Cochrane Library

Cochrane Database of Systematic Reviews

Cranberries for treating urinary tract infections (Review)

Jepson RG, Mihaljevic L, Craig JC

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

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Cranberries for treating urinary tract infections

Ruth G Jepson[1], Lara Mihaljevic[2], Jonathan C Craig[3]

[1]Department of Nursing and Midwifery, University of Stirling, Stirling, UK. [2]Haberfield, Australia. [3]a) Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, b) School of Public Health, The University of Sydney, Westmead, Australia

Contact address: Ruth G Jepson, Department of Nursing and Midwifery, University of Stirling, Stirling, Scotland, FK9 4LA, UK. ruth.jepson@stir.ac.uk.

Editorial group: Cochrane Kidney and Transplant Group
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2010.

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

ABSTRACT

Background

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

Objectives

To assess the effectiveness of cranberries for the treatment of UTIs.

Search methods

The search strategy developed by the Cochrane Renal Group was used. Also, companies involved with the promotion and distribution of cranberry preparations were contacted; electronic databases and the Internet were searched using English and non English language terms; reference lists of review articles and relevant studies were also searched.
Date of last search: July 2010

Selection criteria

All randomised controlled trials (RCTs) or quasi-RCTs of cranberry juice or cranberry products for the treatment of UTIs. Studies of men, women or children were included.

Data collection and analysis

Titles and abstracts of studies that were potentially relevant to the review were screened by one author, RJ, who discarded studies that were clearly ineligible but aimed to be overly inclusive rather than risk losing relevant studies. Authors RJ and LM independently assessed whether the studies met the inclusion criteria. Further information was sought from the authors where papers contained insufficient information to make a decision about eligibility.

Main results

No studies were found which fulfilled all of the inclusion criteria. Two studies were excluded because they did not have any relevant outcomes and two studies are currently being undertaken.

Authors' conclusions

After a thorough search, no RCTs which assessed the effectiveness of cranberry juice for the treatment of UTIs were found. Therefore, at the present time, there is no good quality evidence to suggest that it is effective for the treatment of UTIs. Well-designed parallel group, double blind studies comparing cranberry juice and other cranberry products versus placebo to assess the effectiveness of cranberry juice

in treating UTIs are needed. Outcomes should include reduction in symptoms, sterilisation of the urine, side effects and adherence to therapy. Dosage (amount and concentration) and duration of therapy should also be assessed. Consumers and clinicians will welcome the evidence from these studies.

PLAIN LANGUAGE SUMMARY

Still waiting for evidence about whether cranberries are a useful treatment for urinary tract infections

Cranberries contain a substance that can prevent bacteria from sticking on the walls of the bladder. This may help reduce bladder and other urinary tract infections (UTIs). Cranberries (usually as cranberry juice) have been used to try and treat UTIs, particularly in high risk groups such as older people. Cranberries have few adverse effects. The review found no evidence from studies about the effects of cranberry juice or other cranberry products on UTIs.

BACKGROUND

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

Although UTIs can occur in both men and women, they are about 50 times more common in adult women than adult men. This may be because women have a shorter urethra that may allow bacteria to ascend more easily into the bladder. Symptomatic infection of the bladder (lower tract UTI) has been estimated to occur in up to 30% of women at some stage during their lives (Kelly 1977). Most UTIs arise from the 'ascending' route of infection. The first step is colonisation of periurethral tissues with uropathogenic organisms, followed by the passage of bacteria through the urethra. Infection arises from bacterial proliferation (growth) within the otherwise sterile urinary tract. In children, UTI occurs more commonly in boys up to the age of 6 to 12 months, but overall occurs about three times more often in girls (1% to 3% in boys, 3% to 7% in girls) (Hellstrom 1991; Winberg 1974).

Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the prevention and treatment of UTIs. Cranberries contain quinic acid, malic acid and citric acid as well as glucose and fructose. Until recently, it was suggested that the quinic acid caused large amounts of hippuric acid to be excreted in the urine which then acted as an antibacterial agent (Kinney 1979). Several studies, however, have shown no difference in the levels, or only a transient (short lived) effect thus casting some doubt on this theory (Kahn 1967; McLeod 1978). More recently, it has been demonstrated that cranberries prevent bacteria (particularly *E. coli*) from adhering (sticking) to uroepithelial cells that line the wall of the bladder (Schmidt 1988; Sobota 1984). Cranberries contain two compounds which inhibit adherence - fructose and a polymeric compound of unknown nature (Zafriri 1989). Although many juices contain fructose, only cranberries and blueberries contain the polymeric compound (Ofek 1991).

