

The role of cranberry juice in the treatment of urinary tract infections

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Urinary tract infections (UTIs) are a common problem in the community. Community practitioners may be called on to give advice on the treatment or prevention of the problem in diverse groups from young children to the institutionalized elderly. Both clients and practitioners consider 'natural' remedies for common ailments, and this review seeks to examine the evidence base for one such remedy - the American cranberry (*Vaccinium macrocarpon*).

In preparing this review, the web-based service KA24 has been used extensively. KA24 is currently available to health professionals in the south of England and aims to provide access to knowledge 24 hours a day, 7 days a week. The website gives practitioners access to full text journals and major biomedical databases (*Box 1*).

Although a lower UTI can be asymptomatic, severe illness is a possibility, with pyelonephritis (infection of the kidneys) presenting a threat to older people, young children and people with suppressed immune systems. The generally agreed diagnostic criterion for infection is the presence of 100 000 or more bacteria (colony forming units or cfu) per ml of urine (Jepson et al, 2003a). However, treatment is frequently initiated on presentation of symptoms, which include cloudy urine, frequency and urgency of urination, pain on urination and pain in the lower back (Henig and Leahy, 2000; Jepson et al, 2003a). Apart from the youngest of children, females are more vulnerable than males in all age groups, with adult women at 50 times higher risk than men (Henig and Leahy, 2000; Jepson et al, 2003a). It has been estimated that nearly one-third of all women will experience a symptomatic bladder infection at some point in their life (Krieger, 2002). Pregnant women, the institutionalized older people and those with catheters are most at risk.

Cranberries, especially cranberry juice, have long been advocated as a possible intervention for the problem. They have been considered as both preventive therapy for those at high risk and as a treatment (Jepson et al, 2003a,b). The possible role of cranberries in managing UTIs is widely recognized and it is

estimated that 48% of American consumers are aware of the link (Henig and Leahy, 2000).

Unlike a number of alternative therapies, there is a plausible biological mechanism for the action of cranberry juice. It was originally believed that cranberry acted by rendering the urine acidic (Henig and Leahy, 2000) or by causing the excretion of a bacteriostatic compound (Jepson et al, 2003a). However, although neither of these hypotheses withstood detailed scrutiny it does appear that cranberries contain one or more compounds, in addition to fructose (common to all fruit juices) that inhibit the ability of *Escherichia coli* to adhere to uroepithelial cells that line the bladder (Henig and Leahy, 2000; Jepson et al, 2003a). *E. coli* is the most frequent cause of community-acquired UTI (Sobel, 1991).

The failure to demonstrate the originally supposed antibacterial mechanisms of cranberry *in vivo* clearly illustrates why evidence that a treatment works

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ABSTRACT

There has long been an interest in the use of cranberry, usually as a juice, to prevent and treat urinary tract infections (UTI). This mini-review examined the evidence available using a simple search on an internet-based resource designed to make evidence readily available to practitioners in the South Eastern NHS regions of the UK. The resource, known as KA24, provides access to a range of databases and full text of journal articles. The first stage of the review identified two existing Cochrane Reviews, one examining cranberry as a treatment, the other as prevention. Both concluded that there was insufficient evidence to recommend the use of cranberry in treating UTIs, although some weak research did offer support for cranberry juice in preventing UTIs. A search for further evidence not included in the Cochrane review identified several new reviews and two randomized controlled trials (RCTs) of cranberry as prevention. The reviews were not systematic and came to contradictory conclusions. They were based on a selective reading of the evidence base and gave no criteria for determining the inclusion or validity of studies. One of the RCTs was available for full scrutiny and was appraised as a valid study. Both RCTs found that cranberry (as juice or capsule) significantly reduced the rate of UTI in sexually active women. There is evidence to support the use of cranberry to prevent UTI in some populations but none to support its use as a treatment.

