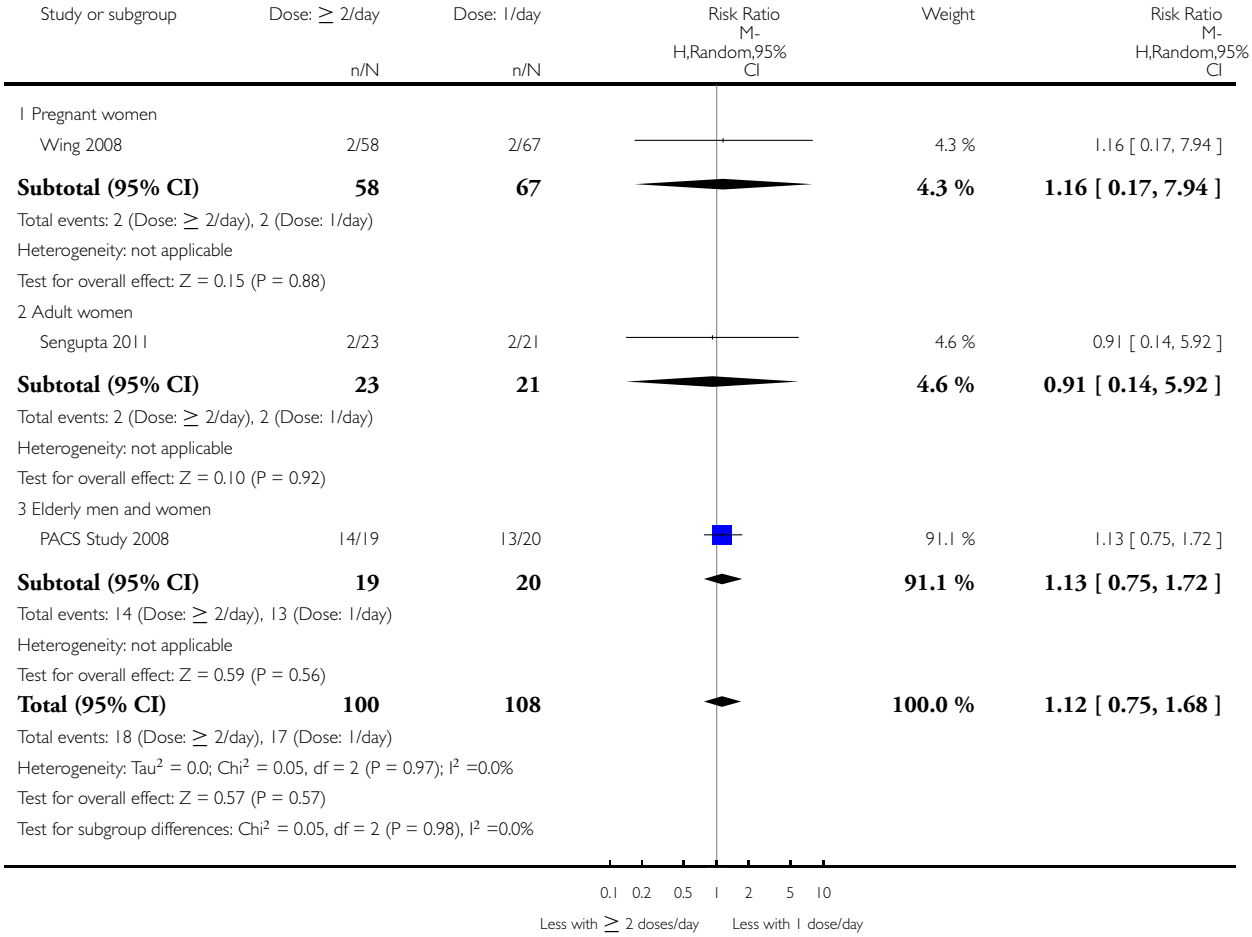


Analysis 3.1. Comparison 3 Cranberry dose: 2 or more/day versus 1 dose/day, Outcome 1 Symptomatic UTI.

Review: Cranberries for preventing urinary tract infections

Comparison: 3 Cranberry dose: 2 or more/day versus 1 dose/day

Outcome: 1 Symptomatic UTI



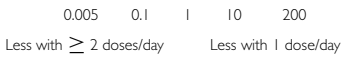
Analysis 3.2. Comparison 3 Cranberry dose: 2 or more/day versus 1 dose/day, Outcome 2 Adverse effects.