UTIs are one of the most common medical conditions requiring outpatient treatment, and complications resulting from persistent and repeated infections necessitate well over one million hospital admissions annually in the USA (Patton 1991). Traditionally UTIs have been treated by antibiotic therapy, but these are expensive, can have side effects and may lead to resistance. The aim of this review is to assess the effectiveness of cranberries in treating symptomatic and asymptomatic UTIs. Although cranberry juice is the form of cranberries most widely used, other cranberry products include cranberry powder in hard or soft gelatin capsules. The amount and concentration of cranberry juice needed to be effective for the treatment of UTIs has not yet been ascertained. One uncontrolled trial, however, found that over 50% of patients had a positive clinical response after consuming 450 mL of cranberry juice for three weeks (Papas 1966).

Cranberries for the prevention of UTIs in susceptible populations is examined in another review by the same authors (Jepson 2008).

OBJECTIVES

We wished to test the following hypotheses:

- Cranberry juice and other cranberry products are more effective than placebo/no treatment for the treatment UTIs.
- Cranberry juice and other cranberry products are more effective than any other therapy for the treatment of UTIs.

If studies are included in this review in the future, an attempt will be made to quantify the side effects of cranberry juice and the findings will be taken into account in the discussion to determine the benefit-risk of the treatment.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of cranberry juice (or derivatives) versus placebo, no treatment or any other treatment. Quasi-RCTs (e.g. those studies which randomised participants by date of birth, or case record number) will be included, but the quality of the studies will be taken into account during the analysis. Cross-over studies will be excluded, because they are not appropriate for short term treatment of acute conditions.

Types of participants

Inclusion criteria

Studies of men, women or children with one the following:

1. a symptomatic lower UTI,
2. a symptomatic upper UTI,
3. an asymptomatic UTI.

- Symptomatic is defined as having one or more or the following symptoms: dysuria, frequency, urgency.
- Studies of participants with either a history recurrent UTIs or an in-dwelling catheter must have specified that participants have a confirmed UTI (asymptomatic or symptomatic) prior to randomisation.
- If studies become available for inclusion in this review, these three groups will be analysed separately. Furthermore, the

causative organism (e.g. *E. coli*) and the methods used to diagnose upper and lower UTIs will be subjected to sensitivity analysis.
- The participants in the studies can be from any setting (hospital, clinic, community).

Exclusion criteria

- Studies of the prevention of UTIs in susceptible groups of the population (these will be analysed in a separate review by the same authors)
- Studies of any urinary tract condition not caused by bacterial infection (e.g. interstitial cystitis which is a is a chronic inflammation of the bladder wall)

Types of interventions

Cranberry juice or a cranberry product (e.g. cranberry capsules) given for at least five days. If studies become available for inclusion in this review, dosage (amount and concentration), duration of treatment and length of treatment will be taken into account in subgroup analyses (see methods section for more details).

Types of outcome measures

Primary outcomes

- Number of symptomatic and asymptomatic UTIs in each group at the end of the treatment period.

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

Secondary outcomes

- Reduction in severity of symptoms.
- Adherence to therapy.
- Side effects.

Search methods for identification of studies

Initial search

Relevant studies were obtained from the following sources:

- The search strategy developed by the Cochrane Renal Group.
- Cochrane Controlled Trials Register (CCTR) and CENTRAL (Issue 3 of *The Cochrane Library* 1998).
- Registry of randomised trials for the Cochrane Collaboration Field in Complementary Medicine.
- Companies involved with the promotion and distribution of cranberry preparations were approached and asked to provide information on both published and unpublished studies.
- Electronic databases including PsycLit, LILACS, CINAHL, MEDLINE, EMBASE, Biological Abstracts, Current Contents.

