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Review

A systematic review of the evidence for cranberries and blueberries in UTI prevention

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In this review we assess the effectiveness of cranberry and blueberry products in preventing symptomatic urinary tract infections (UTIs). Selection criteria were randomised or quasi-randomised controlled trials of cranberry or blueberry juice/products for the prevention of symptomatic UTIs. A comprehensive search was undertaken in November 2006 whereupon two reviewers independently assessed and extracted data. Quality was assessed using Cochrane criteria. Relative risks (RR) were calculated where appropriate; otherwise a narrative synthesis was undertaken. No relevant trials of blueberry products were identified. Nine trials of cranberry products met the inclusion criteria. In four good quality randomised controlled trials (RCTs), cranberry products significantly reduced the incidence of symptomatic UTIs in 12 months (overall RR 0.65, 95% CI: 0.46–0.90) compared with placebo/control. Five trials were not included in the *meta*-analyses due to the lack of appropriate data. However, only one reported a significant result. Side effects were common, and losses to followup/withdrawals in several of the trials were high (>40%). There is some evidence from four good quality RCTs that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period, particularly in women with recurrent UTIs. It is uncertain whether it is effective in other susceptible groups.

Keywords: Blueberry / Cranberry / Systematic review / Urinary tract infections

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1 Introduction

The term urinary tract infection (UTI) refers to the presence of a certain threshold number of bacteria in the urine (usually greater than 100 000/mL). It consists of cystitis (bacteria in the bladder), urethral syndrome and pyelonephritis (infection of the kidneys). Bacterial cystitis (also called acute cystitis) can occur in men and women and the signs and symptoms include dysuria (pain on passing urine), frequency, cloudy urine, occasionally haematuria (blood in the urine), and is often associated with pyuria (urine white cell count greater than 10 000/mL). Some people also have recurrent UTIs with an average of two to three episodes *per* year [1, 2].

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Abbreviations: RCTs, randomised controlled trials; **RR,** relative risks; **UTI,** urinary tract infection

Although UTIs can occur in both men and women, they are about 50 times more common in adult women than adult men. This may be because women have a shorter urethra that allows bacteria to ascend more easily into the bladder. Symptomatic infection of the bladder (lower UTI) has been estimated to occur in up to 30% of women at some stage during their lives [3]. Most UTIs arise from the 'ascending' route of infection. The first step is colonisation of periurethral tissues with uropathogenic organisms, followed by the passage of bacteria through the urethra. Infection arises from bacterial proliferation (growth) within the otherwise sterile urinary tract. The second step is adherence of the bacteria to the bladder wall. In children, UTI occurs more commonly in boys up to the age of 6–12 months, but overall occurs about three times more often in girls (1–3% in boys, 3–7% in girls) [4, 5]. Most people who present to the doctor or hospital have symptomatic UTIs. Some infections can also be asymptomatic, but only those who are at high risk of developing further infections (pregnant women, those with indwelling catheters and the elderly) may require treatment.

Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the preven-

tion and treatment of UTIs. Cranberries and blueberries are part of the *Vaccinium* species which are rich sources of dietary flavonoids including anthocyanins and proanthocyanidins (condensed tannins) [6]. Cranberries comprise nearly 90% water, but also contain various organic substances such as quinic acid, malic acid and citric acid as well as glucose and fructose.

No definite mechanism of action has been established for cranberry or blueberry in the prevention or treatment of UTIs. Until recently, it was suggested that the quinic acid in the berries caused large amounts of hippuric acid to be excreted in the urine. This acidification of the urine acted resulting in an antibacterial effect [7]. Several trials, however, have shown no difference in the levels of hippicuric acid, or only a transient (short lived) effect thus casting some doubt on this theory [8, 9]. The current theory is that cranberries prevent bacteria (particularly *E. coli*) from adhering to uroepithelial cells that line the wall of the bladder [8, 10, 11]. Without adhesion, *E. coli* cannot infect the mucosal surface of the urinary tract. *In vitro*, this adhesion is mediated by two components of cranberry; fructose, which inhibits adherence of type 1 (mannose specific) fimbriated *E. coli* [12], and proanthocyanidins, which inhibit the adherence of p-fimbriated (a-galactose-(1-4) specific) *E. coli* [11]. Blueberries also contain proanthocyanidins, and at least one *in vitro* trial suggests that both antiadhesion and antiproliferation activity are associated with high molecular weight proanthocyanidin oligomers found in wild blueberry fruits [13].

