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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 contain proanthocyanidins (PACs), which inhibit the adherence of p-fimbriated *Escherichia coli* to the urothelial cells lining the bladder. Cranberry products have been used widely for several decades to prevent urinary tract infections (UTIs). This is the fifth update of a review first published in 1998 and updated in 2003, 2004, 2008, and 2012.

Objectives

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

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register up to 13 March 2023 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register Search Portal (ICTRP) and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) or quasi-RCTs of cranberry products compared with placebo, no specific treatment or other intervention (antibiotics, probiotics) for the prevention of UTIs were included.

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) with 95% confidence intervals (CI) were calculated where appropriate. Study quality was assessed using the Cochrane risk of bias assessment tool. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

For this update 26 new studies were added, bringing the total number of included studies to 50 (8857 randomised participants). The risk of bias for sequence generation and allocation concealment was low for 29 and 28 studies, respectively. Thirty-six studies were at low risk of performance bias, and 23 studies were at low risk of detection bias. Twenty-seven, 41, and 17 studies were at low risk of attrition bias, reporting bias and other bias, respectively.

Forty-five studies compared cranberry products with placebo or no specific treatment in six different groups of participants. Twenty-six of these 45 studies could be meta-analysed for the outcome of symptomatic, culture-verified UTIs. In moderate certainty evidence, cranberry

products reduced the risk of UTIs (6211 participants: RR 0.70, 95% CI 0.58 to 0.84; I^2 = 69%). When studies were divided into groups according to the treatment indication, cranberry products probably reduced the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs (8 studies, 1555 participants: RR 0.74, 95% CI 0.55 to 0.99; I^2 = 54%), in children (5 studies, 504 participants: RR 0.46, 95% CI 0.32 to 0.68; I^2 = 21%) and in people with a susceptibility to UTIs due to an intervention (6 studies, 1434 participants: RR 0.47, 95% CI 0.37 to 0.61; I^2 = 0%). However, in low certainty evidence, there may be little or no benefit in elderly institutionalised men and women (3 studies, 1489 participants: RR 0.93, 95% CI 0.67 to 1.30; I^2 = 9%), pregnant women (3 studies, 765 participants: RR 1.06, 95% CI 0.75 to 1.50; I^2 = 3%), or adults with neuromuscular bladder dysfunction with incomplete bladder emptying (3 studies, 464 participants: RR 0.97, 95% CI 0.78 to 1.19; I^2 = 0%).

Other comparisons were cranberry products with probiotics (three studies) or antibiotics (six studies), cranberry tablets with cranberry liquid (one study), and different doses of PACs (two studies).

Compared to antibiotics, cranberry products may make little or no difference to the risk of symptomatic, culture-verified UTIs (2 studies, 385 participants: RR 1.03, 95% CI 0.80 to 1.33; I^2 = 0%) or the risk of clinical symptoms without culture (2 studies, 336 participants: RR 1.30, 95% CI 0.79 to 2.14; I^2 = 68%). Compared to probiotics, cranberry products may reduce the risk of symptomatic, culture-verified UTIs (3 studies, 215 participants: RR 0.39, 95% CI 0.27 to 0.56; I = 0%). It is unclear whether efficacy differs between cranberry juice and tablets or between different doses of PACs as the certainty of the evidence was very low.

The number of participants with gastrointestinal side effects probably does not differ between those taking cranberry products and those receiving placebo or no specific treatment (10 studies, 2166 participants: RR 1.33, 95% CI 1.00 to 1.77; I^2 = 0%; moderate certainty evidence). There was no clear relationship between compliance with therapy and the risk for repeat UTIs. No difference in the risk for UTIs could be demonstrated between low, moderate and high doses of PACs.

Authors' conclusions

This update adds a further 26 studies taking the total number of studies to 50 with 8857 participants. These data support the use of cranberry products to reduce the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs, in children, and in people susceptible to UTIs following interventions. The evidence currently available does not support its use in the elderly, patients with bladder emptying problems, or pregnant women.

PLAIN LANGUAGE SUMMARY

Cranberries for preventing urinary tract infections

What is the issue?

Cranberries (as cranberry juice, tablets or capsules) have been used for many years to prevent urinary tract infections (UTIs). Cranberries contain proanthocyanidins (PACs), substances that can prevent bacteria from sticking to the walls of the bladder. This may help prevent infections and reduce the need for working people to take time for medical appointments. However, there is currently no established regimen for what PACs dose to use and no formal regulation by health authorities of cranberry products. In particular, the dose suggested may not be included on the package.

What did we do?

We analysed the results of randomised controlled trials (RCTs), which compared the occurrence of UTIs in people taking a cranberry product with those taking a placebo or no treatment. We also analysed the results of RCTs comparing a cranberry product with other treatments such as antibiotics or probiotics.

What did we find?

We found 50 RCTs involving 8857 people. Forty-five RCTs compared cranberry with a placebo or no treatment. Taking cranberries as a juice, tablets or capsules reduced the number of UTIs in women with recurrent UTIs, in children with UTIs and in people susceptible to UTIs following an intervention such as bladder radiotherapy. However, UTIs did not appear to be reduced in elderly institutionalised men and women, in adults with neuromuscular bladder dysfunction and incomplete bladder emptying, or in pregnant women. Few people reported any side effects with the most common being tummy pain. We did not find enough information to determine if cranberry products are more or less effective compared with antibiotics or probiotics in preventing further UTIs.

Conclusions

Cranberry products may help to prevent UTIs which cause symptoms in women with frequent UTIs, in children with UTIs and in people who have undergone an intervention involving the bladder. However, further assessment is required in well-designed and prospectively registered RCTs to clarify further who with UTIs would benefit from cranberry products.

SUMMARY OF FINDINGS

Summary of findings 1. Any cranberry product versus placebo or control for preventing urinary tract infection

Cranberry product versus placebo or control for preventing UTI

Patient or population: preventing UTI
Setting: multiple different settings
Intervention: any cranberry product
Comparison: placebo or control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with placebo/control	Risk with any cranberry product			
Symptomatic, culture-verified UTI Women with recurrent UTI	243 per 1,000	180 per 1,000 (134 to 241)	RR 0.74 (0.55 to 0.99)	1555 (8)	⊕⊕⊕⊖ MODERATE [1]
Symptomatic, culture-verified UTI Elderly men and women in institutions	113 per 1,000	105 per 1,000 (76 to 147)	RR 0.93 (0.67 to 1.30)	1489 (3)	⊕⊕⊕⊖ MODERATE [2]
Symptomatic, culture-verified UTI Children	289 per 1,000	153 per 1,000 (104 to 225)	RR 0.53 (0.36 to 0.78)	428 (4)	⊕⊕⊕⊖ MODERATE [3]
Symptomatic, culture-verified UTI Adults with bladder emptying issues or multiple sclerosis	440 per 1,000	427 per 1,000 (343 to 524)	RR 0.97 (0.78 to 1.19)	464 (3)	⊕⊕⊖⊖ LOW [2 3]
Symptomatic, culture-verified UTI People with a susceptibility to a UTI due to an intervention	231 per 1000	109 per 1000 85 to 141	RR 0.47 (o.37 to 0.61)	1434 (6)	⊕⊕⊖⊖ LOW [2 3]
Gastrointestinal adverse events	41 per 1,000	54 per 1,000 (41 to 73)	RR 1.33 (1.00 to 1.77)	2166 (10)	⊕⊕⊕⊖ MODERATE [2]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **UTI:** urinary tract infection

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[1] Inconsistency: increased heterogeneity
[2] Imprecision: small studies and wide CIs
[3] Increased risk of bias: allocation and blinding

BACKGROUND

Description of the condition

The term urinary tract infection (UTI) refers to the presence of a 'threshold' number of bacteria in the urine (usually ≥ 10^8 colony forming units (CFU)/L) with or without pyuria (urinary white cell count (WCC) > 100/µL) together (usually) with symptoms involving the bladder, ureters and kidneys. UTIs are classified into UTIs which involve only the bladder (cystitis) or urethra (urethritis and febrile UTIs which also involve the kidneys (pyelonephritis).

Most UTIs involve the lower urinary tract (acute cystitis). These can occur in women and men but are more common in women. About 60% of women over the age of 18 years will suffer one or more UTIs (Kwok 2022). The symptoms include dysuria, urgency, frequency and occasionally haematuria. Many women have symptoms suggestive of UTIs but have either no bacterial growth or counts < 10^8 CFU/L on repeated urine cultures. It is now accepted that the microbiological diagnosis of UTIs in an otherwise normal symptomatic woman is a colony count of ≥ 10^6 CFU/L. Symptoms of pyelonephritis include flank or back pain, fever, chills with shaking, general ill feeling plus those symptoms of a lower UTI. Although most people who present to a doctor or hospital have symptomatic UTIs, some people can be asymptomatic, and only those asymptomatic people, who are at high risk of developing further infections (pregnant women and the elderly) are considered to need treatment (Kwok 2022). About 30% of women may have recurrent UTIs, with an average of two to three episodes per year (Roberts 1979; Kwok 2022; Wong 1984).

UTIs are one of the most common medical conditions requiring inpatient or outpatient treatment. In Australia, recurrent episodes of pyelonephritis account for more than 76,000 hospital admissions per year at an annual cost of AUD$909 million. In the USA, recurrent episodes of pyelonephritis and associated complications necessitate over one million hospital admissions annually (Patton 1991) with costs estimated to be greater than two billion dollars per year (Foxman 2002). Specific subpopulations are at increased risk of developing symptomatic UTIs. These groups include infants, pregnant women, patients with spinal cord injuries with or without catheters, patients with diabetes or multiple sclerosis, patients with acquired immunodeficiency disease syndrome, patients with underlying urologic abnormalities, and patients with asymptomatic bacteriuria who undergo an invasive procedure (Foxman 2002). Although UTIs can occur in both men and women, they are about 50 times more common in young adult women than in young adult men. Most UTIs arise from the ascending route of infection so the shorter urethra in women may allow bacteria to ascend more easily into the bladder. The annual incidence of acute uncomplicated UTIs is 7% for all ages of women peaking at 15 to 24 years and in women older than 65 (Giesen 2010). Up to 30% of women who have a UTI may have a recurrence within six to 12 months (Epp 2010). UTIs often occur in clusters with long periods (several months) where patients are symptom-free (Stapleton 1997). In children, UTIs occur more commonly in boys than girls up to the age of 12 months, but overall UTIs occur about three times more often in girls than boys (1% to 3% in boys, 3% to 7% in girls) (Hellstrom 1991; Winberg 1974). Children often present with a fever and non-specific symptoms such as lethargy (tiredness), vomiting or poor feeding.

Description of the intervention

Cranberries belong to a group of evergreen dwarf shrubs of subgenus *Oxycoccus* and genus *Vaccinium.* In North America, cranberry refers to *Vaccinium macrocarpon.* Cranberries comprise nearly 90% water, but they also contain various organic substances such as quinic acid, malic acid and citric acid as well as glucose and fructose. Products made from cranberries include juice, syrup, jam, tablets and powder. The active ingredient of cranberry is proanthocyanidin (PAC) (Howell 2010). Processing cranberries into various products such as tablets or capsules can reduce the PAC concentration (Howell 2010) so that some products may contain little or no PAC. In addition, the complexities of the PACs structures mean that the measurement of PACs content may not be accurate or reproducible (Prior 2010). To ensure potency in cranberry products, levels of PACs must be quantified in a replicable manner, and the 4-dimethylaminocinnamaldehyde method is currently the most validated standard method for quantifying PACs in cranberry products (Prior 2010). A randomised controlled trial (RCT) evaluating the dosage effect of cranberry powder in healthy volunteers compared with placebo found that to achieve an ex-vivo bacterial anti-adhesion effect in urine, 36 mg of cranberry PACs equivalence was effective though 72 mg offered more prolonged efficacy (Howell 2010). Therefore, based on this study in healthy volunteers, cranberry products containing PACs levels of 36 to 72 mg are currently recommended.

How the intervention might work

The belief that eating cranberries would be beneficial may have started centuries ago from the Native Americans who would eat cranberries as a remedy for UTIs and other illnesses. Early studies attributed the antibacterial effects of cranberry to acidification of the urine by increasing the excretion of hippuric acid (Blatherwick 1923; Kinney 1979). Several studies, however, found no difference or only transient differences in the level of hippuric acid (Kahn 1967; McLeod 1978). More recent research suggests that cranberries prevent bacteria (particularly *Escherichia coli*) from adhering to the uroepithelial cells lining the bladder wall (Schmidt 1988; Zafriri 1989). Without adhesion, *E coli* cannot infect the mucosal surface of the urinary tract. In vitro, this adhesion is reduced by two components of cranberry; fructose, which inhibits adherence of type 1 (mannose specific) fimbriated *E coli* (Foo 2000; Howell 2007), and PACs, which inhibits the adherence of p-fimbriated (a-galactose-(1-4) specific) *E coli* (Zafriri 1989). PACs have A- and B-type linkages, but It is only the PACs with A-type linkages (found in cranberry juice) which prevent the adhesion of *E coli* to the bladder wall (Howell 2002; Howell 2005). PACs with B-type linkages are present in other sources including commercial apple and grape juice and dark chocolate, but these products do not have any anti-adhesion properties (Howell 2005). As the anti-adhesion activity decreases over time, it is recommended that cranberry products should be consumed in the morning and in the evening (Howell 2010).

Why it is important to do this review

UTIs are an important public health problem since they affect more than 150 million people each year worldwide (Flores-Mireles 2015). Most people experience uncomplicated UTIs without fever. Some people experience recurrent uncomplicated UTIs resulting in a significant health problem which impacts their quality of life. Prevention of recurrence has often relied on long-term use

of low-dose antibiotics, but there are adverse effects including diarrhoea as well as the development of antibiotic-resistant bacteria. Cranberry products have been suggested in some but not all guidelines as an alternative to antibiotic prophylaxis in people with recurrent uncomplicated UTIs without fever and other systemic symptoms (Kwok 2022). Therefore, it is important to review the evidence from RCTs in different patient populations to determine the benefits and harms of cranberry for the prevention of uncomplicated UTIs.

The acute treatment of UTIs with cranberry products has been reviewed previously (Jepson 1998b).

OBJECTIVES

The aim of this review was to assess the effectiveness and adverse effects of cranberries in the prevention of UTIs in susceptible populations such as women with recurrent UTIs, children, elderly institutionalised men and women, pregnant women, people with neuromuscular dysfunction of the bladder and reduced bladder emptying, and people with a susceptibility for UTIs due to an intervention. We wished to test the following hypotheses:

1. Cranberry products are more effective than placebo or no treatment in the prevention of UTIs in susceptible populations.
2. Cranberry products are more effective than other treatments in the prevention of UTIs in susceptible populations.
3. Different cranberry products (juice, capsules, tablets, powder, concentrate) may differ in the effectiveness of preventing UTIs in susceptible populations.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs (e.g. those studies which randomised participants by date of birth or case record number) and all types of study design (parallel group, multi-arm and cross-over) of cranberry products (available as juice, tablets, capsules or powder) versus placebo, no treatment or any other treatment were eligible for inclusion.

Types of participants

Inclusion criteria

Studies of susceptible men, women or children as defined below were included. These population groups were analysed separately and in combination.

- Women with a history of recurrent lower UTIs (usually more than two episodes in the previous 12 months)
- Elderly institutionalised men and women
- Pregnant women
- Children
- Adults with neuromuscular dysfunction of the bladder with incomplete bladder emptying
- Adults having undergone an intervention leading to an increased susceptibility to UTIs (e.g. urogenital surgery, radiotherapy to the bladder, or kidney transplant recipients).

Exclusion criteria

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

Types of interventions

Any cranberry product (e.g. cranberry capsules, tablets, powder, juice or extract) taken by participants for at least one month. Cranberry products included in this review could contain small amounts of other compounds (e.g. D-mannose or propolis extract) provided that these were not antibiotics.

Types of outcome measures

We included all studies meeting the inclusion criteria listed above. We did not report all the outcomes reported in individual studies. We limited reporting to the clinically relevant outcomes listed below.

The bacteriological criteria for diagnosis of UTIs include microbiological confirmation from mid-stream urine (MSU) specimen or catheter specimen. An MSU with a single pathogenic organism and a colony count ≥ 10^8 CFU/L is generally considered consistent with a UTI. Some clinicians use a lower colony count (≥ 10^7 CFU/L). Some clinicians also require concurrent pyuria (white cells in the urine) to confirm a UTI. Lower bacterial colony counts may be used if the urine specimen is obtained by a catheter or by supra-pubic aspiration.

Primary outcomes

- The number of participants in each group with symptomatic, culture-verified UTIs. Symptomatic UTIs were defined as having one or more symptoms of dysuria, frequency, urgency, and/or fever
- The number of participants with symptoms of UTIs without culture verification
- The number of participants with culture-verified UTIs without symptoms.

Secondary outcomes

- Death
- Gastrointestinal (GI) adverse effects
- Adherence to therapy.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 13 March 2023 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals and the proceedings and abstracts from major kidney and transplant conferences

4. Searching the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register Search Portal (ICTRP) and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

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

Searching other resources

We searched reference lists of review articles, relevant studies and clinical practice guidelines. We requested information about unpublished or incomplete studies from investigators known to be involved in previous studies. Companies involved with the promotion and distribution of cranberry preparations were approached and asked to provide information on both published and unpublished studies. Conference abstracts from the Proceedings of the Urological Association (1990 to 1998) and the Journal of the American Geriatrics Society (1990 to 1998) were searched for relevant studies for the initial review. We contacted companies involved with the promotion and distribution of cranberry preparations and checked reference lists of review articles and relevant studies.

Data collection and analysis

Selection of studies

The search strategy described was employed to obtain titles and, where possible, abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened independently by at least two authors, who discarded studies that were not applicable; however, studies and reviews that may have included relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, where necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

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, 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 2011; Salo 2010; Stothers 2002; Walker 1997), but no additional information was obtained from three of these communications (NAPRUTI 2011; Salo 2010; Walker 1997). Discrepancies in the data extraction were resolved via discussion.

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2022) (Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)? We chose a cut-off of > 10% missing or excluded data in outcome analysis as a threshold for a high risk of bias in this field.
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

Risk ratio (RR) with 95% confidence intervals (CI) was used as the measure of effect for dichotomous outcomes. Studies with either parallel or cross-over designs were included in the review. For cross-over studies, only the period before the cross-over was used for the meta-analyses. Where available, data were entered into RevMan for meta-analyses, otherwise, it was reported narratively. Infrequent adverse effects and adherence were summarised descriptively in the results.

Unit of analysis issues

Studies used different units of analysis for the outcome of symptomatic UTI. Some used the number of UTIs in the entire study arm as the unit of analysis, whilst others used the number of participants having one or more UTIs during the study period. As UTIs can cluster (so that one participant may have several UTIs over the course of the study period), we believed that the number of UTIs per study population did not provide enough information on those people who had no UTIs. Therefore, we decided that the number of participants who had one or more UTIs was more informative and we used this unit of analysis for the meta-analyses.

In studies using different doses of cranberry product, for our primary analyses, we combined all cranberry treatment groups together. For example, we grouped those given one tablet a day with those given two tablets and compared these data to data from participants taking a placebo, other control medication or no treatment. Several studies reported follow-up results beyond the treatment period. For example, treatment in some studies was six months, but outcomes were reported at six, 12 and 15 months. Our analyses used 'on-treatment' outcome events and did not analyse 'off-treatment' follow-up as there is no biologically plausible reason that the effects of cranberry products would be maintained over a significant period.

Dealing with missing data

Further information was sought from the authors of those papers that contained insufficient information to make a decision about eligibility.

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. Heterogeneity was then analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). A guide to the interpretation of I^2 values is as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for I^2) (Higgins 2022).

Assessment of reporting biases

We had planned to look at funnel plots to assess for the potential existence of small study bias, but most studies were small and funnel plots did not demonstrate variation in relative risk with sample size (Higgins 2022).

Data synthesis

The outcome used for the meta-analyses was the number of people experiencing at least one UTI by the end of the treatment period. Data were pooled using the random-effects model.

Studies were not included in the meta-analyses for the following reasons:

- The design was a cross-over study, and data were not reported separately for the first phase
- They did not report data using the same unit of analysis, see above
- There were no UTI outcomes reported (and no information could be obtained from the authors).

The data for these studies have been described narratively in the text.

Subgroup analysis and investigation of heterogeneity

Studies were sub-grouped by the population types described in the inclusion criteria (e.g. older people, women with recurrent UTIs).

Sensitivity analysis

- Diagnostic criteria for UTIs ($< 10^8$ CFU/L versus $\geq 10^8$ CFU/L)
- High-dose versus low-dose cranberry product
- Cranberry product versus placebo or control according to the amount of the active ingredient (PAC)
- Sponsor type (any commercial involvement versus no commercial involvement).

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in a summary of findings (SOF) table. This table presents key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2022a). The SOF table also includes an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schunemann 2022b). We presented the following outcome in the SOF tables.

- Symptomatic, culture-verified UTIs in all participant groups taking any cranberry product compared with a placebo or no specific treatment
- GI adverse effects
- Death

RESULTS

Description of studies

Results of the search

We undertook the updated search on 13 March 2023. For articles identified up to 2016, two reviewers checked the abstracts or full-text publications of articles for further information, a single author (GW) reviewed articles identified between 2016 and 2020 and three authors reviewed articles identified between 2020 and 2023. After applying the inclusion criteria, we included 26 new studies for a total of 50 studies (See Figure 1).

Figure 1. Flow diagram of study identification and selection

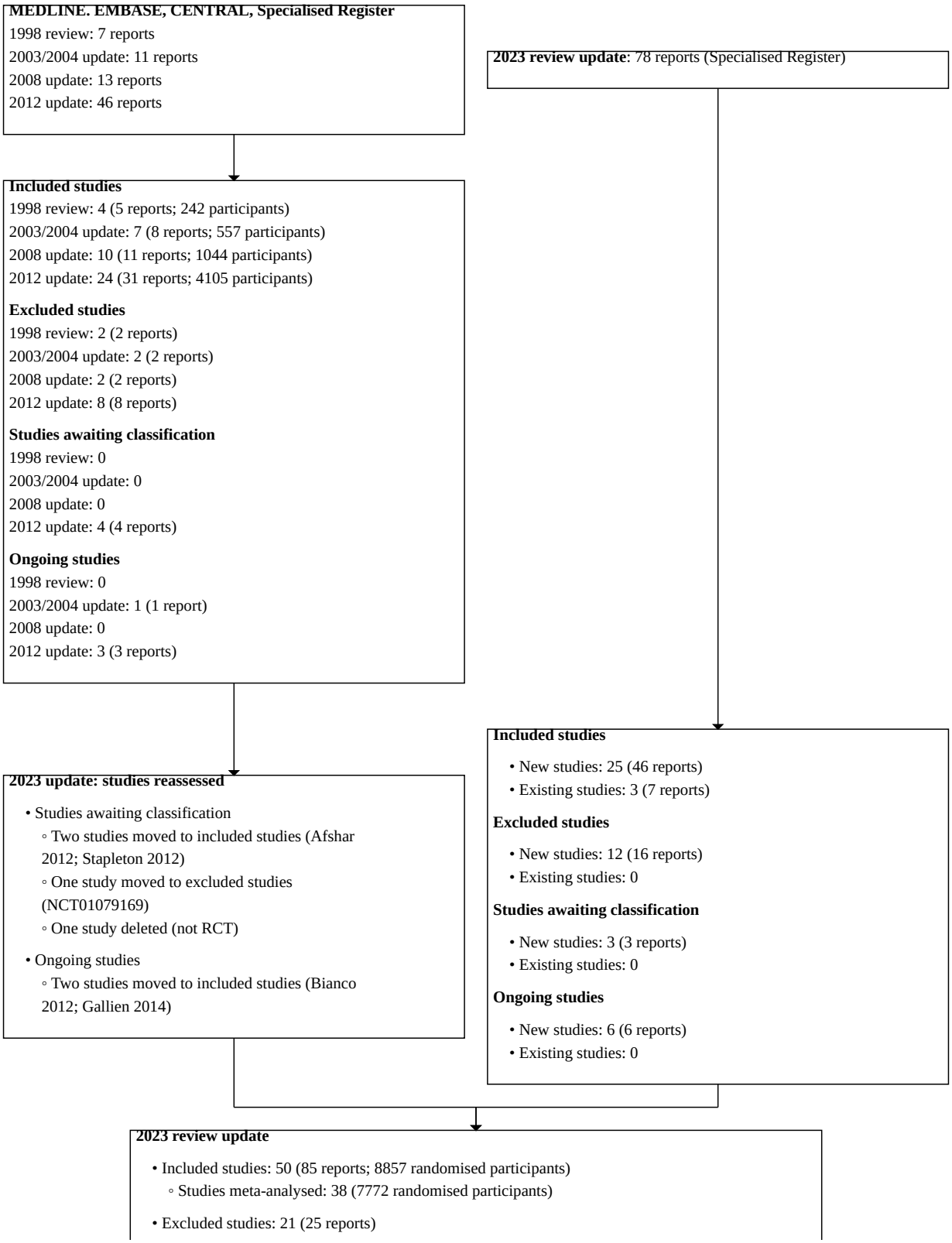
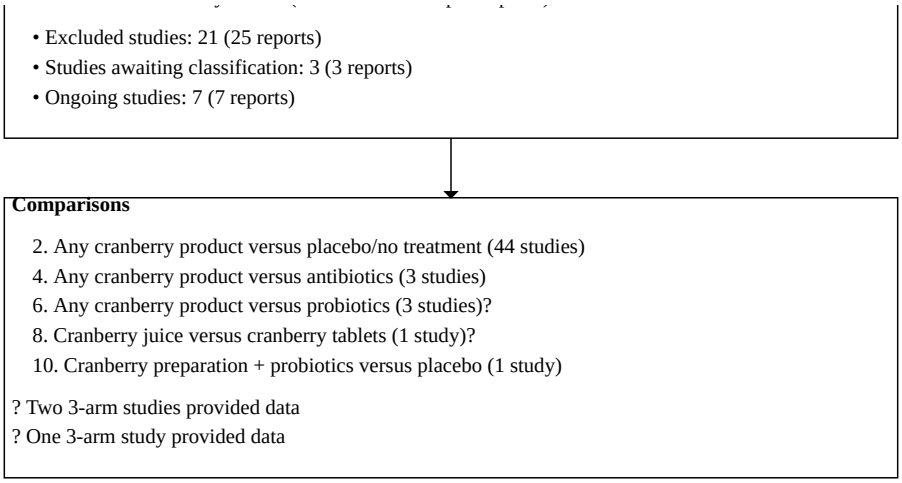


Figure 1. (Continued)



Included studies

See Characteristics of included studies

This updated review includes 50 studies: six cross-over studies (Foda 1995; Haverkorn 1994; Hess 2008; Linsenmeyer 2004; Schlager 1999; Walker 1997); 34 parallel group studies with two arms; eight studies with three arms (Ferrara 2009; Juthani-Mehta 2010; Sengupta 2011; Stapleton 2012; Stothers 2002; Stothers 2016; Temiz 2018; Wing 2008) and two studies with four arms and a factorial design (Bianco 2012; SINBA 2007) with a total of 8857 randomised participants.

The number of included studies has increased steadily over the years. Four studies (Avorn 1994; Foda 1995; Haverkorn 1994; Walker 1997) were included in the first version of this review (Jepson 1998a); three studies (Kontiokari 2001; Schlager 1999; Stothers 2002) were added in 2003/2004; three studies (Linsenmeyer 2004; McMurdo 2005; Waites 2004) were added in the 2008 update; and 14 studies were included in the 2012 update (Barbosa-Cesnik 2011; Cowan 2012; Essadi 2010; Ferrara 2009; Hess 2008; Juthani-Mehta 2010; SINBA 2007; McGuiness 2002; McMurdo 2009; NAPRUTI 2011; Salo 2010; Sengupta 2011; Uberos 2012; Wing 2008). In this latest update, 26 additional studies were included (Afshar 2012; Babar 2021; Bianco 2012; Bonetta 2017; Bruyere 2019; Caljouw 2014; De Leo 2017; Dotis 2014; Fernandes 2016; Foxman 2015; Gallien 2014; Juthani-Mehta 2016; Koradia 2019; Lopes de Carvalho 2012; Maki 2016; Mohammed 2016; Mooren 2020; Scovell 2015; Singh 2016; Stapleton 2012; Stothers 2016; Takahashi 2013; Temiz 2018; Vostalova 2015; Wan 2016; Wing 2015).

Types of participants

The studies were grouped by the types of participants included in the studies and analysed separately due to clinical heterogeneity.

Women with a history of recurrent urinary tract infections

Sixteen studies included non-pregnant, adult women with previous UTIs (Babar 2021; Barbosa-Cesnik 2011; Bruyere 2019; De Leo 2017; Kontiokari 2001; Koradia 2019; Maki 2016; McMurdo 2009; NAPRUTI 2011; Sengupta 2011; Stapleton 2012; Stothers 2002; Stothers 2016; Takahashi 2013; Vostalova 2015; Walker 1997). The age of the women varied considerably, with some studies including a broad range (e.g. > 18 years) and others very narrow (e.g. 40 to 50 years). Generally, to be included in the studies women had to have had at least two UTIs in the past 12 months.

Of these studies, six used cranberry juice, 10 used tablets or powder, and one study used both (Stothers 2002). Ten studies used a placebo as a comparison (Barbosa-Cesnik 2011; Bruyere 2019; Maki 2016 Koradia 2019; Stapleton 2012; Stothers 2002; Stothers 2016; Takahashi 2013; Vostalova 2015; Walker 1997), one study used very low dose cranberry in the control arm (Babar 2021), three studies used no treatment as their comparator (De Leo 2017; Kontiokari 2001; Sengupta 2011), and two compared cranberry products with antibiotics (McMurdo 2009; NAPRUTI 2011).

Elderly institutionalised men and women

Seven studies evaluated cranberry juice for the prevention of UTIs in elderly populations (Avorn 1994; Bianco 2012; Caljouw 2014; Haverkorn 1994; Juthani-Mehta 2010; Juthani-Mehta 2016; McMurdo 2005). All participants were residents in nursing homes, care homes or hospital in-patients.

Participants in some of these studies did not require a history of UTIs to be involved, as increased age is a risk factor for UTIs.

Four studies used cranberry tablets as the intervention (Bianco 2012; Caljouw 2014; Juthani-Mehta 2010; Juthani-Mehta 2016) and three used juice (Avorn 1994; Haverkorn 1994; McMurdo 2005). Four studies used a placebo for the comparison (Avorn 1994; Caljouw 2014; Juthani-Mehta 2016; McMurdo 2005), two studies compared cranberry with no treatment (Bianco 2012; Juthani-Mehta 2010), and one study used water as the comparative treatment (Haverkorn 1994).

Pregnant women

Three studies included a total of 708 pregnant women (Essadi 2010; Wing 2008; Wing 2015). Two studies recruited participants in their late first or early second trimesters (Wing 2008; Wing 2015) while Essadi 2010 did not report this information. Wing 2008 was a three-arm study comparing a single daily dose (240 mL) or

two to 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 and Wing 2015 compared four cranberry tablets per day with placebo tablets.

Children

Eight studies enrolled children either at risk of repeat UTIs (Afshar 2012; Dotis 2014; Ferrara 2009; Salo 2010; Uberos 2012; Wan 2016) or who had a neurogenic bladder (Foda 1995; Schlager 1999).

In the six studies of children at risk of UTIs but without a neurogenic bladder, five studies included children who had experienced more than one UTI (Afshar 2012; Dotis 2014; Ferrara 2009; Uberos 2012; Wan 2016) and one enrolled children at their first UTI (Salo 2010). Three studies compared cranberry juice with placebo (Afshar 2012; Salo 2010; Wan 2016), Uberos 2012 compared cranberry syrup with antibiotics (trimethoprim syrup), Ferrara 2009 compared cranberry plus lingonberry concentrate with lactobacillus, and Dotis 2014 compared cranberry capsules with no treatment.

In the two studies of children susceptible to UTIs because of a neurogenic bladder (Foda 1995; Schlager 1999), the children were managed by clean intermittent catheterisation. Both were cross-over studies which compared cranberry juice to placebo or water and included 40 and 15 children, respectively.

Adults with neuromuscular dysfunction of the bladder and incomplete bladder emptying

Nine studies evaluated the effectiveness of cranberry products in people with bladder emptying issues caused by a number of conditions including multiple sclerosis and spinal cord injuries (Gallien 2014; Hess 2008; Linsenmeyer 2004; Lopes de Carvalho 2012; McGuiness 2002; Scovell 2015; SINBA 2007; Singh 2016; Waites 2004).

Three studies enrolled people diagnosed with multiple sclerosis. McGuiness 2002 compared cranberry capsules with a placebo in patients who voided naturally or who used intermittent self-catheterisation. Lopes de Carvalho 2012 compared two daily capsules of a cranberry compound with a placebo, and Gallien 2014 compared cranberry powder with a placebo powder.

Five studies evaluated the effect of cranberry products in people needing either indwelling catheters or intermittent catheterisation (Hess 2008; Linsenmeyer 2004; Scovell 2015; SINBA 2007; Waites 2004). These studies evaluated the effectiveness of cranberry tablets versus placebo in adults with spinal cord injuries of which two were cross-over studies (Hess 2008; Linsenmeyer 2004), one was a parallel study (Waites 2004), and one used a four-arm factorial design comparing cranberry product with methenamine hippurate and placebo (SINBA 2007).

One study enrolled people with asymptomatic bacteriuria with or without recurrent UTIs (Singh 2016); 14 participants required intermittent catheterisation or bladder drainage via a suprapubic catheter.

Adults with susceptibility to urinary tract infection associated with an intervention

Seven studies included participants prone to UTIs with or without an intervention (Bonetta 2017; Cowan 2012; Fernandes 2016; Foxman 2015; Mohammed 2016; Mooren 2020; Temiz 2018).

Medical and surgical interventions can cause an increased susceptibility to UTIs. Seven studies included participants undergoing such interventions. Three studies included patients undergoing radiation treatment for bladder, prostate, pelvic or cervical cancer and compared cranberry juice or capsules with a placebo (Cowan 2012; Mohammed 2016) or no treatment (Bonetta 2017). Two studies included women undergoing gynaecological surgery and compared cranberry tablets with placebo tablets (Foxman 2015; Mooren 2020). Fernandes 2016 enrolled adult female kidney transplant recipients and compared a daily cranberry capsule to a placebo. Temiz 2018, a three-armed study, enrolled patients with a ureterostomy who underwent ileal conduit diversion, and compared cranberry tablets with no treatment or bladder training.

Interventions and comparisons

Although most of the early studies evaluated cranberry juice, later studies tested a range of other products including tablets, capsules, concentrate, or powder. Of the 50 included studies, 19 studies (3936 randomised participants) evaluated cranberry juice or juice concentrate (Afshar 2012; Avorn 1994; Barbosa-Cesnik 2011; Cowan 2012; Essadi 2010; Ferrara 2009; Foda 1995; Haverkorn 1994; Kontiokari 2001; Maki 2016; McMurdo 2005; Salo 2010; Schlager 1999; Stapleton 2012; Stothers 2016; Takahashi 2013; Uberos 2012; Wan 2016; Wing 2008). Twenty-nine studies (4682 randomised participants) evaluated cranberry tablets, capsules or powder (Babar 2021; Bianco 2012; Bonetta 2017; Bruyere 2019; Caljouw 2014; De Leo 2017; Dotis 2014; Fernandes 2016; Foxman 2015; Gallien 2014; Hess 2008; Juthani-Mehta 2010; Juthani-Mehta 2016; Linsenmeyer 2004; Lopes de Carvalho 2012; McGuiness 2002; McMurdo 2009; Mohammed 2016; Mooren 2020; NAPRUTI 2011; Scovell 2015; Sengupta 2011; SINBA 2007; Singh 2016; Temiz 2018; Vostalova 2015; Waites 2004; Walker 1997; Wing 2015); one study (148 analysed participants) compared cranberry juice and tablets with placebo (Stothers 2002), and one study (89 randomised participants) compared cranberry tablets plus a probiotic with placebo (Koradia 2019).

