DOCTOR'S FORMULAS

ΦΟΡΜΟΥΛΕΣ ΥΓΕΙΑΣ

βιβλιογραφία

NEFROLIN

περιεχόμενα

NEFROLIN

ΦΟΡΜΟΥΛΑ
νεφρών
για τη βελτίωση της ουροποιητικής οδού
και των νεφρών

100ml

Cranberry | Orthosiphon

χτυπήστε τις πέτρες στα νεφρά

Οι μολύνσεις του Ουροποιητικού Συστήματος

ΣΟΒΑΡΕΣ ΝΟΣΟΙ

- Ουρηθρίτιδες και κυστίτιδες
- Οξείες πυελονεφρίτιδες

ΣΥΜΠΤΩΜΑΤΑ

- Αίσθηση καψίματος κατά την ούρηση
- Συχνοουρία
- Έντονη βραδυνή συχνοουρία
- Πόνος στα νεφρά

ΑΙΤΙΕΣ

- Υπεύθυνο είναι το GRAM- (80% Escherichia Coli)

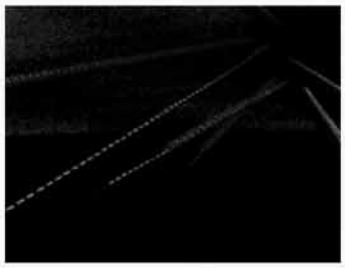
*Οι **μολύνσεις** του **ουροποιητικού συστήματος** μπορούν να δημιουργήσουν **πέτρες**.*

Η λύση είναι το:

NEFROLIN

Διάλυμα με βάση φυτικά εκχυλίσματα σε υγρή μορφή με τις εξής δράσεις:

Αντιμικροβιακή:	▪ Arctostaphylos uva ursi (Αρκουδοστάφυλλο) ▪ Arbutina vaccinium vitis idea (Γλυκοσίδια φαινόλης) ▪ Junipesis Communis (Τερπένιο)
Διουρητική:	▪ Solidago virgaurea (Φλεβονοειδές)
Εξυγιαντική:	▪ Fumaria officinalis (Προποτίνη)
Αντιλιθιασική:	▪ Ceterach officina rum (Φλαβονοειδές)
Αντιφλεγμονώδη:	▪ Ceterach officina rum (Φλαβονοειδές)