Preventive treatments such as antibiotics are often given to susceptible population such as elderly hospitalised patients, people requiring catheterisation (*e.g.* those with spinal cord injuries), children with urological abnormalities, and women with recurrent UTIs. However, one major drawback is the potential for antibiotic resistance. In addition, not all patients wish to take antibiotics as a preventative measure. Cranberry and blueberry products are potentially useful preventative therapies as they are natural products which do not lead to antibiotic resistance. The paper presented here includes findings from a recently published Cochrane review [14] to evaluate the effectiveness of cranberries for the prevention of UTIs. It also includes trials published since the review, and is expanded to include trials which have evaluated the effectiveness of blueberry products. The treatment of UTIs with cranberry products is evaluated in another review by the same reviewers [15].

The aim of this review was to assess the effectiveness of cranberry or blueberry products (*e.g.* juice, capsules, tablets) in the prevention of symptomatic UTIs in susceptible populations. Although cranberry juice is the form of cranberries most widely used for the prevention of UTIs, other cranberry products include cranberry powder in hard or soft gelatine capsules or in tablet form. Any blueberry products were also included.

2 Materials and methods

The following criteria were used to determine which trials should be included in the review:

2.1 Types of trials

Randomised controlled trials (RCTs) of cranberry or blueberry products *versus* placebo, no treatment or any other treatment. Quasi-RCTs (*e.g.* those trials which randomised participants by date of birth, or case record number) were included, but the quality of the trials was taken into account during the analysis and discussion. Both parallel group and crossover designs were included.

2.2 Types of participants

Trials of susceptible men, women or children as defined below. These categories were analysed separately.
(i) Participants with a history of recurrent lower UTIs (more than two episodes in the previous 12 months).
(ii) Elderly men and women.
(iii) Participants needing intermittent catheterisation.
(iv) Pregnant women.
(v) Participants with an indwelling catheter.
(vi) Participants with an abnormality of the urinary tract.

2.3 Types of interventions

Cranberry or blueberry products (*e.g.* juice, capsules, tablets) given for at least 1 month. The comparison group could be placebo, no intervention, or any other intervention (*e.g.* antibiotics).

2.4 Primary outcome measure

Number of symptomatic UTIs in each group (confirmed by a catheter specimen of urine, midstream specimen of urine if possible, or a 'clean catch' specimen). The 'gold standard' bacteriological criteria for diagnosis of UTI includes microbiological confirmation from a midstream specimen of urine (MSU) (or similar method) with greater than 100 000 bacterial cfu/mL, often associated with pyuria (white cells in the urine). In some situations a bacterial count < 100 000/mL is acceptable, for example, when a supra-pubic bladder tap or a catheter urine specimen is obtained. Symptoms must include one or more of the following: dysuria (pain on passing urine), frequency, cloudy urine, haematuria (blood in the urine).

2.5 Secondary outcome measures

Side effects and adherence to therapy.

2.6 Exclusion criteria

Any trials not meeting *all* of the inclusion criteria described previously were excluded. In addition, the following trials were also excluded:
(i) Trials which only measured asymptomatic UTIs.
(ii) Trials of the *treatment* of asymptomatic or symptomatic UTI (these are analysed in a separate review by the same reviewers) [15].
(iii) Trials of any urinary tract condition not caused by bacterial infection (*e.g.* interstitial cystitis, which is a chronic inflammation of the bladder wall).
(iv) Trials involving healthy volunteers with no pre-existing UTI.

2.7 Search strategy for identification of trials

The following key words were translated into the appropriate searching syntax for each of the databases listed below:
(i) Vaccinium, cranberry, blueberry, fruit beverage, fruit drink, fruit juice, beverage.
(ii) UTIs, cystitis, bacteriuria, pyelonephritis, urinary infection or bacterial infection.

The following databases were searched (from date of first issue until December 2006) to identify relevant studies:
(i) The Cochrane Renal Group Register of Trials.
(ii) Cochrane Controlled Trials Register (CCTR) and CENTRAL (issue 1 of The Cochrane Library 2006)
(iii) Registry of randomised trials for the Cochrane Collaboration Field in Complementary Medicine.
(iv) Electronic databases including PsycLit, LILACS, CINAHL, MEDLINE, EMBASE, Biological Abstracts, Current Contents

In addition, companies involved with the promotion and distribution of cranberry preparations were approached and asked to provide information on both published and unpublished trials. The Internet and reference lists of review articles and relevant trials were also searched.