The control or comparison groups also varied considerably. The control arms used placebo in 34 studies, no treatment in eight studies (Bonetta 2017; De Leo 2017; Dotis 2014; Ferrara 2009; Juthani-Mehta 2010; Kontiokari 2001; Sengupta 2011; Temiz 2018) and water in three studies (Essadi 2010; Foda 1995; Haverkorn 1994). Three studies used antibiotics as the comparison groups (McMurdo 2009; Uberos 2012; NAPRUTI 2011), and one study used *Lactobacillus acidophilus* probiotic (Singh 2016).

Four studies had additional comparisons: methenamine hippurate (SINBA 2007), *Lactobacillus* (Kontiokari 2001; Ferrara 2009), and bladder training (Temiz 2018). Seven studies compared different doses of cranberry or different cranberry products (Babar 2021; Bianco 2012; Juthani-Mehta 2010; Sengupta 2011; Stothers 2002; Stothers 2016; Wing 2008).

Dosage, concentration and formulation of cranberry products

One of the difficulties of undertaking a review of cranberry products is the lack of standardisation of PAC dose in the product evaluated in the studies. This is important because the dose and the type of cranberry product could impact effectiveness. There was considerable variation between the studies in terms of:

- Type of cranberry product
- Amount of the component believed to be the active ingredient (PAC) in the products
- Dosage of the products.

Type of cranberry product

There were two main types of products, those that used a liquid form (juice or concentrate) and those that used a dried form (tablets, capsules or powder). Early studies almost exclusively used the liquid form and low adherence was common for people drinking it over long periods, reducing the likelihood that it could be effective. In more recent years, tablet and dried forms are used most commonly in studies.

Cranberry juice, cranberry concentrate or syrup

Nineteen studies used cranberry juice only with daily volumes ranging from 30 mL to 1 litre and 0.2 mL/kg to 5 mL/kg. One study used cranberry juice and tablets (Stothers 2002). Two studies stated only that 'low dose' juice was given (Stothers 2002) or juice given twice daily (Cowan 2012) with no further details.

Cranberry tablets, capsules or powder

Thirty studies (including the Stothers 2002 juice and tablets study), evaluated the effectiveness of cranberry tablets, capsules or powder. Doses ranged from 1 tablet/day up to 4 tablets/day, and 250 mg powder up to an 8 g tablet.

Amount of proanthocyanidin administered

PACs are believed to be the active ingredient of cranberry products, so it is probable that the amount of PAC in a product determines the efficacy of that product. The importance of PAC was less well or not recognised in the early studies, and therefore the amount prescribed was infrequently formally measured or described by study authors.

Of the 19 studies evaluating juice or concentrate, six reported estimates of PAC concentrations. In Afshar 2012, the PAC dose was reported as 37% of liquid volume with doses of 2 mL/kg/day, but data on actual volumes taken were not provided. McMurdo 2005 reported the PAC dose as 11.17 µg/g of dry solids, but the amount taken was reported as 300 mL. The remaining four studies reported PAC amounts of 112 mg/day (Barbosa-Cesnik 2011), 40 mg/day (Takahashi 2013), 80 to 240 mg/day (Wing 2008), and 18 mg/kg/day (Uberos 2012).

Of the 30 studies evaluating cranberry in a tablet, capsule or powder form, 18 reported an estimated dose of PAC administered, ranging from 1.4 mg to 120 mg/day (Babar 2021; Bianco 2012; Bonetta 2017; Caljouw 2014; De Leo 2017; Gallien 2014; Juthani-Mehta 2010; Juthani-Mehta 2016; Koradia 2019; Mohammed 2016; Mooren 2020; NAPRUTI 2011; Scovell 2015; Sengupta 2011; Singh 2016; Temiz 2018; Vostalova 2015; Wing 2015).

Of the 24 studies estimating the PAC dose administered, only seven studies provided a rationale behind the dosage and amount of PAC administered (Babar 2021; Bianco 2012; Caljouw 2014; Gallien 2014; Juthani-Mehta 2016; Mooren 2020; Uberos 2012). Babar 2021 referenced Howell 2010 and Lavigne 2008 as the rationale for the dosage of PAC used. Bianco 2012, a dosing study itself, investigated the effect of 36 mg, 72 mg or 108 mg PAC daily and referenced Avorn 1994 and Lavigne 2008 as the rationale for the dosage range for the study. Caljouw 2014, Mooren 2020 and Uberos 2012 referenced Howell 2010. Gallien 2014 referenced an earlier version of this review (Jepson 2008), and Juthani-Mehta 2016 referenced both Bianco 2012 and Haverkorn 1994 for the rationale behind the dosages studied. The lack of a standardised PAC dosage was identified as a limitation in several studies, with some calling for a well-designed, dose-finding study in their discussions (Caljouw 2014; Singh 2016).

Dosage of cranberry products

The dosage of cranberry products was difficult to determine across the studies, especially in those in children where it was calculated per kg of body weight. The volume of cranberry products does not equate to the amount of PAC and concentrations probably vary with individual products, and some may contain no PAC at all.

Four studies compared different doses of cranberry products (Bianco 2012; Juthani-Mehta 2010; Sengupta 2011; Wing 2008) and, while not comparable across different studies because each used different products, can be used individually to determine whether there appears to be a dose effect within the single study. Three of these studies reported the PAC amounts; 16.25 mg versus 32.5 mg in Juthani-Mehta 2010, 7.5 mg versus 15 mg in Sengupta 2011 and 36 mg versus 72 mg versus 108 mg in Bianco 2012.

Definitions of urinary tract infection

Our primary outcome *a priori* was symptomatic UTIs, verified with a positive urine culture of ≥ 10^6 CFU/L. In 34 studies, the outcome was reported to be symptomatic, culture-verified UTIs; of these 25 studies reported the threshold used for diagnosis. Sixteen studies used a threshold of ≥ 10^8 CFU/L (Afshar 2012; Barbosa-Cesnik 2011; Bonetta 2017; Caljouw 2014; Cowan 2012; Ferrara 2009; Foda 1995; Gallien 2014; Juthani-Mehta 2016; Koradia 2019; Salo 2010; Stapleton 2012; Stothers 2002; Temiz 2018; Uberos 2012; Vostalova 2015), four used ≥ 10^7 CFU/L (Hess 2008; McMurdo 2009; Schlager 1999; Sengupta 2011) and five used ≥ 10^6 CFU/L (Babar 2021; Koradia 2019; Maki 2016; NAPRUTI 2011; Singh 2016). Seven studies reported asymptomatic UTIs including Foda 1995, which reported also symptomatic UTIs. Of these, six studies used a threshold of ≥ 10^8 CFU/L (Avorn 1994; Bianco 2012; Foda 1995; Juthani-Mehta 2010; Waites 2004; Wing 2008) and one used a threshold of ≥ 10^9 CFU/L (McGuiness 2002). Nine studies did not report symptoms of UTIs, but four of these reported the threshold used to diagnose UTIs: two studies used a threshold of ≥ 10^8 CFU/L (Haverkorn 1994; Kontiokari 2001 and two used ≥ 10^7CFU/L (Linsenmeyer 2004; McMurdo 2005).

Excluded studies

Twenty-one studies were excluded.

- Duration of treatment was less than four weeks: 12 studies (Amin 2018; Barnoiu 2015; Gunnarsson 2017; Howell 2010; Kaspar

2015; Letouzey 2017; Liu 2019b; Occhipinti 2016; Radulescu 2020; Russo 2019; Sappal 2018; Schultz 1984)

- No clinically relevant outcomes: eight studies (Hamilton 2015; Howell 2010; Jackson 1997; Jass 2009; Lavigne 2008; Tempera 2010; Valentova 2007; Vidlar 2010)
- Terminated with no results reported: one study (NCT01079169).

See Characteristics of excluded studies

Ongoing studies and studies awaiting classification

Three potentially relevant studies were identified prior to publication (Cotellese 2023; Hakkola 2023; Madhavan 2021). There are also seven ongoing studies (ACTRN12605000626662; Amador-Mulero 2014; ISRCTN55813586; NCT00100061; NCT00247104; NCT03597152; NCT05730998). These 10 studies will be assessed in a future update of this review.

See Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

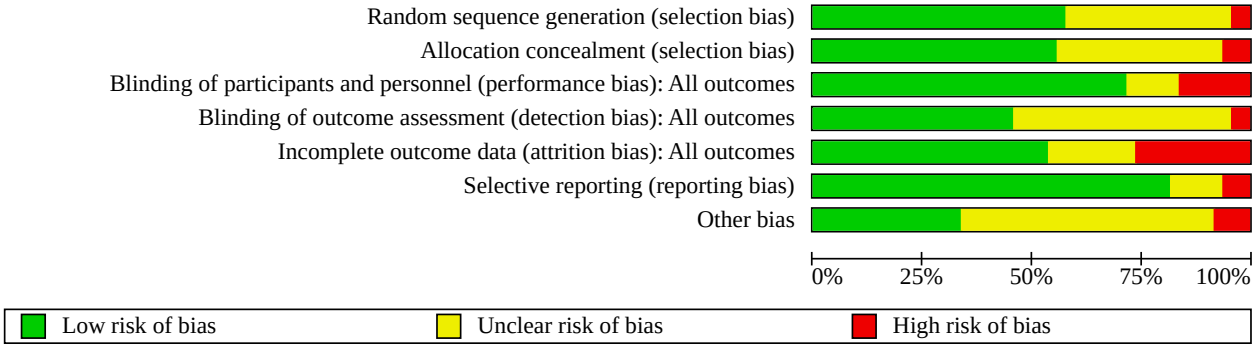


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

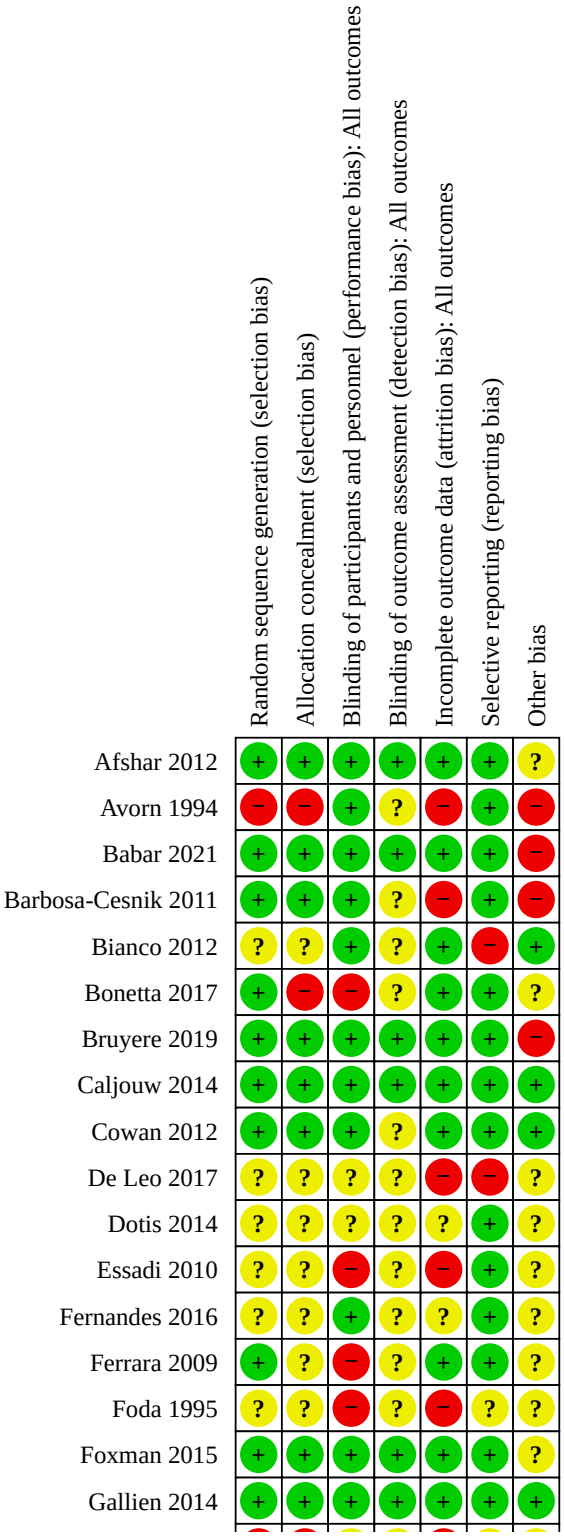
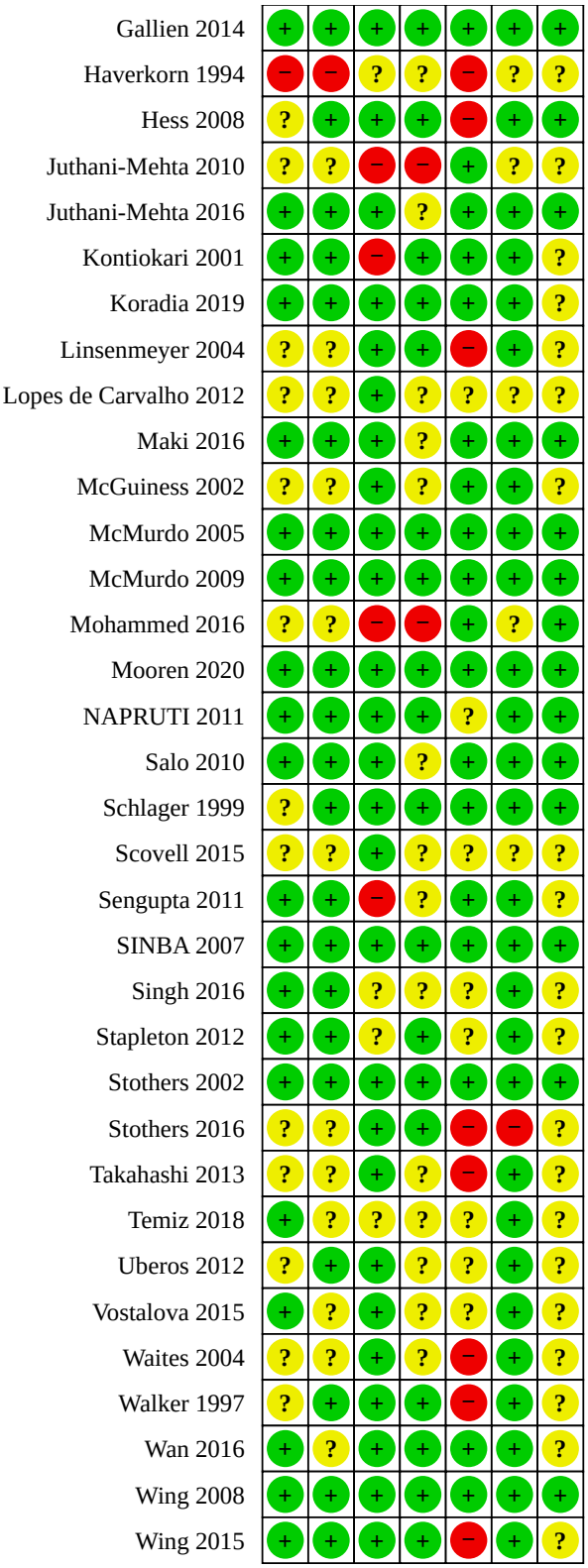


Figure 3. (Continued)



Allocation

Random sequence generation

Twenty-nine studies reported a method of random sequence generation that was judged to be at low risk bias (Afshar 2012; Babar 2021; Barbosa-Cesnik 2011; Bonetta 2017; Bruyere 2019; Caljouw 2014; Cowan 2012; Ferrara 2009; Foxman 2015; Gallien 2014; Juthani-Mehta 2016; Kontiokari 2001; Koradia 2019; Maki 2016; McMurdo 2005; McMurdo 2009; Mooren 2020; NAPRUTI 2011; Salo 2010; Sengupta 2011; SINBA 2007; Singh 2016; Stapleton 2012; Stothers 2002; Temiz 2018; Vostalova 2015; Wan 2016; Wing 2008; Wing 2015), two studies were judged to be at high risk of bias (Avorn 1994; Haverkorn 1994), and the remaining 19 studies were judged to have unclear risk of bias.

Allocation concealment

Twenty-eight studies reported a method of allocation concealment that was judged to be at low risk of bias (Afshar 2012; Babar 2021; Barbosa-Cesnik 2011; Bruyere 2019; Caljouw 2014; Cowan 2012; Foxman 2015; Gallien 2014; Hess 2008; Juthani-Mehta 2016; Kontiokari 2001; Koradia 2019; Maki 2016; McMurdo 2005; McMurdo 2009; Mooren 2020; NAPRUTI 2011; Salo 2010; Schlager 1999; Sengupta 2011; SINBA 2007; Singh 2016; Stapleton 2012; Stothers 2002; Uberos 2012; Walker 1997; Wing 2008; Wing 2015), three studies were judge to be at high risk of bias (Avorn 1994; Bonetta 2017; Haverkorn 1994), and the remaining 19 studies were judged to have unclear risk of bias.

Blinding

Performance bias

Thirty-six studies stated that participants and study personnel were blind to treatment allocation (Afshar 2012; Avorn 1994; Babar 2021; Barbosa-Cesnik 2011; Bianco 2012; Bruyere 2019; Caljouw 2014; Cowan 2012; Fernandes 2016; Foxman 2015; Gallien 2014; Hess 2008; Juthani-Mehta 2016; Koradia 2019; Linsenmeyer 2004; Lopes de Carvalho 2012; Maki 2016; McGuiness 2002; McMurdo 2005; McMurdo 2009; Mooren 2020; NAPRUTI 2011; Salo 2010; Schlager 1999; Scovell 2015; SINBA 2007; Stothers 2002; Stothers 2016; Takahashi 2013; Uberos 2012; Vostalova 2015; Waites 2004; Walker 1997; Wan 2016; Wing 2008; Wing 2015), eight studies had no blinding (Bonetta 2017; Essadi 2010; Ferrara 2009; Foda 1995; Juthani-Mehta 2010; Kontiokari 2001; Mohammed 2016; Sengupta 2011), and for the remaining six studies this issue was unclear.

Detection bias

In 23 studies the outcome assessor was stated as blinded (Afshar 2012; Babar 2021; Bruyere 2019; Caljouw 2014; Foxman 2015; Gallien 2014; Hess 2008; Kontiokari 2001; Koradia 2019; Linsenmeyer 2004; McMurdo 2005; McMurdo 2009; Mooren 2020; NAPRUTI 2011; Schlager 1999; SINBA 2007; Stapleton 2012; Stothers 2002; Stothers 2016; Walker 1997; Wan 2016; Wing 2008; Wing 2015). Two studies had a high risk of bias due to unblinded outcome assessment (Juthani-Mehta 2010; Bonetta 2017), and in the remaining 25 studies it was unclear whether the outcome assessor was blinded to the treatment allocation.

Incomplete outcome data

Twenty-seven studies were judged as at low risk of bias from incomplete data because they had ≤ 10% lost or excluded data from their outcome analysis of UTIs (Afshar 2012; Babar 2021; Bianco 2012; Bonetta 2017; Bruyere 2019; Caljouw 2014; Cowan 2012; Ferrara 2009; Foxman 2015; Gallien 2014; Juthani-Mehta 2010; Juthani-Mehta 2016; Kontiokari 2001; Koradia 2019; Maki 2016; McGuiness 2002; McMurdo 2005; McMurdo 2009; Mohammed 2016; Mooren 2020; Salo 2010; Schlager 1999; Sengupta 2011; SINBA 2007; Stothers 2002; Wan 2016; Wing 2008). Thirteen studies were judged as being at high risk of attrition bias due to incomplete data because they had > 10% of patients data excluded or missing data from UTIs outcome analysis (Avorn 1994; Barbosa-Cesnik 2011; De Leo 2017; Essadi 2010; Foda 1995; Haverkorn 1994; Hess 2008; Linsenmeyer 2004; Stothers 2016; Takahashi 2013; Waites 2004; Walker 1997; Wing 2015). The remaining 10 studies were assessed as unclear for attrition bias because quantifying lost or excluded data was not possible as numbers were not reported.

Selective reporting

Forty-one studies were assessed as at low risk for selective reporting since they reported a UTIs outcome (Afshar 2012; Avorn 1994; Babar 2021; Barbosa-Cesnik 2011; Bonetta 2017; Bruyere 2019; Caljouw 2014; Cowan 2012; Dotis 2014; Essadi 2010; Fernandes 2016; Ferrara 2009; Foxman 2015; Gallien 2014; Hess 2008; Juthani-Mehta 2016; Kontiokari 2001; Koradia 2019; Linsenmeyer 2004; Maki 2016; McGuiness 2002; McMurdo 2005; McMurdo 2009; Mooren 2020; NAPRUTI 2011; Salo 2010; Schlager 1999; Sengupta 2011; SINBA 2007; Singh 2016; Stapleton 2012; Stothers 2002; Takahashi 2013; Temiz 2018; Uberos 2012; Vostalova 2015; Waites 2004; Walker 1997; Wan 2016; Wing 2008; Wing 2015). Although this varied in definition, 27 studies reported the most rigorous definition of UTIs (clinical symptoms combined with a verified positive culture result). Three studies were considered at high risk of bias for selective reporting: one for using UTIs events as their units instead of patients (De Leo 2017), one only reported the number of positive cultures rather than the number of patients with symptomatic UTIs (Bianco 2012), and one stated their primary outcome was symptomatic UTIs, but no data were reported (Stothers 2016; abstract-only publication). In the remaining six studies, the risk of bias from selective reporting was unclear because UTI definitions or units were unclear.

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

The proportion of participants who were randomised but not included in the outcome analysis varied from 0% to 55%. Twenty-eight studies included all randomised participants in their analysis and five studies excluded less than 10% of the randomised group in the outcome analysis. Thirteen studies excluded more than 10% of their randomised participants from outcome analysis, and four studies did not report data in sufficient detail to determine if any or how many participants were excluded from their analyses.

Several studies stated that the 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 doubled 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).

Samples sizes across studies differed. Twelve studies randomised fewer than 50 participants, 11 studies randomised between 50 and 100 people, 15 studies randomised between 100 and 200 participants, and nine studies randomised between 200 and 500 people. Three studies randomised more than 500 but fewer than 1000 participants. One study randomised 21 patients but did not report any numerical data for the outcomes so the size of the analysed sample was unknown (Lopes de Carvalho 2012). Twenty-five studies reported a sample size calculation and 24 studies did not. Nine studies with sample size calculations used a 10% to 15% absolute risk difference for UTIs risk between cranberry and placebo or no treatment groups, while 14 studies chose a sample size based on a much higher expected absolute risk difference of 20% to 50% and two did not quantify the expected difference.

Other potential sources of bias

Seventeen studies were judged to be at low risk of other sources of bias (Bianco 2012; Caljouw 2014; Cowan 2012; Gallien 2014; Hess 2008; Juthani-Mehta 2016; Maki 2016; McMurdo 2005; McMurdo 2009; Mohammed 2016; Mooren 2020; NAPRUTI 2011; Salo 2010; Schlager 1999; SINBA 2007; Stothers 2002; Wing 2008), four were judged to be at high risk of bias (Avorn 1994; Babar 2021; Barbosa-Cesnik 2011; Bruyere 2019), and the remaining 29 studies were judged to have unclear risk of bias.

Commercial involvement

Twenty-three studies reported some involvement of a for-profit organisation and for five of these it was Ocean Spray, a company that sells cranberry products. Twelve studies reported that the for-profit organisation donated the cranberry products and most claimed the company had no influence over the reporting of the results. In eight studies it was not clear what involvement the organisation had in running or reporting the study results.

In 17 studies funding was reported as provided by not-for-profit grants such as health departments and research foundations while four studies reported funding from commercial organisations. In 29 studies it was unclear clear if any funding or sponsorship was involved as insufficient details were reported.

Effects of interventions

See: **Summary of findings 1** Any cranberry product versus placebo or control for preventing urinary tract infection

Included studies compared cranberry products with a range of alternatives including placebo, no specific treatment, different cranberry products or doses, antibiotics, and probiotics. Some compared cranberry products to more than one alternative. All the comparisons are considered separately and are as follows:

1. Cranberry product versus placebo, control or no treatment (Analysis 1.1 to Analysis 1.5)
2. Cranberry juice or syrup versus placebo or control (Analysis 2.1 to Analysis 2.2)
3. Cranberry tablets or powder versus placebo or control (Analysis 3.1 to Analysis 3.2)
4. Cranberry juice versus cranberry tablets or powder (Analysis 4.1)
5. Cranberry dose: high versus low dose (Analysis 5.1 to Analysis 5.2)
6. Cranberry product versus probiotics (Analysis 6.1)
7. Cranberry product versus antibiotics (Analysis 7.1 to Analysis 7.2)
8. Cranberry product + probiotic tablet versus placebo or control (Analysis 8.1)
9. Cranberry product versus placebo or control: PAC dose (Analysis 9.1 to Analysis 9.3)
10. Cranberry product versus placebo or control: sponsor type (Analysis 10.1 to Analysis 10.2)
11. Cranberry product versus placebo or control: culture threshold (Analysis 11.1 to Analysis 11.2)

1. Cranberry products versus placebo, control or no treatment

The assessment of the certainty of the evidence is shown in Summary of findings 1.

Symptomatic, culture-verified urinary tract infection

Overall, cranberry products reduced the risk of symptomatic, culture-verified UTIs in all patient groups (Analysis 1.1 (26 studies, 6211 participants): RR 0.70, 95% CI 0.58 to 0.84; I^2 = 69%; moderate certainty evidence).

Women with recurrent urinary tract infections

Eleven studies evaluated cranberry products in women with recurrent UTIs (Barbosa-Cesnik 2011; Bruyere 2019; Kontiokari 2001; Maki 2016; Sengupta 2011; Stapleton 2012; Stothers 2002; Stothers 2016; Takahashi 2013; Vostalova 2015; Walker 1997).

Cranberry products probably reduce the risk of symptomatic culture-verified UTIs in women with recurrent UTIs (Analysis 1.1.1 (8 studies, 1555 participants): RR 0.74, 95% CI 0.55 to 0.99; I^2 = 54%; moderate certainty evidence). There was moderate heterogeneity in the results primarily resulting from a single study (Barbosa-Cesnik 2011), in which the point estimate was in the opposite direction to all other studies. Omitting this study in a sensitivity analysis resulted in a RR of 0.68 (95% CI 0.52 to 0.89) and reduced the heterogeneity (I^2 = 32%). There may be several reasons why Barbosa-Cesnik 2011 showed different results from the other studies (i.e. no effect of cranberries) including bias introduced when 100 randomised patients were excluded, the use of a lower CFU count leading to over-diagnosis of UTIs, or a chance effect.

Three studies (Bruyere 2019; Stothers 2016; Walker 1997) were not included in the meta-analyses as they did not report the number of participants treated (Stothers 2016; Walker 1997) or reported the mean numbers of UTIs (Bruyere 2019).

Elderly institutionalised men and women

Five studies evaluated the effectiveness of cranberry products for elderly institutionalised men and women in residential care (Bianco 2012; Caljouw 2014; Haverkorn 1994; Juthani-Mehta 2016; McMurdo 2005).

Cranberry products may provide little or no benefit in preventing symptomatic, culture-verified UTIs in this group of older people (Analysis 1.1.2 (3 studies, 1489 participants): RR 0.93, 95% CI 0.67 to 1.30; I^2 = 9%; moderate certainty evidence).

Two studies could not be included in meta-analyses. Haverkorn 1994 was a cross-over study and did not provide data separately for the first part of the study, and Bianco 2012 reported the number of UTIs in each group but not the number of participants with UTIs.

Pregnant women

Three studies evaluated cranberry products for the prevention of symptomatic, culture-verified UTIs in pregnant women (Essadi 2010; Wing 2008; Wing 2015). The number of withdrawals from Wing 2008 was very high because of intolerance to the volume of juice required.

Cranberry products may have little or no effect on preventing UTIs in pregnant women (Analysis 1.1.3 (3 studies, 765 participants): RR 1.06, 95% CI 0.75 to 1.50; I^2 = 3%).

Children

Seven studies evaluated cranberry products compared with placebo or control in children with previous UTIs (Afshar 2012; Dotis 2014; Ferrara 2009; Foda 1995; Salo 2010; Schlager 1999; Wan 2016).

Cranberry products probably reduce the risk of subsequent symptomatic UTIs (Analysis 1.1.4 (5 studies, 504 participants): RR 0.46, 95% CI 0.32 to 0.68; I^2 = 21%; moderate certainty evidence).

Two studies in children with neurogenic bladders were cross-over studies and the data could not be included in meta-analyses (Foda 1995; Schlager 1999). Neither study identified a benefit of cranberry preparations.

Adults with neuromuscular dysfunction of the bladder and insufficient bladder emptying

Eight studies compared cranberry products with placebo or no treatment in people with bladder emptying issues (Gallien 2014; Hess 2008; Linsenmeyer 2004; Lopes de Carvalho 2012; Scovell 2015; SINBA 2007; Singh 2016; Waites 2004).

Cranberry products had little or no effect on preventing UTIs in people with bladder emptying issues (Analysis 1.1.5 (3 studies, 464 participants): RR 0.97, 95% CI 0.78 to 1.19; I^2 = 0%; low certainty evidence).

Four studies could not be included in the meta-analyses. Two studies (Hess 2008; Linsenmeyer 2004) were cross-over studies and data from the first part of the study were not available separately. In two studies the numbers with UTIs were not reported (Lopes de Carvalho 2012; Scovell 2015). A fifth study was not included in meta-analyses as only 14 of 72 participants had bladder emptying issues, and the definition of further UTIs in participants was unclear (Singh 2016).

Adults with susceptibility to urinary tract infection associated with an intervention

Seven studies compared cranberry products with a placebo or no specific treatment in participants undergoing an intervention (Bonetta 2017; Cowan 2012; Fernandes 2016; Foxman 2015; Mohammed 2016; Mooren 2020; Temiz 2018).

Cranberry products reduced the risk of UTIs in participants undergoing an intervention (Analysis 1.1.6 (6 studies, 1434 participants): RR 0.47, 95% CI 0.37 to 0.61; I^2 = 0%; low certainty evidence)

Cowan 2012 could not be included in the meta-analyses as it reported the results according to the number of cultures rather than the number of participants.

Clinical urinary tract infection (symptoms without urine culture)

Overall, cranberry products may reduce clinical UTIs (Analysis 1.2 (6 studies, 2001 participants): RR 0.73, 95% CI 0.58 to 0.90; I^2 = 45%).

Included were two studies of women with recurrent UTIs (518 participants: RR 0.69, 95% CI 0.51 to 0.94; I^2 = 39%) (Babar 2021; Maki 2016), two studies of elderly institutionalised men and women (1113 participants: RR 0.91, 95% CI 0.77 to 1.08; I^2 = 0%) (Caljouw 2014; Juthani-Mehta 2016), and two studies of people with a susceptibility to UTIs after an intervention (370 participants: RR 0.55, 95% CI 0.36 to 0.82; I^2 = 0%) (Foxman 2015; Mooren 2020). Thus, there may be a benefit of cranberry products to prevent clinical symptoms of UTIs in these different patient groups.

Microbiological urinary tract infection (positive culture without known symptoms)

Three studies reported the outcome of microbiological UTIs. Two studies (209 participants) were in the elderly (Avorn 1994; Juthani-Mehta 2010), and one study (135 participants) studied adults with bladder emptying issues related to multiple sclerosis (McGuiness 2002).

Overall, there may be no benefit of cranberry products in preventing positive urine cultures (Analysis 1.3 (3 studies, 344 participants): RR 0.92, 95% CI 0.71 to 1.21; I^2 = 0%).

Death

Four studies reported the number of deaths occurring in each arm of the study (Bruyere 2019; Caljouw 2014; Juthani-Mehta 2016; McMurdo 2005).

Cranberry products may make no difference to the risk of death (Analysis 1.4 (4 studies, 1574 participants): RR 1.07, 95% CI 0.89 to 1.28; I^2 = 0%).

Gastrointestinal adverse events

Ten studies reported GI adverse events (Babar 2021; Bonetta 2017; Gallien 2014; Koradia 2019; McMurdo 2005; Mooren 2020; Sengupta 2011; Singh 2016; Stothers 2002; Wing 2015).

Cranberry products probably make no difference to the risk of GI adverse events (Analysis 1.5 (10 studies, 2166 participants): RR 1.33, 95% CI 1.00 to 1.77; I^2 = 0%; moderate certainty evidence).

2. Cranberry juice or syrup versus placebo or control

Symptomatic culture-verified urinary tract infection

Overall, cranberry juice may reduce the risk of symptomatic, culture-verified UTIs (Analysis 2.1 (13 studies, 2831 participants): RR 0.78, 95% CI 0.62 to 0.97; I^2 = 57%).

Women with recurrent urinary tract infections

Six studies compared cranberry juice or concentrate with a placebo or no treatment in women with recurrent UTIs (Barbosa-Cesnik 2011; Kontiokari 2001; Maki 2016; Stapleton 2012; Stothers 2002; Takahashi 2013).

Cranberry juice or syrup may make little or no difference to the risk of symptomatic culture-verified UTIs in women with recurrent UTIs (Analysis 2.1.1 (6 studies, 1322 participants): RR 0.84, 95% CI 0.63 to 1.10; I^2 = 45%).

Children

Four studies compared cranberry juice to placebo or no treatment in children (Afshar 2012; Ferrara 2009; Salo 2010; Wan 2016).

Cranberry juice may reduce the risk of symptomatic culture-verified UTIs in children (Analysis 2.1.2 (4 studies, 401 participants): RR 0.57, 95% CI 0.37 to 0.87; I^2 = 21%).

Elderly institutionalised men and women

McMurdo 2005 reported little or no difference between cranberry juice or syrup and placebo in the risk of symptomatic culture-verified UTIs in elderly men and women in institutions (Analysis 2.1.3 (1 study, 376 participants): RR 0.51, 95% CI 0.21 to 1.22).

Pregnant women

Two studies compared cranberry juice with a placebo or no treatment in pregnant women (Essadi 2010; Wing 2008).

Cranberry juice or syrup may make little or no difference to the risk of symptomatic culture-verified UTIs in pregnant women (Analysis 2.1.4 (2 studies, 732 participants): RR 1.06, 95% CI 0.75 to 1.50; I^2 = 3%).

Clinical urinary tract infection (symptoms without urine culture)

Maki 2016 reported cranberry juice may reduce the risk of UTIs in women with symptoms of UTIs with or without culture results (Analysis 2.2 (373 participants): RR 0.59, 95% CI 0.42 to 0.83).

3. Cranberry tablets or powder versus placebo or no treatment

Symptomatic, culture-verified urinary tract infection

Overall, cranberry tablets or powder compared to placebo or no treatment may reduce the risk of symptomatic, culture-verified UTIs (Analysis 3.1 (16 studies, 3473 participants): RR 0.65, 95% CI 0.49 to 0.84; I^2 = 64%).

Women with recurrent urinary tract infections

Three studies compared cranberry tablets or powder with a placebo or no treatment in women with recurrent UTIs (Sengupta 2011; Stothers 2002; Vostalova 2015).

Cranberry tablets or powder may reduce the risk of UTI in women with recurrent UTIs (Analysis 3.1.1 (3 studies, 333 participants): RR 0.45, 95% CI 0.28 to 0.72; I^2 = 0%).