Review: Cranberries for preventing urinary tract infections

Comparison: 3 Cranberry dose: 2 or more/day versus 1 dose/day

Outcome: 2 Adverse effects

Study or subgroup	Dose: ≥ 2/day n/N	Dose: 1/day n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Weakness and abdominal pain				
Sengupta 2011	1/23	3/21		0.30 [0.03, 2.70]
2 Mild fever				
Sengupta 2011	3/23	0/21		6.42 [0.35, 117.34]
3 Heart burn				
Sengupta 2011	2/23	0/21		4.58 [0.23, 90.30]
4 Stomach burn and general weakness				
Sengupta 2011	0/23	0/21		Not estimable

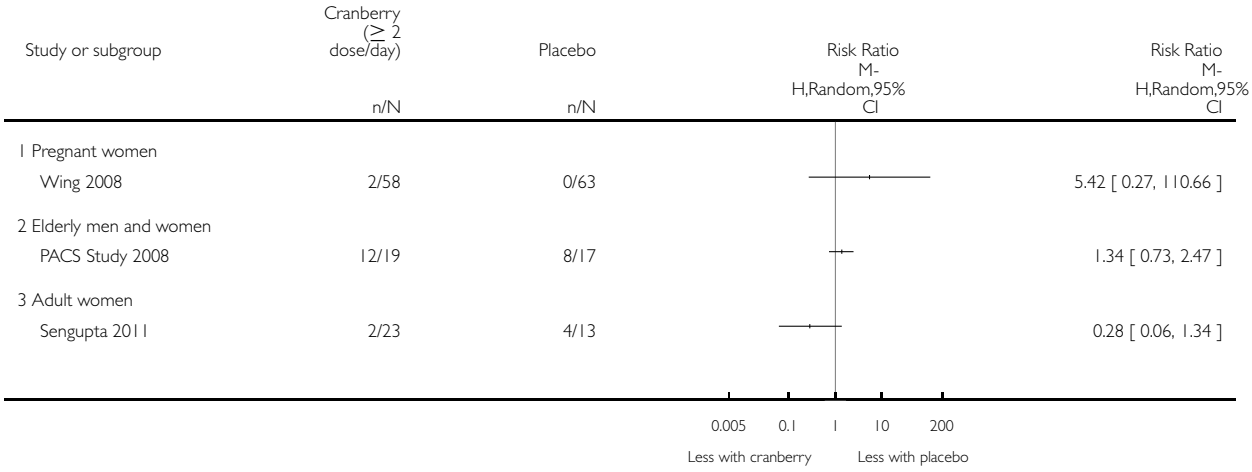


Analysis 4.1. Comparison 4 Cranberry (dose: ≥ 2/day) versus placebo, Outcome 1 Symptomatic UTI.

Review: Cranberries for preventing urinary tract infections

Comparison: 4 Cranberry (dose: ≥ 2/day) versus placebo

Outcome: 1 Symptomatic UTI



Analysis 4.2. Comparison 4 Cranberry (dose: ≥ 2/day) versus placebo, Outcome 2 Adverse effects.

Review: Cranberries for preventing urinary tract infections

Comparison: 4 Cranberry (dose: ≥ 2/day) versus placebo

Outcome: 2 Adverse effects

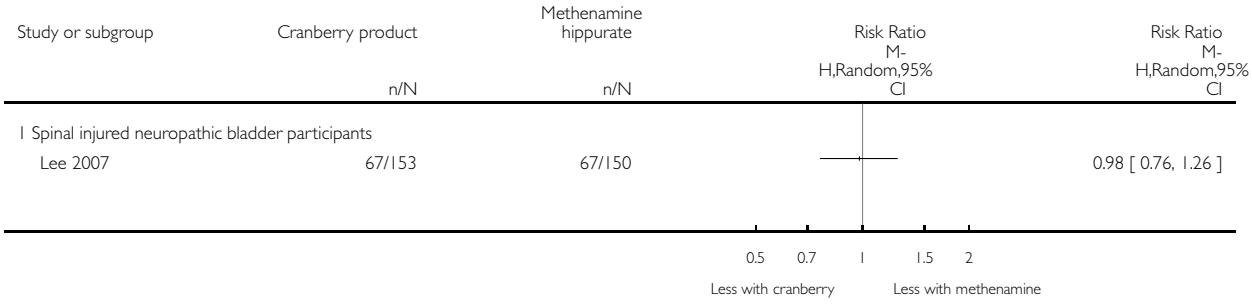
Study or subgroup	Cranberry (≥ 2 dose/day) n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Vomitting				
PACS Study 2008	2/19	0/17		4.50 [0.23, 87.61]
2 Nausea				
PACS Study 2008	1/19	1/17		0.89 [0.06, 13.23]
3 Diarrhoea				
PACS Study 2008	0/19	1/17		0.30 [0.01, 6.91]
4 Gastroenteritis				
PACS Study 2008	0/19	1/17		0.30 [0.01, 6.91]
5 Stomach burn and general weakness				
Sengupta 2011	0/23	2/13		0.12 [0.01, 2.26]