Box 1. KA24

- KA24 gives access to health-care knowledge resources 24 hours a day, 7 days a week to anyone working for or with the NHS in London, Kent, Surrey, Sussex, Hampshire, the Isle of Wight, Berkshire, Buckinghamshire and Oxfordshire
- To access it you need a computer that is linked to the NHS network or world wide web
- All NHS staff can apply for an individual password to access it from non-NHS net computers
- It gives access to a range of databases including Medline, Embase, British Nursing Index, CINAHL, AMED (complementary health) and Evidence-Based Medicine Reviews (which includes much of the content of the Cochrane Library and other evidence-based resources). It also includes direct online access to the full text of many journals
- It is currently a pilot project for what is hoped to be a national service after February 2004
- To access the service or to get further information go to:
<http://www.hilo.nhs.uk/> (London) or <http://stlis.thenhs.com/hln/ka24/> (rest of the South East)

should be sought from studies where the treatment has been used in the relevant population. A plausible mechanism might be a reason to consider a treatment but it does not mean that it works. This review seeks to identify high-quality evidence where cranberries have been used in the prevention or treatment of UTIs in order to determine what role (if any) it might have in practice.

Methods

This review was conducted in a series of stages. The source of data was full text reports and abstracts available on the KA24 service in November 2003. To be included, studies had to compare cranberries (as juice, berry or extract) with no treatment or a recognized standard treatment, and the outcome had to be a measure of incidence of UTI (for prevention) or resolution (for treatment).

Stage 1

The first stage involved the use of the evidence-based medicine reviews database which is a compendium of quality assessed resources, e.g. the Cochrane database of systematic reviews and papers that have been selected and abstracted for 'evidence-based' journals like *Evidence Based Medicine* by the American College of Physicians journal club. The material selected for this database is selected on the basis of validity. The need to critically appraise the research is less since it has already been done. Instead practitioners can concentrate on determining whether a paper answers the questions asked and if so what the implications of the answers are. As high-quality systematic reviews bring together all the available valid evidence on a topic, the first stage of

the search sought only such reviews as opposed to individual studies.

It must be stressed that this strategy differs from the assumption that traditional peer review in academic journals provides an assurance of quality. Peer review in itself does not assure the reader of the validity of research (Griffiths, 1999). Similarly the use of high-quality systematic reviews identified from these sources differs from basing conclusions on the results on non-systematic reviews where the method of identifying and selecting material for review is undocumented (Griffiths, 1999).

The database was searched using the key word 'cranberry' and truncated in order to find alternative word endings, such as cranberries (*Box 2*). The search identified 19 papers which included two systematic reviews (Jepson et al, 2003a,b). Both of these reviews are Cochrane reviews, which are conducted to a rigorous standard and only allow high-quality evidence to be considered.

The first review found no valid evidence regarding the treatment of UTI with cranberry. One study was found that did not report any relevant outcomes (Nahata et al, 1982) while another only reported urinary odours and did not appear to be a randomized controlled trial (DuGan and Cardaciotto, 1966). A further paper identified in the background for the review reported a favourable response in 50% of patients drinking 450 ml of cranberry juice for 3 weeks, but the study was not controlled (Papas et al, 1966).

The second review (Jepson et al, 2003b) examined prevention of UTI in susceptible people, defined as those suffering recurrent UTI, e.g. older people, people undergoing intermittent catheterization, pregnant women, those with an indwelling catheter or abnormality of the urinary tract. Five studies were included in the review, studying 304 patients in total. Four compared cranberry juice to placebo juice or water while one used cranberry capsules and a placebo. The amount of cranberry juice used varied from 300ml in one trial to 30ml in another. Two studies examined older people, one investigated people with a history of recurrent UTI and one researched people undergoing intermittent catheterization. The review rated the overall quality of studies as poor, and all had methodological shortcomings. In particular, all but one study had a high proportion of dropouts, which threatens validity as their outcomes are not known.

One trial reported a significant reduction in symptomatic UTI and one reported a reduction in asymptomatic UTI. However, the reviewers questioned the validity of these results on a number of counts and concluded that there was insufficient evidence of

effectiveness. They also speculated that the high number of dropouts observed might be an indication that the treatment was unacceptable.

Stage 2

The evidence identified in stage one was insufficient to recommend cranberry juice. More evidence of a higher quality was required to answer the question. Importantly, both the reviews found used a highly comprehensive search strategy. Therefore, it is unlikely that this review could identify further papers published in the period covered by searches for those reviews. Cochrane reviews are regularly updated, but integration of new evidence into a review can be subject to some delay. The most recent search for the reviews was conducted in January 2001.