Elderly institutionalised men and women

Two studies compared the effectiveness of cranberry tablets or powder in elderly institutionalised men and women (Caljouw 2014; Juthani-Mehta 2016).

Cranberry tablets or powder may make little or no difference to the risk of UTIs in elderly institutionalised men and women (Analysis 3.1.2 (2 studies, 1113 participants): RR 1.02, 95% CI 0.75 to 1.39; I^2 = 0%).

Pregnant women

Wing 2015 (33 pregnant women) reported no events in either the cranberry tablet or placebo group.

Children

Dotis 2014 reported cranberry tablets may reduce the risk for UTIs in children (Analysis 3.1.4 (76 participants): RR 0.29, 95% CI 0.14 to 0.59).

Adults with neuromuscular dysfunction of the bladder with insufficient bladder emptying capacity and residual urine

Three studies compared cranberry tablets or powder with a placebo or no treatment in adults with neuromuscular dysfunction of the bladder with insufficient bladder emptying capacity and residual urine (Gallien 2014; SINBA 2007; Waites 2004).

Cranberry tablets or powder may make no difference to the risk for UTIs in adults with neuromuscular dysfunction of the bladder with insufficient bladder emptying capacity and residual urine (Analysis 3.1.5 (3 studies, 464 participants): RR 0.97, 95% CI 0.78 to 1.19; I = 0%)

People with susceptibility to UTIs due to an intervention

Six studies compared cranberry tablets or powder with a placebo or no treatment in people with susceptibility to UTIs due to an intervention (Bonetta 2017; Ferrara 2009; Foxman 2015; Mohammed 2016; Mooren 2020; Temiz 2018).

Cranberry tablets or powder probably reduces the risk of UTIs in people with susceptibility to UTIs due to an intervention (Analysis 3.1.6 (6 studies, 1454 participants): RR 0.48, 95% CI 0.37 to 0.61; I^2 = 0%).

Clinical urinary tract infection (symptoms without urine culture)

Four studies compared cranberry tablets or powder with a placebo or no treatment (Babar 2021; Caljouw 2014; Foxman 2015; Juthani-Mehta 2010).

Cranberry tablets may make no difference to the risk of clinical UTIs not confirmed on culture (Analysis 3.2 (4 studies, 1418 participants): RR 0.80, 95% CI 0.63 to 1.02; I^2 = 34%). However, the efficacy may vary according to the population.

- In women with recurrent UTIs (Analysis 3.2.1 (1 study, 145 participants): RR 0.80, 95% CI 0.63 to 1.02; Babar 2021) and in the elderly (Analysis 3.2.2 (2 studies, 1113 participants): RR 0.91, 95% CI 0.77 to 1.08; I^2 = 0%) (Caljouw 2014; Juthani-Mehta 2010), cranberry tablets may have little or no effect on UTIs.
- In contrast, Foxman 2015 reported in people with a susceptibility to UTIs due to an intervention (Analysis 3.2.3 (1 study, 160 participants): RR 0.50, 95% CI 0.29 to 0.86) cranberry tablets may be more effective than placebo.

These findings reflect the results seen in participant groups for the outcome of symptomatic culture-verified UTIs.

Microbiological urinary tract infection (positive culture without known symptoms)

In two studies, one in the elderly (Juthani-Mehta 2010) and one in adults with bladder emptying issues (McGuiness 2002), cranberry tablets may make little or no difference in the risk for positive urine culture without symptoms overall, and in these patient groups (Analysis 3.3 (2 studies, 191 participants): RR 0.92, 95% CI 0.71 to 1.21; I^2 = 0%).

4. Cranberry juice versus cranberry tablets

Stothers 2002 reported little or no difference in the risk for symptomatic UTIs between cranberry juice and cranberry tablets in women with recurrent UTIs (Analysis 4.1 (100 participants): RR 0.90, 95% CI 0.40 to 2.02).

5. Cranberry dose: high versus low

Symptomatic, culture-verified urinary tract infection

Two studies, one in women with recurrent UTIs (Sengupta 2011) and one in pregnant women (Wing 2008), compared different amounts of cranberry either as juice or tablets. It is uncertain whether the risk for clinical UTIs differs between groups as the certainty of the evidence is very low (Analysis 5.1: (2 studies, 169 participants): RR 1.02, 95% CI 0.27 to 3.91; I^2 = 0%).

Microbiological urinary tract infection (positive culture without known symptoms)

One study in elderly people (Juthani-Mehta 2010) compared different doses of cranberry tablets. It is uncertain whether the risk for microbiological UTIs differs between groups as the certainty of the evidence is very low (Analysis 5.2: (39 participants): RR 1.13, 95% CI 0.75 to 1.72).

6. Cranberry products versus probiotics

Symptomatic, culture-verified urinary tract infection

Three studies compared cranberry products with probiotics; one in children (Ferrara 2009), one in women with recurrent UTIs (Kontiokari 2001), and one in men and women (Singh 2016). Overall, cranberry products may reduce the risk of symptomatic UTIs in all patient groups (Analysis 6.1 (3 studies, 215 participants): RR 0.39, 95% CI 0.27 to 0.56; I = 0%).

7. Cranberry products versus antibiotic prophylaxis

Symptomatic, culture-verified urinary tract infection

Two studies, one in women with recurrent UTIs (NAPRUTI 2011) and one in children (Uberos 2012), compared cranberry products (tablets in women, syrup in children) with antibiotics. Cranberry products may make little or no difference in the risk for symptomatic culture-verified UTIs (Analysis 7.1 (2 studies, 385 participants): RR 1.03, 95% CI 0.80 to 1.33; I^2 = 0%).

Clinical urinary tract infection (symptoms without urine culture)

Two studies in women with recurrent UTIs compared cranberry tablets with antibiotic tablets (NAPRUTI 2011; McMurdo 2009). It is uncertain whether the risk for clinical UTIs differs between groups as the certainty of the evidence is very low (Analysis 7.2 (2 studies, 336 participants): RR 1.30, 95% CI 0.79 to 2.14; I^2 = 68%). There was considerable heterogeneity between these studies.

8. Cranberry plus probiotic tablet versus placebo or no treatment

Koradia 2019 reported cranberry plus probiotic reduced the number of symptomatic, culture-verified UTIs in women with recurrent UTIs compared to placebo (Analysis 8.1 (89 participants): RR 0.27, 95% CI 0.10 to 0.76).

9. Cranberry product versus placebo or no treatment: proanthocyanidin dose

Symptomatic, culture-verified UTIs

Low-dose proanthocyanidin (< 40 mg/day)

Seven studies compared a cranberry product with a PAC dose < 40 mg/day with a placebo or no treatment (Caljouw 2014; Gallien 2014; Mooren 2020; Sengupta 2011; Takahashi 2013; Temiz 2018; Vostalova 2015).

Overall, low PAC dose may make little or no difference to the risk for symptomatic UTIs (Analysis 9.1 (7 studies, 1712 participants): RR 0.75, 95% CI 0.54 to 1.04; I^2 = 48%).

There may be little or no difference in the risk for UTIs between low PAC dose and placebo or no treatment in women with recurrent UTIs (Analysis 9.1.1 (3 studies, 423 participants): RR 0.58, 95% CI 0.32 to 1.06; I^2 = 49%); in elderly men and women (Analysis 9.1.2 (1 study, 928 participants): RR 1.03, 95% CI 0.74 to 1.42), in adults with neuropathy or neuropathic bladders (Analysis 9.1.3 (1 study, 111 participants): RR 1.03, 95% CI 0.66 to 1.62), or in those with a susceptibility to UTIs due to an intervention (Analysis 9.1.4 (2 studies, 250 participants): RR 0.36, 95% CI 0.08 to 1.74).

Moderate-dose proanthocyanidin (40 to 80 mg/day)

Three studies compared a cranberry product with a moderate dose PAC of 40 to 80 mg/day with a placebo or no treatment (Juthani-Mehta 2016, Mohammed 2016; Wing 2015).

Overall, there may be little or no difference in the risk for symptomatic UTIs when using 40 to 80 mg PAC/day (Analysis 9.2 (3 studies, 263 participants): RR 0.64, 95% CI 0.13 to 3.28; 263 participants; 3 studies; I^2 = 37%).

In elderly men and women (Analysis 9.2.1 (1 study, 185 participants): RR 1.01, 95% CI 0.42 to 2.43), or in those with a susceptibility to UTIs due to an intervention (Analysis 9.2.2 (1 study, 45 participants): RR 0.15, 95% CI 0.01 to 2.73) there may be little or no difference in the risk for UTIs between moderate PAC dose and placebo or no treatment. There were no reported events in 33 pregnant women (Wing 2015).

High-dose proanthocyanidin (> 80 mg/day)

Two studies, one in women with recurrent UTIs (Sengupta 2011) and one in pregnant women (Wing 2008) compared a PAC dose > 80 mg/day with a placebo or no treatment.

Overall, there may be little or no difference in the risk for symptomatic UTIs (Analysis 9.3 (2 studies, 507 participants): RR 1.47, 95% CI 0.91 to 2.39; I^2 = 0%).

In women with recurrent UTIs (Analysis 9.3.1 (1 study, 319 participants): RR 1.43, 95% CI 0.87 to 2.33) and pregnant women (Analysis 9.3.2 (1 study, 188 participants): RR 4.57, 95% CI 0.25 to 83.60) there may be little or no difference in the risk for UTIs between high PAC dose and placebo or no treatment.

10. Cranberry product versus placebo or no treatment: sponsor type

An analysis was conducted to explore whether the involvement of a commercial entity in the studies had an effect on reported results. A study which declared either financial support or provision

of the cranberry product by a for-profit organisation was classified as having commercial involvement. Only the most robust outcome, symptomatic, culture-verified UTIs was used for this analysis.

Symptomatic, culture-verified urinary tract infection

Commercial involvement

Thirteen studies reported commercial involvement. Overall, there may be a reduction in the risk for symptomatic UTIs in studies with commercial involvement (Analysis 10.1 (13 studies, 3020 participants): RR 0.86, 95% CI 0.76 to 0.99; I^2 = 0%). However, within the individual populations, the risk of UTIs with a cranberry product may be reduced only in participants with a susceptibility to UTIs due to an intervention (Analysis 10.1.6 (2 studies, 370 participants): RR 0.57, 95% CI 0.35 to 0.92; I^2 = 0%).

No commercial involvement

Twelve studies compared a cranberry product with a placebo or no treatment and did not involve commercial involvement. Overall, there may be a reduction in the risk for symptomatic culture-verified UTIs in studies without commercial involvement (Analysis 10.2 (13 studies, 2753 participants): RR 0.62, 95% CI 0.44 to 0.86; I^2 = 61%). Within the individual populations, the risk of UTIs with a cranberry product may be reduced only in participants with a susceptibility to UTIs due to an intervention (Analysis 10.2.6 (4 studies, 1219 participants): RR 0.45, 95% CI 0.34 to 0.59; I^2 = 0%).

11. Cranberry products versus placebo or no treatment: culture threshold

Twenty-six studies used a threshold of # 10^8 CFU/L to define a positive urine culture result. Of these, 18 studies reported data on symptomatic, culture-verified UTIs (Analysis 11.1) with a reduction in symptomatic, culture-verified UTIs overall. In individual analyses, the number of symptomatic UTIs was reduced in children and in people at risk of UTIs following an intervention.

Eleven studies used a threshold of < 18^8 CFU/L to define a positive urine culture. Of these, three studies (Analysis 11.2) reported data on symptomatic, culture-verified UTIs; two studies of women with recurrent UTIs and one of elderly men and women in institutions. There was insufficient data to make any conclusions.

Thirteen studies stated that they had obtained urine cultures but did not report the results according to the culture threshold.

Adverse events

Adverse events were reported in 32 studies (Appendix 3; Appendix 4). In four studies numbers were not reported within study arms (Barbosa-Cesnik 2011; SINBA 2007; Schlager 1999), seven studies only reported there were no adverse events (Cowan 2012; De Leo 2017; Dotis 2014; Ferrara 2009; Kontiokari 2001; Vostalova 2015; Wan 2016), and 21 studies reported numbers of specific adverse events within the study arms.

The number of deaths and the number of participants with GI events were included in meta-analyses as these outcomes were considered potentially relevant to treatment. Four studies comparing cranberry products with placebo or no treatment provided data on the number of deaths (Analysis 1.4 (4 studies, 1574 participants): RR 1.07, 95% CI 0.89 to 1.28; I^2 = 0%). Ten studies included data on GI adverse events (Analysis 1.4 (10 studies, 2166 participants): RR 1.33, 95% CI 1.00 to 1.77; I^2 = 0%) suggesting that these may be increased in participants receiving a cranberry product.

Other adverse events were not analysed, as these were considered too diverse or there were too few data for the different comparator groups. Three studies reported hospitalisations (Caljouw 2014; Fernandes 2016; Juthani-Mehta 2016) but only two reported these within treatment groups. Seven studies reported the numbers of serious adverse events without specifying what these events were (Barbosa-Cesnik 2011; Foxman 2015; Gallien 2014; Juthani-Mehta 2016; Maki 2016; NAPRUTI 2011; Sengupta 2011; Stapleton 2012) and five studies reported occurrences of rash, reported within treatment arms in four studies (three with antibiotics as the comparator and one with placebo) and only as a total for one study (placebo comparator).

Adherence to therapy

Twenty-nine of the 50 studies reported compliance rates in participants. Appendix 5 provides the individual study estimates for compliance, the methods of measuring compliance in the studies and each study's risk ratio for repeat UTIs. There was no clear relationship between compliance with therapy and the RR for repeat UTIs.

DISCUSSION

Summary of main results

This is the fifth update of a review first published in 1998 (updated: 2003, 2004, 2008, 2012). We evaluated the efficacy and safety of cranberry products to prevent UTIs in 50 RCTs (8857 participants) including different populations at risk of UTIs.

- Studies evaluated cranberry products overall and separately in six different populations; women with recurrent UTIs, elderly men and women in institutions, pregnant women, children with recurrent UTIs with or without urinary tract abnormalities, adults with neuromuscular dysfunction of the bladder and incomplete bladder emptying, and people with a susceptibility to UTIs following an intervention.
- Overall, cranberry products reduce the risk of symptomatic, culture-verified UTIs (Analysis 1.1).
- Cranberry products probably reduce the risk of symptomatic, culture-verified UTIs in the subgroups of women with recurrent UTIs (moderate certainty evidence), in children with UTIs but without neurogenic bladders (moderate certainty evidence), and in people with a susceptibility to UTIs following an intervention (low certainty evidence)
- Cranberry products may reduce the risk of UTIs symptoms when urine culture was not obtained in women with recurrent UTIs and in people with a susceptibility to UTIs following an intervention (Analysis 1.1.2)
- Cranberry products may not influence the likelihood of symptomatic, culture-verified UTIs, UTIs symptoms without a positive culture or of positive cultures without symptoms in elderly men and women in institutions, and adults with neuromuscular dysfunction of the bladder and incomplete bladder emptying (Analysis 1.1.3).
- Cranberry products may not influence the likelihood of death, but this outcome was only evaluated in four studies (1574 participants) (Analysis 1.4).

- Cranberry products may be associated with GI adverse events (Analysis 1.5). Other adverse events did not appear to differ between groups (Appendix 3; Appendix 4).
- Cranberry tablets (Analysis 3.1) or cranberry juice (Analysis 2.1) compared with a placebo or control may reduce the risk of symptomatic, culture-verified UTIs.
- It remains uncertain whether cranberry tablets differ from cranberry juice in efficacy as only one small study compared these two different interventions so the level of evidence is very low.
- It remains uncertain whether cranberry products are more or less effective than antibiotics or probiotics alone because few studies investigated these comparisons so the level of evidence is very low.
- In other comparisons:
  - There may be no differences in efficacy between high- and low-dose PAC
  - There were insufficient data to determine any differences in efficacy according to the threshold cut-off for diagnosing UTIs ($< 10^8$ CFU/L or $\geq 10^8$ CFU/L)
  - There may be no differences in efficacy related to the presence or absence of industry involvement.
- There appeared to be no clear relationship between compliance with therapy and the RR for repeat UTIs in individual studies (Appendix 5).

Overall completeness and applicability of evidence

In this 2023 update, 26 additional studies of cranberry products to prevent UTIs were added for a total of 50 studies (8857 participants). Compared with the previous update of this review (Jepson 2012), analyses now show that cranberry products probably reduce the risk of repeat symptomatic, culture-verified UTIs in women with recurrent UTIs, in children, and in people at risk of UTIs following an intervention (Analysis 1.1). The most abundant data are in women with recurrent UTIs and, in this group, the data suggest a 26% reduction in the risk of further UTIs with a cranberry product. Previous versions of this review did not find this result because the individual studies were fewer and small. In this update, combining data from more studies reduced the influence of chance and increased the precision of the overall estimate. Six of the eight analysed studies of women with recurrent UTIs included in the meta-analysis reported a point estimate in favour of cranberry products but 95% CIs often crossed the point of no effect. Additionally, for this update, we combined studies reporting more specific outcomes, the most robust of these being symptomatic, culture-verified UTIs. Prior versions did not clearly differentiate between the outcomes of symptomatic, culture-verified UTIs, clinical UTIs symptoms without culture, and microbiological UTIs-positive culture without symptoms. Improved reporting of the specific details of UTIs definition enabled more certainty in this grouping. Clinical UTIs without culture verification showed a similar pattern of efficacy as the more robust outcome symptoms plus culture, although there were fewer data. For the outcome of microbiological UTIs, there may be little or no benefit of cranberry with all estimates including the point of no difference, but data were limited in these analyses. GI side effects were the most frequent side effect reported, but there may be little or no difference in the risk for these between cranberry and placebo or no treatment groups. There may be no difference in risk of death, but this outcome was reported in only four studies.

Only one small study compared cranberry tablets with cranberry juice and found that there may be little or no difference in efficacy between tablets and juice (Stothers 2002). However, comparisons of cranberry juice or tablets or powder with placebo or control raised the possibility that tablets may be more effective than juice because almost all point estimates suggested a greater benefit with tablets in the various populations taking tablets compared with placebo or control (Analysis 2.1; Analysis 3.1). It is possible that these data are confounded by adherence issues as people taking juice may be less adherent than those taking tablets because of the bitter taste of the juice. However, available data were insufficient to analyse the effect of medication adherence on outcomes. Alternatively, the dose of PAC may be more consistent in the tablet format compared with juice.

There were insufficient data to draw conclusions about the efficacy of cranberry compared with other active interventions. Two studies (385 participants) compared a cranberry product with antibiotics and found no difference in symptomatic, culture-verified UTIs. Since the certainty of the evidence is very low, It is uncertain whether cranberry reduces the risk of UTIs compared with antibiotics. Three studies (215 participants) compared a cranberry product with probiotics in the prevention of symptomatic, culture-positive UTIs. Thus cranberry may be more effective than probiotics in reducing the risk of UTIs, but the certainty of the evidence is low.

It remains unclear what the optimum dose of cranberry should be. Ex-vivo studies suggest that the PAC dose should be at least 36 mg/day (Babar 2021). Only 13 studies could be included in meta-analyses, which evaluated the efficacy of different doses of PAC on symptomatic, culture-verified UTIs, with most evaluating low-dose PAC. No conclusions could be drawn from these analyses as to the relative efficacy of different doses of PAC. Proper standardisation of cranberry products for PAC content and correlation of the PAC content with anti-adhesion bioactivity may be important to ensure that particular cranberry products contain sufficient PAC to be effective (Howell 2010).

Studies that had some involvement from a for-profit organisation did not report different results for the risk of UTIs with cranberry products from those studies with no commercial involvement. However, our definition of commercial involvement was broad and included studies that reported receiving the cranberry product at no cost and with no further involvement of the supplier in the reporting of the study.

The majority of studies used a urine culture for diagnosing UTIs of $\geq 10^8$ CFU/L with results for symptomatic, culture-positive UTIs reflecting the overall results. There were insufficient studies to determine the relative efficacy of studies using a lower threshold for diagnosis.

Comparisons between cranberry products and antibiotics or probiotics were limited so no definite conclusions can be drawn. The three studies with antibiotics showed no difference between the interventions, but precision was poor. Three studies comparing cranberry products with probiotics suggested that there could be a greater benefit with cranberry, but further studies are required to confirm or refute this finding.

Our review lists six studies as ongoing. However, only one study (NCT03597152) may be underway though there are no updates to confirm whether or not the study has commenced. The remaining

five studies were identified from study registries between 2004 and 2015, and to date, no publications of these studies have been identified despite extensive searching of the literature and emails sent to listed principal investigators. Failure to complete a study and/or report a completed study could indicate that studies, which showed no difference between cranberry and placebo, were not published.

Quality of the evidence

Study design in approximately half of the studies was relatively robust and free from significant bias. Only 58% and 56% of studies were at low risk of selection bias (sequence generation and allocation concealment). Selection bias was a concern in many studies as it was unclear how and why people were identified for admission to the study. Similarly, performance and detection bias were at low risk in only 72% and 46% of studies, respectively. Attrition bias and reporting bias were at low risk in 54% and 82% of studies, respectively. Other biases were low in 34% of studies. Many studies failed to report adherence numbers including some of the studies that reported a method for measuring adherence. Quantitation of the apparent active ingredient, PAC, was uncommon, possibly due to the technicalities in doing so, but surprising given the importance of the issue.

Forty-five of the 50 included studies compared a cranberry product to placebo, no specific treatment, or water. However, data from only 32 of these 45 studies could be included in our meta-analyses most commonly because the number of participants suffering a UTI was not reported adequately in the treatment and control arms. The certainty of the evidence was considered to be moderate for the analyses of women with recurrent UTIs, for children and for people with a susceptibility to UTIs due to an intervention, but was considered to be low for elderly men and women and for adults with bladder emptying issues because of imprecision and heterogeneity between studies (Summary of findings 1). There were too few studies to assess the certainty of the evidence in studies satisfactorily in studies comparing cranberry to other interventions such as probiotics or antibiotics.

It should be pointed out that some studies, particularly older studies, were not prospectively registered with ClinicalTrials.gov or equivalent bodies. In future updates of this review, subgroup analyses could include analyses comparing the results from studies that were prospectively registered with those not registered.

Potential biases in the review process

For this update, a comprehensive search of Cochrane Kidney and Transplant's Specialised Register was performed, which reduced the likelihood that eligible published studies were omitted from the review. Eligible studies published after the last search date or published in conference proceedings not routinely searched could have been missed. Important information particularly on study risk of bias may not have been available from the published results, particularly in studies only available as abstracts. Data extraction was completed independently by two authors or by a single author with extensive experience in data extraction. This limited the risk of errors in determining study eligibility, data extraction, risk of bias assessment and data synthesis. No author had a financial interest in the outcome of the studies. The authors believe that the review update resulted from an unbiased process limited primarily by the adequacy of reporting in the included studies.

Agreements and disagreements with other studies or reviews

Two recent systematic reviews have evaluated cranberry products relative to placebo or no treatment (Fu 2017; Luis 2017). Fu 2017 focused on women with recurrent UTIs, identified seven studies, and reported a RR of 0.74 (95%CI 0.55 to 0.98) which is almost identical to that obtained in this review, which included eight studies in the participant group (Analysis 1.1: RR 0.74, 95% CI 0.55 to 0.99; 1555 participants). This is unsurprising given the only difference was that we included one additional study (Sengupta 2011) and data from one study (Maki 2016) differed in that we analysed symptomatic, culture-positive UTIs, while Fu 2017 used the outcome clinical UTIs-no urine culture, for their analysis. The risk of bias assessments between the two reviews was quite different and somewhat perplexing. This systematic review considered an open-label study to be at high risk of bias for blinding issues, while Fu 2017 deemed these studies to be at low risk while classifying a study reported as double-blinded, as high risk of bias for blinding. Additionally, this review considered a loss to follow-up or dropout rate of less than 10% as a low risk of incomplete outcome bias, while Fu 2017 did not appear to use a consistent classification for this, for example, an 8.7% dropout rate in one study was deemed high risk but a 23.6% loss in another was classified as low risk. The second systematic review by Luis 2017 included a wider at-risk population, similar to ours, but identified only 25 studies, three of which were not randomised. The point estimate from these 25 studies was 0.675 (95% CI 0.5516 to 0.7965). While not very different to our findings, some of the difference was probably due to the inclusion of the three non-randomised studies and grouping all types of UTI outcomes together (symptomatic-culture verified, clinical UTIs-no culture, microbiological UTIs-no symptoms). There were also many differences in the risk of bias assessments in the 22 studies, which were included in our review and that of Luis 2017. For example, Luis 2017 classified one study at high risk of bias for random sequence generation although the study authors reported that the randomisation sequence was obtained using a "computer generated random number table". In this review, that study was classified as at low risk of bias for random sequence generation. Similarly, Luis 2017 classified a study, in which "the identities of the treatment assignments were not known to the subjects, research coordinators or investigators and unblinding did not occur until termination of the investigation", as at high risk of bias while the current review considered this study to be at low risk of bias for those parameters.

AUTHORS' CONCLUSIONS

Implications for practice

- The current body of evidence suggests that cranberry products (either in juice or as tablets or powder) compared to placebo or no treatment probably reduces the risk of symptomatic UTIs in women with recurrent UTIs, in children, and in people at risk of UTIs following an intervention.
- The data did not support the use of cranberry products to reduce the risk of symptomatic UTIs in elderly men and women, in pregnant women or in adults with neuromuscular dysfunction of the bladder and incomplete bladder emptying. However, data in these latter groups are limited to small studies with considerable uncertainty around the results.

Implications for research

- There remains considerable uncertainty about the appropriate dose of PAC intake via cranberry product required to reduce the risk of UTIs so further studies using different doses of PAC intake are required to determine the dose with the highest efficacy and tolerability and the lowest risk of adverse effects in the patient groups at risk of symptomatic UTIs.
- The amount of PAC within cranberry products needs to be standardised between products with products clearly labelled to include PAC content.
- More studies are required to assess the relative efficacy and safety of cranberry products compared with antibiotics or probiotics to prevent symptomatic UTIs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Afshar 2012

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes, based on UTIs rate over 12 months • ITT analysis: yes, stated Time frame • Duration of study: not reported • Duration of follow-up: 12 months
Participants	Study characteristics • Country: Canada • Setting: single centre • Inclusion criteria: aged 5 to 8 years; toilet trained; 2 symptomatic, culture-proven UTIs in the calendar year before recruitment; living in metropolitan Vancouver • Exclusion criteria: posterior urethral valves; neurogenic bladder; obstruction Baseline characteristics

Afshar 2012 *(Continued)*

- Number: intervention group (20); control group (20)
- Median age, range (years): intervention group (7, 5 to 18); control group (7, 5 to 17)
- Sex (M/F): intervention group (1/19); control group (0/20)

Interventions	Intervention group • Cranberry juice: 2 cc/kg cranberry juice containing 37% PAC Control roup • Placebo: identical in terms of colour, taste and packaging, same volume of juice with no PAC or other cranberry products Intervention duration: 12 months
Outcomes	Outcomes of interest/reported • Symptomatic UTI rate/participant/year • UTI rate ratio
Notes	Additional information • Six patients in each group did not complete the study, average follow-up for these children was 3 months; all included in analysis • Culture threshold: 10^8 CFU/L, or 10^7 CFU/L plus positive WCC and or nitrites in dipstick • Symptomatic: any one of: fever, dysuria, frequency or hematuria • Funding source: Lions Gate HealthCare Research Foundation grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number table
Allocation concealment (selection bias)	Low risk	States that randomisation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States participants and clinicians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 of 40 patients did not complete the study but all included in the analysis
Selective reporting (reporting bias)	Low risk	States number for repeat UTIs
Other bias	Unclear risk	Patient selection is poorly detailed and uncertain how representative these children are of the wider group of children with UTIs

Avorn 1994

Study characteristics	
Methods	Study design • Quasi-RCT • Power calculation: yes • ITT analysis: no Time frame • Duration of study: not reported • Duration of follow-up: 6 months
Participants	Study characteristics • Country: USA • Setting: multicentre (10 sites) • Inclusion criteria: women were recruited from a single long-term care facility for the elderly and 9 housing complexes for the elderly; participants had to be willing to ingest at least 300 mL of cranberry juice daily for a 6-month period • Exclusion criteria: terminal disease or severe dementia; men Baseline characteristics • Number: intervention group (72); control group (81) • Mean age ± SD (years): intervention group (78.1 ± 8.3); control group (79.0 ± 9.4) • Sex (M/F): all female
Interventions	Intervention group • Cranberry juice cocktail: 300 mL/day (30% cranberry concentrate) • PAC content: not reported Control group • Placebo beverage: looked and tasted similar but contained no cranberry juice Intervention duration: 6 months
Outcomes	Outcomes of interest/reported • Presence of bacteriuria (≥ 10^8 CFU/L) with the presence of pyuria • Presence of bacteriuria • Presence of bacteriuria with the presence of pyuria plus symptoms of a UTI
Notes	Additional information • 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: MSU, clean-voided • Definition of bacteriuria: organisms ≥ 10^8 CFU/L regardless of organism • Definition of pyuria: not reported • Exclusions post randomisation: none • Adherence; bottle caps collected and counted • Funding source: research grant from Ocean Spray Cranberries Inc
Risk of bias	

Avorn 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Odd versus even numbers in institutional identification number or telephone number (quasi-RCT)
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	Quote: "Neither participants nor investigators were aware of whether a given subject was receiving cranberry beverage or placebo beverage"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
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	Study includes an outcome of symptomatic culture-verified UTI
Other bias	High risk	Source of funding: Research grant from Ocean Spray Cranberries, Inc

Babar 2021

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes, based on 25% difference between groups • ITT analysis: yes, stated Time frame • Duration of study: August 2015 to April 2017 • Duration of follow-up: 6 months
Participants	Study characteristics • Country: Canada • Setting: Laval University community in Quebec City, Canada • Inclusion criteria: sexually active healthy women; aged ≥ 18 years; recent history of recurrent UTI; ≥ 2 UTIs in the past 6 months and/or ≥ 3 UTIs in the past 12 months; no consumption of cranberry juice, polyphenol or antioxidant supplements in the last 2 weeks • Exclusion criteria: pregnancy; history of anatomical urogenital anomalies, urogenital tract surgery; history of AKI or CKD; nephrolithiasis; history of intestinal diseases causing malabsorption; anticoagulant medication in the last month; known allergy or intolerance to cranberry Baseline characteristics • Number: intervention group (72); control group (73) • Mean age ± SD (years): intervention group (27.2 ± 8.8); control group (32.5 ± 14.2)

Babar 2021 *(Continued)*

	• Sex (M/F): all female
Interventions	Intervention group • Cranberry extract: formulated in high PAC content capsules (2 capsules of 18.5 mg PAC/day) Control group • Cranberry extract: formulated in low PAC content capsules (2 capsules of 1 mg PAC/day) Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Symptomatic UTI: defined as acute urinary symptoms (frequency, urgency, dysuria, pelvic pain, haematuria) in the absence of alternate diagnoses as assessed by study staff • Symptomatic UTI with pyuria on leucocyte esterase test • Symptomatic UTI with bacteriuria in the presence of ≥ 10^6 CFU/ml of uropathogenic bacteria
Notes	Additional information • Funding source: "Ministry of Agriculture, Fisheries and Food of Quebec and Nutra Canada (now part of Diana Food Canada)." "Diana Food scientists did have a role in the approval of the manuscript and the decision to submit the manuscript for publication. Diana Food Canada manufactured and donated the cranberry capsules used in this study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Concealed randomization was generated using computer assisted randomization by blocks of 10"
Allocation concealment (selection bias)	Low risk	Quote: "Concealed randomization was generated using computer assisted randomization by blocks of 10"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “All clinical investigation, laboratory analysis, data collection and assessment were blinded to the randomization allocation” Quote: “Capsules were distributed in opaque packaging in order to conceal slight colour variations from the research team”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “All clinical investigation, laboratory analysis, data collection and assessment were blinded to the randomization allocation” Quote: “Capsules were distributed in opaque packaging in order to conceal slight colour variations from the research team”
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for: 86% completed study, 18 (12%) lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Quote: “This research project was funded by the Ministry of Agriculture, Fisheries and Food of Quebec and Nutra Canada (now part of Diana Food Canada). The funders had no role in the design and conduct of this clinical trial nor the collection, management, analysis, and interpretation of data. Diana Food scientists did have a role in the approval of the manuscript and the decision to

Babar 2021 *(Continued)*

	submit the manuscript for publication. Diana Food Canada manufactured and donated the cranberry capsules used in this study"

Barbosa-Cesnik 2011

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes • ITT analysis: no Time frame • Duration of study: August 2005 and October 2007 • Duration of follow-up: 6 months
Participants	Study characteristics • Country: USA • Setting: single centre • Inclusion criteria: women presenting to a health service with symptoms of UT aged 18 to 40 years; residing in Ann Arbor next 6 months 3 to 4 previous UTIs, 1 in previous year • Exclusion criteria: antibiotics in past 48 hours; hospitalisation or catheterisation within past 2 weeks; kidney stones; DM; pregnancy; cranberry allergy; negative urine culture Baseline characteristics • Number (randomised/analysed): intervention group (205/155); control group (214/184) • Mean age ± SD (years): intervention group (21.2 ± 3.4); control group (21.2 ± 3.5) • Sex (M/F): all female
Interventions	Intervention group • Low-calorie cranberry cocktail: 240 mL twice/day • Mean PAC: 112 mg/240 mL Control group • Placebo drink: same volume matched for flavour and colour Intervention duration: 6 months
Outcomes	Outcomes of interest/reported • UTI: ≥ 10^3 CFU/L of known pathogen • Urinary symptoms and vaginal symptoms at day 3, 1 to 2 weeks, and ≥ 1 month
Notes	Additional information • Compliance measured by direct questioning • Source of funding: National centre for alternative medicine at NIH

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Barbosa-Cesnik 2011 *(Continued)*

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	Insufficient information to permit judgement
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 those who consented is questionable

Bianco 2012

Study characteristics	
Methods	Study design • Parallel, 4-arm RCT ○ Stratification on the presence or absence of baseline bacteriuria • Power calculation: no • ITT analysis: not reported Time frame • Duration of study: not reported • Duration of follow-up: 4 weeks
Participants	Study characteristics • Country: USA • Setting: multicentre (11 sites) • Inclusion criteria: female long-term nursing home residents with past history of UTIs aged ≥ 65 years; English speaking • Exclusion criteria: total incontinence; warfarin therapy; < 4 weeks residence; chronic indwelling catheter; terminal prognosis; antibiotic therapy; kidney stones; dialysis; currently on cranberry therapy; cranberry allergy Baseline characteristics • Number: intervention group 1 (20); intervention group 2 (20); intervention group 3 (20); control group (20) • Mean age ± SD: 89.2 ± 7 years • Sex (M/F): all female

Bianco 2012 *(Continued)*

Interventions	Intervention group 1 • Cranberry tablet/s: 1 (36 mg) • Placebo tablet/s: 2 Intervention group 2 • Cranberry tablet/s: 2 (72 mg) • Placebo tablet/s: 1 Intervention group 3 • Cranberry tablet/s: 3 (108 mg) Control group • Placebo tablets: 3 Each cranberry tablet contained 36 mg of PAC Intervention duration: 30 days
Outcomes	Outcomes of interest/reported • Episodes of bacteriuria and pyuria at 7, 14, 21 and 28 days of tablet taking
Notes	Additional information • Data not included in meta-analysis, unit of analysis was urine samples, not people • Culture threshold; > 10^8 CFU/L • Funding source: Cranberry and placebo donated by Pharmatoka Inc, and National Institute on Aging, National Institutes of Health, Claude D. Pepper Older Americans Independence Center and the National Center for Research Resources at the National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of randomisation process but stratification stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of exclusions and lost data for outcome analysis: 22/320 urine samples
Selective reporting (reporting bias)	High risk	Does not specify patients with UTIs, unit of analysis is urine specimen and participants had multiple of these