Analysis 5.1. Comparison 5 Cranberry products versus methenamine hippurate, Outcome 1 Symptomatic UTI.

Review: Cranberries for preventing urinary tract infections

Comparison: 5 Cranberry products versus methenamine hippurate

Outcome: 1 Symptomatic UTI

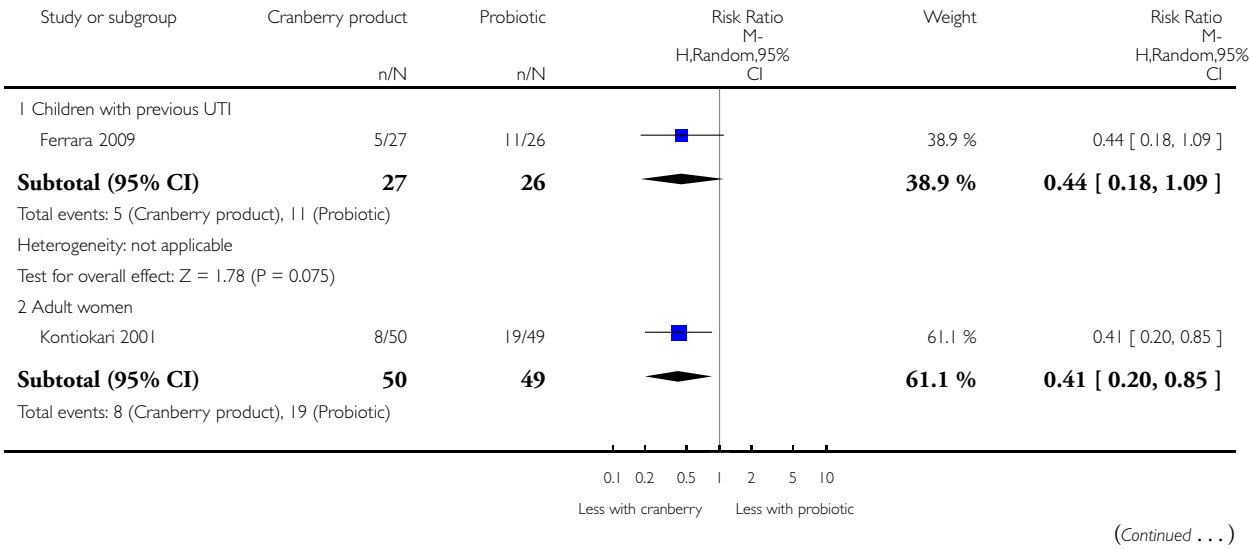


Analysis 6.1. Comparison 6 Cranberry versus probiotics, Outcome 1 Symptomatic UTI.