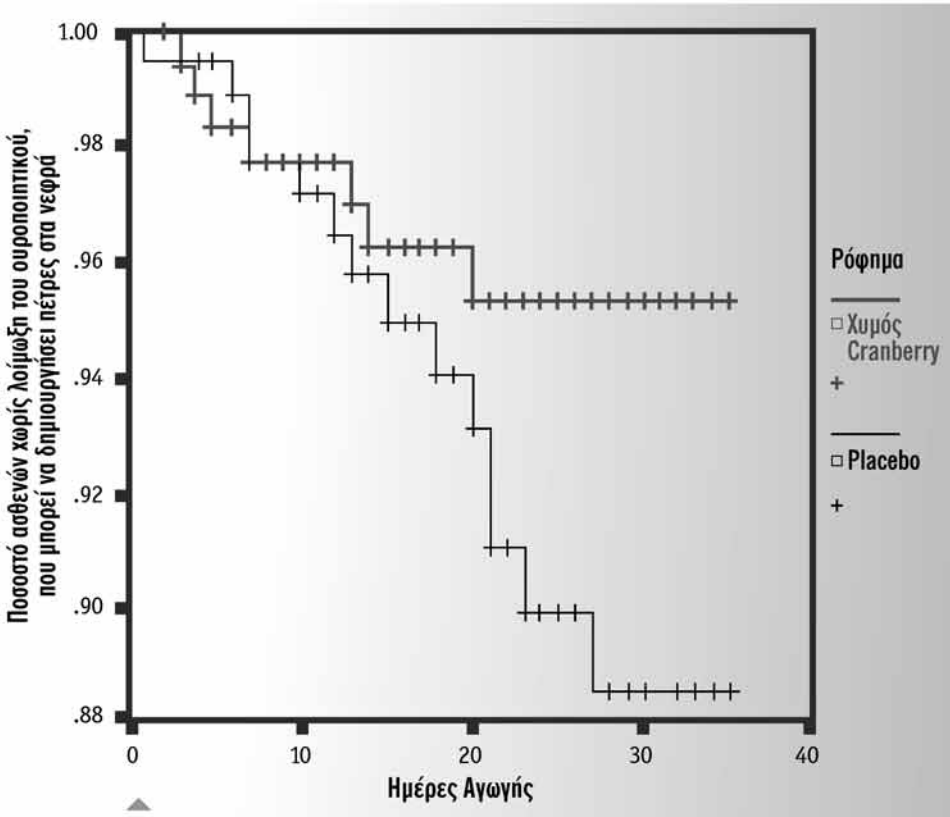
Το CRANBERRY ES 23% σε ΑΝΘΟΚΥΑΝΟΣΙΔΙΕΣ

(Vaccinium macrocarpon) έδειξε σε αρκετές κλινικές μελέτες, ότι μειώνει την εισχώρηση του E-Coli, εμποδίζοντας την εκδήλωση μολύνσεων.

Age and ageing 2005;
34: 256-261
The author 2005. Published by Oxford University Press on Behalf of the British Geriatrics Society.
doi:10.1093/ageing/afi101

Μπορεί η κατανάλωση χυμού από εκχύλισμα cranberry να ελαττώσει τις μολύνσεις του ουροποιητικού που προκαλούν συμπτώματα σε ηλικιωμένους που νοσηλεύονται στο νοσοκομείο; Μια διπλά-τυφλή ελεγχόμενη μελέτη με Placebo.

Marione E.T. McMURDO



Σύγκριση των ασθενών στην διάρκεια των συμπτωμάτων από μολύνσεις της ουροποιητικής οδού. Η κόκκινη γραμμή, χυμός cranberry (n=7 στάδια μόλυνσης) η μαύρη γραμμή, placebo (n=14 στάδια μόλυνσης). Test σε κλίμακα ιεραρχίας P=0,122.

ΣΥΝΙΣΤΑΤΑΙ ΣΕ ΠΕΡΙΠΤΩΣΕΙΣ

- **Νεφρολιθίασης**
- **Ψαμμίασης**
- **Νεφρίτιδας**
- **Κυστίτιδας**
- **Ουρηθρίτιδας**

ΔΟΣΟΛΟΓΙΑ

- 5ml, 3 φορές την ημέρα.
- Διαλύστε **5ml** διαλύματος σ' ένα ποτήρι νερό.

ΔΙΑΤΡΟΦΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ	ανά 100ml	ανά ημερήσια δόση 15ml
Γιόβα	3g	0,45g
Αρκτοστάφυλος υγρό εκχύλισμα	15g	2,25g
Σολιτάγκο - χρυσόβεργα	7g	1,05g
Σκορπίδι	5g	0,75g
Άρκευθος υγρό εκχύλισμα	5g	0,75g
Φουμαριά	5g	0,75g
Κόκκινο μύρτιλλο (Άμπελος της ίδης)	3g	0,45g
Κράνμπερρυ (εκχύλισμα) 30% σε προανθοκυανιδίνη	1g	0,15g

Age and Ageing 2005; 34: 256–261
doi:10.1093/ageing/afi101

Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial

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Abstract

Background: cranberry juice is often given to older people in hospital to prevent urinary tract infection (UTI), although there is little evidence to support its use.
Objective: to assess whether cranberry juice ingestion is effective in reducing UTIs in older people in hospital.
Design: randomised, placebo-controlled, double-blind trial.
Setting: Medicine for the Elderly assessment and rehabilitation hospital wards.
Subjects: 376 older patients in hospital.
Methods: participants were randomised to daily ingestion of 300 ml of cranberry juice or matching placebo beverage. The primary outcome was time to onset of first UTI. Secondary outcomes were adherence to beverage drinking, courses of antibiotics prescribed, and organisms responsible for UTIs.
Results: 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, $P=0.122$). Although there were significantly fewer infections with *Escherichia coli* in the cranberry group (13 versus 4) RR 0.31 [95% CI 0.10–0.94, $P=0.027$], this should be interpreted with caution as it was a secondary outcome.
Conclusion: despite having the largest sample size of any clinical trial yet to have examined the effect of cranberry juice ingestion, the actual infection rate observed was lower than anticipated, making the study underpowered. This study has confirmed the acceptability of cranberry juice to older people. Larger trials are now required to determine whether it is effective in reducing UTIs in older hospital patients.