Bianco 2012 *(Continued)*

Other bias	Low risk	Good detail on screened patients and exclusion groups

Bonetta 2017

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: no • ITT analysis: not reported Time frame • Duration of study: 2006 to 2016 • Duration of follow-up: 6 weeks
Participants	Study characteristics • Country: Italy • Setting: single centre • Inclusion criteria: men diagnosed with prostatic adenocarcinoma were treated with radiotherapy to the prostatic area and also to the pelvic area • Exclusion criteria: history of pelvic external beam radiotherapy; previous pelvic malignancies; a Karnofsky score < 8; kidney failure; refusal of preventive daily intervention with cranberry extract Baseline characteristics • Number: intervention group (489); control group (435) • Mean age ± SD (years): intervention group (69.63 ± 7.16); control group (70.15 ± 6.45) • Sex (M/F): all males
Interventions	Intervention group • One tablet/day of enteric-coated, highly standardized extract, titred as 30% PAC according to the European Pharmacopoeia method (version 6.0) ○ Sold as MonoselectMacrocarpon® by PharmExtracta (Italy) and in the rest of the world as Ressuro® by Helsinn Integrative Care (Helsinn Healthcare SA, Switzerland) Control group • No intervention Duration of intervention: 6 to 7 weeks
Outcomes	Outcomes of interest/reported • UTI: culture verified (> 10^8 CFU/L) with symptoms • Recurrent UTI infection • *E coli* in culture • *E faecalis* in culture • Days on antibiotics • Days on NSAIDs • Dysuria • Nocturia • Urgency

Bonetta 2017 *(Continued)*

- Change in average daily urination frequency

Notes	Additional information • Funding source: not reported • Conflict of interest: FRP involved with company selling cranberry products

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin toss
Allocation concealment (selection bias)	High risk	Easy to manipulate by repeating toss if unhappy with result
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study, all aware of intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Does not state details on whether analysis done blind to intervention arm
Incomplete outcome data (attrition bias) All outcomes	Low risk	All who were reported to be randomised are included in the analyses
Selective reporting (reporting bias)	Low risk	Wide range of outcomes, patient centred and UTI required culture and symptoms
Other bias	Unclear risk	No description of who was screened for the study and who or how many refused

Bruyere 2019

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: yes • ITT analysis: yes, for those who had taken the product at least once Time frame • Duration of study: October 2013 to June 2015 • Duration of follow-up: 6 months
Participants	Study characteristics • Country: France • Setting: multicentre (9 sites) • Inclusion criteria: women aged > 18 years; at least 4 episodes of cystitis in the previous 12 months

Bruyere 2019 *(Continued)*

	• Exclusion criteria: cystitis due to microorganisms other than *E coli*; anatomical abnormalities or history of surgery of the urinary tract; urinary stones; kidney failure; DM; immune deficiency acquired or linked to long-term corticosteroid medication; pregnant or whose were not receiving effective contraception; undergoing continuous or discontinuous antibiotic prophylaxis or treatment with antivitamin K; an intolerance to beehive products or red fruits Baseline characteristics • Number (randomised/analysed): intervention group (43/38); control group (43/36) • Mean age ± SD (years): intervention group (53.0 ± 17.4); control group (53.0 ± 19.2) • Sex (M/F): all women
Interventions	Intervention group • Cranberry and Propolis extract: 4 capsules on day 1, then 2 capsules/day ○ (Propolis is a chemically complex sticky "glue" collected from beehives. It contains resins collected from the buds and leaves of plants, volatile oils, and wax) Control group • Placebo: 4 capsules on day 1, then 2 capsules/day Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Mean number of infections • Total number of cystitis episodes • Time to onset of first UTI: positive urine culture was defined as > 10^5 CFU/mL urinary enterobacteria • Tolerance to intervention
Notes	Additional information • Funding source: "This study was funded by Nutrivercell"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was generated by the statistician at Euraxi Pharma (Tours, France) using SAS software version 8.2 and was centralized in block size 4 with no stratification"
Allocation concealment (selection bias)	Low risk	Quote: "The centralized randomization list was kept and securely managed by Euraxi Pharma."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigator at each site completed a Randomization Request Form for each subject after protocol eligibility criteria were met and the completed form was faxed to Euraxi Pharma. The subject was randomized according to the randomization schedule and the Randomization Request Form faxed back to the site with details of the treatment allocation for the subject"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an independent CRO of Nutrivercell, performed the statistical analyses of this trial in accordance with the protocol and the statistical analysis plan at the end of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient asked to stop the study in the intervention group and was excluded from the ITT analysis; all patients accounted for

Bruyere 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes of interest were reported
Other bias	High risk	Funded by Nutricercell, and all analyses carries out by Nutricercell

Caljouw 2014

Study characteristics	

Methods	Study design
	• Parallel RCT
	• Stratified into high and low risk
	  ○ High risk: long-term catheterisation (> 1 month), DM, or at least 1 UTI in the preceding year
	  ○ Low risk: does not fulfil high risk criteria (assumed)
	• Power calculation: yes, based on 40% reduction in incidence of UTIs with cranberry intervention
	• ITT analysis: not reported, but analysed all who were randomised, within their randomised group
	Time frame
	• Duration of study: November 2008 to August 2009
	• Duration of follow-up: study stopped in June 2011

Participants	Study characteristics
	• Country: Netherlands
	• Setting: multicentre (number of sites not reported)
	• Inclusion criteria: long-term aged care home residents. aged ≥ 65 years
	• Exclusion criteria: use of coumarin; life expectancy ≤ 1 month
	Baseline characteristics
	• Number
	  ○ Low-risk group: intervention group (205); control group (207)
	  ○ High-risk group: intervention group (253); control group (263)
	• Mean age, IQR (years)
	  ○ Low-risk group: intervention group (84.0, 78.5 to 88.5); control group (83.0, 79.0 to 88.0)
	  ○ High-risk group: intervention group (85.0, 79.0 to 89.0); control group (84.0, 79.0 to 88.0)
	• Sex (M/F)
	  ○ Low-risk group: intervention group (62/143); control group (48/153)
	  ○ High-risk group: intervention group (65/188); control group (50/213)

Interventions	Intervention group • Cranberry tablet: 1 tablet, twice/day, containing 500 mg cranberry product, 1.8% (9 mg) PAC Control group • Placebo: 1 tablet twice/day Treatment duration: 12 months
Outcomes	Outcomes of interest/reported • Clinical UTI: clinical symptoms alone • Strict UTI: symptoms plus positive culture (> 10^8 CFU/L)

Caljouw 2014 *(Continued)*

- Hospitalisation
- Death

Notes	Additional information
	• Clinical UTI: a minimum of one of the following
	  ◦ Specific and nonspecific micturition-related symptoms and signs
	  ◦ Positive test (nitrite, leukocyte esterase test, dip slide, or culture)
	  ◦ Antibiotic intervention for UTI
	  ◦ UTI reported in the medical record
	• Funding; Dutch Organization for Health Research, Springfield Nutraceuticals B.V. supplied the cranberry and placebo capsules and Dutch Organization of Scientific Research (NWO) for Open Access publication of this paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (blocks of 6) was used, stratified for risk profile and ability to give informed consent, generated using a computer random number generator External randomisation
Allocation concealment (selection bias)	Low risk	Random number in sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants,family, nursing staff, physicians, pharmacists, and research nurses were blinded to intervention"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, family, nursing staff, physicians, pharmacists, and research nurses were blinded to intervention"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of excluded data for outcome analysis: 0/928
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes reported
Other bias	Low risk	Good detail on study design and recruitment/selection of patients

Cowan 2012

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: yes, assumed 20% reduction in bladder problems • ITT analysis: yes Time frame

Cowan 2012 *(Continued)*

- Duration of study: recruitment between March 2003 and June 2006
- Duration of follow-up: 6 weeks

Participants	Study characteristics • Country: UK • Setting: single centre • Inclusion criteria: > 18 years with cervical or bladder cancer requiring radiation therapy • Exclusion criteria: pregnant or lactating women; irritable bowel syndrome; DM; rheumatoid arthritis; > Common Toxicity Criteria grade 1 urinary symptoms or UTI at baseline; receiving antispasmodics or antibiotics for urinary symptoms; indwelling urinary catheter; receiving warfarin therapy Baseline characteristics • Number (randomised/analysed): intervention group (64/57); control group (64/56) • Median age, range (years): intervention group (67.5, 27 to 89); control group (69.0, 28 to 85) • Sex (M/F): all women
Interventions	Intervention group • Cranberry juice twice/day; volume and PAC not reported Control group • Matched placebo juice twice/day; volume not reported Duration of intervention: 6 weeks
Outcomes	Outcomes of interest/reported • Urinary symptoms • UTI: single organism, ≥ 10^8 CFU/L in a non-catheterised patient and/or other abnormal findings such as pus cells in the urine with or without subjective symptoms
Notes	Additional information • Funding source: "West Research Endowment Fund, NHS Greater Glasgow and Clyde; the juice and placebo were supplied by Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based deterministic minimisation algorithm
Allocation concealment (selection bias)	Low risk	Externally allocated; c omputer algorithm generated a blinded juice pack
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding stated, patients blinded to intervention 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)	Low risk	Very little missing/excluded data for outcome analysis: 9/128

Cowan 2012 *(Continued)*

All outcomes

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

De Leo 2017

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: not reported • ITT analysis: not reported Time frame • Duration of study: not reported • Duration of follow-up: 3 months
Participants	Study characteristics • Country: Italy • Setting: multicentre (number of sites not reported) • Inclusion criteria: women aged 40 to 50 years with ≥ 8 episodes of cystitis/year • Exclusion criteria: cancer; endocrine diseases; urinary calculus; drug intervention that could create interactions with therapy Baseline characteristics • Number: intervention group (100); control group (50) • Mean age ± SD (years): intervention group (47.3 ± 4.1); control group (47.9 ± 4) • Sex (M/F): all women

Interventions	Intervention group
	• 1 sachet once/day for the first 10 days of the month, for 3 months containing:
	  ○ Cranberry: 90 mg (PAC 72 mg)
	  ○ Noxamicin (Kistinox Forte): 100 mg (from propolis extract)
	  ○ D-mannose: 500 mg
	Control group
	• No intervention

Outcomes	Outcomes of interest/reported • Episodes of cystitis • Frequency of symptoms (dysuria, frequency, intensity of urination pain)
Notes	Additional information • UTI definition: not reported • Cystitis: self-reported episodes

De Leo 2017 *(Continued)*

- Funding source: not reported, states there were no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	3 dropouts (of 45) but 4 missing
Selective reporting (reporting bias)	High risk	UTI definition poor
Other bias	Unclear risk	Selection bias, unable to determine how and where patients were recruited from

Dotis 2014

Study characteristics

Methods

Study design

- Parallel RCT
- Power calculation: not reported
- ITT analysis: not reported

Time frame

- Duration of study: not reported
- Duration of follow-up: 12 months

Participants

Study characteristics

- Country: Greece
- Setting: not reported
- Inclusion criteria: children aged 2 to 18 years with a history of recurrent UTI
- Exclusion criteria: children with VUR ≥ grade III

Baseline characteristics

- Number: intervention group (38); control group (38)
- Mean age ± SD (years): not reported

Dotis 2014 *(Continued)*

	• Sex (M/F): 23/53
Interventions	Intervention group • Cranberry capsules (Mirtygil, Istituto Ganassini, SpA, Epsilon Health): 2/day, for at least 3 months Control group • No intervention
Outcomes	Outcomes of interest/reported • UTI: definition not specified, no culture threshold reported • Initiation of antimicrobial intervention • Days on antimicrobial intervention • Side effects
Notes	Additional information • Abstract-only publication • Contacted author for further details (18 May 2017), no response • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unsure, no denominators given so uncertain if all children included in the analysis
Selective reporting (reporting bias)	Low risk	Repeat UTIs reported
Other bias	Unclear risk	Abstract-only publication; unable to determine representativeness of sample, and study design issues incomplete

Essadi 2010

Study characteristics

Methods	Study design

Essadi 2010 *(Continued)*

- Parallel RCT
- Power calculation: not reported
- ITT analysis: not reported

Time frame

- Duration of study: October 2008 to December 2009
- Duration of follow-up: not reported

Participants	Study characteristics • Country: Libya • Setting: single centre • Inclusion criteria: pregnant women attending an antenatal clinic • Exclusion criteria: not reported Baseline characteristics • Number (randomised/analysed): intervention group (380/258); control group (380/286) • Mean age ± SD (years): not reported • Sex (M/F): all women
Interventions	Intervention group • Cranberry juice: 250 mL 4 times/day Control group • Water: 250 mL 4 times/day Duration of intervention: not reported
Outcomes	Outcomes of interest/reported • UTI: definition not reported, no culture threshold reported • Premature delivery
Notes	Additional information • Abstract-only publication, few details • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No, participants could tell difference between intervention and drinking water
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Essadi 2010 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up excluded and no best-worst case scenario analysis High rate of losses to follow-up/withdrawals/exclusions for UTI outcome analysis: 196/760
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Fernandes 2016

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: not reported • ITT analysis: not reported; unclear from outcomes data Time frame • Duration of study: not reported • Duration of follow-up: not reported
Participants	Study characteristics • Country: Portugal • Setting: not reported • Inclusion criteria: women ≥ 18 years; received kidney transplant > 1 year earlier; eGFR ≥ 30 mL/min/1.72 m^2 • Exclusion criteria: pregnancy; urological anomaly; cranberry intolerance; ongoing antibiotics or cotrimoxazole prophylaxis Baseline characteristics • Number: intervention group (25); control group (30) • Mean age ± SD (years): not reported • Sex (M/F): all women
Interventions	Intervention group • Daily cranberry capsule Control group • Daily placebo capsule intervention duration: 6 months
Outcomes	Outcomes of interest/reported • UTI: culture threshold not stated • UTI caused by *E coli* • UTI caused by *Klebsiella pneumoniae* • UTI caused by *Proteus mirabilis*

Fernandes 2016 *(Continued)*

- Antibiotic resistance to amoxicillin-clavulanate
- Quinolones resistance
- SMP-TMP resistance
- ESBL bacterial infections
- Number of hospitalised patients

Notes	Additional information • Abstract-only publication • Funding source: not reported • Authors contacted for further details 18 May 2017: no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to determine, no denominators and no lost to follow-up reported
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Ferrara 2009

Study characteristics

Methods	Study design • Parallel, 3-arm RCT • Power calculation: not reported • ITT analysis: no Time frame • Duration of study: June 2005 to July 2007 • Duration of follow-up: 6 months
Participants	Study characteristics

Ferrara 2009 *(Continued)*

- Country: Italy
- Setting: single centre
- Inclusion criteria: girls aged 3 to 14 years attending an ambulatory paediatric nephrology clinic; > 1 UTI in previous 12 months
- Exclusion criteria: structural abnormalities; deformities of the urinary tract; impaired kidney function

Baseline characteristics

- Number (randomised/analysed): intervention group 1 (28/27); intervention group 2 (27/26); control group (29/27)
- Mean age ± SD (years): not reported
- Sex (M/F): all girls

Interventions	Intervention group 1
	• Cranberry-lingonberry concentrate
	  ○ Cranberry concentrate: 50 mL/day for 6 months (97.5 g cranberry concentrate)
	  ○ Lingonberry concentrate: 1.7 g in 50 mL water
	  ○ No sugar additive
	Intervention group 2
	• Lactobacillus GG drink: 100 mL on 5 days each month for 6 months (contains 4 x 10^7 CFU/100 mL)
	Control group
	• No intervention
	Duration of intervention: 6 months

Outcomes	Outcomes of interest/reported • Symptomatic UTI (symptoms being frequency, dysuria, urgency, haematuria, nocturia, fever, back or hip pain) and ≥ 10^8 CFU/L
Notes	Additional information • Funding source: not reported

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	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No, participants knew what intervention they were taking
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Low risk	Low rate of those excluded from outcome analysis: 4/84

Ferrara 2009 *(Continued)*

All outcomes		
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 not reported

Foda 1995

Study characteristics	
Methods	Study design • Cross-over RCT • Power calculation: not reported • ITT analysis: no Time frame • Duration of study: not reported • Duration of follow-up: 12 months total
Participants	Study characteristics • Country: Canada • Setting: single centre • Inclusion criteria: children with neuropathic bladder managed by clean intermittent catheterisation; outpatients' residence at a distance not exceeding 150 km from the Children's Hospital of Eastern Ontario • Exclusion criteria: not reported Baseline characteristics • Number (randomised/analysed): 40/21 • Mean age (range): 9.35 years (1.4 to 18) • Sex (M/F): 19/21
Interventions	Intervention group • Cranberry cocktail: 15 mL/kg/day (30% cranberry concentrate) Control group • Water Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • 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	Additional information • Method of urine collection

Foda 1995 *(Continued)*

- Sterile catheter urine samples
- Definition of bacteriuria
  - ≥ 10^8 CFU/L of a pathogenic organism after 24 hours incubation
  - Any growth in a symptomatic patient was considered significant
- Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
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	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of losses to follow-up/withdrawals excluded for outcome analysis: 19/40 excluded
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Foxman 2015

Study characteristics

Methods

Study design

- Parallel RCT
- Power calculation: yes, based on 65% to 75% relative risk reduction in cranberry group, compared to placebo, based on recurrence risk of 15% to 18% recurrence risk in placebo
- ITT analysis: not reported but group tallies with numbers randomised to each group

Time frame

- Duration of study: recruited between August 2011 and January 2013
- Duration of follow-up: 6 weeks

Participants

Study characteristics

- Country: USA
- Setting: single centre
- Inclusion criteria: non-pregnant women; > 18 years; undergoing gynaecological surgery

Foxman 2015 *(Continued)*

	• Exclusion criteria: history of nephrolithiasis; congenital urogenital anomaly; neurogenic bladder; known allergy to cranberry; on anticoagulant medicine; fistula repair or vaginal mesh removal Baseline characteristics • Number: intervention group (80); control group (80) • Mean age ± SD (years): intervention group (56 ± 12.5); control group (56 ± 14.3) • Sex (M/F): all women
Interventions	Intervention group • Cranberry capsules (Theracran): 2 capsules twice/day (4/day) equivalent to 2 x 8-ounce servings of cranberry juice Control group • Placebo: no details, made by Theralogix, LLC Duration of intervention: 6 weeks
Outcomes	Outcomes of interest/reported • Symptomatic UTI: confirmed with culture, no threshold reported • Clinical UTI: not confirmed with culture • Median time to UTI • Adverse events • Severe adverse events
Notes	Additional information • Funding source: NIH (R21-DK-085290) and University of Michigan (for 1 CIs salary) • Pills supplied free from Theralogix

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated permuted blocks
Allocation concealment (selection bias)	Low risk	Data coordinating centre managed allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "masked to intervention assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cultures performed by laboratory
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for in analysis Low rate of missing data for outcome analysis: 0/160
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported, includes culture-verified UTI

Foxman 2015 *(Continued)*

Other bias	Unclear risk	Few details on why so many eligible women (n = 359) were not randomised

Gallien 2014

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes, based on estimation of 35% recurrence rate in placebo, and 15% reduction in cranberry group • ITT analysis: yes, stated; reports results within randomised groups with correct totals Time frame • Duration of study: recruitment from 26 January 2006 to 5 November 2007 • Duration of follow-up: 12 months
Participants	Study characteristics • Country: France • Setting: multicentre (8 sites) • Inclusion criteria: MS with an EDSS score ≥ 3; clinically stable for at least 3 months; able to undergo evaluation; aged 18 to 70 years; urinary disorders (at least one of these 4 symptoms: pollakiuria, urgency, dysuria and urinary incontinence); agree to a 1-year follow-up • Exclusion criteria: pregnant or breast-feeding; kidney failure; risk of uric acid lithiasis; peptic ulcer; intolerance to cranberry and/or excipients; receiving UTI antibiotic prophylaxis; receiving oral anticoagulants; consumed cranberry in some form within the previous 3 months; indwelling catheter; UTI at the time of randomisation Baseline characteristics • Number: intervention group (82); control group (89) • Mean age ± SD (years): intervention group (49 ± 9); control group (48 ± 11) • Sex (M/F): intervention group (19/63); control group (27/62)
Interventions	Intervention group • Cranberry powder: twice/day (36 mg PAC/day) Control group • Placebo: matching powder Duration of intervention: 12 months
Outcomes	Outcomes of interest/reported • Rate of UTIs • UTIs in 12 months • Number of UTIs per person in 12 months • MS relapses in 12 months • Number of patients who took at least one script for antibiotics • Mean number of days on antibiotics
Notes	Additional information

Gallien 2014 *(Continued)*

- Culture threshold: ≥ 10^8 CFU/L
- Funding source: French Ministry of Health (PHRC 2005)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of four according to a computer generated random number table with a 1:1 allocation reported
Allocation concealment (selection bias)	Low risk	Centrally performed across 8 centres
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated, patients, pharmacists, medical staff and nurses all blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated, patients, pharmacists, medical staff and nurses all blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients included in analysis, denominators reported
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes reported
Other bias	Low risk	Well reported and all patients accounted for, selection bias probably limited

Haverkorn 1994

Study characteristics

Methods	Study design • Cross-over RCT • Power calculation: not reported • ITT analysis: no Time frame • Duration of study: end of 1992 to early 1994 • Duration of follow-up: not reported
Participants	Study characteristics • Country: the Netherlands • Setting: single centre • Inclusion criteria: those who had hospital treatment and were waiting transfer to a nursing home • Exclusion criteria: not reported Baseline characteristics • Number (randomised/analysed): 38/7

Haverkorn 1994 *(Continued)*

- Mean age: 81 years
- Sex (M/F): 9/29

Interventions	Intervention group • Cranberry juice: 30 mL/day mixed with water (PAC not reported) Control group • Water: same volume as intervention Duration of intervention: 4 weeks active intervention (8 weeks total)
Outcomes	Outcomes of interest/reported • Bacteriuria
Notes	Additional information • Method of obtaining urine sample: not reported • Definition of bacteriuria ○ ≥ 10^8 CFU/L of one of the *Enterobacteriaceae* • Report is a letter only, so very few methodological details • Funding source: not reported

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	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of missing or excluded data from outcome analysis: 21/38 (55%)
Selective reporting (reporting bias)	Unclear risk	Few details, can't be certain all outcomes collected were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Hess 2008

Study characteristics

Hess 2008 *(Continued)*

Methods	Study design • Cross-over RCT • Power calculation: yes • ITT analysis: no Time frame • Duration of study: enrolled between August 2002 to August 2004 • Duration of follow-up: 12 months
Participants	Study characteristics • Country: USA • Setting: single centre • Inclusion criteria: clinically documented spinal cord injury with neurogenic bladder • Exclusion criteria: spinal cord injury duration < 12 months; GFR < 30 mL/min; immunosuppression; current malignancy Baseline characteristics • Number (randomised/analysed): 57/47 • Median age (range): 53 years (28 to 79) • Sex (M/F): all men
Interventions	Intervention group • Cranberry tablet: 500 mg twice/day Control group • Placebo tablet: rice flour, matched to cranberry tablet Duration of intervention: 6 months then crossed over
Outcomes	Outcomes of interest/reported • Symptomatic UTI: ≥ 10^7 CFU/L • Significant bacteriuria: at least 1 UTI over 6 months; rate of UTI/person-years
Notes	Additional information • Cross-over design without data on 1st phase being separate, not analysed • Funding source: Spinal Cord Research Foundation, sponsored by the Paralyzed Veterans of America

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Concealed, managed by the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding stated

Hess 2008 *(Continued)*

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	High rate of missing or excluded data for outcome analysis: 10/57
Selective reporting (reporting bias)	Low risk	Appropriate outcome
Other bias	Low risk	No apparent additional bias Source of funding: Spinal Cord Research Foundation, sponsored by the Paralyzed Veterans of America

Juthani-Mehta 2010

Study characteristics	
Methods	Study design • Parallel, 3-arm RCT • Power calculation: not reported • ITT analysis: appears all were included Time frame • Duration of study: September 2007 to June 2008 • Duration of follow-up: 6 months
Participants	Study characteristics • Country: USA • Setting: multicentre (4 sites) • Inclusion criteria: > 60 years with dementia and a resident of a nursing home or assisted living facility for > 30 days • Exclusion criteria: chronic indwelling catheter; residence < 4 weeks; prednisone therapy; active UTI symptoms; terminal; ESKD; < 60 years; chronic suppressive antibiotic therapy; history of kidney stones; unable to provide baseline urine; warfarin therapy Baseline characteristics • Number: intervention group 1 (20); intervention group 2 (19); control group (17) • Mean age: 87 years • Sex (M/F): 82.1% female
Interventions	Intervention group 1 • Cranberry: 650 mg capsule once/day (16.25 mg PAC) Intervention group 2 • Cranberry: 650 mg capsule twice/day (32.50 mg PAC) Control group • No intervention

Juthani-Mehta 2010 *(Continued)*

	Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Number of urine cultures collected • Number of participants with *E coli* isolated from urine culture • Number of participants with ≥ 10^8 CFU/L of any organism
Notes	Additional information • 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 • Funding source: Patrick and Catherine Weldon Donaghue Medical Research Foundation GrantDF06-005 (KG, MJM) • The cranberry capsules used in the study were donated by Theralogix Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
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 study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of exclusions from outcome analysis; 0/56
Selective reporting (reporting bias)	Unclear risk	Outcomes are about feasibility not efficacy
Other bias	Unclear risk	Many details missing or poorly detailed

Juthani-Mehta 2016

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: yes, based on a rate of bacteriuria and pyuria of 0.45 in placebo and a 33% reduction in cranberry • ITT analysis: yes, stated and groups analysed as randomised Time frame

Juthani-Mehta 2016 *(Continued)*

- Duration of study: 24 August 2012 to 7 October 2014
- Duration of follow-up: 12 months

Participants	Study characteristics • Country: USA • Setting: multicentre (21 sites) • Inclusion criteria: women in long-term care facilities > 60 years; English speaking; with or without bacteriuria plus pyuria • Exclusion criteria: not expected to be a resident for at least 1 month; taking chronic suppressive antibiotics or anti-infective agents; on dialysis; unable to produce urine sample; on warfarin; nephrolithiasis; indwelling bladder catheter; allergy to cranberry; intervention with cranberry product; nursing home resident < 4 weeks Baseline characteristics • Number: intervention group (92); control group (93) • Mean age ± SD (years): intervention group (86.4 ± 8.2); control group (87.1 ± 8.4) • Sex (M/F): all women
Interventions	Intervention group • Cranberry capsules (made by Pharmatoka): 2 capsules once/day (72 mg PAC) Control group • Placebo: 2 capsules once/day Duration of intervention: 360 days
Outcomes	Outcomes of interest/reported • Bacteriuria plus pyuria (culture threshold ≥ 10^8 CFU/L) • Symptomatic UTI • Death (any cause) • Hospitalisation (any cause) • Multi-drug resistance organisms • Antibiotics for suspected UTI • Antimicrobial prescriptions
Notes	Additional information • Funding source: Pepper Older Americans Independence Centre, National Institute of Health • Cranberry and placebo capsules donated by Pharmatoka

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block design with variable block size, 4-6, stratified by nursing home. States designed by statistician, implemented by statistical programmer
Allocation concealment (selection bias)	Low risk	Investigational drug services pharmacist made intervention assignments. Only programmer and pharmacist had access to randomisation codes during enrolment
Blinding of participants and personnel (performance bias)	Low risk	States double blinded

Juthani-Mehta 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 lost to follow-up in cranberry group, and 19 lost to follow-up in placebo, included in analysis Low rate of missing or excluded data for outcome analysis: 0/185
Selective reporting (reporting bias)	Low risk	Comprehensive list of outcomes and clinically relevant ones reported
Other bias	Low risk	Well reported study with clear selection process

Kontiokari 2001

Study characteristics	
Methods	Study design • Parallel, 3-arm RCT • Power calculation: yes, but recruitment stopped before appropriate number recruited • ITT analysis: yes Time frame • Duration of study: 1993 to 1997 • Duration of follow-up: 12 months
Participants	Study characteristics • Country: Finland • Setting: single centre • Inclusion criteria: women who had a UTI caused by *E coli* (10^5 CFU/mL in clean voided MSU) and were not taking antimicrobial prophylaxis • Exclusion criteria: not reported Baseline characteristics • Number: intervention group 1 (50); intervention group 2 (50); control group (50) • Mean age ± SD (years): intervention group 1 (30 ± 9.8); intervention group 2 (30 ± 11.8); control group (29 ± 10.5) • Sex (M/F): all women

Interventions	Intervention group 1
	• Cranberry-lingonberry juice concentrate (Maija, Marli, Finland): 50 mL/day
	  ○ Cranberry concentrate: 7.5 g
	  ○ Lingonberry concentrate: 1.7 g
	  ○ Water: 50 mL with no added sugars
	Intervention group 2
	• Lactobacillus GG drink (Gefilus, Valio, Finland): 100 mL for 5 days/week
	Control group

Kontiokari 2001 *(Continued)*

	• No intervention Duration of intervention • Cranberry-lingonberry concentrate: 6 months • Lactobacillus GG drink: 12 months
Outcomes	Outcomes of interest/reported • First recurrence of symptomatic UTI
Notes	Additional information • Method of obtaining urine sample: clean voided MSU specimen • Definition of bacteriuria ○ Bacterial growth ≥ 10^8 CFU/L • 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 • Funding source: Emil Aaltonen, Juho Vainio, and Alma and K A Snellman Foundations • Marli and Valio provided the study products

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	Low rate of excluded or missing data from outcome analysis: 13/150
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Unclear risk	Uncertain about selection bias, few details

Koradia 2019

Study characteristics

Methods	Study design

Koradia 2019 *(Continued)*

- Parallel RCT
- Power calculation: yes, based on a reduction from 0% to 10%
- ITT analysis: yes, also gives per protocol

Time frame

- Duration of study: August 2016 to June 2018
- Duration of follow-up: 180 days

Participants	Study characteristics • Country: India • Setting: multicentre (4 sites) • Inclusion criteria: females aged 18 to 55 years; ≥ 2 episodes of uncomplicated acute UTI in the last 6 months, or ≥ 3 episodes of uncomplicated acute UTI in the last 12 months; agree to avoid pregnancy • Exclusion criteria: active UTI; any use of antibiotics within 2 weeks of screening; use of any natural product one month prior to starting the study; a positive pregnancy test; postmenopausal; concurrent use of corticosteroids, anticoagulants, antidepressants, other mood-stabilizing medications, or any medication that could interact with the supplement; significant concurrent illness or conditions including, psychiatric, cardiac, poorly-controlled hypertension, renal (including anatomical irregularities, catheterisation, kidney stones or kidney transplant), hepatic, neurological, endocrine, metabolic, or lymphatic disease that, in the opinion of the investigator, could adversely affect the subjects participation in the study; immunosuppressive disease; active participation in any clinical trial within 1 month of study entry; known allergy to any ingredient Baseline characteristics • Number (randomised/analysed): intervention group (44/40); control group (45/44) • Mean age ± SD (years): intervention group (34.6 ± 9.6); control group (34.8 ± 10.1) • Sex (M/F): all women

Interventions	Intervention group
	• Cranberry and probiotic capsule (BKPro-Cyan (ADM Protexin, Somerset, UK): 1 capsule, twice/day
	  ◦ Cranberry: minimum of 18 mg PAC/capsule
	  ◦ Probiotic: > 500 x 10^6 live probiotic microorganisms/capsule
	Control group
	• Placebo
	Duration of intervention: 26 weeks

Outcomes	Outcomes of interest/reported • Repeat UTI by 26 weeks • Days to first UTI after randomisation • Days of active UTI • Number of patients requiring antibiotics for active UTI • Days of antibiotics for active UTI • Number of antibiotic courses
Notes	Additional information • UTI definition: ≥ 10^6 CFU/L of uropathogens in an MSU in participants presenting with symptoms of uncomplicated cystitis (dysuria, urinary frequency, urgency, suprapubic pain, and haematuria) • Funding source: ADM Protexin Ltd

Risk of bias

Koradia 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Performed by an independent statistician using unique three-digit subject identification numbers [based upon a single-digit study center number followed by a two-digit individual number"
Allocation concealment (selection bias)	Low risk	Independent data monitor maintained codes and records locked
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States patients blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	States blinding
Selective reporting (reporting bias)	Low risk	Includes most appropriate outcome of microbiologically verified symptomatic UTI
Other bias	Unclear risk	No details on how and where patients were recruited; 1 author and a reviewer stated involvement with commercial entities selling cranberry and probiotics

Linsenmeyer 2004

Study characteristics	
Methods	Study design • Cross-over RCT • Power calculation: not reported • ITT analysis: no Time frame • Duration of study: not reported • Duration of follow-up: 9 weeks
Participants	Study characteristics • Country: USA • Setting: single centre • Inclusion criteria: neurogenic bladders secondary to spinal cord injury • Exclusion criteria: not reported Baseline characteristics • Number (randomised/analysed): 37/21 • Mean age ± SD (years): not reported • Sex (M/F): 16/5

Linsenmeyer 2004 *(Continued)*

Interventions	Intervention group • Cranberry tablets: 400 mg standardised tablets Control group • Placebo Duration of intervention: 9 weeks (4 weeks on each, plus one week wash out)
Outcomes	Outcomes of interested/reported • Urinary bacterial counts and WBC counts and the combination of bacterial and WBC counts

Notes	Additional information
	• Method of obtaining urine sample
	  ○ CSU or MSU
	• Definition of bacteriuria
	  ○ MSU: ≥ 10^7 CFU/L
	  ○ CSU: ≥ 10^5 CFU/L
	• Funding source: Eastern Paralyzed Veterans Association

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States participants and researchers blinded
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	High risk	High proportion excluded from outcome analysis: 16/37
Selective reporting (reporting bias)	Low risk	Primary outcome is appropriate
Other bias	Unclear risk	Some methods are vague, not a well reported study

Lopes de Carvalho 2012

Study characteristics

Methods	Study design

Lopes de Carvalho 2012 *(Continued)*

- Parallel RCT
- Power calculation: not reported
- ITT analysis: not reported

Time frame

- Duration of study: not reported
- Duration of follow-up: 90 days

Participants	Study characteristics • Country: Italy • Setting: not reported • Inclusion criteria: fulfil McDonald criteria for MS diagnosis • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (11); control group (10) • Mean age ± SD (years): not reported • Sex (M/F): not reported

Interventions	Intervention group
	• Cranberry-D-mannose-vitamin C: 2 capsules/day
	  ◦ Cranberry extract: 40 mg/capsule
	  ◦ D-mannose: 100 mg/capsule
	  ◦ Vitamin C: 60 mg/capsule
	Control group
	• Placebo: 2 capsules/day
	Intervention duration: 90 days

Outcomes	Outcomes of interest/reported • Number of UTIs • Number of urine cultures (threshold not reported) • Bladder symptoms • Post void residual
Notes	Additional information • Abstract-only publication • Funding source: not reported • Author emailed for further details, no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Lopes de Carvalho 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	States examiner physicians and subjects blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	No data reported for any outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Maki 2016

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes, based on 32% of women having a UTI and 17.8% reduction in this rate for cranberry group • ITT analysis: yes, stated and numbers in groups reflect randomised numbers Time frame • Duration of study: February 2013 to March 2015 • Duration of follow-up: 24 weeks
Participants	Study characteristics • Countries: USA, France • Setting: multicentre (18 sites) • Inclusion criteria: women aged 20 to 70 years; BMI < 40; ≥ 2 UTIs treated by a health professional in the past year, of which ≥ 1 UTI treated ≤ 6 months before screening visit • Exclusion criteria: currently using prophylactic antibiotics; active UTI infection with symptoms; bladder catheter; polycystic disease; interstitial cystitis; previous urologic surgery; stones; anatomical abnormality of urinary tract; spinal cord injury; immunocompromised; kidney impairment; DM with HbA1c ≥ 8%; DM treated with insulin; cancer in past 2 years; major trauma or surgery; oral anticoagulants ≤ 4 weeks before screening; pregnancy; lactating Baseline characteristics • Number: intervention group (185); control group (188) • Mean age ± SEM (years): intervention group (40.9 ± 1.1); control group (41.0 1.0) • Sex (M/F): all women
Interventions	Intervention group • Cranberry juice (Ocean Spray Cranberries Inc): 240 mL bottle/day Control group

Maki 2016 *(Continued)*

	• Placebo beverage (Ocean Spray Cranberries Inc): 240 mL bottle/day, matched for smell and taste intervention duration: 24 weeks
Outcomes	Outcomes of interest/reported • Clinical UTI • Annual UTI incidence density • UTI by 24 weeks • Microbiologically-proven UTI (≥ 10^6 CFU/L) • Adverse effects
Notes	Additional information • Funding source: Ocean Spray Cranberries Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated, SAS for Windows software
Allocation concealment (selection bias)	Low risk	Coded data trak system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of missing or excluded data from outcome analysis: 0/373
Selective reporting (reporting bias)	Low risk	Amongst the outcomes was the most relevant, symptomatic UTI verified by culture
Other bias	Low risk	Detailed reporting

McGuiness 2002

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: not mentioned in methods but mentioned in discussion • ITT analysis: reported to be "yes" (although percentages in results do not make sense) Time frame • Duration of study: not reported

McGuiness 2002 *(Continued)*

- Duration of follow-up: 6 months

Participants	Study characteristics • Country: Canada • Setting: single centre • Inclusion criteria: MS diagnosis (Poser criteria), EDSS 0–8; consented; refrain from cranberries during study; no indwelling or condom catheter, if intermittent catheterisation, no more than 6 times/day; symptoms of neurogenic bladder; no current UTI • Exclusion criteria: not reported Baseline characteristics • Number (randomised/analysed): 135/106 (number per group not reported) • Mean age ± SD (years): intervention group (44.8 ± 9.9); control group (45.4 ± 9.8) • Sex (M/F): intervention group (21%/79%); control group (21.9%/78.1%)
Interventions	intervention group • Cranberry-containing tablet (NOW Natural Foods): 8000 mg tablet, one tablet/day Control group • Beetroot powder placebo tablet: identical appearance to cranberry, one tablet/day Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Microbiological UTI (≥ 10^9 CFU/L) "with leucocytes, blood or nitrites on microscopy" • Symptoms were not required because these are usually masked in people with MS
Notes	Additional information • 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 intervention groups are not provided • Very poorly reported study and percentages reported for incidence of UTIs do not make sense • Funding source: Alberta Association of Registered Nurses, American Association of Neuroscience Nurses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Title states the study was double-blinded, assume this refers to participants and healthcare 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

McGuiness 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of exclusions from outcome analysis: 12/135 participants withdrew or were lost to follow-up but the numbers in each intervention 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

McMurdo 2005

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes • ITT analysis: yes • Stratified by gender and hospital Time frame • Duration of study: not reported • Duration of follow-up: 35 days following randomisation or until hospital discharge
Participants	Study characteristics • Country: UK • Setting: multicentre (5 sites) • Inclusion criteria: ≥ 60 years admitted to either acute medicine for the elderly assessment or rehabilitation units for elderly people • Exclusion criteria: MSQ score < 5/10; dysphagia; symptoms of a UTI; antibiotic intervention; anticipated length of stay < 1 week; regular drinkers of cranberry juice; presence of an indwelling 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 Baseline characteristics • Number: intervention group (187); control group (189) • Mean age ± SD (years): intervention group (81.3 ± 7.3); control group (81.4 ± 7.6) • Sex (M/F): intervention group (56/133); control group (65/122)
Interventions	Intervention group • Cranberry juice: 300 mL Control group • Matching placebo beverage: 300 mL Duration of intervention: unclear
Outcomes	Outcomes of interest/reported

McMurdo 2005 *(Continued)*

- Time to onset of first symptomatic UTI: defined as a culture-positive urine growing a single organism of > 10^7 CFU/L urine specimen
- Adherence to beverage drinking, courses of antibiotics prescribed, and organisms responsible for UTI

Notes	Additional information • Method of obtaining urine sample: clean catch • Definition of bacteriuria ◦ Only pure growths of ≥ 10^7 CFU/L were reported with an antibiotic sensitivity • Funding source: "funded by project grant K/OPR/2/2/D398 from the Chief Scientist Office at the Scottish Executive Department of Health. The cranberry juice and matching placebo were supplied by Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA, USA."