Review: Cranberries for preventing urinary tract infections

Comparison: 6 Cranberry versus probiotics

Outcome: 1 Symptomatic UTI



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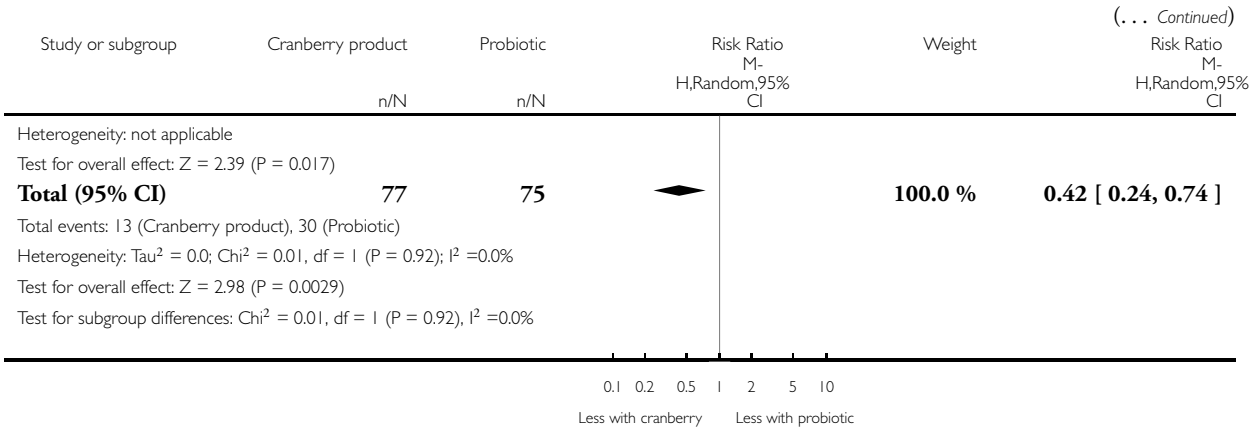

ADDITIONAL TABLES

Table 1. Characteristics of studies

Stduy name	Year	N	Country	Setting	Participants	Intervention
Avorn 1994	1994	192	USA	Nursing homes	Elderly women, mean age 78.5 years	Cranberry juice cocktail: 300 mL/d (30% cranberry concentrate) Placebo beverage PAC content: NS
Haverkorn 1994	1994	38	Netherlands	Hospital	Elderly men (9) and women (29), mean age 81 years	Cranberry juice: 15 mL, twice a day (30 mL cranberry juice/d, concentration not specified) PAC content: NS
Foda 1995	1995	40	Canada	Hospital clinic	Children with neuropathic bladder requiring clean intermittent catheterisation, mean age 9.35 years	Cranberry juice cocktail: 15 mL/kg/d (30% cranberry concentrate) 3-4 times a day PAC content: NS
Walker 1997	1997	19	USA	Family practice	Young women with recurrent UTI, median age 37 years	Cranberry capsules: 400 mg of cranberry solids (total amount/d: NS) PAC content: NS
Schlager 1999	1999	15	USA	Hospital clinic	Children with neuropathic bladder	Cranberry juice cocktail: 300 mL/d (30% cranberry

Table 1. Characteristics of studies (*Continued*)

					requiring clean intermittent catheterisation, aged 2-18 years	concentrate) PAC content: NS
Kontiokari 2001	2001	150	Finland	Student health service	Young women (mean age 29-32 years) with previous UTI	Cranberry-lingonberry juice: 50 mL once/d, 5 days/week (7.5 g cranberry concentrate) PAC content: NS
McGuiness 2002	2002	135	Canada	Outpatient clinic for MS patients	Patinets with multiple sclerosis	Cranberry tablet: 8000 mg, once/d (am) for 6 months PAC content: NS
Stothers 2002	2002	150	Canada	Unclear	Women with recurrent UTI (aged 21-72 years)	Cranberry juice: 250 mL three times/d or one concentrated cranberry juice tablet twice daily (dose NS apart from 'at least 1:30 parts concentrated juice) PAC content: NS (study authors did not know if the product contained active PAC or not)
Linsenmeyer 2004	2004	21	USA	Urology rehabilitation clinic	Spinal cord injury patients with neuropathic bladders	Cranberry tablets: 1200 mg/d (3 x 400 mg tablets) PAC content: NS
Waites 2004	2004	48	USA	Hospital clinic	Spinal cord injury patients with neuropathic bladders	Cranberry juice capsule: 2000 mg/d PAC content: NS
McMurdo 2005	2005	376	Scotland	Hospital	Elderly inpatients	Cranberry juice: 300 mL once/d PAC concentration: 11.175 µg/g (dry solids basis)
Lee 2007	2007	305	Australia	Community	Spinal cord injury patients	Cranberry tablets: 1600 mg/d Methenamine hippurate tablet: 2 mg PAC content: NS
Wing 2008	2008	115	USA	Pre-natal clinic	Pregnant women	Cranberry juice - Group 2: 240 mL cranberry drink at breakfast, placebo juice at other