Keywords: *urinary tract infection, randomised clinical trial, cranberry juice, hospital, elderly*

Introduction

Although cranberry juice is commonly given to older people to prevent urinary tract infection (UTI), there is little evidence to support its use. Only one large trial to date has studied the effect of cranberry juice in older people. Avorn and colleagues randomised 153 elderly women from housing complexes in a controlled trial using a matching placebo. Ingestion of 300 ml of cranberry juice daily for 6 months was associated with a lower incidence of bacteriuria with pyuria [1]. However, analysis was not by intention to treat and substantially more of the placebo group (25%) than the cranberry group (7%) had a history of UTI in the 6 months prior to the study. This has led to criticism of the randomisation or blinding employed [2]. Furthermore, as asymptomatic bacteriuria is a condition which does not require

treatment, there seems little value, even if cranberry juice is effective in preventing it.

The mechanism by which an effect of cranberry might be mediated has been the source of much debate. Berries of the *Vaccinium* species, such as cranberries and blueberries, contain tannins called proanthocyanidins. Proanthocyanidins are stable phenolic compounds, which exhibit potent anti-adhesion activity against both sensitive and resistant strains of P-fimbriated *Escherichia coli*, preventing adherence to uroepithelial cells which line the wall of the bladder [3].

Cranberry juice is an attractive therapy as it is a cheap, natural product which should not lead to antibiotic resistance. Given that UTI occurs more frequently in old age than at any other time of life [4], and is common in hospitalised older people, this study was designed to examine whether ingestion of cranberry juice was associated with a reduction in symptomatic UTIs in elderly hospital patients.

Methods

Study population

In contrast to other studies of cranberry juice and UTI, the target population was older hospital patients, not those with a history of recurrent UTIs.

Inclusions: Patients aged 60 years or over admitted to either acute Medicine for the Elderly assessment or rehabilitation units (Royal Victoria Hospital, Ashludie Hospital, Ninewells Hospital, Dundee and Perth Royal Infirmary) for elderly people in Tayside, Scotland.

Exclusions: Mental State Questionnaire (MSQ) score <5/10; dysphagia; symptoms of a UTI; antibiotic treatment; anticipated length of stay less than 1 week; regular drinkers of cranberry juice; presence of an in-dwelling catheter; and terminal illness. In light of a UK Committee on Safety of Medicines alert about a potential interaction between cranberry juice and warfarin which emerged during the final 8 weeks of recruitment, warfarin was added as an exclusion for that period only [5].

Written informed consent was obtained from participants and the study was approved by the Tayside Committee on Medical Research Ethics. Potential participants were given the opportunity to taste a sample of the juice prior to giving consent.

Randomisation

Participants were stratified by gender and by hospital and randomised to receive either 150 ml of cranberry juice or 150 ml of placebo beverage twice daily. To optimise adherence, the juice was prescribed in the ward drug kardex and administered by nursing staff. Randomisation was performed by opening sealed envelopes in numbered sequence prepared by an individual not otherwise involved in the study, and prepared from a computer-generated random numbers program. The treatment code was held in a sealed envelope by the Clinical Trials Pharmacist, The Pharmacy, Ninewells Hospital.

Cranberry juice and placebo juice

Both beverages looked and tasted identical. Both the Light Cranberry low calorie juice and the matching placebo beverage were provided by Ocean Spray Cranberries, Inc. (Lakeville-Middleboro, MA, USA) and produced annually by Gerber Foods Soft Drinks Ltd (Bridgewater, Somerset, UK). The juice contained water, cranberry juice from concentrate (25%), sugar, vitamin C and a non-nutritive sweetener (aspartame). The cranberry concentrate used to produce the juice had a proanthocyanidin concentration of 11.175 μg/g (dry solids basis). The placebo beverage contained no cranberry solids, but contained water, sugar (sucrose), elderberry extract, quinic acid, citric acid, malic acid, vitamin C and non-nutritive sweetener (aspartame).

Urine culture methods

Clean catch urine samples were taken and sent on a 'Dipslide' (Medical Wire & Equipment Co. (Bath) Ltd) to the microbiology laboratory for culture. Patients who displayed symptoms or signs of UTI (i.e. frequency, dysuria, or a non-specific deterioration in clinical condition) and in whom ward-based urine dip stick tests found the presence of leucocyte esterase and/or nitrites were cultured. Only pure growths of greater than or equal to 10^4 colony-forming units per ml (cfu/ml) were reported with an antibiotic sensitivity. Two or more strains were regarded as mixed growths and repeat samples requested. Given the age of the population and the practical difficulties of obtaining such urine specimens, no restriction was put on the amount of time the urine had to be in the bladder before sampling.