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	Low rate of excluded or missing data from outcome analysis: 0/376
Selective reporting (reporting bias)	Low risk	Appropriate clinical outcomes
Other bias	Low risk	No other bias apparent, well reported study

McMurdo 2009

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: yes • ITT analysis: yes • Recruited predominantly through primary care services but also from newspaper ads Time frame • Duration of study: not reported • Duration of follow-up: 6 months

McMurdo 2009 *(Continued)*

Participants	Study characteristics • Country: UK • Setting: single centre • Inclusion criteria: community-dwelling women ≥ 45 years with at least 2 antibiotic-treated UTIs in previous 12 months confirmed by GP, but not necessarily culture proven • Exclusion criteria: previous urological surgery, stones or anatomical abnormalities of the urinary tract; urinary catheter; DM; immunocompromised; pyelonephritis; severe kidney impairment; blood dyscrasias; symptomatic UTI at baseline; cognitive impairment precluding informed consent; resident in institutional care; on long-term antibiotic therapy; on warfarin therapy; regular cranberry consumers; childbearing potential; unwilling to participate Baseline characteristics • Number: intervention group (69); control group (68) • Mean age ± SD (years): intervention group (62.6 ± 10.8); control group (63.3 ± 10.1) • Sex (M/F): all women
Interventions	Intervention group • Cranberry: 500 mg capsule, once/day Control group • TMP: 100 mg capsule, once/day Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Clinical UTI treated with antibiotics (with or without culture), time to recurrence of clinical UTI • Symptomatic and culture-verified UTI (culture threshold ≥ 10^7 CFU/L) • Adherence • Adverse events
Notes	Additional information • Matched tablets with over-coating • Funding source: Moulton Charitable Foundation; Buckton Scott Health ProductsLtd, UK supplied the Cran-Max™ free of charge

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)	Low risk	Stated as blinded

McMurdo 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for No lost or missing data from outcome analysis: 0/137
Selective reporting (reporting bias)	Low risk	Symptomatic UTI is most appropriate
Other bias	Low risk	Well reported, no other bias apparent

Mohammed 2016

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: not reported • ITT analysis: not reported Time frame • Duration of study: recruitment period November 2014 to April 2016 • Duration of follow-up: 6 weeks
Participants	Study characteristics • Country: Iraq • Setting: single centre • Inclusion criteria: patients with bladder cancer (stage 2 or above = MIBC) undergoing radiation • Exclusion criteria: cranberry allergy; UTI and/or severe lower urinary tract symptoms at baseline; urethral catheterisation during or around the course of radiation therapy, previous pelvic radiation therapy, prostate and other pelvic malignancy; MIBC stages T4a and T4b; on chemotherapy or receiving chemotherapy in 3 months before the study; DM; neurogenic bladder; history of kidney dysfunction; severe macrohaematuria; irritable bowel syndrome; using medications such as NSAIDs, corticosteroids, antibiotics, antispasmodics and other analgesics; on warfarin therapy Baseline characteristics • Number: intervention group (22); control group (23) • Mean age ± SD (years): not reported • Sex (M/F): intervention group (16/6); control group (17/6)
Interventions	Intervention group • Cranberry: 2 tablets/day of pure PAC (36 mg) extracted from American cranberry according to the American extraction method (Urinal Akut®, by Walmark) Control group • Placebo: 2 capsules/day of pure lactose (500 mg) Duration of intervention: 6 weeks during radiation therapy
Outcomes	Outcomes of interest/reported • Number with UTI

Mohammed 2016 *(Continued)*

	• Number with urinary tract symptoms (frequency, nocturia, urgency) in participants without UTI
Notes	Additional information • Primarily a study of urinary tract symptoms in those without UTI • Funding source: 'nil'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomly allocated
Allocation concealment (selection bias)	Unclear risk	Said to be randomly allocated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	All outcomes were clinically based and not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	UTIs reported for all participants; 13% (6/45) excluded from other reported outcomes
Selective reporting (reporting bias)	Unclear risk	No report on adverse effects
Other bias	Low risk	Study appears free of other biases

Mooren 2020

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: not reported • ITT analysis: yes Time frame • Duration of study: recruitment period October 2016 to September 2018 • Duration of follow-up: 6 weeks
Participants	Study characteristics • Country: the Netherlands • Setting: single centre • Inclusion criteria: women > 18 years undergoing elective surgery for pelvic organ prolapse or incontinence surgery (with use of an indwelling catheter); able to understand the Dutch language

Mooren 2020 *(Continued)*

	• Exclusion criteria: pregnant Baseline characteristics • Number: intervention group (105); control group (105) • Mean age (years): intervention group (61); control group (64) • Sex (M/F): all women
Interventions	Intervention group • Cranberry capsules: 36 mg PAC + small portion of grape seed extract; 1 capsule twice/day started on the evening before surgery Control group • Placebo capsules: 1 capsule twice/day started on the evening before surgery Co-interventions in both groups • Clean intermittent catheterisation or indwelling catheter if required for urinary retention Duration of intervention: 6 weeks
Outcomes	Outcomes of interest/reported • UTI symptoms postoperatively • Culture-positive UTI: definition not reported • Compliance rates • Adverse effects: GI, allergic reactions, others
Notes	Additional information • The study protocol was registered with trial number NL57693.101.16 • Funding source: "OrthoBasics for providing the study medication for our trial" "The costs of the study medication were equally shared by OrthoBasics and the research department of our clinic. OrthoBasics was not involved in the design, analysis nor publication of the results."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “After signing informed consent, women were randomly allocated (1:1) to cranberry capsules or placebo capsules using block randomization with a block size of 10 that was created with a computerized random number generator”
Allocation concealment (selection bias)	Low risk	Quote: “After signing informed consent, women were randomly allocated (1:1) to cranberry capsules or placebo capsules using block randomization with a block size of 10 that was created with a computerized random number generator”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “All investigators, participants, and medical staff were blinded for the randomization during the trial. Study medication was produced and packed by the manufacturer in identical packages for both groups and numbered according to the randomization list. Placebo capsules were identical to the cranberry capsules with regard to color and flavor and differed only in the absence of the extract from cranberry and grapefruit”
Blinding of outcome assessment (detection bias)	Low risk	The outcome (urine culture) was laboratory based and unlikely to be influenced by lack of blinding

Mooren 2020 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Quote: "All study medication was produced and packed by OrthoBasics, Midwoud, the Netherlands." Quote: "The costs of the study medication were equally shared by OrthoBasics and the research department of our clinic. OrthoBasics was not involved in the design, analysis nor publication of the results"

NAPRUTI 2011

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes • ITT analysis: no Time frame • Duration of study: recruitment period 1 January 2005 to 21 August 2007 • Duration of follow-up: 15 months
Participants	Study characteristics • Country: the Netherlands • Setting: multicentre (10 sites) • Inclusion criteria: premenopausal women > 18 years with at least 3 symptomatic UTIs in the year prior to enrolment, self-reported • 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; kidney transplantation Baseline characteristics • Number (randomised/analysed): intervention group (111/104); control group (110/95) • Medina age, IQR (years): intervention group (34.8, 22.8 to 44.4); control group (36.1, 26.9 to 46.3) • Sex (M/F): all women
Interventions	intervention group • Cranberry extract: 500 mg capsule twice/day (9.1 mg/g type A PAC) • Placebo tablet: 1 tablet at night Control group • TMP-SMX: 480 mg tablet at night • Placebo capsule: 1 capsule twice/day

NAPRUTI 2011 *(Continued)*

	Duration of intervention: 12 months
Outcomes	Outcomes of interest/reported • Mean number of clinically defined UTIs over 12 months • Microbiological confirmed symptomatic UTI • Median time to microbiologically confirmed symptomatic UTI • Bacterial resistance to active intervention • Asymptomatic culture-positive UTI • Serious adverse events
Notes	Additional information • Recruited through direct advertising and primary care facilities as well as secondary and tertiary level hospital referrals • Placebo and active tablets were identical • Culture threshold: $\geq 10^6$ CFU/L • Email correspondence from Marielle Beerepoot on 5 June 2012 provided the actual numbers of participants in each arm who experienced a UTI • Cranberry and placebo capsules supplied by Springfield Nutraceuticals BV • Funding source: Netherlands Organisation for Health Research and Development

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 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	Unclear risk	High rate of exclusions from outcome analysis: 22/221
Selective reporting (reporting bias)	Low risk	Many outcomes reported, clinically appropriate
Other bias	Low risk	Appears to be a representative sample

Salo 2010

Study characteristics

Salo 2010 *(Continued)*

Methods	Study design • Parallel RCT • Power calculation: yes • ITT analysis: no Time frame • Duration of study: 2001 to 2008 • Duration of follow-up: 12 months
Participants	Study characteristics • Country: Finland • Setting: multicentre (7 sites) • Inclusion criteria: children referred to paediatric departments for verified UTI in previous 2 months; aged 1 to 16 years • Exclusion criteria: grade III-V VUR or severe genitourethral malformations Baseline characteristics • Number (randomised/analysed): intervention group (129/126); control group (134/129) • Mean age ± SD (years): intervention group (3.8 ± 2.5); control group (4.5 ± 2.9) • Sex (M/F): intervention group (11/115); control group (12/117)
Interventions	Intervention group • Cranberry juice: 5mL/kg up to 300mL; 1 to 2 doses/day Control group • Placebo juice: same volume and dose/day as cranberry Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Symptomatic, culture-verified repeat UTI (≥ 10^8 CFU/L of 1 species in a midstream catch, bag or catheter sample or any amount of bacteria in a suprapubic bladder aspirate sample in 2 consecutive samples • UTI incidence density • Antimicrobial use
Notes	Additional information • 27 dropped out by 12 months (16 in cranberry group, 11 in placebo group) • Funding source: Paivikki and Sakari Sohlberg Foundation, Foundation for Paediatric Research, Paulo Foundation, Ocean Spray

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

Salo 2010 *(Continued)*

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	Insufficient information to permit judgement
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, low rate of missing or excluded data from outcome analysis; 11/263
Selective reporting (reporting bias)	Low risk	Most appropriate outcome used
Other bias	Low risk	Well reported study

Schlager 1999

Study characteristics	
Methods	Study design • Cross-over RCT • Power calculation: no • ITT analysis: yes Time frame • Duration of study: November 1996 to November 1997 • Duration of follow-up: 6 months
Participants	Study characteristics • Country: USA • Setting: single centre • Inclusion criteria: children aged 2 to 18 years with neuropathic bladder and managed by clean intermittent catheterisation; lived at home; normal findings on kidney ultrasonography and voided cystourethrogram; lived within a 1 hour drive of the hospital • Exclusion criteria: not reported Baseline characteristics • Number: 15 • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group • Cranberry juice cocktail: 300 mL/day (30% cranberry concentrate) Control group • Placebo beverage: looked and tasted similar but contained no cranberry juice

Schlager 1999 *(Continued)*

	Duration of intervention: 3 months
Outcomes	Outcomes of interest/reported • Presence of bacteriuria • Symptomatic UTI

Notes	Additional information
	• 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
	  ○ ≥ 10^7 CFU/L
	• Funding source: Grants from Spinal Cord Research Foundation and the Pendleton Pediatric Infectious Disease Research Laboratory

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, no data excluded or missing from outcome analysis: 0/15
Selective reporting (reporting bias)	Low risk	Symptomatic UTI reported as appropriate
Other bias	Low risk	Study appears free of other biases

Scovell 2015

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: yes, "based on prior in vivo studies" • ITT analysis: not reported

Scovell 2015 *(Continued)*

	Time frame • Duration of study: March 2012 to July 2014 • Duration of follow-up: 16 weeks
Participants	Study characteristics • Country: USA • Setting: not reported • Inclusion criteria: women > 18 years who self-catheterise for neurogenic bladder > 3 times/day • Exclusion criteria: augmentation cystoplasty; pregnancy Baseline characteristics • Number: intervention group (14); control group (10) • Mean age: 46.5 years • Sex (M/F): all women
Interventions	Intervention group • Cranberry supplement: 36 mg PACBL^{-DMAC} daily Control group • Placebo: no further details reported Duration of intervention: 16 weeks
Outcomes	Outcomes of interest/reported • Bacterial colony count (culture threshold not reported) • Symptomatic UTI • Time to symptomatic UTI
Notes	Additional information • Abstract-only publication • Funding source: TROPHIKOS "funded the study drug, placebo, and some administrative expenses"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Unclear risk	Low rate of exclusions from outcome analysis: 2/24

Scovell 2015 *(Continued)*

All outcomes		24 randomised, 22 completed the study, uncertain if all randomised included, no data provided
Selective reporting (reporting bias)	Unclear risk	Outcomes included symptomatic UTI, but no data are given
Other bias	Unclear risk	Insufficient information to permit judgement

Sengupta 2011

Study characteristics	
Methods	Study design • Parallel, 3-arm RCT • Power calculation: no • ITT analysis: no Time frame • Duration of study: not reported • Duration of follow-up: 90 days
Participants	Study characteristics • Country: India • Setting: unclear • Inclusion criteria: females with a history of recurrent UTIs, with dysuria, frequency, blood in urine or pain in suprapubic region and negative pregnancy test • Exclusion criteria: antibiotics in past 48 hours; catheterised within last 2 weeks; DM; cardiovascular disease; pyelonephritis; kidney stones Baseline characteristics • Number: intervention group 1 (21); intervention group 2 (23); control group (16) • Age range: 18 to 40 years • Sex (M/F): all women
Interventions	Intervention group 1 • Cranberry: 500 mg/day (PAC standardized whole cranberry powder, PS-WCP; 1.5% PAC, Decas Botanical Synergies) Intervention group 2 • Cranberry: 1000 mg/day (PAC standardized whole cranberry powder, PS-WCP; 1.5% PAC, Decas Botanical Synergies) Control group • No intervention Duration of intervention: 90 days
Outcomes	Outcomes of interest/reported • Symptomatic UTI with > 10^7 CFU/L *E coli* pure growth

Sengupta 2011 *(Continued)*

Notes	Additional information • Funding source: not reported

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
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Uncertain if researchers or assessors were blind to allocated intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of exclusions from outcome analysis: 3/60
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

SINBA 2007

Study characteristics

Methods	Study design • Parallel, 4-group factorial design RCT • Power calculation: yes • ITT analysis: yes Time frame • Duration of study: November 2000 to August 2002 • Duration of follow-up: 6 months
Participants	Study characteristics • Country: Australia • Setting: multicentre (2 sites; spinal cord injuries database, predominantly community-dwelling patients) • Inclusion criteria: spinal cord injured people with neurogenic bladder; bladder management with either indwelling urethral or suprapubic catheter, intermittent catheterisation, or reflex voiding with or without a condom drainage divide; absence of complex urological or serious kidney or hepatic pathol-

SINBA 2007 *(Continued)*

	ogy; not being prescribed antibiotics at the time of enrolment and absence of symptoms of a UTI at enrolment; willing to stop any intercurrent urinary antiseptics before entering the study • Exclusion criteria: previous allergy to any of the test interventions Baseline characteristics • Number: intervention group 1 (75); intervention group 2 (75); intervention group 3 (78); control group (77) • Mean age ± SD: 53.5 ± 13.5 years • Sex (M/F): 83%/17%
Interventions	Intervention group 1 • Methenamine hippurate: 2 g • Cranberry: 1600 mg Intervention group 2 • Methenamine hippurate: 2 g • Cranberry placebo Intervention group 3 • Cranberry: 1600 mg • Methenamine hippurate placebo Control group • Methenamine hippurate placebo • Cranberry placebo Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Symptomatic UTI: current criteria for treating patients in the spinal injured population (culture threshold ≥ 10^8 CFU/L)
Notes	Additional information • Funding source: Motor Accidents Authority and Brucia Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dynamically balanced, centralised 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

SINBA 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All accounted for in results. Rate of excluded or missing data from outcome analysis: 34/305
Selective reporting (reporting bias)	Low risk	Well described
Other bias	Low risk	No other bias apparent, well reported study

Singh 2016

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes, based on 30% change in mean • ITT analysis: not stated but totals in analysed group match number randomised to each group Time frame • Duration of study: November 2011 to March 2013 • Duration of follow-up: 12 weeks
Participants	Study characteristics • Country: India • Setting: single centre • Inclusion criteria: patients aged 15 to 76 years with subclinical asymptomatic bacteriuria and/or recurrent UTI, not responding to antimicrobials; patients prone to repeat UTIs • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (25/11); control group (24/12) • Mean age, range (years): intervention group (41.6, 15 to 76); control group (35.8, 18 to 70) • Sex (M/F): not reported
Interventions	Intervention group • Cranberry: Cranpac PAC-A 60 mg/capsule, 1 capsule twice/day Control group • *Lactobacillus acidophilus*: 400 mg/capsule, 1 capsule twice/day Duration of intervention: 12 weeks
Outcomes	Outcomes of interest/reported • Number with UTI by 12 weeks: does not state UTO definition but references European guideline; symptomatic and culture > 10^6 CFU/L • Mean urinary pH • Burning micturition score • Micro pyuria score • Bacterial growth number • Bacterial adhesion

Singh 2016 *(Continued)*

- Biofilm formation
- Mannose-resistant haemagglutination assay

Notes	Additional information • Included 8 patients with indwelling catheters or on intermittent catheterisation in each group • Funding source: within regular running expenditure available to the government institution and no extra-institutional financial grant or funding was required • Additional data on gender of patients received from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used www.randomization.com
Allocation concealment (selection bias)	Low risk	Managed externally
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Denominators given in one outcome, not for many others
Selective reporting (reporting bias)	Low risk	Symptomatic UTI is reported but many outcomes are primarily surrogates and may not reflect clinical effects
Other bias	Unclear risk	Uncertainty about blinding (participants and clinicians)

Stapleton 2012

Study characteristics

Methods	Study design • Parallel, 3-arm RCT ○ Study flowchart shows 4 groups; control groups are different volumes of placebo juice • Power calculation: yes, based on 35% risk UTi in placebo, and 15% absolute risk reduction in cranberry • ITT analysis: yes, though modified due to drop-out before first follow-up Time frame • Duration of study: 16 November 2005 to 21 December 2008 • Median duration of follow-up: 186 days
Participants	Study characteristics • Country: USA

Stapleton 2012 *(Continued)*

- Setting: multicentre (2 sites)
- Inclusion criteria: premenopausal women, 18 to 45 years; history of ≥ 1 clinician diagnosed UTI in past 12 months
- Exclusion criteria: prediagnosed anatomical abnormality of the urinary tract; history of kidney stones; DM; malignant neoplasm; allergy or intolerance to cranberry; symptoms of vaginitis or cystitis or asymptomatic bacteriuria; pregnant or lactating; not using contraceptives; on prophylactic antibiotics; taking warfarin; antibiotics used in past 7 days; investigational drug in past 30 days

Baseline characteristics

- Number (randomised/completed): intervention group 1 (63/41); intervention group 2 (62/44); control group 1 (31/17); control group 2 (30/18)
- Mean age ± SD (years): intervention group (25.3 ± 6.6); control group (26.4 ± 6.5)
- Sex (M/F): all women

Interventions	Intervention group 1 • Cranberry juice: 4 oz (118 mL)/day Intervention group 2 • Cranberry juice: 8 oz (236 mL)/day Control group 1 • Placebo juice: 4 oz (118 mL)/day Control group 2 • Placebo juice: 8 oz (236 mL)/day Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Clinical: UTI (dysuria+one or more of; frequency, urgency, suprapubic pain, haematuria, and pyuria > 10 cells/µL in un-spun urine or positive leucocyte esterase on dipstick) • Symptomatic, culture-verified UTI: clinical UTI + positive culture (threshold > 10^6 CFU/L) • Time to symptomatic UTI • Asymptomatic bacteriuria (> 10^8 CFU/L) with no symptoms • Adverse effects • Adherence
Notes	Additional information • Dose groups combined for analysis • Reports results for people with at least 1 follow-up, not all who were randomised • Funding source: Grant ROI AT002105 from the National Centre for Complementary and Alternative Medicine and Clinical and Translational Science Award grant ULI RR024139 from National Centre for Research Resources

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list, performed by biostatistician; stratified by site
Allocation concealment (selection bias)	Low risk	Web-based system to allocate and store randomisation codes

Stapleton 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated as blinded but placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States laboratory procedures performed blind to intervention allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 randomised women were excluded from analysis, failed to attend first assessment
Selective reporting (reporting bias)	Low risk	Clinically important outcomes reported
Other bias	Unclear risk	Some uncertainties over 10 excluded post-randomisation

Stothers 2002

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: no • ITT analysis: yes Time frame • Duration of study: not reported • Duration of follow-up: 12 months
Participants	Study characteristics • Country: Canada • Setting: single centre • Inclusion criteria: women, 21 to 72 years; 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 • Exclusion criteria: neurogenic bladder dysfunction; insulin-dependent diabetes; immunosuppressive disease; steroid use; intermittent or indwelling catheterisation Baseline characteristics • Number: intervention group 1 (50); intervention group 2 (50); control group (50) • Mean age, range (years): intervention group 1 (40, 23 to 68); intervention group 2 (44, 21 to 70); control group (43, 21 to 72) • Sex (M/F): all women
Interventions	Intervention group 1 • Cranberry tablets: 1 tablet of 1:30 parts concentrated juice, twice/day • Placebo juice: filtered water with food colouring + 20 mL pineapple juice, 3 times/day Intervention group 2

Stothers 2002 *(Continued)*

	• Cranberry juice: 250 mL, 3 times/day • Placebo tablets: 1 placebo tablet, twice/day Control group • Placebo juice: filtered water with food colouring + 20 mL pineapple juice • Placebo tablets: 1 placebo tablet, twice/day Duration of intervention: 1 year
Outcomes	Outcomes of interest/reported • Cost-effectiveness of cranberry juice and tablets • Compliance rates • Side effects and complications • Symptomatic culture-positive UTI: threshold > 10^8 CFU/L of a single organism • Mean number of UTIs in a calendar year
Notes	Additional information • Method of obtaining urine sample: CSU • Definition of bacteriuria ○ Bacteria in the urine ≥ 100,000/mL • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomised in 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 intervention 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

Stothers 2016

Study characteristics

Stothers 2016 *(Continued)*

Methods	Study design • Parallel, 3-arm RCT • Power calculation: not reported • ITT analysis: yes, stated Time frame • Duration of study: not reported • Duration of follow-up: 1 year
Participants	Study characteristics • Country: Canada • Setting: not reported • Inclusion criteria: women only, no other information provided • Exclusion criteria: not reported Baseline characteristics • Number: 263; numbers per group not reported • Age range: 19 to 85 years • Sex (M/F): all women
Interventions	Intervention group 1 • Cranberry juice: low dose, twice/day (dose not reported) Intervention group 2 • Cranberry juice: medium dose, twice/day (dose not reported) Control group • Placebo, twice/day Intervention duration: 1 year
Outcomes	Outcomes of interest/reported • Number of symptomatic, culture-positive UTI (culture threshold not stated, single organism only) • Urine chemistry P3Ga levels
Notes	Additional information • Abstract-only publication • Funding source: NIH NCCAM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Stothers 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians blinded, unsure about participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors stated as blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No data given, cannot determine completeness
Selective reporting (reporting bias)	High risk	Primary outcome appropriate, symptomatic UTI, but no data
Other bias	Unclear risk	Insufficient information to permit judgement

Takahashi 2013

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: not done to justify sample size, power calculated for the sample size obtained • ITT analysis: excluded the 5 males and 9 self-catheterised women from the analysis Time frame • Duration of study: October 2007 to September 2009 • Duration of follow-up: 200 days
Participants	Study characteristics • Country: Japan • Setting: multicentre (40 sites) • Inclusion criteria: aged 20 to 79 years; acute exacerbation of uncomplicated cystitis or chronic complicated cystitis (including self-catheterising); past history of multiple relapses of UTI and in whom healing by antimicrobial agents had been confirmed by expert urologists • Exclusion criteria: current or past history of uric acid stone disease in the urinary tract or hyperuricaemia that required urological manipulation for urinary tract stone disease; urinary tract obstruction; urinary tract malignant disease; indwelling urinary catheter; urogenital infection such as urethritis, acute or chronic bacterial prostatitis, or acute epididymitis; systemic diseases or severe complications such as uncontrolled DM, collagen disease, leukaemia, advanced cancer, congenital heart failure, or severe hepatic or kidney dysfunction; history of allergic reaction to cranberry products; non-eligibility for this study as judged by the doctor in the clinic Baseline characteristics • Number: intervention group (107); control group (106) • Mean age, range (years): intervention group (55, 20 to 79); control group (59, 20 to 79) • Sex (M/F): 5/232 randomised; 213 women analysed
Interventions	Intervention group • Cranberry juice: 125 mL/day before sleep (40 mg PAC)

Takahashi 2013 *(Continued)*

	Control group • Placebo juice: 125 mL/day before sleep, colour and taste matched to cranberry juice intervention duration: 24 weeks
Outcomes	Outcomes of interest/reported • Repeat UTI (defined as when antibiotics were administered), no culture mentioned • Adverse event
Notes	Additional information • Funding source; Partly supported, in regard to data collection, by Kikkoman Food Products Company and The Nisshin Oillio Group, Ltd., Tokyo, Japan • No definition of UTI, no culture threshold or verification stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinded and used a matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	States 5 men, and 9 women who self-catheterised were excluded from the analysis
Selective reporting (reporting bias)	Low risk	Repeat UTI, probably symptomatic, was the only outcome but is clinically the most important one
Other bias	Unclear risk	Many details missing so unable to determine other biases

Temiz 2018

Study characteristics

Methods	Study design • Parallel, 3-arm RCT • Power calculation: yes, 2 "unit" difference • ITT analysis: not reported Time frame

Temiz 2018 *(Continued)*

- Duration of study: June 2013 to November 2014
- Duration of follow-up: 3 months

Participants	Study characteristics • Country: Turkey • Setting: single centre • Inclusion criteria: ≥ 18 years; underwent ileal conduit diversion; conscious, cooperative, and fully oriented • Exclusion criteria: UTI; pregnant; irritable bowel syndrome; DM; rheumatoid arthritis; taking antibiotics; on warfarin Baseline characteristics • Number: intervention group 1 (20); intervention group 2 (20); control group (20) • Mean age ± SD: 68.83 ± 4.72 years • Sex (M/F): 68% men
Interventions	Intervention group 1 • Cranberry capsule: 400 mg cranberry (1.8% PAC (9 mg)), 2 capsules/day, before breakfast and dinner for 3 months Intervention group 2 • Training about preventing UTI: verbal information from the researcher at the appropriate time and place about UTI, and they were also given informational brochures that could be taken home and used later Control group • No intervention
Outcomes	Outcomes of interest/reported • Mean body temperature • Mean flank pain scores • Mean urine pH • Mean WCC and C-reactive protein • Period of time passed without a UTI • *E coli* positive cultures (culture positive threshold > 10^8 CFU/L) • *Pseudomonas* positive cultures • *Klebsiella* positive cultures
Notes	Additional information • Funding source: not reported, states no conflicts of interest and no disclosures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated using a software program (https://www.random.org/lists/)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Temiz 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reports that 87 were "reached" 13 left the cranberry group, may have excluded these and kept recruiting specifically to the cranberry group, numbers (20 in each) are very convenient
Selective reporting (reporting bias)	Low risk	Patient centred outcome of symptomatic UTI was reported, others were lab measures
Other bias	Unclear risk	No details on patient recruitment, screening, selection

Uberos 2012

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: yes, based on equivalence of ± 10% from 20% baseline risk of recurrent UTI in antibiotic group • ITT analysis: yes, stated as performed Time frame • Duration of study: 1 January 2009 to 31 October 2010 • Duration of follow-up: 1 year
Participants	Study characteristics • Country: Spain • Setting: single • Inclusion criteria: children with a history of recurrent UTI (more than 2 episodes of infection in the past 6 months) with or without VUR of any grade • Exclusion criteria: concurrent presence during episodes of UTI of other infectious diseases; metabolic disorders; CKD; kidney stones; liver failure; allergy or intolerance to any components of cranberry or TMP; the presence of blood dyscrasias; the express desire of the legal guardian that the child not participate in the study Baseline characteristics • Number (randomised/analysed): intervention group (75/72); control group (117/114) ○ VUR: intervention group (17/75); control group (23/117) • Mean age ± SD (months): intervention group (28.3 ± 30.7); control group (30.7 ± 33.9) • Sex (M/F): intervention group (32/43); control group (48/69)
Interventions	Intervention group • Cranberry: glucose syrup with 2.8% cranberry extract, 0.2 mL/kg/night Control group

Uberos 2012 *(Continued)*

	• TMP: glucose syrup with 8 mg/mL TMP, 0.2 mL/kg/night Duration of intervention: maximum of 12 months
Outcomes	Outcomes of interest/reported • Symptomatic UTI (culture threshold 10^8 CFU/L for clean catch or bag, 10^7 CFU/L for catheter) • GI intolerance • Rash • Multi-drug resistance in repeat UTI organism
Notes	Additional information • Funding source: Fundo de Investigacianos Sanitarias (Health Research Fund) of the Instituo de Salud Carlos III Madrid • Study design detail in Uberos publications are no more detailed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Register numbers held by the Hospital Pharmacy Service (2012 reference)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up: cranberry group (3); antibiotic group (3); denominators include losses
Selective reporting (reporting bias)	Low risk	UTI reported, microbial resistance reported
Other bias	Unclear risk	Screening and selection of participants is not clear, unable to determine representativeness of sample

Vostalova 2015

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: yes, based on 30% baseline risk of repeat UTI reduced to 15% in cranberry group • ITT analysis: yes stated, analysis reflects randomised group numbers, loss to follow-up included but 6 excluded from cranberry group for ineligibility

Vostalova 2015 *(Continued)*

	Time frame • Duration of study: January 2010 and April 2011 • Duration of follow-up: 180 days
Participants	Study characteristics • Country: Czech Republic • Setting: single centre • Inclusion criteria: women, 18 to 75 years; at least 2 episodes of symptomatic UTI in the previous 12 months treated with antibiotics; clinical laboratory tests within normal range • Exclusion criteria: symptomatic UTI at baseline; antibiotic intervention for reasons other than UTI; pregnancy or breastfeeding; anatomical anomalies; insulin-dependent DM; cardiovascular disease; immunocompromised; indwelling catheter; use of narcotics; heavy alcohol use; participating in another trial Baseline characteristics • Number: intervention group (89); control group (93) • Mean age ± SD (years): intervention group (35.61 ± 12.97); control group (38.03 ± 13.40) • Sex (M/F): all women
Interventions	Intervention group • Cranberry: 2 capsules once/day after breakfast. Each capsule contained 250 mg cranberry fruit powder, with total PAC 0.56% Control group • Placebo: identical to cranberry capsules Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Symptomatic UTI: bacteriuria ≥ 10^8 CFU/L on culture plus symptoms of UTI • UTI caused by *E coli* • Average count of UTIs • Haematology measurements
Notes	Additional information • Funding source: Palacky University Olomouc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Online software QuickCalcs
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double blinded