Table 1. Characteristics of studies (*Continued*)

						meals - Group 3: 240 mL cranberry juice 3 times/d (dosage changed throughout) Mean PAC content: 80 mg/240 mL
Hess 2008	2008	47	USA	SpInal cord injury patients in Veterans Admin Hospital	Spinal cord injury patients with neurogenic bladders	Cranberry tablet: 1000 mg/d (500 mg tablet) PAC concentration: NS
Ferrara 2009	2009	80	Italy	Paediatric nephrology ambulatory clinic	Girls with > 1 UTI in past year	Cranberry concentrate, 50 mL in 50 mL water Lactobacillus GG drink: 100 mL PAC content: NS
McMurdo 2009	2009	137	UK	Scottish primary care research network	Women ≥ 45 years with ≥ 2 UTIs in the previous 12 months	Cranberry tablet: 500 mg Antibiotic: 100 mg TMP PAC content: NS
Essadi 2010	2010	544	Unsure	Antenatal clinic	Pregnant women	Cranberry juice: 250 mL, 4 times/d PAC content: NS
PACS Study 2008	2010	56	USA	Nursing home	Elderly men and women (> 60 years) with dementia	Cranberry tablet: 1 x 650 mg or 2 x 1300 mg PAC content: NS
Salo 2010	2010	252	Finland	Hospital	Children with UTI	Cranberry juice: 5 mL/kg up to 300 mL PAC concentration: NS
Uberos 2010	2010	51	Spain	Unclear, possibly hospital	Children with UTI	Cranberry syrup: 0.2 mL/kg Antibiotic: 8 mg/kg TMP 'The concentration guarantees that 5 mL of the syrup contains 36 mg of highly bioactive PAC extracted from the cranberry syrup, measured by the BL-DMAC method.'
Barbosa-Cesnik 2011	2011	319	USA	University Health Service	Adult women with urinary symptoms	Cranberry juice: 2 x 240 mL (480 mL/d) PAC concentration: 112 mg (range 83-136 mg; SD 614.1 mg)

Table 1. Characteristics of studies (*Continued*)

NAPRUTI Study 2011 I	2011	199	Netherlands	Primary care physicians	Adult women (premenopausal) with at least 3 UTIs in previous 12 months	Cranberry tablet: 2 x 500 mg/d Antibiotic: 480 mg TMP-SMX Type A PAC in cranberry extract: 9.1 mg/g
Sengupta 2011	2011	57	India	Medical clinic	Adult women	Cranberry tablets: 500 mg/d or 1000 mg/d PAC content: 1.5%
Cowan 2012	2012	128	UK	Oncology unit	Adults with bladder or cervical cancer	Cranberry juice: twice daily, volume (NS), PAC concentration (NS)

DMAC - dimethylaminocinnamaldehyde; NS - not stated; PAC - proanthocyanidin; SD - standard deviation; SMX - sulfamethoxazole; TMP - trimethoprim

Table 2. Study design and quality of reporting

Study name	Design	Study duration	Urine collection	Threshold	Other definitions	Allocation	Loss to follow-up	Blinding	Intention-to-treat
Avorn 1994	Parallel	6 months	Voided	$\geq 10^8$/L	Pyuria (not defined)	No (quasi-RCT by ID or phone number)	39/192 (20%)	Participants: yes Investigators: yes	No
Haverkorn 1994	Cross-over	4 weeks	NS	$= 10^8$/L	NS	No (quasi-RCT by date of birth)	21/38 (55%)	Unclear	Unclear
Foda 1995	Cross-over	12 months (6 months of each treatment)	CSU	$\geq 10^8$/L (1 or 2 organisms)	Symptoms (not defined)	Unclear	19/40 (47.5%)	Investigators: yes	Unclear
Walker 1997	Cross-over	3 months	NS	NS	Symptoms present (not defined)	Unclear	9/19 (47.4%)	Participants: yes Investigators: yes	Unclear
Schlager 1999	Cross-over	3 months	CSU	$= 10^7$/L	Symptoms present (defined)	Yes, pharmacy	0/15 (0%)	Participants: yes Investiga-	Yes