Outcome measures

Primary outcome

All outcomes were assessed by an individual who was blind to treatment group. The primary outcome was time to onset of first symptomatic UTI. This was defined as a culture-positive urine growing a single organism of greater than 10^4 cfu/ml urine specimen [6].

Secondary outcomes

Courses of antibiotics prescribed. All courses of antibiotics prescribed for any indication were noted to assess any potential impact of cranberry juice ingestion on antimicrobial use.

Adherence. The beverages were prescribed by the ward doctor in the ward drug kardex, and the amount consumed was recorded daily by ward nursing staff on an adherence sheet.

Responsible organisms. The Dipslides were incubated in air at 37° C overnight. Pure cultures of greater than 10^4 cfu/ml of urine were identified using the VITEK 1 (Biomerieux). Cultures with less than 10^4 cfu/ml were reported as 'no significant growth' or 'no growth' accordingly. Cultures with more than a single colony type were reported as 'mixed growth – suggestive of contamination'.

Other information

History of positive urine culture

Participants' microbiology results were examined for the 12 months prior to admission using the computerised regional reporting system, to determine the number of

positive urine culture specimens received by the local microbiology laboratory during that period.

Follow-up

Participants were followed up for 35 days following randomisation or until hospital discharge. Withdrawals were censored at hospital discharge or at occurrence of first symptomatic UTI. All adverse events and reasons for withdrawal were noted.

Statistical methods

Sample size

Based on local pilot data, it was predicted that a final sample of 380 participants would be required to have 80% power at $P<0.05$ of detecting a reduction in the proportion of patients having at least one episode of UTI in the cranberry juice group to 11% compared to 22% in the control group. Anticipating a dropout rate of 15%, we aimed to recruit 440 patients, to give a final evaluable sample of 380.

Statistical analysis

Data were entered onto Excel database and analysed using SPSS version 11.5. Full statistical analysis was performed prior to breaking the treatment code. Analysis was by intention to treat. Between-group comparisons were made using the unpaired *t*-test for normally distributed variables. Categorical variables were compared using the Chi squared test. Time to first episode of infection is presented as a Kaplan–Meier curve and differences between groups were assessed using the log rank test.

Results

A total of 3,228 patients were admitted to the study wards during the trial period, and the reasons for exclusion are given in the participant recruitment and follow-up chart in Figure 1. The reasons for potential participants failing to meet the inclusion criteria were: significant cognitive impairment with MSQ score of less than five out of ten, 530/2,238 (23.6%); the presence of a urinary catheter, 384/2,238 (17.1%); anticipated hospital stay of less than 1 week, 315/2,238 (14.1%); being terminally ill, 263/2,238 (11.7%); symptomatic UTI, 111/2,238 (4.9%); dysphagia, 106/2,238 (4.7%); regular cranberry juice drinkers, 71/2,238 (3.2%); respite admission, 63/2,238 (2.8%); on antibiotic therapy, 39/2,238 (1.7%); not assessed, 174/2,238; and other, 182/2,238. Of the 501 who were eligible to participate, 158/501 (31.5%) cited dislike of the taste of the juice as their reason for declining.

Only 376 participants were randomised compared to the target of 440 as a consequence of changes in ward organisation and a reduction in subsequent patient throughput. Participants were similar at baseline with no significant differences between the groups (Table 1). Between 25 and 28% had a history of culture-positive urine in the previous 12 months. Participants in the placebo group were observed for a