Vostalova 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 post-randomisation exclusions all in the cranberry group
Selective reporting (reporting bias)	Low risk	Appropriate outcome of symptomatic UTI reported
Other bias	Unclear risk	Unclear because of uncertainty of some design details

Waites 2004

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: no • ITT analysis: no Time frame • Duration of study: not reported • Duration of follow-up: 6 months
Participants	Study characteristics • Country: USA • Setting: single centre • Inclusion criteria: community residing men and women at least 1-year post spinal cord injury; ≥ 16 years; neurogenic bladder managed by clean intermittent catheterisation 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; agreement not to ingest and cranberry-containing products whilst participation in the clinical study; baseline urine culture demonstrating at least 10^5 CFU/mL • Exclusion criteria: not reported Baseline characteristics • Number (randomised/analysed): intervention group (36/26); control group (38/22) • Age range (years): intervention group (20 to 73); control group (27 to 71) • Sex (M/F): intervention group (20/6); control group (22/0)
Interventions	Intervention group • Concentrated cranberry extract: 2 g in capsule form Control group • Placebo capsule Duration of intervention: 6 months
Outcomes	Outcomes or interest/reported

Waites 2004 *(Continued)*

- Baseline urinalysis and cultures were performed at the time of the initial clinic visit and monthly for 6 months

Notes	Additional information • Microbiologic data were evaluated using analysis of variance with repeated measures • Method of obtaining urine sample: CSU or clean catch • Definition of bacteriuria: ≥ 10^8 CFU/L • Funding source: not reported, but Cranberry capsules were provided by Aim This Way, Cambridge, Massachusetts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and clinicians were blind to intervention allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Probably likely that microbiology staff assessing culture results were blind to intervention, but this wasn't stated
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of missing or excluded data from outcome analysis: 26/74
Selective reporting (reporting bias)	Low risk	The primary outcome was symptomatic UTI which is appropriate
Other bias	Unclear risk	Insufficient information to permit judgement

Walker 1997

Study characteristics

Methods	Study design • Cross-over RCT • Power calculation: no • ITT analysis: no Time frame • Duration of study: not reported • Duration of follow-up: 6 months
Participants	Study characteristics • Country: USA

Walker 1997 *(Continued)*

- Setting: single centre
- Inclusion criteria: non-pregnant, sexually active women; 18 and 45 years; recurrent UTI (4 UTIs during the past year or at least one during the previous 3 months)
- Exclusion criteria: not reported

Baseline characteristics

- Number (randomised/analysed): 19/10
- Median age (range): 37 years (28 to 44)
- Sex (M/F): all women

Interventions	Intervention group • Cranberry capsules: 400 mg of cranberry solids Control group • Placebo capsule Duration of intervention: each patient had 3 months of active intervention and 3 months of placebo
Outcomes	Outcomes of interest/reported • Symptomatic, culture-verified UTI (no culture threshold reported, but culture performed as bacterial species known)
Notes	Additional information • Letter to the Editor • Method of obtaining urine sample: not reported • Definition of symptomatic UTI • Women notified the physician and then submitted a urine sample (method: not reported) • 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 • Capsules provided by Solaray a health supplements, for-profit organisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
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 intervention arm
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear reporting of results, culture appears the units rather than patients High rate of lost or excluded data from outcome analysis: 9/19

Walker 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	Symptomatic UTI most appropriate outcome
Other bias	Unclear risk	Insufficient information to permit judgement

Wan 2016

Study characteristics

Methods	Study design • Parallel RCT • Power calculation: not reported • ITT analysis: not specified but numbers are correct for analysis within randomised groups Time frame • Duration of study: not reported • Duration of follow-up: 12 months
Participants	Study characteristics • Country: Taiwan • Setting: single centre • Inclusion criteria: uncircumcised boys aged 6 to 18 years with uncomplicated UTI who were patients at the hospital • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (28); control group (27) • Mean age (years): intervention group (9.6); control group (9.7) • Sex (M/F): all boys
Interventions	Intervention group • Cranberry juice: 120 mL/day of commercial brand Control group • Placebo juice: 120 mL/day, diluted tomato juice with sugar Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Symptomatic, culture-verified UTI (> 10^8 CFU/L) • Adverse events
Notes	Additional information • 3rd group reported, but not randomised to intervention, all were circumcised and received placebo juice • Funding source: Chih Kuang Liu (President of U Best Innovative Technology Company, which produces chemicals and other products)

Risk of bias

Wan 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not specifically reported, questionable placebo used (diluted tomato juice)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Specified outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All children completed the study and were included in the analysis Missing data: 0/55
Selective reporting (reporting bias)	Low risk	Most clinically relevant outcome, symptomatic UTI was reported as were adverse events
Other bias	Unclear risk	Uncertainty over how representative these patients are

Wing 2008

Study characteristics	
Methods	Study design • Parallel, 3-arm RCT • Power calculation: no, feasibility pilot • ITT analysis: yes Time frame • Duration of study: June 2005 to July 2007 • Duration of follow-up: until delivery
Participants	Study characteristics • Country: USA • Setting: multicentre (2 sites) • Inclusion criteria: women < 16 weeks gestation presenting for prenatal care • Exclusion criteria: underlying medical conditions (e.g. DM, kidney failure, sickle cell disease, chronic hypertension, CKD); previous or current antimicrobial therapy; known urological abnormalities Baseline characteristics • Number: intervention group 1 (67); intervention group 2 (58); control group (63) • Mean age ± SD (years): intervention group 1 (27.7 ± 5.4); intervention group 2 (25.8 ± 5.6); control group (25.6 ± 5.0) • Sex (M/F): all women

Wing 2008 *(Continued)*

Interventions	Intervention group 1 • Cranberry juice: 240 mL (106 mg PAC) at breakfast, placebo juice at other meals Intervention group 2 • Cranberry drink: 240 mL, 3 times/day (720 mL/day, 318 mg PAC) reduced to twice/day (480 mL, 212 mg PAC) after 52 enrolments because not well tolerated Control group • Placebo: 3 doses/day of matched juice product Duration of intervention: until delivery
Outcomes	Outcomes of interest/reported • Asymptomatic bacteriuria: > 10^8 CFU/L of a single organism and no symptoms • Acute cystitis/symptomatic bacteriuria: > 10^8 CFU/L of single organism and dysuria or frequency or urgency • Pyelonephritis: "urinalysis and/or urine culture" as above, + flank 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	Additional information • Funding source: National Institute of Diabetes, and Digestive and Kidney Diseases (NIDDK) and the National Center for Complementary and Alternative Medicine

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	Intervention 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 Low rate of missing or excluded data from outcome analysis: 0/188
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Low risk	Details suggest free of bias, although selection methods a little unclear

Wing 2015

Study characteristics	
Methods	Study design • Parallel RCT • Power calculation: no, feasibility study • ITT analysis: yes, analysed within randomised groups Time frame • Duration of study: 2009 to 2012 • Duration of follow-up: until birth
Participants	Study characteristics • Country: USA • Setting: multicentre (2 sites) • Inclusion criteria: pregnant with non-anomalous foetuses between 12 and 16 weeks of gestation • Exclusion criteria: DM; kidney failure; sickle cell disease; chronic hypertension; CKD; previous or current antibiotics within 2 weeks Baseline characteristics • Number: intervention group (24); control group (25) • Mean age ± SD (years): intervention group (30.9 ± 6.2); control group (31.0 ± 7.1) • Sex (M/F): all women
Interventions	Intervention group • Cranberry tablets (TheraCran): 4/day (2 at night, 2 in the morning), equivalent to 250 mL juice (4 tablets = 64 to 68 mg PAC) Control group • Placebo tablet: matched for colour and taste intervention duration: 34 to 38 weeks (until delivery of baby)
Outcomes	Outcomes of interest/reported • Asymptomatic bacteriuria • Cystitis • Pyelonephritis • GI intolerance • Nausea • Constipation • Vomiting • Heartburn • Loss of appetite • Diarrhoea • Stomach ache • Taste intolerance • Pathogen in culture • Fetal malformation, Intrauterine growth retardation, oligo- and polyhydramnios • Preterm delivery • Low birth weight (< 2500 g)

Wing 2015 *(Continued)*

- Neonatal intensive care admission
- Apgar score
- Birthweight
- Delivery route
- Compliance

Notes	Additional information • Culture threshold: ≥ 10^8 CFU/L of single pathogen • Funding source: Ocean Spray Cranberries donated cranberry capsules and placebo. National Centre for research resources, National Centre for Advancing translational sciences, NIH • TheraCran, contains dried cranberry powder from Vaccinium macrocarpon Aiton berries. Provided by Ocean Spray Cranberries Inc • Placebo provided by Ocean Spray

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	Stated as concealed and bottles managed by individual not associated with study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as blinded and placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of missing or excluded data from outcome analysis;:16/49
Selective reporting (reporting bias)	Low risk	Many outcomes reported, clinically relevant cystitis and pyelonephritis included
Other bias	Unclear risk	Uncertain about representativeness of sample with many drop outs

AKI: acute kidney injury; BMI: body mass index; CFU: colony forming units; CKD: chronic kidney disease; CSU: catheter specimen of urine; DM: diabetes mellitus; EDSS: Expanded Disability Status Scale; ESBL: extended spectrum beta-lactamase; ESKD: end-stage kidney disease; GFR: glomerular filtration rate; GI: gastrointestinal; HbA1c: glycated haemoglobin; IQR: interquartile range; ITT: intention-to-treat; M/F: male/female; MIBC: muscle-invasive bladder cancer; MS: multiple sclerosis; MSQ: Mental State Questionnaire; MSU: mid-stream urine; NSAID/s: nonsteroidal anti-inflammatory drug/s; PAC: proanthocyanidin; SD: standard deviation; SEM: standard error of the mean; SMP: sulphamethoxazole; TMP: trimethoprim; UTI: urinary tract infection; VUR: vesicoureteral reflux; WBC: white blood cell; WCC: white cell count

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

Study	Reason for exclusion
Amin 2018	Intervention duration < 4 weeks
Barnoiu 2015	Acute intervention study: 5 days
Gunnarsson 2017	Acute intervention study: 5 days
Hamilton 2015	No clinically relevant outcomes: focused on radiation cystitis
Howell 2010	No clinically relevant outcomes: only laboratory measures
Howell 2015	Acute intervention study: < 7 days; single dose given
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
Kaspar 2015	Acute intervention study: 24 hours
Lavigne 2008	No clinically relevant outcomes: only laboratory measures of urine kinetics
Letouzey 2017	Acute intervention study: 10 days
Liu 2019b	Intervention duration < 4 weeks
NCT01079169	Study terminated, no results available
Occhipinti 2016	Acute intervention study: 7 days
Radulescu 2020	Intervention duration < 4 weeks
Russo 2019	Intervention duration < 4 weeks
Sappal 2018	Intervention duration < 4 weeks
Schultz 1984	Intervention < 4 weeks (20 days)
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 classification *[ordered by study ID]*

Cotellese 2023

Methods	Study design • Pilot RCT • Power calculation: not reported • ITT analysis: unclear

Cotellese 2023 *(Continued)*

	Time frame • Duration of study: not reported • Duration of follow-up: variable
Participants	Study characteristics • Country: Italy • Setting: unclear • Inclusion criteria: healthy subjects (BMI < 26) who underwent a non-complicated surgical procedure (i.e. intestinal resection for localized tumours with no metastasis, no occlusion and no complication) and required urinary catheterisation during the perioperative period because of a history of recurrent UTI or risk for UTI. Subjects were defined as at risk if they had reported at least two symptomatic UTIs in the previous year or an episode of UTI in the previous month. During the peri-surgical period, patients also received appropriate antibiotic coverage (cephalosporin as individually appropriate for each subject) • Exclusion criteria: diabetes, any other chronic clinical condition or risk conditions, immune-compromising diseases, co-morbidities, corticosteroids treatment for any reason, mycosis or chemotherapy treatment within 6 months before inclusion, chronic inflammatory bowel disease, and any possible or suspected intolerance or allergy to PS supplements and specifically cranberry Baseline characteristics • Number: intervention group (24); control group (18) • Mean age ± SD (years): unclear • Sex (M/F): unclear

Interventions	Intervention group
	• standardized cranberry extract at the dose of either
	  ◦ 120 mg/day (n = 12)
	  ◦ 240 mg/day (n = 12)
	Control group
	• standard management: (n = 18) or nitrofurantoin administration (n = 22)
	Duration of intervention: 4 weeks

Outcomes	Outcomes of interest/reported • UTI symptoms • Haematuria • Urine bacterial contamination • Recurrence of signs and symptoms • Adverse events • Dropouts
Notes	Additional information • Funding source: unclear

Hakkola 2023

Methods	Study design • Parallel RCT • Power calculation: yes

Hakkola 2023 *(Continued)*

	• ITT analysis: no Time frame • Duration of study: 12 July 2013 to 27 February 2018 • Duration of follow-up: 12 months
Participants	Study characteristics • Country: Finland • Setting: • Inclusion criteria: children aged 1 year and 16 years and a confirmed UTI within 7 days of entry. UTI at entry was defined as fever and/or a local urinary tract symptom, the presence of pyuria or nitrite and a positive urine culture, defined as the growth of > 10^5 CFU/mL of the same pathogen in clean-voided urine or a urine collection pad sample. If the child had two urine samples available, growth of > 10^5 CFU of the same pathogen in one sample and at least $10^{4–5}$ CFU in the other was required • Exclusion criteria: continuous antimicrobial prophylaxis or a severe congenital kidney or urinary tract anomaly as seen in ultrasound Baseline characteristics • Number: intervention group (56); control group (57) • Mean age ± SD (years): intervention group (7.2 ± 4.0); control group (5.2 ± 2.9) • Sex (M/F): intervention group (1/55); control group (1/56)
Interventions	Intervention group • Cranberry-lingonberry juice Control group • Placebo juice Duration of intervention: 6 months
Outcomes	Outcomes of interest/reported • Gut and urinary microbiome • UTI and time to recurrence
Notes	Additional information • Funding source: "This was an investigator-driven academic clinical study. The cranberry-lingonberry juice was donated by Eckes-Granini, Turku, Finland. Eckes-Granini did not participate in the study design, analysis, or writing of the manuscript"

Madhavan 2021

Methods	Study design • Parallel RCT • Power calculation: unclear • ITT analysis: unclear Time frame • Duration of study: 1 February 2017 to 20 July 2017

Madhavan 2021 *(Continued)*

	• Duration of follow-up: 7 days post stent removal
Participants	Study characteristics • Country: India • Setting: single centre • Inclusion criteria: aged 18 to 65 years, who underwent unilateral elective DJ stenting (polyurethane 6 Fr and 26 cm in length) following various urological procedures • Exclusion criteria: unclear Baseline characteristics • Number: intervention group 1 (48); intervention group 2 (46); control group (40) • Medina age, range SD (years): intervention group 1 (39, 21 to 59); intervention group 2 (36, 19 to 64); control group (33, 18 to 55) • Sex (M/F): intervention group 1 (40/8); intervention group 2 (35/11); control group (31/9)
Interventions	Intervention group 1 • Cranberry extract 300 mg and D-mannose 600 mg twice daily throughout the period of the in-dwelling stent Intervention group 2 • Low dose continuous antibiotic prophylaxis: nitrofurantoin 100 mg once daily throughout the period of the indwelling stent Control group • No prophylaxis Duration of intervention: 15 to 45 days (till stent removal)
Outcomes	Outcomes of interest/reported • Stent-related symptoms such as urgency, frequency, dysuria or flank pain and febrile UTI prior to DJ stent removal • Febrile UTI • Adverse events
Notes	Additional information • Funding source: not reported

BMI: body mass index; CFU: colony-forming units; M/F: male/female; PS: Pharma Standard; RCT: randomised controlled trial; SD: standard deviation; UTI: urinary tract infection

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

ACTRN12605000626662

Study name	Cranberry capsules for the prevention of urinary tract infection in an elderly population
Methods	Cross-over RCT
Participants	Elderly people
Interventions	Cranberry tablets compared with placebo
Outcomes	The incidence of UTI in elderly clients

ACTRN12605000626662 *(Continued)*

	To determine the effectiveness of urine clarity tests for diagnostic use in an elderly population To examine the extent to which agitation in clients is associated with UTI
Starting date	1/11/2005 (anticipated)
Contact information	Ms Stacey Hassall Blue Care Research Unit PO Box 1539 Milton BC QLD 4064 Australia Phone +61 7 33773346 Fax +61 7 33773377 Email s.hassall@bluecare.org.au
Notes	Commercial funder: Mayne Consumer Pty Ltd Charity funded: Blue Care Research Unit No publication found, email contact failed

Amador-Mulero 2014

Study name	Effectiveness of red cranberries ingestion on urinary tract infections in pregnant women
Methods	RCT; triple-blind study
Participants	Healthy first-time mothers belonging to these healthcare centers, who are subject to accidental non-probability sampling and randomly assigned to test or control group
Interventions	1 capsule daily cranberry extract (118 mg PAC)
Outcomes	Incidence of UTI
Starting date	
Contact information	L. Amador Mulero - lorenaam82@hotmail.com
Notes	Matronas Profession 2017; 15(2):50-55 (protocol paper)

ISRCTN55813586

Study name	Clinical dosage and effectiveness study of ShanStar® cranberry supplement for prevention and intervention against women's urinary tract infections
Methods	Double-blind, placebo-controlled RCT
Participants	Women
Interventions	ShanStar® cranberry extract 150 mg and 300 mg/day

ISRCTN55813586 *(Continued)*

	Participants in each group are given 3-months supply of pills. Participants are instructed to take one tablet twice a day by mouth for 3 months. At 1, 2 and final 3 months follow-up, they will score the UTI symptoms and provide urine for complete urine analysis and urine culture Total duration of the intervention will be 3 months
Outcomes	Effectiveness of ShanStar® cranberry extract against recurrent UTIs on the basis of symptoms, bacteriuria and pyuria in the urine and urine culture At 1, 2 and 3 months, the participants will return to answer urinary tract symptoms questions and provide urine for complete urinalysis and culture
Starting date	31/01/2011 to 30/04/2011
Contact information	Dr Albert Chang - shadycanyon@yahoo.com
Notes	Completed, awaiting publication of results (last edited 18/03/2011) Have not located a publication, searched Google scholar, PubMed and Google Email contact failed

NCT00100061

Study name	Dose response to cranberry of women with recurrent UTIs
Methods	RCT
Participants	Women with recurrent UTI
Interventions	Cranberry juice
Outcomes	UTI
Starting date	May 2007
Contact information	Principal investigator: Lynn Stothers, Bladder Care Centre, University of British Columbia
Notes	Although due to finish in 2011, the website states 'This study is ongoing, but not recruiting participants'. Possibly same as Stothers 2016, which has only been published as an abstract as of 2017. Email contact failed

NCT00247104

Study name	The use of cranberries in women with preterm premature rupture of membranes
Methods	RCT
Participants	Pregnant with premature rupture of membranes
Interventions	Cranberry, comparison not reported
Outcomes	Length (in days) of the latent period

NCT00247104 *(Continued)*

	Neonatal infection Respiratory distress Admission to NICU (in days) Neonatal complications rate (e.g. NEC, IVH) Maternal infections (uterus, UTI) • Urinary and vaginal flora before and after intervention • Vaginal pH before and after intervention • Amniotic fluid pH before and after intervention
Starting date	May 2007
Contact information	Contact: Arik Tzukert, DMD 00 972 2 6776095 arik@hadassah.org.il Contact: Hadas Lemberg, PhD 00 972 2 6777572 lhadas@hadassah.org.il
Notes	Searched on author names in PubMed, Google and Google scholar. No publication found. No response to emails

NCT03597152

Study name	Nutritional supplementation for recurrent urinary tract infections in women
Methods	Double-blind placebo-controlled cross-over RCT
Participants	250 women, aged 18 to 75 years, who have suffered from 3 to 4 uncomplicated UTI in the past 12 months
Interventions	Dietary supplement: WelTract (contains extracts from hibiscus flowers and cranberry fruit, lactoferrin, D-mannose, and vitamins C and D) compared with placebo
Outcomes	The primary outcome will be time to recurrence of next UTI
Starting date	Estimated starting date 1-8-2020; estimated completion date 31-12-2020
Contact information	Katie O'Brien, Arkansas Urology (katie@arkansasurology.com); Richard Dennis, AmPurity Nutraceuticals, LLC (protocols@att.net)
Notes	Unclear whether recruitment has commenced

NCT05730998

Study name	Cranberry for the prevention of urinary tract infections
Methods	Parallel RCT
Participants	Diabetic women ≥ 70 years
Interventions	Anthocran phytosome or placebo will be taken in the quantity of 1 capsule of 120 mg, once/day, for 6 months

NCT05730998 *(Continued)*

Outcomes	Urinalysis, urine culture
Starting date	1 September 2022
Contact information	Azienda di Servizi alla Persona di Pavia
Notes	

IVH: intraventricular haemorrhage; NEC: necrotizing enterocolitis; NICU: neonatal intensive care unit; PAC: proanthocyanidin; RCT: randomised controlled trial; UTI: urinary tract infection

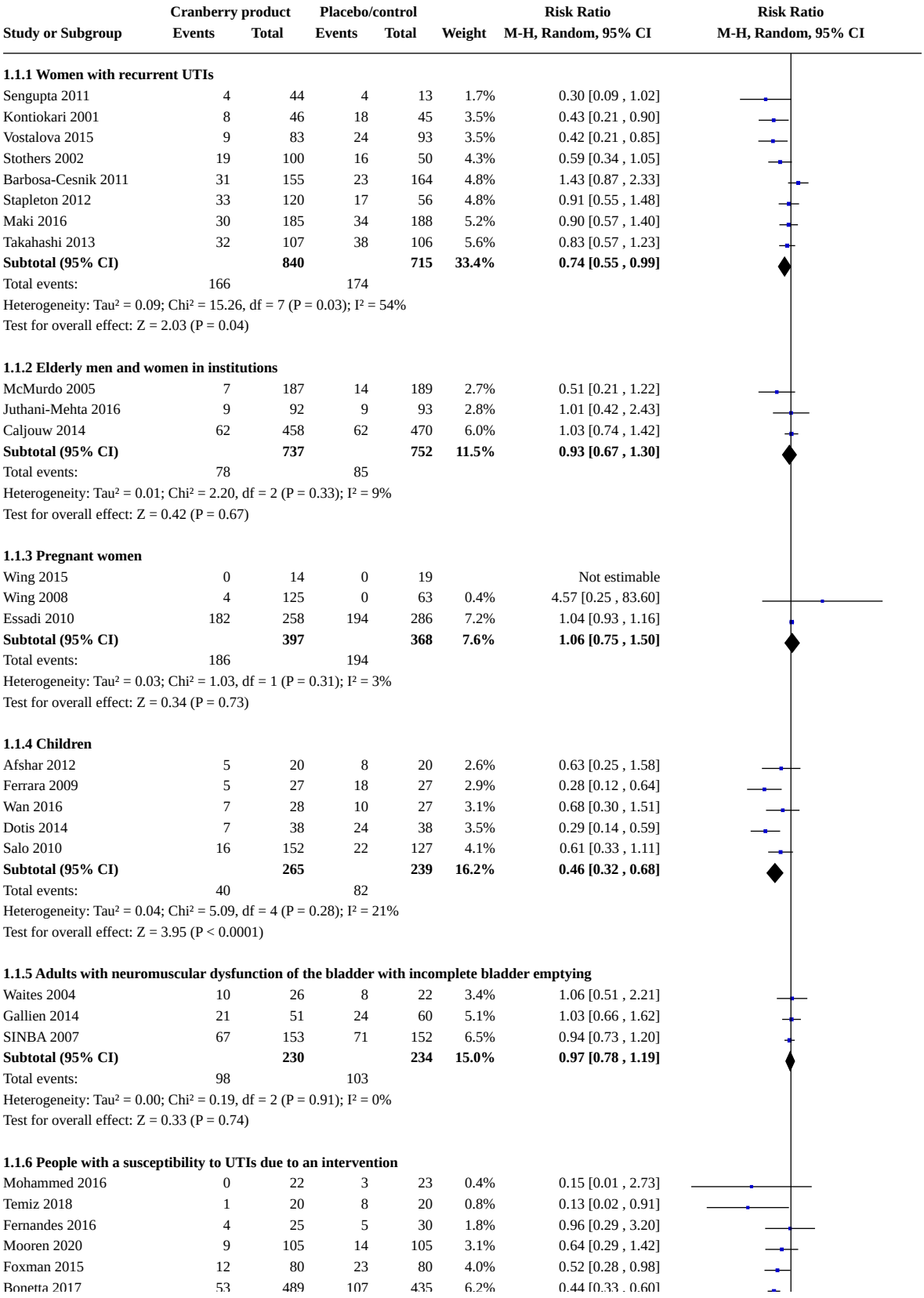
DATA AND ANALYSES

Comparison 1. Any cranberry product versus placebo, control or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Symptomatic UTI: culture-verified UTI	28	6211	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
1.1.1 Women with recurrent UTIs	8	1555	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 0.99]
1.1.2 Elderly men and women in institutions	3	1489	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.67, 1.30]
1.1.3 Pregnant women	3	765	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.50]
1.1.4 Children	5	504	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.32, 0.68]
1.1.5 Adults with neuromuscular dysfunction of the bladder with incomplete bladder emptying	3	464	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]
1.1.6 People with a susceptibility to UTIs due to an intervention	6	1434	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.37, 0.61]
1.2 Clinical UTI: symptoms, no culture	5	1791	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.57, 0.94]
1.2.1 Women with recurrent UTI	2	518	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.94]
1.2.2 Elderly men and women in institutions	2	1113	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.08]
1.2.3 People with a susceptibility to UTI due to interventions	1	160	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.29, 0.86]
1.3 Microbiological UTI: positive culture without known symptoms	3	344	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.1 Elderly men and women in institutions	2	209	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.54, 1.32]
1.3.2 Adults with neuromuscular dysfunction of the bladder with incomplete bladder emptying	1	135	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.66]
1.4 Death	4	1574	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.89, 1.28]
1.5 Gastrointestinal adverse events	10	2166	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.00, 1.77]

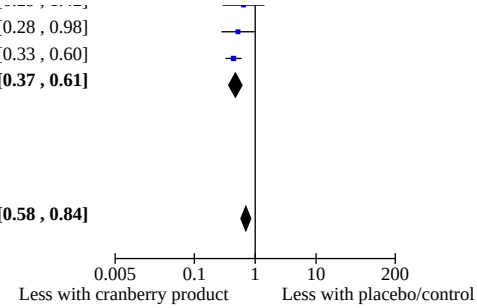
Analysis 1.1. Comparison 1: Any cranberry product versus placebo, control or no treatment, Outcome 1: Symptomatic UTI: culture-verified UTI



Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Women with recurrent UTIs						
Sengupta 2011	4	44	4	13	1.7%	0.30 [0.09 , 1.02]
Kontiokari 2001	8	46	18	45	3.5%	0.43 [0.21 , 0.90]
Vostalova 2015	9	83	24	93	3.5%	0.42 [0.21 , 0.85]
Stothers 2002	19	100	16	50	4.3%	0.59 [0.34 , 1.05]
Barbosa-Cesnik 2011	31	155	23	164	4.8%	1.43 [0.87 , 2.33]
Stapleton 2012	33	120	17	56	4.8%	0.91 [0.55 , 1.48]
Maki 2016	30	185	34	188	5.2%	0.90 [0.57 , 1.40]
Takahashi 2013	32	107	38	106	5.6%	0.83 [0.57 , 1.23]
Subtotal (95% CI)		**840**		**715**	**33.4%**	**0.74 [0.55 , 0.99]**
Total events:	166		174			
Heterogeneity: Tau² = 0.09; Chi² = 15.26, df = 7 (P = 0.03); I² = 54%						
Test for overall effect: Z = 2.03 (P = 0.04)						
1.1.2 Elderly men and women in institutions						
McMurdo 2005	7	187	14	189	2.7%	0.51 [0.21 , 1.22]
Juthani-Mehta 2016	9	92	9	93	2.8%	1.01 [0.42 , 2.43]
Caljouw 2014	62	458	62	470	6.0%	1.03 [0.74 , 1.42]
Subtotal (95% CI)		**737**		**752**	**11.5%**	**0.93 [0.67 , 1.30]**
Total events:	78		85			
Heterogeneity: Tau² = 0.01; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%						
Test for overall effect: Z = 0.42 (P = 0.67)						
1.1.3 Pregnant women						
Wing 2015	0	14	0	19		Not estimable
Wing 2008	4	125	0	63	0.4%	4.57 [0.25 , 83.60]
Essadi 2010	182	258	194	286	7.2%	1.04 [0.93 , 1.16]
Subtotal (95% CI)		**397**		**368**	**7.6%**	**1.06 [0.75 , 1.50]**
Total events:	186		194			
Heterogeneity: Tau² = 0.03; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.1.4 Children						
Afshar 2012	5	20	8	20	2.6%	0.63 [0.25 , 1.58]
Ferrara 2009	5	27	18	27	2.9%	0.28 [0.12 , 0.64]
Wan 2016	7	28	10	27	3.1%	0.68 [0.30 , 1.51]
Dotis 2014	7	38	24	38	3.5%	0.29 [0.14 , 0.59]
Salo 2010	16	152	22	127	4.1%	0.61 [0.33 , 1.11]
Subtotal (95% CI)		**265**		**239**	**16.2%**	**0.46 [0.32 , 0.68]**
Total events:	40		82			
Heterogeneity: Tau² = 0.04; Chi² = 5.09, df = 4 (P = 0.28); I² = 21%						
Test for overall effect: Z = 3.95 (P < 0.0001)						
1.1.5 Adults with neuromuscular dysfunction of the bladder with incomplete bladder emptying						
Waites 2004	10	26	8	22	3.4%	1.06 [0.51 , 2.21]
Gallien 2014	21	51	24	60	5.1%	1.03 [0.66 , 1.62]
SINBA 2007	67	153	71	152	6.5%	0.94 [0.73 , 1.20]
Subtotal (95% CI)		**230**		**234**	**15.0%**	**0.97 [0.78 , 1.19]**
Total events:	98		103			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.1.6 People with a susceptibility to UTIs due to an intervention						
Mohammed 2016	0	22	3	23	0.4%	0.15 [0.01 , 2.73]
Temiz 2018	1	20	8	20	0.8%	0.13 [0.02 , 0.91]
Fernandes 2016	4	25	5	30	1.8%	0.96 [0.29 , 3.20]
Mooren 2020	9	105	14	105	3.1%	0.64 [0.29 , 1.42]
Foxman 2015	12	80	23	80	4.0%	0.52 [0.28 , 0.98]
Bonetta 2017	53	489	107	435	6.2%	0.44 [0.33 , 0.60]

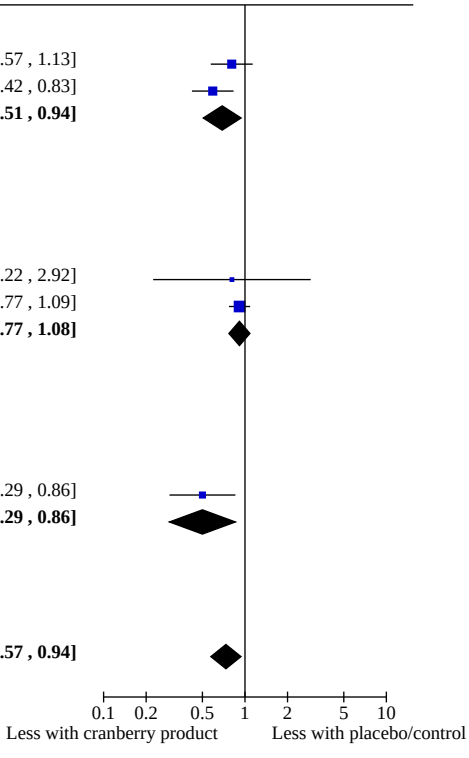
Analysis 1.1. (Continued)

Foxman 2015	12	80	23	80	4.0%	0.52 [0.28 , 0.98]
Bonetta 2017	53	489	107	435	6.2%	0.44 [0.33 , 0.60]
Subtotal (95% CI)		**741**		**693**	**16.2%**	**0.47 [0.37 , 0.61]**
Total events:	79		160			
Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 5 (P = 0.47); I² = 0%						
Test for overall effect: Z = 5.90 (P < 0.00001)						
Total (95% CI)		**3210**		**3001**	**100.0%**	**0.70 [0.58 , 0.84]**
Total events:	647		798			
Heterogeneity: Tau² = 0.12; Chi² = 83.48, df = 26 (P < 0.00001); I² = 69%						
Test for overall effect: Z = 3.78 (P = 0.0002)						
Test for subgroup differences: Chi² = 30.53, df = 5 (P < 0.0001), I² = 83.6%						



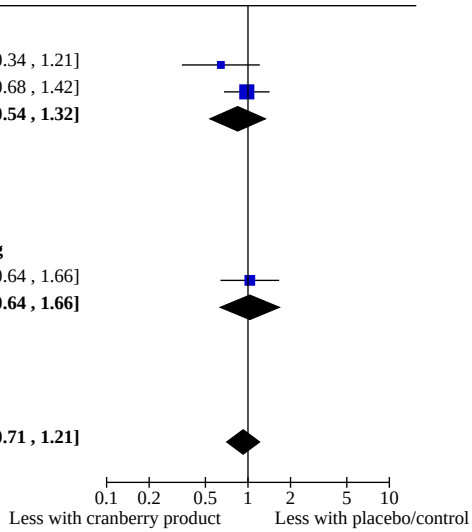
Analysis 1.2. Comparison 1: Any cranberry product versus placebo, control or no treatment, Outcome 2: Clinical UTI: symptoms, no culture

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Women with recurrent UTI						
Babar 2021	31	72	39	73	23.5%	0.81 [0.57 , 1.13]
Maki 2016	39	185	67	188	23.6%	0.59 [0.42 , 0.83]
Subtotal (95% CI)		**257**		**261**	**47.1%**	**0.69 [0.51 , 0.94]**
Total events:	70		106			
Heterogeneity: Tau² = 0.02; Chi² = 1.64, df = 1 (P = 0.20); I² = 39%						
Test for overall effect: Z = 2.36 (P = 0.02)						
1.2.2 Elderly men and women in institutions						
Juthani-Mehta 2016	4	92	5	93	3.4%	0.81 [0.22 , 2.92]
Caljouw 2014	157	458	176	470	35.5%	0.92 [0.77 , 1.09]
Subtotal (95% CI)		**550**		**563**	**38.9%**	**0.91 [0.77 , 1.08]**
Total events:	161		181			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.2.3 People with a susceptibility to UTI due to interventions						
Foxman 2015	15	80	30	80	14.0%	0.50 [0.29 , 0.86]
Subtotal (95% CI)		**80**		**80**	**14.0%**	**0.50 [0.29 , 0.86]**
Total events:	15		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.53 (P = 0.01)						
Total (95% CI)		**887**		**904**	**100.0%**	**0.73 [0.57 , 0.94]**
Total events:	246		317			
Heterogeneity: Tau² = 0.04; Chi² = 8.40, df = 4 (P = 0.08); I² = 52%						
Test for overall effect: Z = 2.48 (P = 0.01)						
Test for subgroup differences: Chi² = 6.00, df = 2 (P = 0.05), I² = 66.7%						



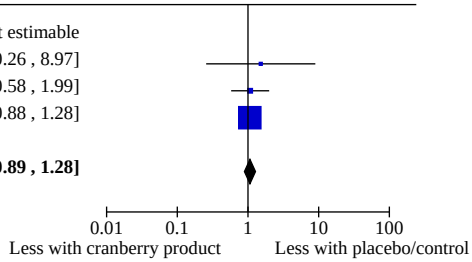
Analysis 1.3. Comparison 1: Any cranberry product versus placebo, control or no treatment, Outcome 3: Microbiological UTI: positive culture without known symptoms