2.8 Applying the inclusion criteria and assessing trial quality

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

The quality of all trials which were deemed eligible for the review were then assessed independently by two of the reviewers. The quality of allocation concealment was graded as either (A) adequate, (B) unclear or (C) inadequate, following the detailed descriptions of these categories provided by the Cochrane Collaboration. It was intended to use this grading in investigation of any heterogeneity and in sensitivity analyses. Other aspects of trial quality assessed included the extent of blinding, whether groups were comparable at baseline, the extent of losses to followup, nonparticipation, whether the outcome assessment was standardised, and whether an 'intention-to-treat' analysis was undertaken.

Two reviewers independently extracted information using specially designed data extraction forms. For each included trial, information was collected regarding the location of the trial, methods of the trial (as per quality assessment checklist), the participants (sex, age, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified previously. Where possible, missing data (including side effects) were sought from the trial authors.

2.9 Methods of analysis

Analysis was undertaken using RevMan, the Cochrane Collaboration's computer software programme for preparing and maintaining Cochrane reviews (Review Manager (RevMan). [Version 4.2 for Windows], 2003, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Only RCTs were included in the *meta*-analysis. The overall relative risk (RR) was used to report the relative rates of symptomatic UTI in the intervention group and placebo groups, with an RR less than one favouring the intervention. Due to heterogeneity in population groups, trials were categorised into predefined subgroups (see under 'Type of participants') and analysed both separately and together using a random effects model. For crossover trials, only the period before the crossover was possible to be analysed in RevMan. These data were not available for any of the crossover trials, so results were reported descriptively. Results were also reported descriptively for the quasi-RCT.

3 Results

3.1 Description of studies

No trials were identified which evaluated the effectiveness of blueberry products for the prevention or treatment of UTIs. Therefore, the rest of this section refers to the cranberry trials that were identified. Nine trials met the inclusion criteria, with a total of 1011 participants randomised to treatment or control [16 – 24]. Of these, one was only published as a letter and no additional data were received from the authors [18]. Table 1 provides further details of the trials.

Seven trials had one intervention arm and one control arm and evaluated the effectiveness of either cranberry juice/cocktail [19 – 22] or cranberry capsules [18, 23, 24]. A

Table 1. Description of included studies

Reference no.	Author and year	*N*[a)]	Country	Setting	Participants	Intervention
[16]	Kontiokari, 2001	150	Finland	Student health service	Young women (mean age 29 – 32 years) with previous UTI	50 mL of cranberry-lingonberry juice 5 days *per* week (7.5 g cranberry concentrate)
[17]	Stothers, 2002	150	Canada	Unclear	Women with recurrent UTI (aged 21 – 72 years)	Cranberry juice (250 mL three times a day) or one concentrated cranberry juice tablet twice daily
[18]	Walker, 1997	19	USA	Family practice	Young women with recurrent UTI, median age 37 years	Cranberry capsules (400 mg of cranberry solids)
[19]	Avorn,1994	192	USA	Nursing homes	Elderly women, mean age 78.5 years	300 mL cranberry juice cocktail *per* day (30% cranberry concentrate)
[20]	McMurdo, 2005	376	Scotland	Hospital	Elderly inpatients	300 mL of cranberry juice
[21]	Schlager, 1999	15	USA	Hospital clinic	Children with neuropathic bladder requiring clean intermittent catheterisation, aged 2 – 18 years	300 mL of cranberry juice cocktail *per* day (30% cranberry concentrate)
[22]	Foda, 1995	40	Canada	Hospital clinic	Children with neuropathic bladder requiring clean intermittent catheterisation, mean age 9.35 years	15/mL/kg cranberry juice cocktail *per* day (30% cranberry concentrate)
[23]	Linsenmeyer, 2004	21	USA	Urology rehabilitation clinic	Spinal cord injury patients with neuropathic bladders	Cranberry tablets (400 mg)
[24]	Waites, 2004	48	USA	Hospital clinic	Spinal cord injury with neuropathic bladder	Cranberry juice concentrate (2 g)

a) Total number randomised to intervention or control, not number analysed. Some studies only report the number analysed in their abstracts. For example, Avorn, 1994 [19] describes a study of 153 people, whereas a total of 192 were initially randomised to intervention or control. See Table 2 for more details of losses to followup and number included in the analysis.

further two trials had two intervention arms and a control arm [16, 17]. One of these randomised participants to either cranberry – lingonberry juice, lactobacillus GG drink or no intervention [16] whilst the other [17] randomised participants to cranberry juice, cranberry tablets or placebo juice.