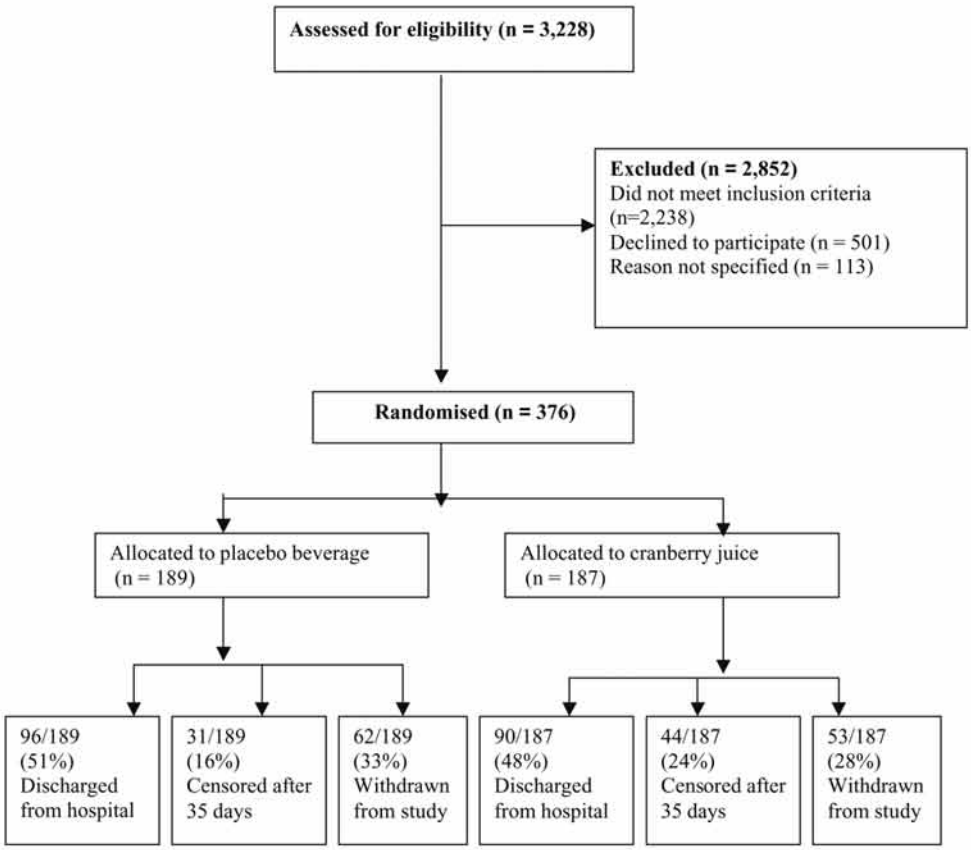

Figure 1. Participant recruitment and follow-up.

Table 1. Baseline characteristics ($n=376$)

	Placebo group ($n=189$)	Cranberry juice group ($n=187$)
Mean (sd) age	81.4 (7.6)	81.3 (7.3)
Males/females	56/133	65/122
Median (range) number of medications per day[a]	8 (1–19)	7 (1–20)
History of culture-positive urine in past 12 months, *n* (%)	48 (25%)	53 (28%)

[a]46 values missing from number of medications.

median [inter-quartile range (IQR)] of 21 [22] days, and those in the cranberry juice group were observed for 24 [23] days ($P=0.999$ Mann–Whitney test.) The placebo beverage was consumed for a median [IQR] of 15 [18.5] days, and cranberry juice for 16 [26] days ($P=0.574$).

Primary outcome

A total of 21/376 (5.6%) patients had at least one symptomatic UTI (14 in the placebo group and 7 in the cranberry juice group); relative risk (RR) 0.51 [95% CI 0.21–1.22, $P=0.122$). Of these, antibiotic therapy was initiated in 14/21 (67%), 8 in the placebo group and 6 in the cranberry juice group. No significant differences were found between treatment groups, although the cranberry juice group had fewer infections. A Kaplan–Meier plot of the proportion of participants free from symptomatic UTI shows a similar initial infection rate, but the curves begin to separate after 15 days (Figure 2).

One patient in the placebo group was treated with an antibiotic for a UTI, but as no confirmatory urine culture was obtained, this individual's results were excluded from the analysis.

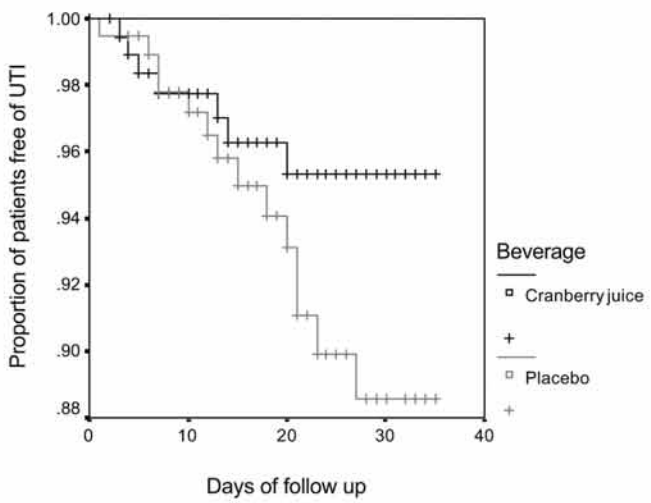

Figure 2. Comparison of the proportion of patients over time free from symptomatic urinary tract infection. Black line, cranberry juice ($n=7$ episodes of infection); grey line, placebo ($n=14$ episodes of infection). Log rank test $P=0.122$.