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Elderly men and women in institutions						
Avorn 1994	12	72	21	81	17.6%	0.64 [0.34 , 1.21]
Juthani-Mehta 2010	27	39	12	17	51.4%	0.98 [0.68 , 1.42]
Subtotal (95% CI)		**111**		**98**	**69.0%**	**0.85 [0.54 , 1.32]**
Total events:	39		33			
Heterogeneity: Tau² = 0.04; Chi² = 1.63, df = 1 (P = 0.20); I² = 39%						
Test for overall effect: Z = 0.73 (P = 0.46)						
1.3.2 Adults with neuromuscular dysfunction of the bladder with incomplete bladder emptying						
McGuiness 2002	21	62	24	73	31.0%	1.03 [0.64 , 1.66]
Subtotal (95% CI)		**62**		**73**	**31.0%**	**1.03 [0.64 , 1.66]**
Total events:	21		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**173**		**171**	**100.0%**	**0.92 [0.71 , 1.21]**
Total events:	60		57			
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%						



Analysis 1.4. Comparison 1: Any cranberry product versus placebo, control or no treatment, Outcome 4: Death

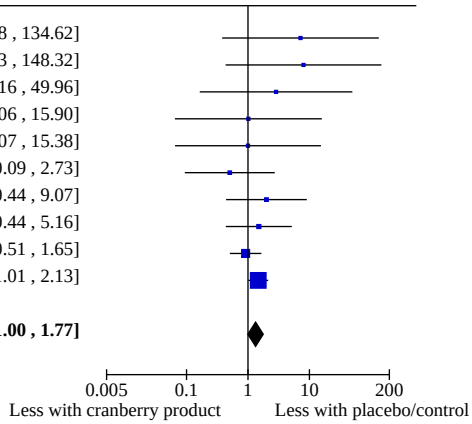
Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bruyere 2019	0	42	0	43		Not estimable
McMurdo 2005	3	187	2	189	1.0%	1.52 [0.26 , 8.97]
Juthani-Mehta 2016	17	92	16	93	8.4%	1.07 [0.58 , 1.99]
Caljouw 2014	150	458	145	470	90.6%	1.06 [0.88 , 1.28]
Total (95% CI)		**779**		**795**	**100.0%**	**1.07 [0.89 , 1.28]**
Total events:	170		163			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						



Analysis 1.5. Comparison 1: Any cranberry product versus placebo, control or no treatment, Outcome 5: Gastrointestinal adverse events

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Koradia 2019	3	44	0	45	1.0%	7.16 [0.38 , 134.62]
Bonetta 2017	4	489	0	435	1.0%	8.01 [0.43 , 148.32]
Sengupta 2011	4	43	0	13	1.0%	2.86 [0.16 , 49.96]
Babar 2021	1	72	1	73	1.1%	1.01 [0.06 , 15.90]
Singh 2016	1	36	1	36	1.1%	1.00 [0.07 , 15.38]
McMurdo 2005	2	187	4	189	2.9%	0.51 [0.09 , 2.73]
Stothers 2002	8	100	2	50	3.6%	2.00 [0.44 , 9.07]
Mooren 2020	6	105	4	105	5.4%	1.50 [0.44 , 5.16]
Gallien 2014	14	51	18	60	23.7%	0.92 [0.51 , 1.65]
Wing 2015	13	14	12	19	59.3%	1.47 [1.01 , 2.13]
Total (95% CI)		**1141**		**1025**	**100.0%**	**1.33 [1.00 , 1.77]**
Total events:	56		42			

Heterogeneity: Tau² = 0.00; Chi² = 6.48, df = 9 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Not applicable

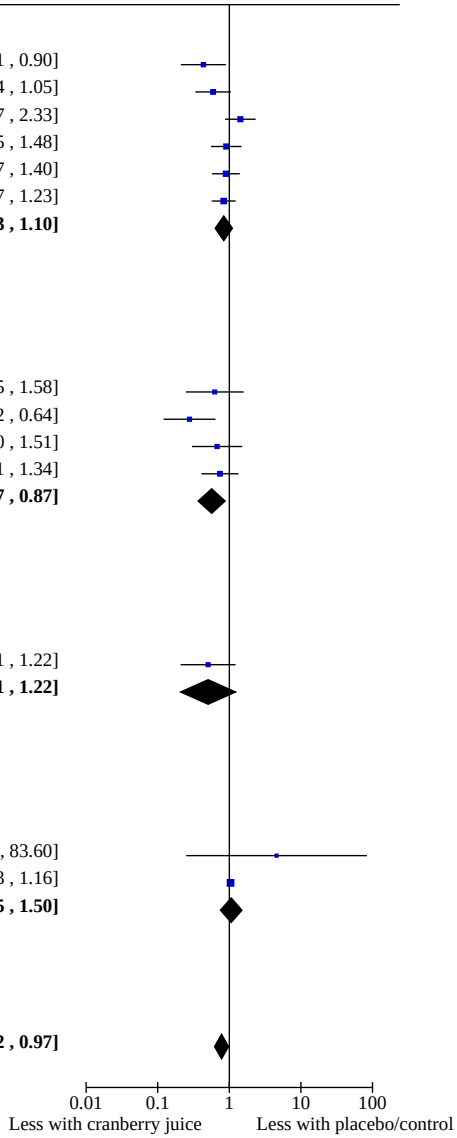


Comparison 2. Cranberry juice or syrup versus placebo or control

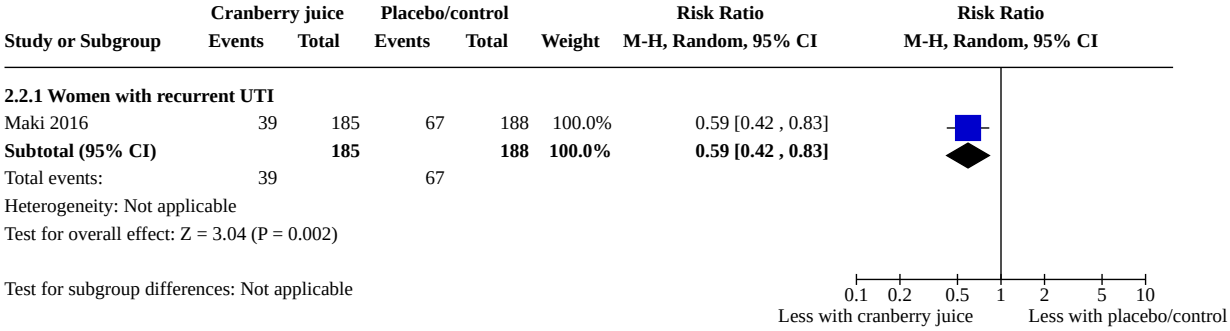
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Symptomatic UTI: culture-verified UTI	13	2831	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
2.1.1 Women with recurrent UTIs	6	1322	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.63, 1.10]
2.1.2 Children	4	401	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.37, 0.87]
2.1.3 Elderly men and women in institutions	1	376	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.21, 1.22]
2.1.4 Pregnant women	2	732	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.50]
2.2 Clinical UTI: symptoms, no culture	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Women with recurrent UTI	1	373	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.42, 0.83]

Analysis 2.1. Comparison 2: Cranberry juice or syrup versus placebo or control, Outcome 1: Symptomatic UTI: culture-verified UTI

Study or Subgroup	Cranberry juice Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Women with recurrent UTIs						
Kontiokari 2001	8	46	18	45	6.2%	0.43 [0.21 , 0.90]
Stothers 2002	19	100	16	50	8.2%	0.59 [0.34 , 1.05]
Barbosa-Cesnik 2011	31	155	23	164	9.5%	1.43 [0.87 , 2.33]
Stapleton 2012	33	120	17	56	9.5%	0.91 [0.55 , 1.48]
Maki 2016	30	185	34	188	10.3%	0.90 [0.57 , 1.40]
Takahashi 2013	32	107	38	106	11.5%	0.83 [0.57 , 1.23]
Subtotal (95% CI)		**713**		**609**	**55.3%**	**0.84 [0.63 , 1.10]**
Total events:	153		146			
Heterogeneity: Tau² = 0.05; Chi² = 9.17, df = 5 (P = 0.10); I² = 45%						
Test for overall effect: Z = 1.27 (P = 0.21)						
2.1.2 Children						
Afshar 2012	5	20	8	20	4.4%	0.63 [0.25 , 1.58]
Ferrara 2009	5	27	18	27	5.1%	0.28 [0.12 , 0.64]
Wan 2016	7	28	10	27	5.4%	0.68 [0.30 , 1.51]
Salo 2010	16	125	22	127	7.9%	0.74 [0.41 , 1.34]
Subtotal (95% CI)		**200**		**201**	**22.7%**	**0.57 [0.37 , 0.87]**
Total events:	33		58			
Heterogeneity: Tau² = 0.04; Chi² = 3.79, df = 3 (P = 0.29); I² = 21%						
Test for overall effect: Z = 2.57 (P = 0.01)						
2.1.3 Elderly men and women in institutions						
McMurdo 2005	7	187	14	189	4.7%	0.51 [0.21 , 1.22]
Subtotal (95% CI)		**187**		**189**	**4.7%**	**0.51 [0.21 , 1.22]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
2.1.4 Pregnant women						
Wing 2008	4	125	0	63	0.6%	4.57 [0.25 , 83.60]
Essadi 2010	182	258	194	286	16.7%	1.04 [0.93 , 1.16]
Subtotal (95% CI)		**383**		**349**	**17.3%**	**1.06 [0.75 , 1.50]**
Total events:	186		194			
Heterogeneity: Tau² = 0.03; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)		**1483**		**1348**	**100.0%**	**0.78 [0.62 , 0.97]**
Total events:	379		412			
Heterogeneity: Tau² = 0.08; Chi² = 28.06, df = 12 (P = 0.005); I² = 57%						
Test for overall effect: Z = 2.18 (P = 0.03)						
Test for subgroup differences: Chi² = 6.12, df = 3 (P = 0.11), I² = 51.0%						



Analysis 2.2. Comparison 2: Cranberry juice or syrup versus placebo or control, Outcome 2: Clinical UTI: symptoms, no culture

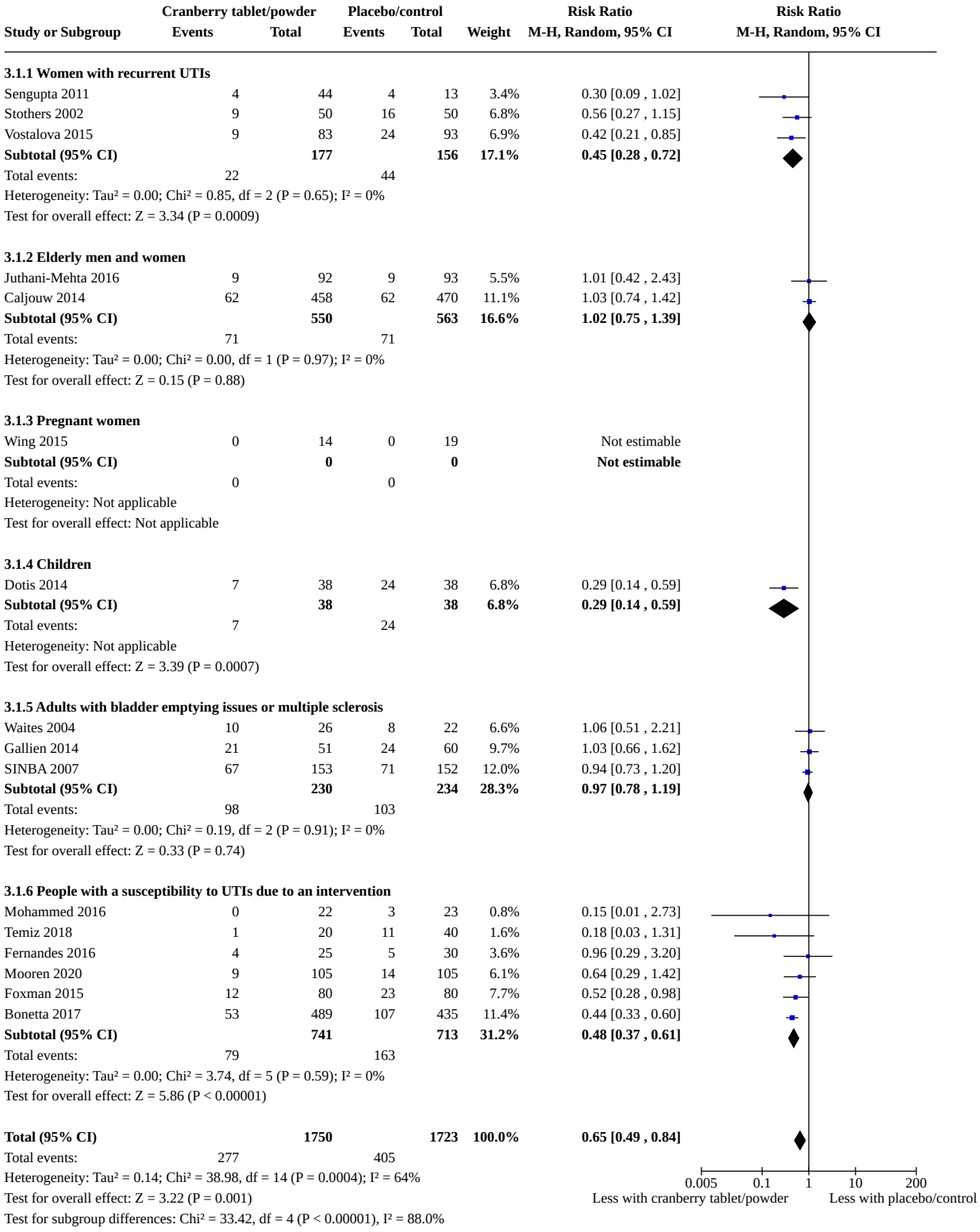


Comparison 3. Cranberry tablets or powder versus placebo or control

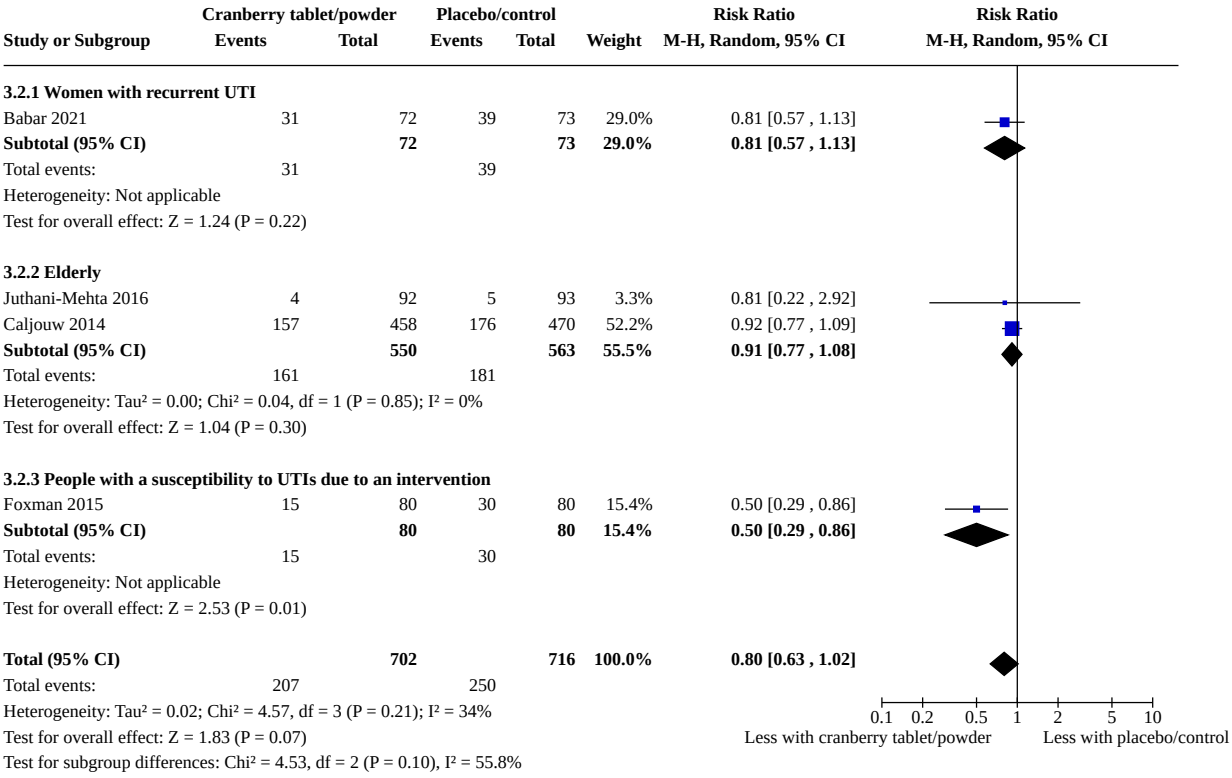
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptomatic UTI: culture-verified UTI	16	3473	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.84]
3.1.1 Women with recurrent UTIs	3	333	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.28, 0.72]
3.1.2 Elderly men and women	2	1113	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.75, 1.39]
3.1.3 Pregnant women	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.1.4 Children	1	76	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.14, 0.59]
3.1.5 Adults with bladder emptying issues or multiple sclerosis	3	464	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]
3.1.6 People with a susceptibility to UTIs due to an intervention	6	1454	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.37, 0.61]
3.2 Clinical UTI: symptoms, no culture	4	1418	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.02]
3.2.1 Women with recurrent UTI	1	145	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.57, 1.13]
3.2.2 Elderly	2	1113	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.08]
3.2.3 People with a susceptibility to UTIs due to an intervention	1	160	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.29, 0.86]
3.3 Microbiological UTI: positive culture without known symptoms	2	191	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 Elderly men and women in institutions	1	56	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.42]
3.3.2 Adults with neuromuscular dysfunction of the bladder with incomplete bladder emptying	1	135	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.66]

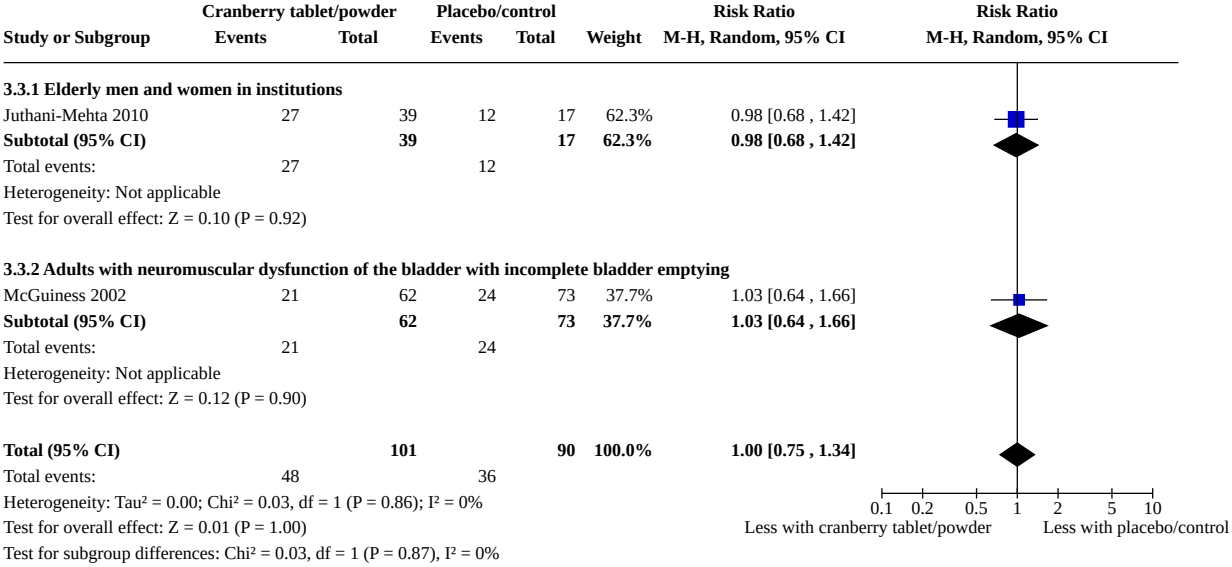
Analysis 3.1. Comparison 3: Cranberry tablets or powder versus placebo or control, Outcome 1: Symptomatic UTI: culture-verified UTI



Analysis 3.2. Comparison 3: Cranberry tablets or powder versus placebo or control, Outcome 2: Clinical UTI: symptoms, no culture



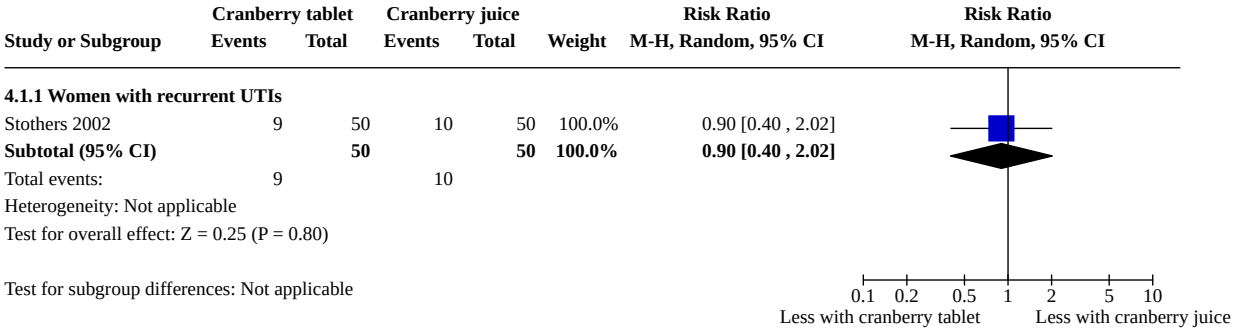
Analysis 3.3. Comparison 3: Cranberry tablets or powder versus placebo or control, Outcome 3: Microbiological UTI: positive culture without known symptoms



Comparison 4. Cranberry juice versus cranberry tablets or powder

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Symptomatic UTI: culture-verified UTI	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 Women with recurrent UTIs	1	100	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.40, 2.02]

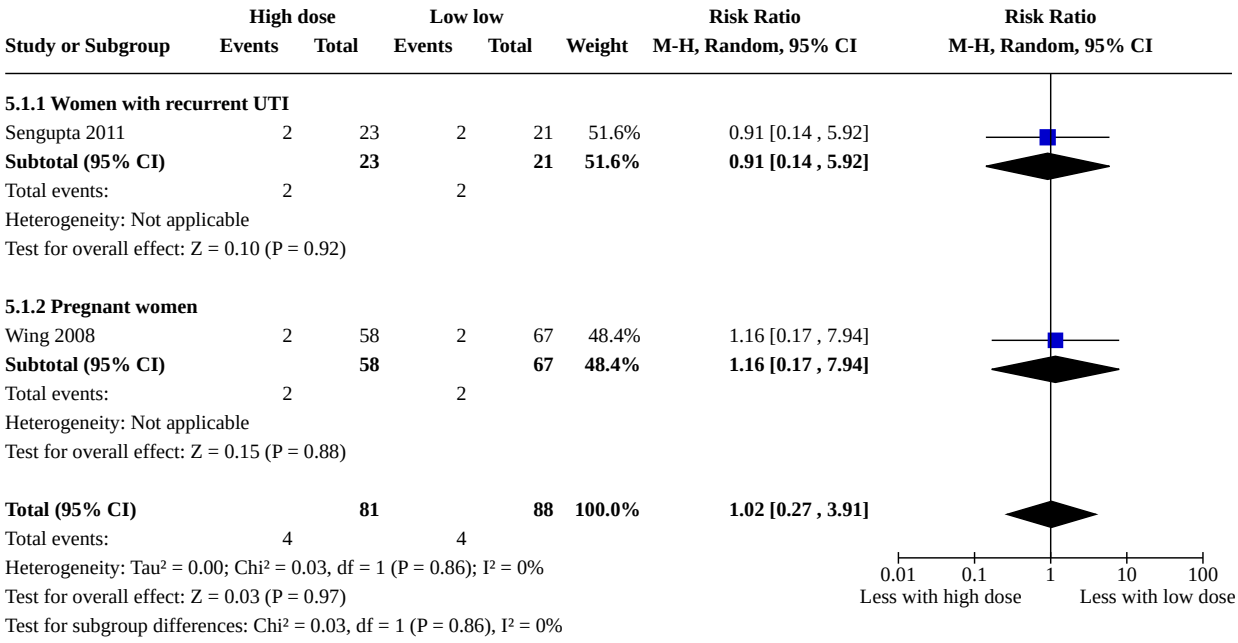
Analysis 4.1. Comparison 4: Cranberry juice versus cranberry tablets or powder, Outcome 1: Symptomatic UTI: culture-verified UTI



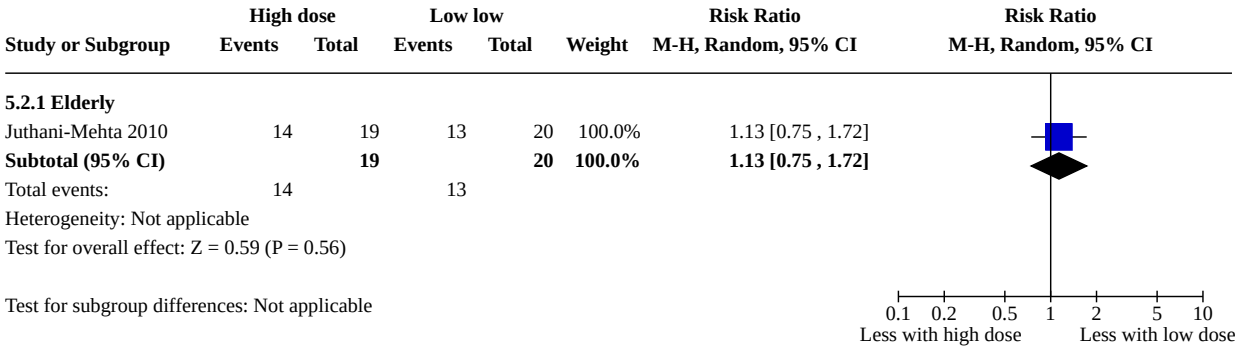
Comparison 5. Cranberry dose: high versus low

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Symptomatic UTI: culture-verified UTI	2	169	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.27, 3.91]
5.1.1 Women with recurrent UTI	1	44	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.14, 5.92]
5.1.2 Pregnant women	1	125	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.17, 7.94]
5.2 Microbiological UTI: positive culture without known symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.2.1 Elderly	1	39	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.75, 1.72]

Analysis 5.1. Comparison 5: Cranberry dose: high versus low, Outcome 1: Symptomatic UTI: culture-verified UTI



Analysis 5.2. Comparison 5: Cranberry dose: high versus low, Outcome 2: Microbiological UTI: positive culture without known symptoms

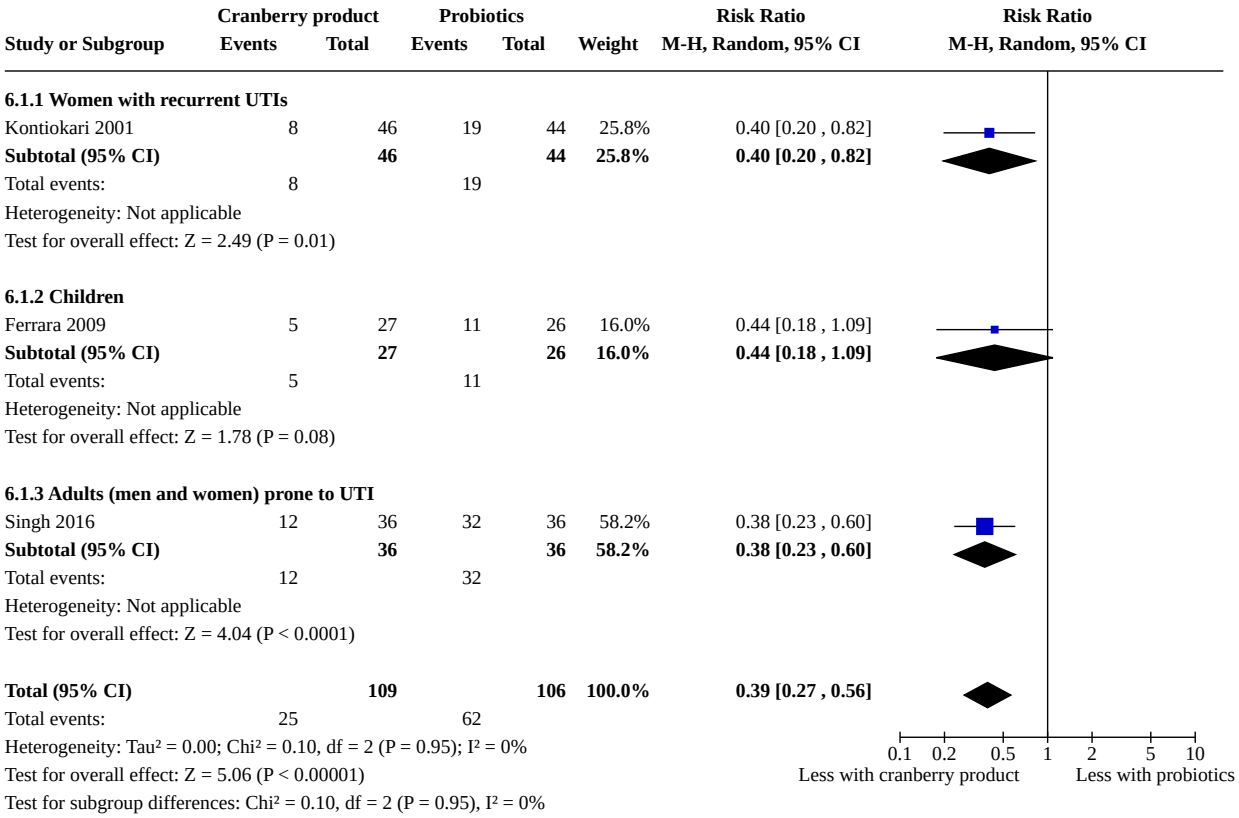


Comparison 6. Cranberry product versus probiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Symptomatic UTI: culture-verified UTI	3	215	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.27, 0.56]
6.1.1 Women with recurrent UTIs	1	90	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.20, 0.82]
6.1.2 Children	1	53	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.18, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.3 Adults (men and women) prone to UTI	1	72	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.23, 0.60]

Analysis 6.1. Comparison 6: Cranberry product versus probiotics, Outcome 1: Symptomatic UTI: culture-verified UTI



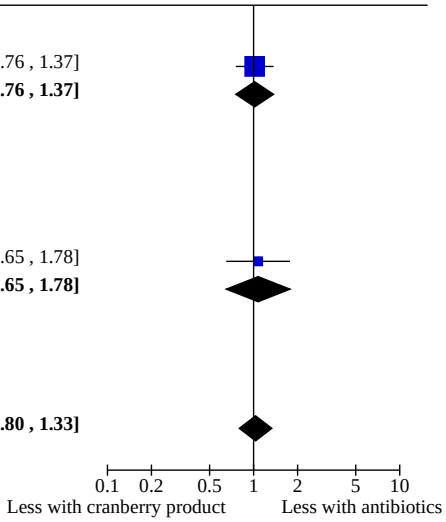
Comparison 7. Cranberry product versus antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Symptomatic UTI: culture-verified UTI	2	385	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.80, 1.33]
7.1.1 Women with recurrent UTI	1	199	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.37]
7.1.2 Children	1	186	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.65, 1.78]
7.2 Clinical UTI: symptoms, no culture	2	336	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.79, 2.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2.1 Women with recurrent UTIs	2	336	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.79, 2.14]

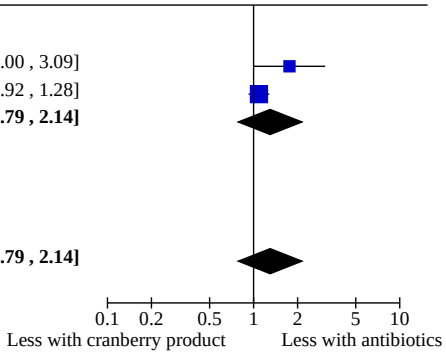
Analysis 7.1. Comparison 7: Cranberry product versus antibiotics, Outcome 1: Symptomatic UTI: culture-verified UTI

Study or Subgroup	Cranberry products Events	Total	Antibiotics Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Women with recurrent UTI						
NAPRUTI 2011	49	104	44	95	74.1%	1.02 [0.76 , 1.37]
Subtotal (95% CI)		**104**		**95**	**74.1%**	**1.02 [0.76 , 1.37]**
Total events:	49		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
7.1.2 Children						
Uberos 2012	19	72	28	114	25.9%	1.07 [0.65 , 1.78]
Subtotal (95% CI)		**72**		**114**	**25.9%**	**1.07 [0.65 , 1.78]**
Total events:	19		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**176**		**209**	**100.0%**	**1.03 [0.80 , 1.33]**
Total events:	68		72			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%						



Analysis 7.2. Comparison 7: Cranberry product versus antibiotics, Outcome 2: Clinical UTI: symptoms, no culture

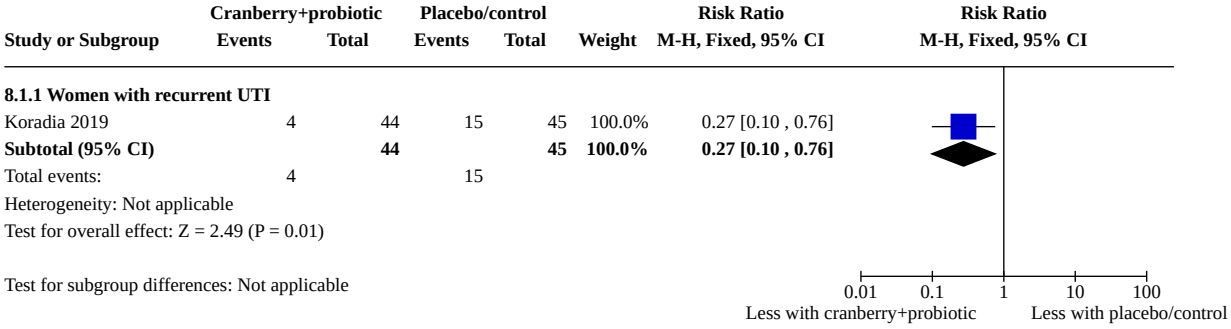
Study or Subgroup	Cranberry products Events	Total	Antibiotics Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 Women with recurrent UTIs						
McMurdo 2009	25	69	14	68	36.6%	1.76 [1.00 , 3.09]
NAPRUTI 2011	81	104	68	95	63.4%	1.09 [0.92 , 1.28]
Subtotal (95% CI)		**173**		**163**	**100.0%**	**1.30 [0.79 , 2.14]**
Total events:	106		82			
Heterogeneity: Tau² = 0.10; Chi² = 3.16, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**173**		**163**	**100.0%**	**1.30 [0.79 , 2.14]**
Total events:	106		82			
Heterogeneity: Tau² = 0.10; Chi² = 3.16, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Not applicable						



Comparison 8. Cranberry + probiotic tablet versus placebo or control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Symptomatic UTI: culture-verified UTI	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1.1 Women with recurrent UTI	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.10, 0.76]

Analysis 8.1. Comparison 8: Cranberry + probiotic tablet versus placebo or control, Outcome 1: Symptomatic UTI: culture-verified UTI