These databases were searched using the following terms*:

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

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

- The following terms were searched to identify non-English language studies:
  * Danish - (Tranebaersaft.ti,ab. or tranebaer.ti,ab. or orkaempetranebaer.ti,ab. or store tranebaer.ti,ab. or cranberry.ti,ab.) and (urinvejsinfektion.ti,ab. or cystitis.ti,ab. or blaerebetaendelse.ti,ab. or pyelonephritis.ti,ab. or pyelonefrit.ti,ab.)
  * Dutch - (veenbes.ti,ab. or lepeltjeheide.ti,ab. or lepeltjesheide.ti,ab. or Amerikaanse veenbes.ti,ab. or cranberry.ti,ab.) and (cystitis.ti,ab. or catarrhus.ti,ab. or vesicalis.ti,ab. or blaasontsteking.ti,ab. or urineweginfectie.ti,ab. or pyelonephritis.ti,ab. or nephropyelitis.ti,ab.)
  * French - (canneberges ronce d'Amerique.ti,ab. or cranberry.ti,ab. or cranberrie.ti,ab.) and (cystite.ti,ab. or infection urinaire.ti,ab. or pyélonéphrite.ti,ab.)
  * German - (moosbeere.ti,ab or kranbeere.ti,ab.) and (zystitis.ti,ab. or cystitis.ti,ab. or harnwegsinfektion.ti,ab. or harninfekt.ti,ab. or pyelonephritis.ti,ab.)
  * Italian - (vaccinium oxycoccus.ti,ab. or ossicocco palustro.ti,ab.) and (cistite.ti,ab. or infezione del tratto urinario.ti,ab or infezione urinaria.ti,ab. or infezione delle vie urinarie.ti,ab. or pielonefrite.ti,ab. or nefropielite.ti,ab.)
  * Portuguese - (cranberry.ti,ab. or oxicoco$.ti,ab. or vaccinium oxycoccos.ti,ab. or oxycoccus palustris) and (cistite.ti,ab. or pielonefrite.ti,ab.)
  * Spanish - (arandano agrio.ti,ab or arandano americano.ti,ab.) and (cistitis.ti,ab. or infección urinaria.ti,ab or pielonefritis.ti,ab.)
- The Internet was searched using the terms listed.
- Reference lists of review articles and relevant studies were searched.
- Conference abstracts from The Proceedings of the Urological Association (1990-1998), and The Journal of the American Geriatrics Society (1990 -1998) were searched for relevant studies.
- The National Research Register was searched for studies currently underway.

Review update

For this update the Cochrane Renal Group's specialised register and CENTRAL was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an

ongoing activity across the Cochrane Collaboration and is both retrospective and prospective. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the complete list of nephrology conference proceedings searched (Renal Group 2010).

Data collection and analysis

Selection of studies

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

Data extraction and management

If studies which meet the inclusion criteria are identified in the future, RJ will provide LM with the full articles of the included studies and both authors will independently extract information using specially designed data extraction forms. For each included trial, information will be collected regarding the location of the study, methods of the study (as per quality assessment checklist), the participants (sex, age, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified previously. Where possible, missing data (including side effects) will be sought from the authors. Discrepancies in the data extraction will be referred to JC for discussion.

Assessment of risk of bias in included studies

The following items will be assessed using the risk of bias assessment tool (Higgins 2008) (*see* Appendix 1).

- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

If studies which meet the inclusion criteria are identified in the future, statistical analyses will be performed where possible. Briefly, the risk ratio (RR) will be used as the measure of effect for each dichotomous outcome. Where continuous scales of measurement are used to assess the effects of treatment, these data will be analysed in continuous form (i.e. mean difference). If different scales have been used in different studies, where possible, the results will be standardised and then combined (i.e. standardised mean difference).

Assessment of heterogeneity

Heterogeneity in the data will be noted and cautiously explored using previously identified characteristics of the studies, particularly assessments of quality.

Data synthesis

Where there is sufficient data, a summary statistic for each outcome will be calculated using both a fixed effects and a random effects model.

Subgroup analysis and investigation of heterogeneity

If studies which meet the inclusion criteria are identified in the future, the groups described previously (see under types of participants) will be analysed separately with the following subgroups:

- dosage (amount and concentration).
- frequency and duration of treatment.