Table 2. Study design and quality of reporting (*Continued*)

								tors: yes	
Kontiokari 2001	Parallel, 3 groups	6 months	Voided	= 10^8/L	Symptoms present (defined)	Yes, sealed opaque envelopes	13/150 (8.7%)	Unclear	Yes
McGuiness 2002	Parallel	6 months	Intermittent catheterisation or voided	≥ 10^9/L	Leucocytes, blood or nitrite plus culture positive (symptoms may be unrecognised in these patients)	Unclear	3 lost to follow-up, 9 withdrew	States double blinded, unsure who	Yes
Stothers 2002	Parallel, 3 group factorial design	12 months	Voided	= 10^8/L	Symptoms present (undefined)	Yes, sealed envelopes	2/150 (1.3%)	Participants: yes Investigators: yes	Yes
Linsenmeyer 2004	Cross-over	9 weeks	CSU or voided	= 10^8/L	WBC count	Unclear	16/37	Participants: yes Investigators: yes	
Waites 2004	Parallel	6 months	CSU or voided	= 10^7/L	Symptoms (defined)	Unclear	26/74	Participants: yes Investigators: yes	No
McMurdo 2005	Parallel	6 months	Voided	= 10^4/L	Symptoms present (not defined)	Yes, sealed envelopes	0/376	Participants: yes Investigators: yes	Yes
Lee 2007	Parallel, 4 group factorial design	6 months	CSU or reflex voided	≥ 10^8/L	Symptoms present (defined)	External and robust	0/305	Participants: yes Investigators: yes Outcome assessors: yes	Yes

Table 2. Study design and quality of reporting (*Continued*)

Wing 2008	Parallel, 3 groups	5-7 months (to delivery)	Voided	$\geq 10^8$/L	Symptoms (defined)	Unclear	0/115	Participants: yes Investigators: yes Outcome assessors: yes	Yes
Hess 2008	Cross-over	6 months	Assume voided	$\geq 10^7$ cfu/L	Symptoms (defined)	Yes, stated	10/57	Participants: yes Clinicians: yes	No
Ferrara 2009	Parallel, 3 groups	6 months	Voided	$\geq 10^8$/L	Symptoms (defined)	Unclear	4/84 (5%)	Participants: no Investigators: unclear Outcome assessors: unclear	Unclear
McMurdo 2009	Parallel	6 months	Voided	$\geq 10^7$/L	Symptoms (defined)	Externally managed, trial number given	0/137	Participants: yes Investigators: yes Outcome assessors: yes	Yes
Essadi 2010	Parallel	NS	Assume voided	NS	NS	NS	216/760	Participants: no Investigators: NS	Unclear
PACS Study 2008	Parallel, 3 groups	6 months	Assume voided	$\geq 10^8$/L	NS	NS	2/56	Stated no blinding	No
Salo 2010	Parallel	6 months	NS	NS	NS	NS	11/263	Participants: yes Investigators: yes	Unclear
Uberos 2010	Parallel	when a UTI was recorded	Voided, MSU	= 10^4/L	Symptoms	Yes, hospital pharmacy	6/198	Participants: yes Clinicians: yes	Yes

Table 2. Study design and quality of reporting (*Continued*)

Barbosa-Cesnik 2011	Parallel	6 months	Voided, MSU	$\geq 10^6$ cfu/L	Symptoms (defined)	Yes, external	100/419	Participants: yes Investigators: yes Outcome assessors: yes	Yes
NAPRUTI Study 2011 I	Parallel	12 months	Voided	$\geq 10^6$ cfu/L	Symptoms (not defined)	Yes	22/221	Participants: yes Investigators: yes Outcome assessors: yes	Unclear
Sengupta 2011	Parallel, 3 groups	90 days	Voided, MSU	$\geq 10^7$ cfu/L	Symptoms (not defined)	Yes, sealed pre prepared envelopes	3/60	High and low dose participants: yes 'no treatment' participants: no Investigators: no	Unclear
Cowan 2012	Parallel	6 weeks	Voided	$\geq 10^8$/L	Symptoms (not defined)	Unclear	15/128	Participants: yes Clinicians: yes Outcome assessors: unclear	Yes

CSU - catheter specimen of urine; NS - not stated; WBC - white blood cell

Table 3. Positive urine culture (bacteriuria)