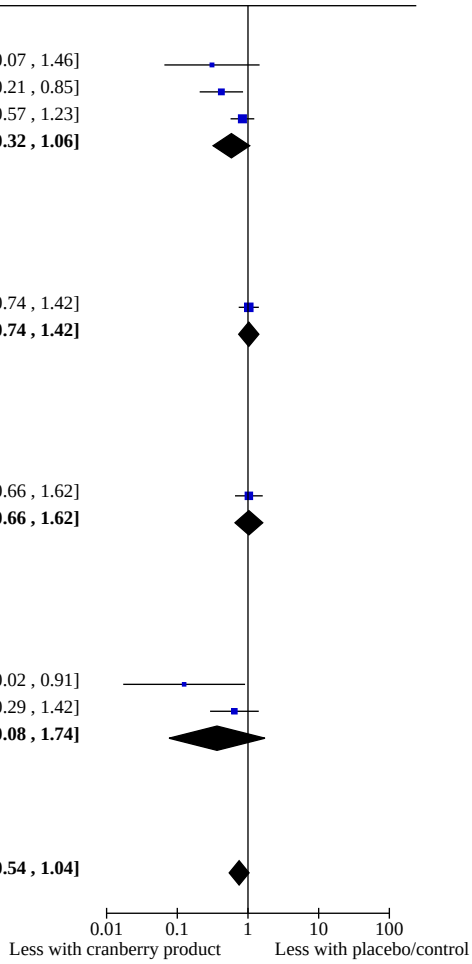
Comparison 9. Cranberry product versus placebo or control: PAC dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Symptomatic UTI: culture-verified UTI (low dose PAC < 40 mg/day)	7	1712	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.54, 1.04]
9.1.1 Women with recurrent UTIs	3	423	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.06]
9.1.2 Elderly men and women	1	928	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.74, 1.42]
9.1.3 Adults with neuropathy or neuropathic bladders	1	111	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.66, 1.62]
9.1.4 People with a susceptibility to UTIs due to an intervention	2	250	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.08, 1.74]
9.2 Symptomatic UTI: culture-verified UTI (moderate dose PAC 40 to 80 mg/day)	3	263	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.13, 3.28]
9.2.1 Elderly men and women	1	185	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.42, 2.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2.2 Pregnant women	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
9.2.3 People with a susceptibility to UTIs due to an intervention	1	45	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.73]
9.3 Symptomatic UTI: culture-verified UTI (high dose PAC > 80 mg/day)	2	507	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.91, 2.39]
9.3.1 Women with recurrent UTIs	1	319	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.87, 2.33]
9.3.2 Pregnant women	1	188	Risk Ratio (M-H, Random, 95% CI)	4.57 [0.25, 83.60]

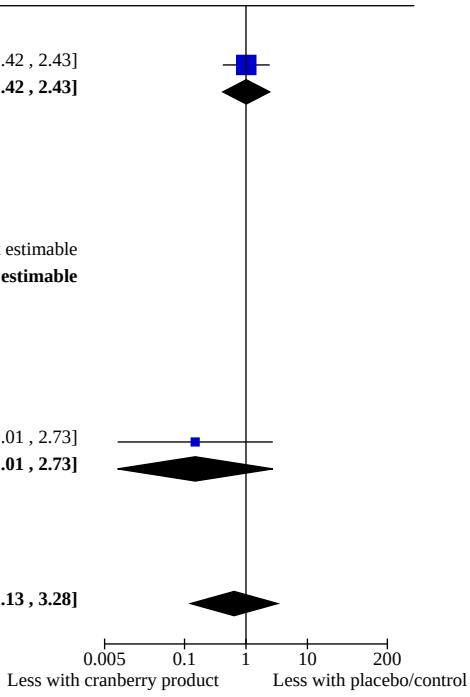
Analysis 9.1. Comparison 9: Cranberry product versus placebo or control: PAC dose, Outcome 1: Symptomatic UTI: culture-verified UTI (low dose PAC < 40 mg/day)

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Women with recurrent UTIs						
Sengupta 2011	2	21	4	13	3.9%	0.31 [0.07 , 1.46]
Vostalova 2015	9	83	24	93	13.0%	0.42 [0.21 , 0.85]
Takahashi 2013	32	107	38	106	23.2%	0.83 [0.57 , 1.23]
Subtotal (95% CI)		**211**		**212**	**40.1%**	**0.58 [0.32 , 1.06]**
Total events:	43		66			
Heterogeneity: Tau² = 0.13; Chi² = 3.94, df = 2 (P = 0.14); I² = 49%						
Test for overall effect: Z = 1.78 (P = 0.08)						
9.1.2 Elderly men and women						
Caljouw 2014	62	458	62	470	25.5%	1.03 [0.74 , 1.42]
Subtotal (95% CI)		**458**		**470**	**25.5%**	**1.03 [0.74 , 1.42]**
Total events:	62		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
9.1.3 Adults with neuropathy or neuropathic bladders						
Gallien 2014	21	51	24	60	20.7%	1.03 [0.66 , 1.62]
Subtotal (95% CI)		**51**		**60**	**20.7%**	**1.03 [0.66 , 1.62]**
Total events:	21		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
9.1.4 People with a susceptibility to UTIs due to an intervention						
Temiz 2018	1	20	8	20	2.5%	0.13 [0.02 , 0.91]
Mooren 2020	9	105	14	105	11.2%	0.64 [0.29 , 1.42]
Subtotal (95% CI)		**125**		**125**	**13.7%**	**0.36 [0.08 , 1.74]**
Total events:	10		22			
Heterogeneity: Tau² = 0.81; Chi² = 2.36, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 1.27 (P = 0.21)						
Total (95% CI)		**845**		**867**	**100.0%**	**0.75 [0.54 , 1.04]**
Total events:	136		174			
Heterogeneity: Tau² = 0.08; Chi² = 11.64, df = 6 (P = 0.07); I² = 48%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 4.28, df = 3 (P = 0.23), I² = 29.8%						



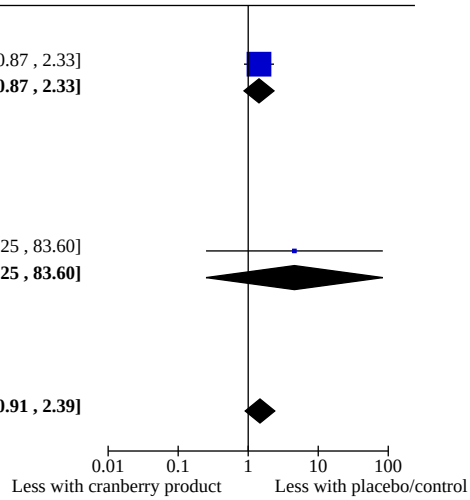
Analysis 9.2. Comparison 9: Cranberry product versus placebo or control: PAC dose, Outcome 2: Symptomatic UTI: culture-verified UTI (moderate dose PAC 40 to 80 mg/day)

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
9.2.1 Elderly men and women						
Juthani-Mehta 2016	9	92	9	93	76.2%	1.01 [0.42 , 2.43]
Subtotal (95% CI)		**92**		**93**	**76.2%**	**1.01 [0.42 , 2.43]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
9.2.2 Pregnant women						
Wing 2015	0	14	0	19		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.2.3 People with a susceptibility to UTIs due to an intervention						
Mohammed 2016	0	22	3	23	23.8%	0.15 [0.01 , 2.73]
Subtotal (95% CI)		**22**		**23**	**23.8%**	**0.15 [0.01 , 2.73]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**128**		**135**	**100.0%**	**0.64 [0.13 , 3.28]**
Total events:	9		12			
Heterogeneity: Tau² = 0.71; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%						
Test for overall effect: Z = 0.53 (P = 0.59)						
Test for subgroup differences: Chi² = 1.53, df = 1 (P = 0.22), I² = 34.5%						



Analysis 9.3. Comparison 9: Cranberry product versus placebo or control: PAC dose, Outcome 3: Symptomatic UTI: culture-verified UTI (high dose PAC > 80 mg/day)

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
9.3.1 Women with recurrent UTIs						
Barbosa-Cesnik 2011	31	155	23	164	97.2%	1.43 [0.87 , 2.33]
Subtotal (95% CI)		**155**		**164**	**97.2%**	**1.43 [0.87 , 2.33]**
Total events:	31		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
9.3.2 Pregnant women						
Wing 2008	4	125	0	63	2.8%	4.57 [0.25 , 83.60]
Subtotal (95% CI)		**125**		**63**	**2.8%**	**4.57 [0.25 , 83.60]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**280**		**227**	**100.0%**	**1.47 [0.91 , 2.39]**
Total events:	35		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%						

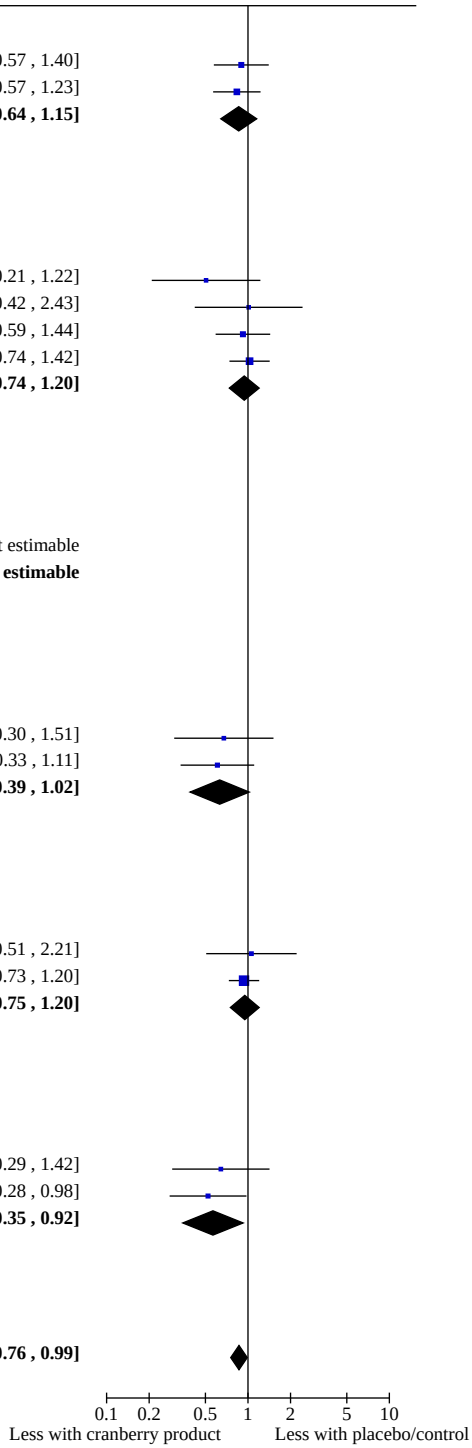


Comparison 10. Cranberry product versus placebo or control: sponsor type

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Symptomatic UTI: culture-verified UTI (commercial involvement)	13	3202	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.76, 0.99]
10.1.1 Women with recurrent UTIs	2	586	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.15]
10.1.2 Elderly men and women	4	1526	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.20]
10.1.3 Pregnant women	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.1.4 Children	2	334	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.02]
10.1.5 Adults with neuropathy or neuropathic bladders	2	353	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.20]
10.1.6 People with a susceptibility to UTIs due to an intervention	2	370	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.35, 0.92]
10.2 Symptomatic UTI: culture-verified UTI (no commercial involvement)	13	2753	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.86]
10.2.1 Women with recurrent UTIs	5	819	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.38, 1.14]
10.2.2 Elderly men and women	1	376	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.21, 1.22]
10.2.3 Pregnant women	1	188	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.06, 36.88]
10.2.4 Children	1	40	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.25, 1.58]
10.2.5 Adults with neuropathy etc	1	111	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.66, 1.62]
10.2.6 People with a susceptibility to UTI due to an intervention	4	1219	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.34, 0.59]

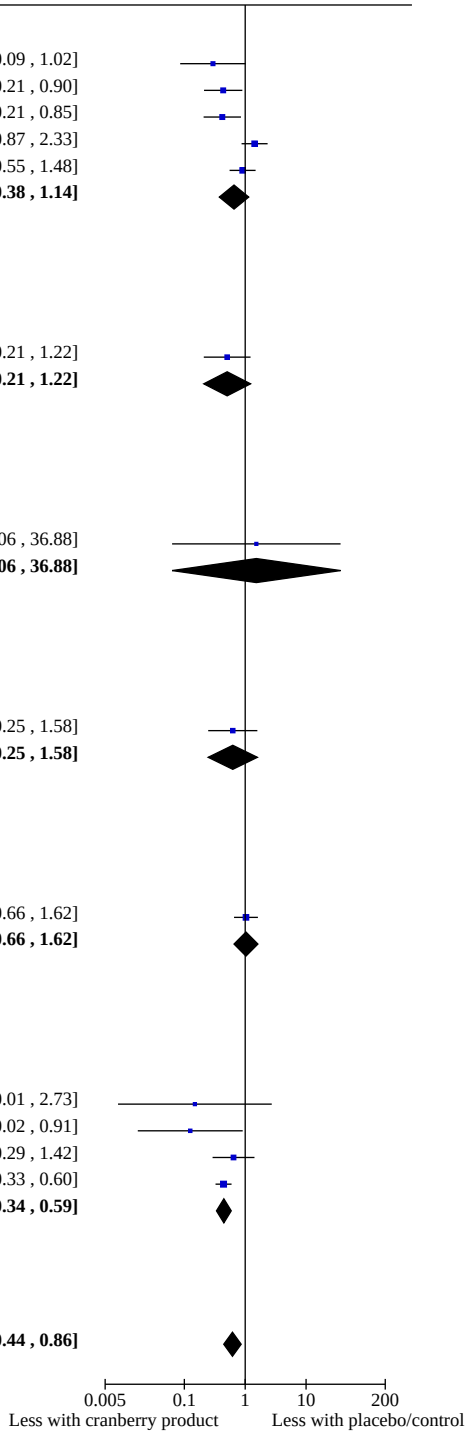
Analysis 10.1. Comparison 10: Cranberry product versus placebo or control: sponsor type, Outcome 1: Symptomatic UTI: culture-verified UTI (commercial involvement)

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 Women with recurrent UTIs						
Maki 2016	30	185	34	188	9.0%	0.90 [0.57 , 1.40]
Takahashi 2013	32	107	38	106	12.1%	0.83 [0.57 , 1.23]
Subtotal (95% CI)		**292**		**294**	**21.2%**	**0.86 [0.64 , 1.15]**
Total events:	62		72			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
10.1.2 Elderly men and women						
McMurdo 2005	7	187	14	189	2.3%	0.51 [0.21 , 1.22]
Juthani-Mehta 2016	9	92	9	93	2.3%	1.01 [0.42 , 2.43]
Juthani-Mehta 2010	13	20	12	17	9.1%	0.92 [0.59 , 1.44]
Caljouw 2014	62	458	62	470	16.8%	1.03 [0.74 , 1.42]
Subtotal (95% CI)		**757**		**769**	**30.6%**	**0.94 [0.74 , 1.20]**
Total events:	91		97			
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
10.1.3 Pregnant women						
Wing 2015	0	14	0	19		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.1.4 Children						
Wan 2016	7	28	10	27	2.8%	0.68 [0.30 , 1.51]
Salo 2010	16	152	22	127	5.0%	0.61 [0.33 , 1.11]
Subtotal (95% CI)		**180**		**154**	**7.8%**	**0.63 [0.39 , 1.02]**
Total events:	23		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.88 (P = 0.06)						
10.1.5 Adults with neuropathy or neuropathic bladders						
Waites 2004	10	26	8	22	3.3%	1.06 [0.51 , 2.21]
SINBA 2007	67	153	71	152	29.6%	0.94 [0.73 , 1.20]
Subtotal (95% CI)		**179**		**174**	**32.9%**	**0.95 [0.75 , 1.20]**
Total events:	77		79			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
10.1.6 People with a susceptibility to UTIs due to an intervention						
Mooren 2020	9	105	14	105	2.9%	0.64 [0.29 , 1.42]
Foxman 2015	12	80	23	80	4.6%	0.52 [0.28 , 0.98]
Subtotal (95% CI)		**185**		**185**	**7.5%**	**0.57 [0.35 , 0.92]**
Total events:	21		37			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.28 (P = 0.02)						
Total (95% CI)		**1607**		**1595**	**100.0%**	**0.86 [0.76 , 0.99]**
Total events:	274		317			
Heterogeneity: Tau² = 0.00; Chi² = 8.23, df = 11 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Chi² = 5.60, df = 4 (P = 0.23), I² = 28.6%						



Analysis 10.2. Comparison 10: Cranberry product versus placebo or control: sponsor type, Outcome 2: Symptomatic UTI: culture-verified UTI (no commercial involvement)

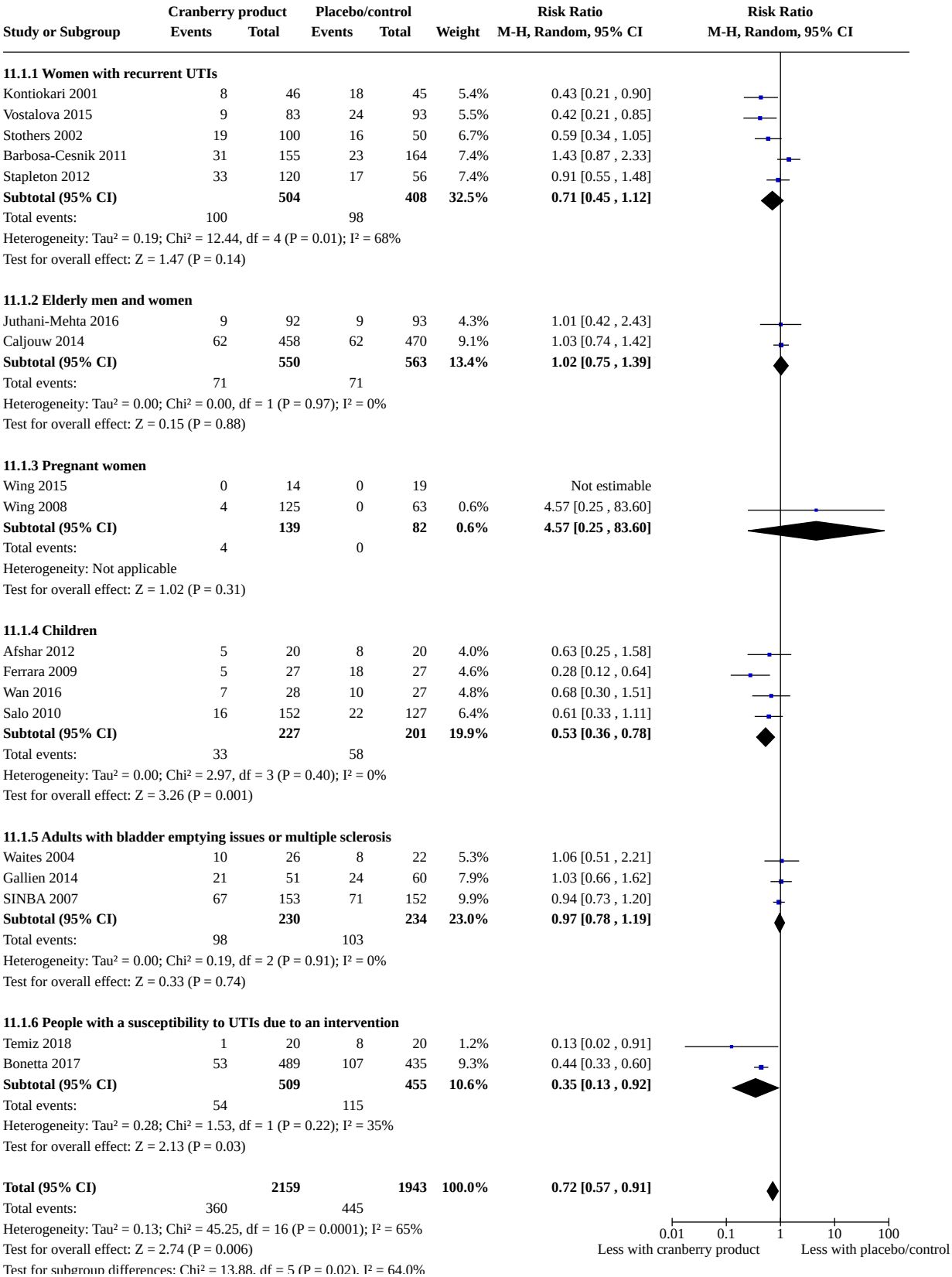
Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.2.1 Women with recurrent UTIs						
Sengupta 2011	4	44	4	13	4.9%	0.30 [0.09 , 1.02]
Kontiokari 2001	8	46	18	45	9.0%	0.43 [0.21 , 0.90]
Vostalova 2015	9	83	24	93	9.2%	0.42 [0.21 , 0.85]
Barbosa-Cesnik 2011	31	155	23	164	11.7%	1.43 [0.87 , 2.33]
Stapleton 2012	33	120	17	56	11.7%	0.91 [0.55 , 1.48]
Subtotal (95% CI)		**448**		**371**	**46.5%**	**0.66 [0.38 , 1.14]**
Total events:	85		86			
Heterogeneity: Tau² = 0.27; Chi² = 13.92, df = 4 (P = 0.008); I² = 71%						
Test for overall effect: Z = 1.49 (P = 0.14)						
10.2.2 Elderly men and women						
McMurdo 2005	7	187	14	189	7.4%	0.51 [0.21 , 1.22]
Subtotal (95% CI)		**187**		**189**	**7.4%**	**0.51 [0.21 , 1.22]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
10.2.3 Pregnant women						
Wing 2008	1	125	0	63	1.0%	1.52 [0.06 , 36.88]
Subtotal (95% CI)		**125**		**63**	**1.0%**	**1.52 [0.06 , 36.88]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
10.2.4 Children						
Afshar 2012	5	20	8	20	7.0%	0.63 [0.25 , 1.58]
Subtotal (95% CI)		**20**		**20**	**7.0%**	**0.63 [0.25 , 1.58]**
Total events:	5		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
10.2.5 Adults with neuropathy etc						
Gallien 2014	21	51	24	60	12.3%	1.03 [0.66 , 1.62]
Subtotal (95% CI)		**51**		**60**	**12.3%**	**1.03 [0.66 , 1.62]**
Total events:	21		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
10.2.6 People with a susceptibility to UTI due to an intervention						
Mohammed 2016	0	22	3	23	1.2%	0.15 [0.01 , 2.73]
Temiz 2018	1	20	8	20	2.3%	0.13 [0.02 , 0.91]
Mooren 2020	9	105	14	105	8.3%	0.64 [0.29 , 1.42]
Bonetta 2017	53	489	107	435	14.0%	0.44 [0.33 , 0.60]
Subtotal (95% CI)		**636**		**583**	**25.8%**	**0.45 [0.34 , 0.59]**
Total events:	63		132			
Heterogeneity: Tau² = 0.00; Chi² = 2.97, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 5.68 (P < 0.00001)						
Total (95% CI)		**1467**		**1286**	**100.0%**	**0.62 [0.44 , 0.86]**
Total events:	182		264			
Heterogeneity: Tau² = 0.18; Chi² = 30.58, df = 12 (P = 0.002); I² = 61%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: Chi² = 10.28, df = 5 (P = 0.07), I² = 51.3%						



Comparison 11. Cranberry product versus placebo or control: culture threshold

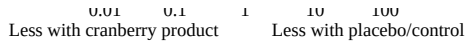
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Symptomatic UTI: culture-verified UTI (# 10^8 CFU/L)	18	4102	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.57, 0.91]
11.1.1 Women with recurrent UTIs	5	912	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.12]
11.1.2 Elderly men and women	2	1113	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.75, 1.39]
11.1.3 Pregnant women	2	221	Risk Ratio (M-H, Random, 95% CI)	4.57 [0.25, 83.60]
11.1.4 Children	4	428	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.78]
11.1.5 Adults with bladder emptying issues or multiple sclerosis	3	464	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]
11.1.6 People with a susceptibility to UTIs due to an intervention	2	964	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.13, 0.92]
11.2 Symptomatic UTI: culture-verified UTI (< 10^8 CFU/L)	3	806	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.34, 1.14]
11.2.1 Women with recurrent UTIs	2	430	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.21, 1.71]
11.2.2 Elderly men and women	1	376	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.21, 1.22]

Analysis 11.1. Comparison 11: Cranberry product versus placebo or control: culture threshold, Outcome 1: Symptomatic UTI: culture-verified UTI (# 10^8 CFU/L)



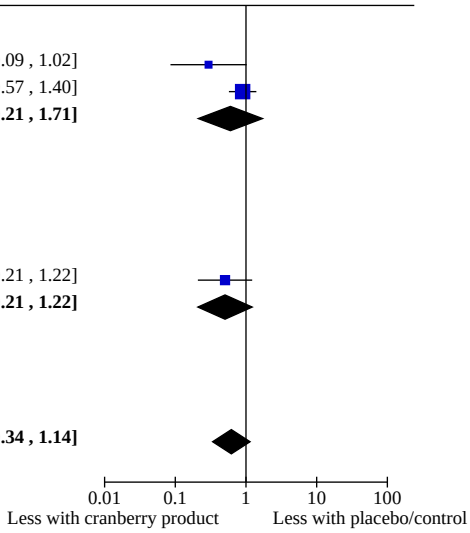
Analysis 11.1. (Continued)

Test for overall effect: Z = 2.74 (P = 0.006)
Test for subgroup differences: Chi² = 13.88, df = 5 (P = 0.02), I² = 64.0%



Analysis 11.2. Comparison 11: Cranberry product versus placebo or control: culture threshold, Outcome 2: Symptomatic UTI: culture-verified UTI (< 10^8 CFU/L)

Study or Subgroup	Cranberry product Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.2.1 Women with recurrent UTIs						
Sengupta 2011	4	44	4	13	18.2%	0.30 [0.09 , 1.02]
Maki 2016	30	185	34	188	52.9%	0.90 [0.57 , 1.40]
Subtotal (95% CI)		**229**		**201**	**71.1%**	**0.60 [0.21 , 1.71]**
Total events:	34		38			
Heterogeneity: Tau² = 0.39; Chi² = 2.73, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 0.95 (P = 0.34)						
11.2.2 Elderly men and women						
McMurdo 2005	7	187	14	189	28.9%	0.51 [0.21 , 1.22]
Subtotal (95% CI)		**187**		**189**	**28.9%**	**0.51 [0.21 , 1.22]**
Total events:	7		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
Total (95% CI)		**416**		**390**	**100.0%**	**0.62 [0.34 , 1.14]**
Total events:	41		52			
Heterogeneity: Tau² = 0.13; Chi² = 3.52, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%						



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms used
CENTRAL	1. MeSH descriptor: [Beverages] this term only 2. MeSH descriptor: [Fruit] this term only 3. MeSH descriptor: [Phytotherapy] this term only 4. MeSH descriptor: [Vaccinium macrocarpon] this term only 5. Vaccinium macrocarpon:ti,ab,kw (Word variations have been searched) 6. vaccinium oxycoccus:ti,ab,kw (Word variations have been searched) 7. vaccinium vitisidaea:ti,ab,kw (Word variations have been searched) 8. cranberry or cranberries:ti,ab,kw (Word variations have been searched) 9. {or #1-#8} 10.MeSH descriptor: [Urinary Tract Infections] this term only 11.MeSH descriptor: [Bacteriuria] this term only 12.MeSH descriptor: [Pyuria] this term only 13.MeSH descriptor: [Cystitis] this term only 14.uti or utis:ti,ab,kw (Word variations have been searched) 15.cystitis:ti,ab,kw (Word variations have been searched)

(Continued)

	16.pyelonephritis:ti,ab,kw (Word variations have been searched) 17.bacteriuria:ti,ab,kw (Word variations have been searched) 18.urinary tract infection*:ti,ab,kw (Word variations have been searched) 19.{or #10-#18} 20.{and #9, #19}
MEDLINE	1. Beverages/ 2. FRUIT/ 3. cranberr$.tw. 4. (fruit$ and (juice$ or beverage$ or drink$)).tw. 5. PHYTOTHERAPY/ 6. Vaccinium macrocarpon/ 7. vaccinium oxycoccus.tw. 8. vaccinium vitisidaea.tw. 9. or/1-8 10.Urinary tract infections/ 11.Bacteriuria/ 12.Pyuria/ 13.Cystitis/ 14.(uti or utis).tw. 15.cystitis.tw. 16.pyelonephritis.tw. 17.bacter$.tw. 18.urinary tract infection$.tw. 19.or/10-18 20.and/9,19
EMBASE	1. cranberry/ 2. cranberry juice/ 3. cranberry extract/ 4. vaccinium macrocarpon.tw. 5. vaccinium vitisidaea.tw. 6. vaccinium oxycoccus.tw. 7. cranberr$.tw. 8. or/1-7 9. urinary tract infection/ 10.pyuria/ 11.bacteriuria/ 12.asymptomatic bacteriuria/ 13.cystitis/ 14.(uti or utis).tw. 15.urinary tract infection$.tw. 16.bacteriuria.tw. 17.cystitis.tw. 18.or/9-17 19.and/8,18

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.
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 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

(Continued)

	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.
	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.

Appendix 3. Adverse events: cranberry product versus control

Adverse event	Cranberry product		Control	
	Patients with event	Total	Patients with event	Total
Death				
McMurdo 2005	3	187	2	189
Caljouw 2014	150	458	145	470
Juthani-Mehta 2016	17	92	16	93
Bruyere 2019	0	42	0	43
Hospitalisations				
Fernandes 2016	1	25	2	30
Juthani-Mehta 2016	33	92	50	93

(Continued)

Serious adverse events (not specified)				
Sengupta 2011	0	44	0	13
Stapleton 2012	0	120	0	56
Gallien 2014	0	51	0	60
Foxman 2015	4	80	4	80
Juthani-Mehta 2016	50 (events)	-	66 (events)	-
Maki 2016	1	185	4	188
Gastrointestinal events				
Stothers 2002	8	100	2	50
McMurdo 2005	2	187	4	189
Sengupta 2011	4	44	0	13
Gallien 2014	14	51	18	60
Wing 2015	13	14	12	19
Singh 2016	1	36	1	36
Bonetta 2017	4	489	0	435
Koradia 2019	3	44	0	45
Babar 2021	1	72	1	73
Mohammed 2016	0	22	0	23
Rash				
McMurdo 2005	1	187	0	189

Appendix 4. Adverse events: cranberry product versus antibiotics

Adverse event	Cranberry product		Antibiotics	
	Patients with event	Total	Patients with event	Total
Gastrointestinal events				
McMurdo 2009	4	69	4	68
NAPRUTI 2011	13	104	16	95

(Continued)

Uberos 2012	2	72	5	114
Rash or urticaria				
McMurdo 2009	0	69	3	68
NAPRUTI 2011	9	104	15	95
Uberos 2012	1	72	1	114
Vaginal problems				
NAPRUTI 2011	15	104	18	95
Allergic reaction				
NAPRUTI 2011	0	109	1	98
Antibiotic resistance (positive cultures)				
Uberos 2012	4	19	9	28
Severe adverse events (unspecified)				
NAPRUTI 2011	8	104	12	95

Appendix 5. Adherence to cranberry product

Study ID	Cranberry type	Adherence (%)	How measured	Reported result for symptomatic UTI (verified on culture unless otherwise specified)
Afshar 2012	Juice	Not reported	Bottle count	RR 0.63 (95% CI 0.25 to 1.58)
Avorn 1994	Juice	80%	Bottle caps counted	Not estimable (units = cultures)
Babar 2021	Pill	92.9% versus 92.7%	Self-reported in a daily journal Pill count	RR 0.69 (95% CI 0.57 to 1.13) (symptomatic UTI not verified by culture)
Barbosa-Cesnik 2011	Juice	70% to 75%	Self-report	RR 1.43 (95% CI 0.87 to 2.33)
Caljouw 2014	Pill	97%	Pill count	RR 1.03 (95% CI 0.74 to 1.42)
Cowan 2012	Juice	79%	Self-report	Not estimable (units = cultures)
Ferrara 2009	Juice	96.4%	Self-report	RR 0.28 (95% CI 0.12 to 0.64)
Foda 1995	Juice	52%	Self-report	Not estimable (cross-over RCT)

(Continued)

Foxman 2015	Pill	85% took pills most or all of the time	Pill count and questioned by staff	RR 0.52 (95% CI 0.28 to 0.98)
Gallien 2014	Powder	80% were > 70%	Sachets counted	RR 1.03 (95% CI 0.66 to 1.62)
Hess 2008	Pill	Not reported	Pill count and questioned	Not estimable (cross-over RCT)
Juthani-Mehta 2016	Pill	77.5%	Pill count	RR 1.01 (95% CI 0.42 to 2.43)
Kontiokari 2001	Juice	91%	Self-report sheet	RR 0.43 (95% CI 0.21 to 0.90)
Koradia 2019	Pill	80%	Self-report-Diary cards	RR 0.27 (95% CI 0.1 to 0.76) (Cranberry+probiotic versus placebo)
Maki 2016	Juice	98%	Bottles returned and self-report diary	RR 0.90 (95% CI 0.57 to 1.4)
McGuiness 2002	Pill	Not reported	Questioned by researcher	RR 1.03 (95% CI 0.64 to 1.66) (microbiological UTI)
McMurdo 2005	Juice	Close to 100%	Self-report	RR 0.51 (95% CI 0.21 to 1.22)
McMurdo 2009	Pill	99%	Pill count	RR 1.76 (95% CI 1.0 to 3.09) (cranberry versus antibiotic; clinical UTI)
Mooren 2020	Pill	85.7% versus 80%	Self-reported on questionnaire Pill count	RR 0.64 (95% CI 0.29 to 1.42)
Salo 2010	Juice	46% were > 90%, 17% were 50% to 90%, 37% were < 50%	Self-report and bottle count	RR 0.61 (95% CI 0.33 to 1.11)
Schlager 1999	Juice	Not reported	Bottle count	Not estimable (cross-over RCT)
Singh 2016	Pill	Not reported	Returned empty pill packets	RR 0.38 (95% CI 0.23 to 0.60)
Stapleton 2012	Juice	91.8%	Questionnaire	RR 0.91 (95% CI 0.55 to 1.48)
Stothers 2002	Pill or Juice	Pills > 85% Juice < 80%	Pill count	RR 0.59 (95% CI 0.34 to 1.05)
Takahashi 2013	Juice	Not reported	Questioned by doctor	RR 0.83 (95% CI 0.57 to 1.23)
Waites 2004	Pill	Not reported	Monthly telephone calls for pill count	RR 1.06 (95% CI 0.51 to 2.21)

(Continued)

Walker 1997	Pill	Not reported	Returned capsule bottles and interviewed	Not estimable (cross-over study)
Wing 2008	Juice	50.7% (2 to 3 dose group) 39.7% (1 dose group)	Self-report	RR 4.57 (95% CI 0.25 to 83.6)
Wing 2015	Pill	82%	Self-report	Not estimable (no UTI events)

Footnotes

CI: confidence interval; RR: relative risk; UTI: urinary tract infection

WHAT'S NEW

Date	Event	Description
17 April 2023	New citation required and conclusions have changed	New studies identified
17 April 2023	New search has been performed	24 new studies added and conclusions changed

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 1998

Date	Event	Description
18 March 2015	Amended	Updated search strategies for MEDLINE, EMBASE & CENTRAL
16 June 2014	Amended	Minor grammatical correction made
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

- JCC: study design, writing review, updating review
- GW: update search, study selection, quality assessment, data extraction, writing, updating review
- EMH: Updating review
- DH: Risk of bias tables, updating review
- JHS: Updating review

DECLARATIONS OF INTEREST

- Gabrielle Williams: no relevant interests were disclosed
- Deirdre Hahn: no relevant interests were disclosed
- Jacqueline H Stephens: no relevant interests were disclosed
- Jonathan C Craig: no relevant interests were disclosed
- Elisabeth M Hodson: no relevant interests were disclosed

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2023: Risk of bias assessment tool has replaced quality assessment checklist. GRADE has been used to describe the certainty of the evidence.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Male