Therefore, it was decided to search for more evidence published after January 2001. The search for additional evidence was undertaken using five databases – Medline, Embase, CINAHL, British Nursing Index and AMED (a database of complementary health-care research) using both free text and index terms for cranberries, papers were identified on three of the five databases (Box 2). The search was limited to papers published from 2000–2003. Items considered were reviews and controlled trials. For a review to be considered as evidence it must have been conducted according to an explicit method and to have selected valid research according to explicitly-stated criteria (i.e. it must be a valid systematic review).

Table 1 contains a brief summary of the material identified. The results were instructive. Of the nine items identified eight were reviews and one was a new randomized controlled trial (Kontiokari et al, 2001). None give any additional support to the use of cranberry in treating UTIs and so further consideration is limited to the prevention of UTI.

Of the seven reviews, only three cite the Cochrane reviews as part of the basis on which their conclusion are drawn. Of these, one (Reisen, 2002) offers no new evidence but chooses to selectively cite one negative study from the review to support a conclusion of no effect. Kiel et al (2003) cite two new controlled trials (Kontiokari et al, 2001; Stothers, 2002) and come to a cautiously positive recommendation. However, the criteria for selecting material for review is not given and so one cannot be confident that the new evidence is valid without scrutinizing it directly. The third paper (Biering-Sorensen, 2002) cites two new studies, one already identified (Kontiokari et al, 2001) and one that is not a controlled trial (identified by scrutinizing its abstract) (Reid et al, 2001). Again, the result is cautiously positive. However, the method of the review is not given and its validity should not be taken at face value.

Box 2. Searches and results

Stage 1

Database: Evidence-Based Medicine Reviews
Search terms: Cranberr\$*
Results: hits 19; relevant to topic 16; systematic reviews 2

Stage 2

Databases: Medline, Cinahl, Embase, BNI, AMED
Search terms: Cranberr\$ or *Vaccinium macrocarpon* (MESH) or cranberry juice (CINAHL index) or cranberry (Embase index)
Results: unique hits 18; relevant to question 8; reviews 7
(* \$ = Ovid truncation operator to find all possible endings of root text)

Of the four reviews that do not cite the Cochrane review, one cites another review, one cites the two favourable studies included in the Cochrane review (Avorn et al, 1994; Walker et al, 1997) and a more recent trial (Kontiokari et al, 2001), and two cite only Avorn et al (1994) and Kontiokari et al (2001). Three of these give conclusions that support the use of cranberry juice in preventing UTIs with only one (Dwyer and O'Reilly, 2002) being anything other than emphatic. Krieger (2002) comes to the opposite conclusion using essentially the same evidence.

The only additional evidence published since the Cochrane review are therefore the two trials, neither of which have been considered in a systematic review. One (Stothers, 2002) was identified from the reference list of the other papers and was not available for full scrutiny from the resources utilized. Therefore only one piece of additional evidence was available for full scrutiny (Kontiokari et al, 2001). This was a randomized controlled trial comparing no intervention to daily *Lactobacillus* drink or 50ml of cranberry-lingonberry juice concentrate containing 7.5g of cranberry concentrate made up into 200ml drinks. Fifty women were randomized to each group, although it is not clear if allocation was concealed prior to randomization. Bias can occur when this is not done (Juni et al, 2001). Unlike most of the studies reviewed previously, the drop out rate was low (less than 10%) and was equal from each group. Outcomes were assessed using a standard microbiological criterion (>100 000 cfu per ml) to diagnose symptomatic women. Over a 6-month follow up period, 8 (16%) of the cranberry juice group experienced one or more UTIs compared to 19 (39%) in the *Lactobacillus* group and 18 (36%) in the no-intervention control. The absolute risk reduction (the difference between cranberry juice and control) was 20% (95% confidence interval 3%–34%).