Study name	Pre cross-over	P value	End of study data	P value	Notes
Schlager 1999	Cranberries: 85/97 Placebo: 33/55	NS	Cranberries: 120/160 (75%) Placebo 114/151 (75%)	NS	
Haverkorn 1994	NS	NS	NS	P = 0.004	Actual number of people in each group: NS

Table 3. Positive urine culture (bacteriuria) (*Continued*)

Avorn 1994	N/A	N/A	Cranberries: 20/473 (4%) of the urine samples Placebo: 7% (37/498)	(P = not significant)	
Foda 1995	NS	NS	Cranberry: 27/112 months (24.1%) Placebo: 34/117 months (29%)	NS	Outcome was months with positive/significant culture but no UTI symptoms
Linsenmeyer 2004	NS	NS	NS	NS	The authors report that, 'We failed to find a statistically significant treatment effect for 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)"
Wing 2008	N/A	N/A	Cranberry, 1 dose: 5/67 Cranberry 2-3 doses: 2/58 Placebo; 7/63	NS	This data are for asymptomatic UTI specifically
Hess 2008	NS	NS	Cranberry: 31 positive culture episodes Placebo: 37 positive culture episodes	P = 0.52	This study reported symptomatic and positive culture results
PACS Study 2008	N/A	N/A	Cranberry, 1 dose: 13/20 Cranberry, 2 doses: 14/19 No treatment: 12/17	NS	
Uberos 2010	N/A	N/A	Cranberry: 8/23 Antibiotic: 15/28	NS	In this report (abstract only) it isn't clear if the repeat UTI was symptomatic or a positive culture result

N/A - not applicable; NS - not stated

Table 4. Symptomatic UTIs

Study name	Pre cross-over	P value	End of study data	P value	Notes
Schlager 1999	NS	NS	Cranberry: 3 UTIs in 2 children Placebo: 3 UTIs in 3 children	NS	
Avorn 1994	N/A	N/A	Cranberry: 20/473 (4%) Placebo: 37/498 (7%)	Not significant (P value NS)	Denominator unclear
Walker 1997	NS	NS	Cranberry: 6 UTIs Placebo: 15 UTIs	P < 0.05	Whilst taking cranberry capsules as opposed to placebo, 7/10 subjects exhibited fewer UTIs, 2 subjects exhibited the same number of UTIs, and 1 subject experienced 1 more UTI
Foda 1995	NS	NS	Cranberry: 19/112 months (17%) Placebo: 20/117 months (17.1%)	NS	Months with positive/significant culture and UTI symptoms
Haverkorn 1994	NS				No details provided
Lee 2007	N/A	N/A	Cranberry: 67/153 Cranberry placebo: 71/152 Methenamine hippurate: 67/150 Methenamine hippurate placebo: 71/55	Hazard ratio cranberry 0.93 (95% CI 0.66-1.29)	
Wing 2008	N/A	N/A	Cranberry 1 dose: 2/67 Cranberry 2-3 doses: 2/58 Placebo: 0/63	NS	This study reported symptomatic UTI and positive culture results, these results are symptomatic UTI
Hess 2008	Pre-trial: 1.3 UTIs/person/y	NS	During the cranberry period, 6 participants had 7 UTI, compared with 16 subjects and 21 UTI in the placebo period The frequency of UTI	P < 0.05	This study reported symptomatic UTI and positive culture results, these results are symptomatic UTI

Table 4. Symptomatic UTIs (*Continued*)

			was reduced to 0.3 UTI/y vs 1.0 UTI/y while receiving placebo		
Ferrara 2009	N/A	N/A	Cranberry: 5/27 Lactobacillus: 11/26 No treatment: 18/27	P < 0.5 cranberry vs Lactobacillus groups and control	
McMurdo 2009	N/A	N/A	Cranberry: 25/69 Antibiotic: 14/68	P = 0.084	Only 19/39 symptomatic UTIs had positive culture results
Salo 2010	N/A	N/A	Cranberry: 20/125 Placebo: 28/127	P = 0.21	This data are during 12 months but participants were only treated for 6 months. On-treatment data are not reported
Barbosa-Cesnik 2011	N/A	N/A	Cranberry: 31/155 Placebo: 23/164	P = 0.21	
NAPRUTI Study 2011 I	N/A	N/A	Cranberry: 78.2% Antibiotic: 71.1%	P = 0.03	These UTI results are for clinical UTI not necessarily microbiologically determined
Sengupta 2011	N/A	N/A	Cranberry (500 mg/d): 2/21 Cranberry (1000 mg/d) : 2/23 No treatment: 4/12	NS	
Cowan 2012	N/A	N/A	Cranberry: 26/59 Placebo: 23/59	P = 0.28	This data are symptomatic UTI not necessarily culture proven