Three trials were excluded from the review because although they were randomised and compared cranberry juice with placebo in susceptible populations, two did not measure any relevant outcomes [25, 26] and the other only measured asymptomatic UTIs [27].

The included studies evaluated the effectiveness of cranberry products in different populations. Three trials evaluated cranberry juice for the prevention of UTIs for women with recurrent UTIs [16 – 18]. Two trials were conducted in elderly populations [19, 20] and four trials were with people (including children) needing either indwelling catheters or intermittent catheterisation [21 – 24]. All the participants in these four trials had neuropathic bladders.

The rationale behind the amount and concentration of cranberry juice given to participants was not mentioned in any of the trials, and only one trial [20] detailed the amount of active component (a proanthocyanidin concentration of 11.175 μg/g (dry solids basis). Of the four trials which evaluated the effectiveness of cranberry capsules, two gave participants capsules containing 400 mg of cranberry solids [18, 23] one gave capsules containing 2 g of concentrated cranberry juice [24] and one [17] gave participants cranberry tablets containing 1:30 parts of concentrated juice twice a day.

3.2 Methodological quality of included trials

3.2.1 General

In general, the methodological quality of the trials was good (see Table 2.) Four used adequate concealment of allocation [16, 17, 20, 21]. Four of the trials did not state the method of randomisation [18, 22 – 24] and were graded B (unclear). One trial [19] used a quasirandomised method of allocation and was graded C (inadequate).

The dropout rate in all of the trials varied considerably. Two of the trials reported no dropouts [17, 21], however, adherence with treatment was reported as being less than 80% in 5 of the 12 months in one of these trials [17]. In the other trials the dropout or withdrawal rates ranged from 8 to 55%. Only two of the trials reported using an intention-to-treat analysis [16, 20].

Table 2. Quality of included studies

Reference no.	Author and year	Design, method of allocation and allocation quality grade (A, B or C)	Duration of trial	Blinding	Losses to followup/withdrawals	No. included in analysis	Intention to treat analysis
[16]	Kontiokari, 2001	Randomised controlled parallel group trial Allocation by sealed opaque envelopes (A)	6 months	Unclear	13/150 (8.7%)	150	Yes
[17]	Stothers, 2002	Randomised controlled parallel group trial Allocation by sealed envelopes (A)	12 months	Participants, investigators	2/150 (1.3%)	148	No
[18]	Walker, 1997	Randomised controlled crossover trial Allocation method not stated (B)	3 months	Participants, investigators	9/19 (47.4%)	9	Unclear
[19]	Avorn, 1994	Quasi-randomised parallel group trial Allocation by ID or phone number (C)	6 months	Participants, investigators	39/192 (20%)	153	No
[20]	McMurdo, 2005	Randomised controlled parallel group trial Allocation by sealed envelopes (A)	6 months	Participants, investigators	115/376 (31%)	376	Yes
[21]	Schlager, 1999	Randomised controlled crossover trial Allocation by pharmacy (A)	3 months	Participants, investigators	None	15	N/A
[22]	Foda, 1995	Randomised controlled crossover trial Allocation method not stated (B)	6 months	Investigators	19/40 (47.5%)	21	Unclear
[23]	Linsenmeyer, 2004	Randomised controlled crossover trial Allocation method not stated (B)	9 wk	Participants, investigators	16/37 (43%)	21	No
[24]	Waites, 2004	Randomised controlled parallel group trial Allocation method not stated (B)	6 months	Participants, investigators	26/74 (35%)	48	No

3.2.2 Symptomatic UTIs

Relative risks (RR) were calculated for four trials [16, 17, 20, 24]. The overall RR using a random effects model was 0.65 (95% CI: 0.46–0.90) (see Fig. 1). For the five trials not included in the *meta*-analyses [18, 21–23, 28] only one reported a significant result for the outcome of symptomatic UTIs (six incidents in the cranberry arm *versus* 15 in the placebo group, $p < 0.05$) [18]. The following sections outline the results for each of the predefined subgroups for which there were data.