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

Sensitivity analysis

Sensitivity analyses will be undertaken to examine the stability of the results in relation to a number of factors including study quality, the source of the data (published or unpublished), the causative organism (e.g. *E.coli*), the method used for confirming the presence of bacteria in the urine (e.g. catheter specimen of urine or midstream specimen of urine) and the method of diagnosing upper or lower UTI.

R E S U L T S

Description of studies

No studies assessing the treatment of UTIs with cranberry juice (or other cranberry products) which met all of the inclusion criteria were found.

Two studies were excluded from the review. One trial (Nahata 1982) was a randomised cross-over trial, comparing methenamine mandelate alone, methenamine mandelate plus ascorbic acid, or methenamine mandelate plus ascorbic acid and cranberry juice for people with UTIs. No relevant outcomes were presented, however, and the main purpose of the studies was to see the effect of the methenamine on formaldehyde concentration. The author was contacted, but could not provide any further information about the trial. Another cross-over trial (DuGan 1966) compared cranberry juice with no treatment for the reduction of urinary odours (which could have been caused by a UTI). From the description of the trial it is unlikely it was randomised and the report contained no relevant outcomes. See Characteristics of excluded studies for more details about both these studies.

Two ongoing studies have been identified (NCT00093054; NCT00305071).

- NCT00093054 will enrol women aged 18 to 40 years of age with a culture confirmed UTI. They will be randomised to either 8 ounces of cranberry juice or placebo juice twice a day for 6 months. Participants will have follow-up visits at 3 and 6

months and whenever they experience a symptomatic episode. Urine, vaginal and rectal specimens will be taken at each visit to test for the presence of bacteria. Participants will complete a questionnaire at study entry and at day 3, weeks 1 and 2, and then every month or whenever there is a recurrence of symptoms. This study is due to be completed in December 2008.

- NCT00305071 will enrol women aged 20 to 65 with non-complicated acute bacterial cystitis. The intervention group will receive 3-day oral trimethoprim/sulfamethoxazole (80/400 mg) 2 tablets twice a day on day 1 to 3 plus oral compound cranberry extract tablets (UmayC, 900 mg) 2 tablets three times a day on day 1 to 7. The control group will received same oral antibiotics plus identical placebo prescribed as the same protocol of intervention arm. Outcomes to be assessed are time to symptoms relief and pyuria eradication rate. This study has not started recruiting.

Risk of bias in included studies

No studies were found which met the inclusion criteria for this review.

Effects of interventions

No studies were found which met the inclusion criteria for this review.

DISCUSSION

No studies assessing cranberries for the treatment of UTIs which met our inclusion criteria were found. Only a few uncontrolled studies examining the effectiveness of cranberry juice in treating the symptoms of UTI have been reported. Two of these did show a beneficial effect (Papas 1966; Rodgers 1991) but no firm conclusions can be drawn from such studies.

AUTHORS' CONCLUSIONS

Implications for practice

No RCTs have been performed to assess the effectiveness of cranberry juice or cranberry products for the treatment of UTIs. Therefore, at the present time, there is no evidence to suggest that cranberry juice or other cranberry products are effective in treating UTIs.

Implications for research

More research is need to assess the effectiveness of cranberry juice in treating UTIs. Well-designed parallel group, double blind studies of cranberry juice and other cranberry products for the treatment of UTIs are needed. The outcomes should include reduction in symptoms, sterilisation of the urine, side effects and adherence to therapy. Dosage (amount and concentration) and duration of therapy should also be evaluated. Consumers and clinicians will welcome the evidence from these studies.

ACKNOWLEDGEMENTS

- Ruth Jepson would like to thank the Nuffield Trust for giving her a short term fellowship for this review.
- The authors would also like to thank the following people for replying to correspondence, even though they could provide no further information:
  * Prof Nahata (Nahata 1982)
  * Dr RJ Woodward (Larkhill Green Farm - cranberry tablets)

REFERENCES

References to studies excluded from this review

DuGan 1966 *{published data only}*

DuGan CR, Cardaciootto PS. Reduction of ammonial urinary odors by the sustained feeding of cranberry juice. *Journal of Psychiatric Nursing* 1966;**4**(5):467-9.