N/A - not applicable; NS - not stated

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms used
CENTRAL	1. MeSH descriptor Beverages, this term only in MeSH products 2. MeSH descriptor Fruit, this term only in MeSH products 3. cranberr* in All Fields in all products 4. fruit near beverage* in All Fields in all products 5. fruit near drink* in All Fields in all products 6. fruit near juice* in All Fields in all products 7. MeSH descriptor Phytotherapy, this term only in MeSH products 8. MeSH descriptor Vaccinium macrocarpon, this term only in MeSH products 9. MeSH descriptor Vaccinium vitis-idaea, this term only in MeSH products 10. vaccinium oxycoccus in All Fields in all products 11. vaccinium vitis-idaea in All Fields in all products 12. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) 13. MeSH descriptor Urinary Tract Infections explode all trees in MeSH products 14. MeSH descriptor Pyelonephritis explode all trees in MeSH products 15. MeSH descriptor Cystitis explode all trees in MeSH products 16. uti in All Fields in all products 17. bacter* in All Fields in all products 18. cystitis in All Fields in all products 19. pyelonephritis in All Fields in all products 20. MeSH descriptor Urine, this term only in MeSH products 21. (urin* near infect*) in All Fields in all products 22. (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21) 23. (#12 AND #22)
MEDLINE	1. Beverages/ 2. FRUIT/ 3. cranberr$.tw. 4. (fruit adj5 beverage$).tw. 5. (fruit adj5 drink$).tw. 6. (fruit adj5 juice$).tw. 7. PHYTOTHERAPY/ 8. Vaccinium macrocarpon/ 9. vaccinium oxycoccus.tw. 10. vaccinium vitisidaea.tw. 11. or/1-10 12. urinary tract infections/ or bacteriuria/ or pyuria/ 13. PYELONEPHRITIS/ 14. cystitis/ or cystitis, interstitial/ 15. urine/ 16. uti.tw. 17. cystitis.tw. 18. pyelonephritis.tw. 19. bacter$.tw. 20. (urinary adj5 infection$).tw.

(*Continued*)

	21. or/12-20 22. 11 and 21
EMBASE	1. fruit juice/ 2. cranberr$.tw. 3. (fruit adj5 beverage$).tw. 4. (fruit adj5 drink$).tw. 5. (fruit adj5 juice$).tw. 6. vaccinium macrocarpon.tw. 7. vaccinium vitisidaea.tw. 8. vaccinium oxycoccus.tw. 9. or/1-8 10. Urinary Tract Infection/ 11. pyelonephritis/ or acute pyelonephritis/ or chronic pyelonephritis/ 12. exp Cystitis/ 13. Bacteriuria/ 14. ASYMPTOMATIC BACTERIURIA/ 15. uti.tw. 16. cystitis.tw. 17. pyelonephritis.tw. 18. bacteriuria.tw. 19. (urinary adj5 infection$).tw. 20. or/10-19 21. 9 and 20

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement

(*Continued*)

Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar

(*Continued*)

	reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.

(*Continued*)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

WHAT'S NEW

Last assessed as up-to-date: 10 September 2012.

Date	Event	Description
16 June 2014	Amended	Minor grammatical correction made

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 1998

Date	Event	Description
2 April 2013	Amended	Minor spelling corrections made throughout
14 September 2012	New citation required and conclusions have changed	Updated the review in 2012 with 14 new studies. Conclusions have changed to say that the evidence suggests that cranberry products are not effective in preventing UTIs
13 August 2009	Amended	Contact details updated.
13 May 2009	Amended	Contact details updated.
23 September 2008	Amended	Converted to new review format.
10 September 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- RJ: study design, search strategy, study selection, quality assessment, data extraction, data analysis, writing of review, updating of review.
- JCC: study design, writing of review, updating review
- GW: update search, study selection, quality assessment, data extraction, writing

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nuffield Trust, UK.
- NHS - NIHR, UK.

Funding to update the latest version of the review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced quality assessment checklist.

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