3.2.2.1 Women with a history of recurrent lower UTIs

Three trials evaluated the effectiveness of cranberry products for women with recurrent UTIs [16–18]. Data were available for *meta*-analyses from two RCTs (see Fig. 1) [16, 17]. When data from cranberry products (capsules and juice) were combined and compared with placebo/control, the RR was 0.61 (95% CI: 0.40–0.91). The combined RR for both trials for cranberry juice *versus* placebo/water for the reoccurrence of symptomatic UTIs at 12 months was 0.62 (95% CI: 0.40–0.97). For cranberry capsules *versus* placebo the RR was 0.56 (95% CI: 0.27–1.15). For cranberry juice *versus* cranberry capsules, the RR was 1.11 (95% CI: 0.49–2.50). In the third trial [18], there were 21 incidents of UTIs amongst the ten people who completed the trial. Six were in the treatment group and 15 were in the placebo group ($p < 0.005$).

3.2.2.2 Elderly men and women

Two trials were undertaken with elderly populations [19, 20]. In the largest and the best quality trial [20], a total of 21/376 (5.6%) participants developed a symptomatic UTI: 14/189 in the placebo group and 7/187 in the cranberry juice group. These between-group differences were not significant, relative risk (RR) 0.51 (95% CI: 0.21–1.22).

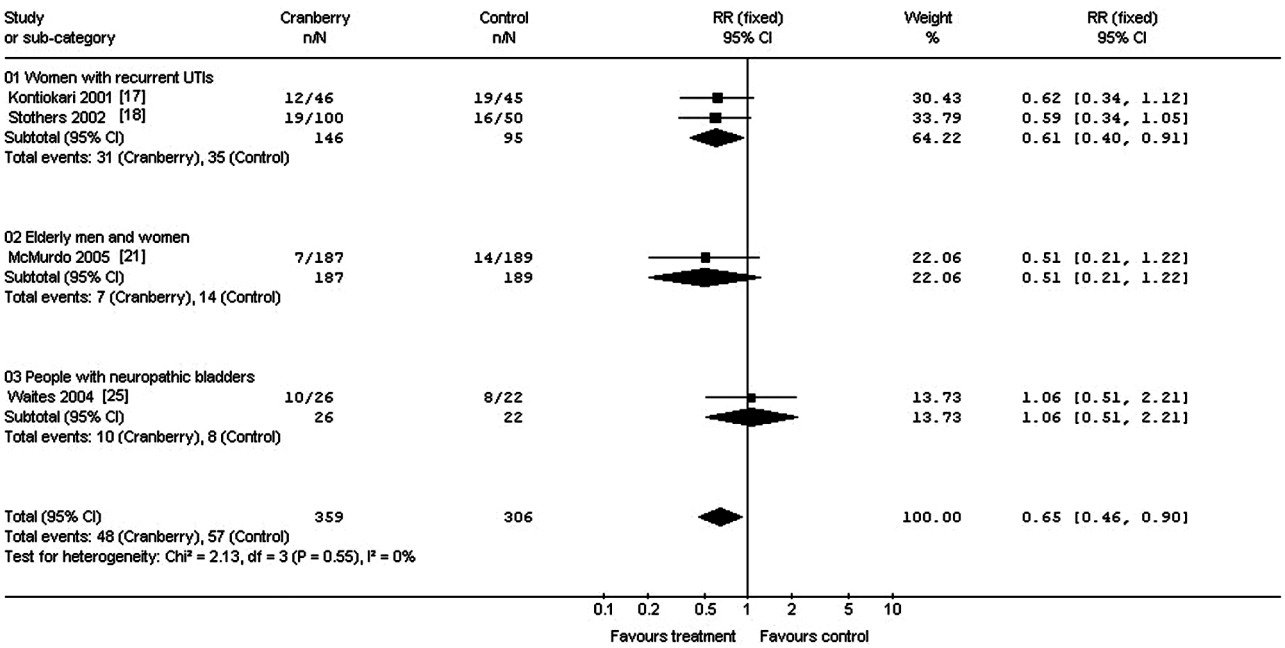

Figure 1. Strength of evidence for studies included in *meta*-analysis.

Although there were significantly fewer infections with *Escherichia coli* in the cranberry group (13 *vs*. 4), RR 0.31 (95% CI 0.10–0.94, $P = 0.027$), the authors suggest that the result should be interpreted with caution as it was a secondary outcome. In the other trial [19], it was reported that 4% (20/473) of the urine samples in the treatment group and 7% (37/498) in the placebo group had bacteriuria and pyuria concurrent with the subjects reporting urinary tract symptoms (p = not significant). There were discrepancies in the data presented in the final report [17] and an initial abstract [28] and further information could not be obtained from the authors. Therefore the results of the trial should be interpreted with caution.