Nahata 1982 *{published data only}*

Nahata MC, Cummins B A, McLeod DC. Effect of urinary acidifiers on formaldehyde concentration and efficacy with methenamine therapy. *European Journal of Clinical Pharmacology* 1982;**22**(3):281-4. [MEDLINE: 7106162]

Nahata MC, Cummins BA, Mcleod DC, Butler R. Predictability of methenamine efficacy based on type of urinary pathogen and pH. *Journal of the American Geriatrics Society* 1981;**29**(5):236-9. [MEDLINE: 7014695]

Nahata MC, McLeod DC. Lack of effect of ascorbic acid, hippuric acid, and methenamine (urinary formaldehyde) on the copper-reduction glucose test in geriatric patients. *Journal of the American Geriatrics Society* 1980;**28**(5):230-3. [MEDLINE: 7365188]

References to ongoing studies

NCT00093054 *{published data only}*

NCT00093054. Cranberry juice and urinary tract infections. clinicaltrials.gov/ct2/show/NCT00093054 (accessed 13 July 2010).

NCT00305071 *{published data only}*

NCT00305071. A double-blind, randomized, placebo-controlled study to evaluate the effect of adjuvant treatment with compound cranberry extract tablets (UmayC) in acute bacterial cystitis. clinicaltrials.gov/ct2/show/NCT00305071 (accessed 19 July 2010).

Additional references

Hellstrom 1991

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

Higgins 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration. 2008. Available from www.cochrane-handbook.org.

Jepson 2008

Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub3]

Kahn 1967

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

Kelly 1977

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

Kinney 1979

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

McLeod 1978

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

Ofek 1991

Ofek I, Goldhar J, Zafriri D, Lis H, Adar R, Sharon N. Anti-Escherichia coli adhesin activity of cranberry and blueberry juices. *New England Journal of Medicine* 1991;**324**(22):1599. [MEDLINE: 1674106]

Papas 1966

Papas PN, Brusch CA, Ceresia GC. Cranberry juice in the treatment of urinary tract infections. *Southwestern Medicine* 1966;**47**(1):17-20. [MEDLINE: 5900988]

Patton 1991

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

Renal Group 2010

Willis NS, Mitchell R, Higgins GY, Webster AC, Craig JC. Cochrane Renal Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2010, Issue 7. Art. No.: RENAL (accessed July 2010).

Roberts 1979

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

Rodgers 1991

Rodgers J. Pass the cranberry juice. *Nursing Times* 1991;**87**(48):36-7. [MEDLINE: 1754454]

Schmidt 1988

Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios* 1988;**55**(224-225):173-82. [MEDLINE: 3063927]

Sobota 1984

Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *Journal of Urology* 1984;**131**(5):1013-6. [MEDLINE: 6368872]

Winberg 1974

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

Wong 1984

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

Zafriri 1989

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

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
DuGan 1966	Cross-over trial of cranberry juice versus no treatment. The 220 participants were elderly and from two hospital wards - one male and one female. The female ward received the cranberry juice first followed by the male ward. Cross-over trial of cranberry juice versus no treatment. This trial was excluded because from the description of the study design, it looked unlikely that this trial had be randomised. Also, the outcome was urinary odours, and no information was given about urinary tract infections. Furthermore, cross-over trials may not be a relevant trial design for acute conditions such as urinary tract infections.
Nahata 1982	Randomised controlled cross-over trial of 27 people with bacteriuria comparing methenamine mandelate alone, with ascorbic acid or with ascorbic acid and cranberry juice. The primary purpose of this review was to assess the effect of methenamine on formaldehyde concentrations. Each patient was randomised to 5 days of each therapy. The trial was excluded because it contained no relevant outcomes. Furthermore, cross-over trials may not be a relevant trial design for acute conditions such as urinary tract infections.