This evidence is far stronger than any presented previously. Stothers (2002) found similar results in a group of sexually active young women with a reduction from 32% experiencing infections in the control group over one year, to 20% when using cranberry

Table 1. Summary of papers recovered by search

Paper	Description	Recommendation*	Review decision
Anonymous, 2002	Review paper	'...sufficient clinical evidence exists to continue recommending that patients consume cranberry products to reduce their risk of developing UTIs' based on an account of another review	Exclude – no evidence of systematic search or critical appraisal
Biering-Sorensen, 2002	Review paper	'...it appears that there may be a future application for cranberry products in the treatment or prevention of UTI...' based on Cochrane review and other non-systematic reviews plus (Kontiokari et al, 2001) and one new uncontrolled study (Reid et al, 2001)	Exclude – the review is selective. No evidence of systematic search or critical appraisal
Dwyer and O'Reilly, 2002	Review paper	'The drinking of cranberry juice for the prevention of UTIreduces bacterial adherence and reduces bacteriuria' based on quoting studies in the Cochrane review (Avorn et al, 1994) and 1 other (Kontiokari et al, 2001)	Exclude – the review is selective. No evidence of systematic search or critical appraisal
Kiel et al, 2003	Review paper	'Despite flaws, the weight of the clinical evidence suggests that cranberry juice is an effective intervention for the prevention of UTIs-especially in high-risk populations.' Cites Cochrane review and 2 new studies (Kontiokari et al, 2001; Stothers, 2002)	Exclude. The review is described as evidence-based** but the criteria for selecting material are not made explicit.
Kontiokari et al, 2001	Randomized controlled trial	'Regular drinking of cranberry juice seems to reduce the recurrence of urinary tract infection'	Include
Krieger, 2002	Review paper	'There is currently no evidence that daily ingestion of cranberry juice improves clinical outcomes' based on quoting one study in the Cochrane review (Avorn et al, 1994) and one other (Kontiokari et al, 2001)	Exclude – the review is selective. No evidence of systematic search or critical appraisal
Leahy et al, 2001	Review paper	'Now a considerable body of science, including clinical, mechanistic and epidemiologic studies, supports cranberry in helping to maintain urinary tract health' based on evidence from 2/4 studies in the Cochrane review (those showing significant results– (Avorn et al, 1994; Walker et al, 1997) and one new study (Kontiokari et al, 2001)	Exclude – the review is selective. No evidence of systematic search or critical appraisal
Reisen, 2002	Review paper	'Preliminary studies in women with recurrent urinary tract infections and in children with neurogenic bladder have not shown substantial benefit' Cites Cochrane review and a study from it (Schlager et al, 1999) which had negative results.	Exclude. No additional evidence presented to Cochrane review (despite selective quotation)

*The recommendation of the paper is reproduced for information only – the claims of valid research will be considered further.

** Often evidence-based reviews are produced according to criteria that are published separately from the paper itself. Knowledge of these criteria might give more confidence in the validity.

juice and 18% when using cranberry capsules. This trial on 150 women was described as random and used placebo controls and is possibly even stronger, but the full report was not available for review. However its inclusion would clearly not contradict a conclusion based on (Kontiokari et al, 2001) alone.

Conclusions

There is no valid evidence to support the use of cranberry juice in treating UTI although of course this does not mean it does not work. However, practitioners would be unwise to recommend it and more

research is needed to establish if there is a role. Evidence supports the effectiveness of using cranberry juice to prevent UTI in sexually active women. Although the mechanism of action is supported by a strong scientific rationale, there is no good evidence to support its use in other groups and the high drop-out rates reported in many studies suggests that the juice may be unpalatable to some. The sample sizes in the valid research have been small and so the extent of the benefit remains unclear. More research is required but practitioners might reasonably recommend this as a possible strategy in preventing

UTI in susceptible populations, although clearly strategies such as giving it to all patients in a nursing home would not be acceptable.

The effective dose is unclear, although a daily glass of juice (200–300 ml) or cranberry capsules are both potentially effective. Cranberry juice is not cheap and it is not to everyone's taste (although use of capsules does get around this). The juice costs around £1.50 per litre in the UK and so a year's treatment would cost about £137 if taking 250 ml per day.

Many of the reviews examined here were quite emphatic about cranberry's benefits based on a selective reading of rather poor literature. Other reviews were negative about this potentially beneficial intervention. The apparent authority of some of them, published as they were in esteemed academic journals, did not guarantee rigour. Reviews sometimes based their conclusions on selective quotation of evidence that supported the authors' point and so came to different conclusions. Sometimes precisely the same evidence was used to make different conclusions when no clear criteria were given for determining a conclusion that evidence was valid (or otherwise). This emphasizes the importance of systematic reviews.