3.2.2.3 Participants needing catheterisation (intermittent or indwelling)

There was neither clinical nor statistical difference in the number of symptomatic UTIs observed in either the cranberry or placebo groups in any of the four trials [21–24] which evaluated cranberries in people who needed catheterisation. The relative risk was only possible to be calculated for one trial [24] and it was not significant RR 1.06 (95% CI: 0.51–2.21).

3.3 Side effects and adherence to therapy

Studies reported side effects of reflux, mild nausea and frequency of bowel movements in the cranberry groups. However, some participants in the placebo group also complained of headache and mild nausea.

The number of withdrawals in some of the trials was high (20–47%). This could indicate that cranberry juice is not an acceptable therapy taken over a long period of time. Children in particular cited taste as the main reason for withdrawal [22]. Furthermore, the cost of consuming large amounts of cranberry juice may limit acceptance in the general population. The trials of cranberry extract [18] and cranberry capsules [17] may have overcome some of these issues of compliance and cost. Withdrawals from the two trials of cranberry capsules/tablets in people with neuropathic bladders [23, 24] were high (>40%), but reasons for the withdrawals were not related to taste.

4 Discussion

There is some evidence from the trials that cranberry juice and derivatives are effective in preventing UTIs in women with recurrent UTI and the elderly but not in children or adults with abnormal bladder function requiring catheterisation. However, none of the trials of cranberry juice justified the dosage of cranberries given to participants. In addition, there was no standardisation of the description of the dosage (*i.e.* concentration) given which made comparison difficult. Generally, the chemical composition of available cranberry products is not standardised, and the bioequivalence between the juice and capsules/tablets is not clear. The strength of cranberry in a cocktail varies, but cocktails commonly contain 25% pure juice.

Furthermore, none of the trials justified the duration of the trial UTIs often occur in clusters with long periods (sev-

eral months) when patients are symptom free [29]. Thus trials may need to cover much longer trial periods to take into account the natural course of the illness. One trial of hospitalised elderly patients gave cranberry juice or placebo for 35 days or until the patient was discharged [20]. The beverages were consumed for a mean of 18 days. The authors suggested that there was evidence from *in vitro* work that the antiadhesion activity of cranberry juice on fimbriated *E. coli* is present in the urine 2 h after ingestion, and that it persists for 10 h following ingestion [30], making it plausible that twice daily ingestion of cranberry juice for 18 days might be effective in reducing episodes of infection.

No published trials have been undertaken that compare cranberry with established interventions (*e.g.* antibacterials) for preventing UTIs. Theoretically, using cranberry instead of antibacterials might reduce the risk for the development of antibacterial-resistant organisms [30], but there is currently no evidence to confirm this. However, a study comparing antibiotic treatment with cranberry capsules for women with recurrent UTIs is currently underway in The Netherlands [31].

Large, properly randomised, parallel group, placebo controlled, double blind trials are needed to determine the effectiveness of cranberries for the prevention of UTIs in susceptible populations. The trial period needs to be longer than 6 months to take into account the natural course of the illness, since UTIs often occur in clusters with long periods (several months) during which patients are symptom free. Furthermore, the dosage and concentration of the cranberry juice/product to be given should be determined scientifically. Outcomes should include the number of symptomatic and asymptomatic UTIs, side effects and adherence to therapy. The large number of dropouts/withdrawals in the cranberry juice trials included in this review indicates that drinking considerable amounts of cranberry juice over a long period may not be acceptable. Further trials of cranberry capsules/tablets or other cranberry products, therefore, are also needed. Several trials are ongoing in this area to address some of these research gaps. For example eight basic and clinical research projects (four clinical trials) of cranberry products and UTIs by the U.S. National Institutes of Health (for more details see http://clinicaltrials.gov) are either underway or completed.

5 Conclusions

The review identified no trials of blueberry products for preventing UTIs. The evidence for cranberry products from four RCTs indicates that it can be effective in reducing UTIs. However, it may only be effective in certain subpopulations. From the results of two well-conducted RCTs, there is some evidence to recommend cranberry juice for the prevention of UTIs in women with symptomatic UTIs. The evidence is more inconclusive as to whether it is effective in older people (both men and women), and current evidence suggests that it is not effective in people with a neuropathic bladder. In addition, the large number of dropouts/withdrawals from some of the trials, indicates that cranberry juice may not be acceptable over long periods of time. Furthermore, there is no clear evidence as to the amount and concentration that needs to be consumed, and the length of time for the intervention to be most effective. A therapeutic dose of cranberry juice or products has not yet been established, but current knowledge suggests a glass of cranberry juice twice a day.

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