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

NCT00093054

Trial name or title	Cranberry Juice and Urinary Tract Infections ClinicalTrials.gov identifier: NCT00093054
Methods	
Participants	400 Females, 18-40 years with a culture-confirmed urinary tract infection at study start. Exclusion Criteria: - Other chronic disease - Antibiotics within 48 hours prior to study start - Hospitalization for any reason within 2 weeks prior to study start - Stones in urinary tract - Plans to leave Ann Arbor within 6 months after study start - Allergy to cranberry or cranberry compounds - Pregnancy
Interventions	Participants in this study will be randomly assigned to consume either 8 ounces of cranberry juice or placebo juice twice a day for 6 months
Outcomes	Participants in this study will be randomly assigned to consume either 8 ounces of cranberry juice or placebo juice twice a day for 6 months. Participants will have follow-up visits at 3 and 6 months,

NCT00093054 *(Continued)*

	and whenever they experience a symptomatic episode. Urine, vaginal and rectal specimens will be taken at each visit to test for the presence of bacteria that cause urinary tract infections. Participants will complete a questionnaire at study entry, day 3, weeks 1 and 2, and monthly thereafter or whenever there is a recurrence of symptoms.
Starting date	November 2004
Contact information	Cibele T. Barbosa-Cesnik 734-764-1350 cibele@umich.edu
Notes	Expected completion December 2008

NCT00305071

Trial name or title	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Effect of Adjuvant Treatment With Compound Cranberry Extract Tablets (UmayC) in Acute Bacterial Cystitis. ClinicalTrials.gov identifier: NCT00305071
Methods	
Participants	60 females, 20-65 years. Inclusion Criteria: - female patient with non-complicated acute bacterial cystitis. Exclusion Criteria: - recent (less than one month) urinary tract infection - partially treated acute cystitis - anatomical or function disease of the lower urinary tract - patients received radical pelvic surgery associated bladder stone disease - upper urinary tract anomaly or urolithiasis systemic - infection with body temperature higher than 38°C - known allergic reaction to cranberry or vitamin C pregnant or prepare to be pregnant.
Interventions	Intervention group will receive 3-day oral trimethoprim/sulfamethoxazole (80/400 mg) 2 tablets twice a day on day 1 to 3 plus oral compound cranberry extract tablets (UmayC, 900 mg) 2 tablets three times a day on day 1 to 7. The control group will received same oral antibiotics plus identical placebo prescribed as the same protocol of intervention arm. For patients with known allergic reaction to sulfa drug, the empirical antibiotics will be replaced by cephalexin (250 mg) 2 capsules four times a day.
Outcomes	Primary Outcome Measures: - Time to symptoms relief Secondary Outcome Measures: - Pyuria eradication rate
Starting date	April 2006
Contact information	Contact: Po-Chien Huang, MD 886-3-3179599 ext 8223 m001435@e-ms.com.tw Contact: Hung-Ju Yang, MD 886-3-3179599 ext 8225 m001436@e-ms.com.tw
Notes	Not yet recruiting

APPENDICES

Appendix 1. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Was there adequate sequence generation?	*Yes (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).
	No (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.
Was allocation adequately concealed?	*Yes (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).
	No (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.
Was knowledge of the allocated interventions adequately prevented during the study?	*Yes (low risk of bias):* No blinding, but the review authors judge that the outcome and the outcome measurement are 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; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
	No (high risk of bias): No blinding or incomplete blinding, and the outcome or outcome measurement 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; either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'
Were incomplete outcome data adequately addressed?	*Yes (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.
	No (high risk of bias): Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among miss-

(Continued)

	ing 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 of 'Yes' or 'No'.
Are reports of the study free of suggestion of selective outcome reporting?	*Yes (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).
	No (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 of 'Yes' or 'No'.
Was the study apparently free of other problems that could put it at a risk of bias?	*Yes (low risk of bias):* The study appears to be free of other sources of bias.
	No (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 permit judgement of 'Yes' or 'No'.

WHAT'S NEW

Date	Event	Description
13 July 2010	Amended	13 July 2010: Searched for new studies, none identified

CONTRIBUTIONS OF AUTHORS

- The titles and abstracts were screened by RJ.
- RJ and LM independently assessed studies.
- Disagreements resolved by discussion and consultation with JC.
- The quality of all studies which were deemed eligible for the review were then assessed independently by two of the reviewers RJ and LM.
- Discrepancies resolved by discussion with the third, JC.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nuffield Trust, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

New Cochrane methodology shall be used (Higgins 2008).

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Beverages; Fruit [*therapeutic use]; Urinary Tract Infections [*therapy]

MeSH check words

Humans