The methods of two systematic reviews might differ and so differing conclusions are still possible. However, because the scope of the review and decisions about what constitutes valid evidence must be made explicit, it should be easier for readers to come to their own conclusions. The appearance of new evidence not incorporated in the Cochrane reviews also emphasizes the need to revisit knowledge and update reviews. Evidence moves on and practitioners need to keep up to date with it. ■

NB The Committee on Safety of Medicines has issued advice to health professionals, via the September 2003 issue of Current Problems in Pharmacovigilance of the possibility of interaction between warfarin and cranberry juice. This advice may also be relevant to cranberry juice extract tablets and can be seen at <http://medicines.mhra.gov.uk/ourwork/monitorsafeequalmed/currentproblems/cpsept2003.pdf>. The advice concludes that until the possible interaction between cranberry juice has been investigated further it would be prudent for patients taking warfarin to limit or avoid drinking cranberry juice.

Anonymous (2002) Nutrition matters. *The Nurse Practitioner: The American Journal of Primary Health Care* 27(4 Suppl 20): 10

Avorn J, Monane M, Gurwitz JH, et al (1994) Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 271(10): 751–4

Biering-Sorensen F (2002) Urinary tract infection in individuals with spinal cord lesion. *Curr Opin Urol* 12(1): 45–9

DuGan C, Cardaciotto P (1966) Reduction of amonial urinary odors by the sustained feeding of cranberry juice. *Journal of Psychiatric Nursing* 4: 467–70

Dwyer PL, O'Reilly M (2002) Recurrent urinary tract

infection in the female. *Curr Opin Obstet Gynecol* 14(5): 537–43

Griffiths P (1999) The challenge of implementing evidence-based health care. *Br J Community Nurs* 4(3): 142–48

Henig YS, Leahy MM (2000) Cranberry juice and urinary-tract health: science supports folklore. *Nutrition* 16(7–8): 684–7

Jepson RG, Mihaljevic L, Craig J (2003a) Cranberries for treating urinary tract infections. *Cochrane Database Syst Rev* 4

Jepson RG, Mihaljevic L, Craig JC (2003b) Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 4

Juni P, Altman DG, Egger M (2001) Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 323(7303): 42–6

Kiel RJ, Nashelsky J, Robbins B (2003) Does cranberry juice prevent or treat urinary tract infection? *J Fam Pract* 52(2): 154–5

Kontiokari T, Sundqvist K, Nuutinen M et al (2001) Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ* 322(7302): 1571–3

Krieger JN (2002) Urinary tract infections: what's new? *J Urol* 168(6): 2351–8

Leahy M, Roderick R, Brilliant K (2001) The cranberry — promising health benefits, old and new. *Nutrition Today* 36(5): 254–65

Nahata MC, Cummins BA, McLeod DC, Schondelmeyer SW, Butler R (1982) Effect of urinary acidifiers on formaldehyde concentration and efficacy with methenamine therapy. *Eur J Clin Pharmacol* 22(3):281–4

Papas PN, Brusca CA, Ceresia GC (1966) Cranberry juice in the treatment of urinary tract infections. *Southwest Med* 47(1): 17–20

Reid G, Hsieh J, Potter P et al (2001) Cranberry juice consumption may reduce biofilms on uroepithelial cells: pilot study in spinal cord injured patients. *Spinal Cord* 39(1): 26–30

Reisen S (2002) Dietary supplement use for pediatric infections. *Pediatr Infect Dis J* 21(7): 683–4

Schlager TA, Anderson S, Trudell J, Hendley JO (1999) Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. *J Pediatr* 135(6): 698–702

Sobel JD (1991) Bacterial etiologic agents in the pathogenesis of urinary tract infection. *Med Clin North Am* 75(2): 253–73

Stothers L (2002) A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol* 9(3): 1558–62

Walker EB, Barney DP, Mickelsen JN et al (1997) Cranberry concentrate: UTI prophylaxis. *J Fam Pract* 45(2): 167–8

KEY POINTS

- Cranberries are often recommended for the prevention and treatment of UTI.
- Existing reviews offer contradictory conclusions because they are based on a selective reading of the evidence or were published prior to new evidence.
- An unbiased appraisal of new evidence leads to the conclusion that cranberry can prevent UTIs in some groups.
- The findings of this review emphasise the need to use only high quality evidence (including systematic reviews) but also the need to keep these reviews updated.
- Practitioners need to update their knowledge of evidence regularly.