Secondary outcomes

Adherence

Median [IQR] adherence from a maximum of 300 ml per day was good at 300 [44] ml for the placebo beverage and 300 [28] ml for the cranberry juice ($P=0.208$, Mann–Whitney test). Adherence data were missing on 11/376 (2.9%) of participants, 5 from the placebo group and 6 from the cranberry juice group.

Antibiotic use

A total of 35/189 (19%) of participants in the placebo group were prescribed antibiotics for any indication during the period of observation, compared to 32/187 (17%) of the cranberry juice group ($P=0.721$). The median (range) duration of antibiotic treatment was 7 (1–19) days and 7 (1–15) days, respectively.

Adverse events

Only 13 adverse events occurred and all resulted in withdrawal from the study. The six in the placebo group comprised two deaths and four episodes of gastrointestinal upset. The seven in the cranberry group comprised three deaths, two episodes of gastrointestinal upset, one episode of skin redness and itching, and one elevated blood glucose level in a known diabetic patient.

Withdrawals

There were 115/376 (30%) withdrawals from the study (62 from the placebo group and 53 from the cranberry juice group), and reasons for withdrawal were similar between groups. The commonest reason for withdrawal was a desire not to continue with the study (25/189 in the placebo group and 23/187 in the cranberry group). Only 13/189 and 12/187 cited dislike of the beverage as the reason for withdrawing, and urinary catheterisation led to withdrawal of 11/189 and 7/187 in the placebo and cranberry groups, respectively.

Responsible organisms

Examining all 21 infections, *E. coli* was responsible for 13 of the infections in the cranberry group, but only 4 in the cranberry group. This between-group difference was significant, RR 0.31 [95% CI 0.10–0.94, $P=0.027$] Chi squared test.

Discussion

Despite having the largest sample size of any clinical trial of cranberry juice ingestion to date, this study still emerged as underpowered to detect a difference between the groups in time to onset of first symptomatic infection. The rate of UTI observed in the placebo group (7.4%) was considerably lower than in our open pilot study, and much lower than the rates of 36% and 32% reported in longer term studies of

younger women with a history of recurrent UTI [7, 8]. There is little in the literature on what the expected rate of UTI might be in elderly hospital patients. This is due to several factors: confusion about the distinction between asymptomatic bacteriuria and symptomatic infection [9]; differences in the bacteriological features of UTI in old versus young patients; and a lack of clarity on the definition of symptomatic UTI in elderly people. Given the rates of symptomatic UTI observed, we would have required 574 participants per group to have 80% power of detecting a difference at $P=0.05$. In reality with the sample size we had of 188 per group, we had less than 50% power to detect a significant difference between the groups.

Escherichia coli was the commonest organism isolated in our study, and is recognised as the most common urinary tract pathogen on elderly people [10]. We found significantly fewer infections with *E. coli* in the cranberry juice group than in the control group. This was only a secondary outcome, but the observation is consistent with there being an effect of cranberry juice. An important reason for evaluating the effectiveness of cranberry juice is because of its potential to reduce antibiotic prescriptions, and hence antimicrobial resistance.

Our trial differs in a number of respects from the two recent positive trials of cranberry juice [7, 8]. The study sample in both these trials were 150 young women (mean age 32 and 43 years, respectively) with a history of UTI, and cranberry product was taken for a period of between 6 months and 1 year. This duration of treatment is considerably longer than the mean of 18 days of beverage consumption in our trial. There is good evidence from *in vitro* work that the anti-adhesion activity of cranberry juice on fimbriated *E. coli* is present in the urine 2 hours after ingestion, and that it persists for 10 hours following ingestion [11], making it plausible that our regime of twice daily ingestion for 18 days might be effective in reducing episodes of infection. An updated Cochrane review which incorporates these trials concludes that cranberry juice 'may decrease the number of symptomatic UTIs over a 12 month period in younger women' [12].

Our trial had a number of methodological strengths, addressing many of the criticisms of the existing literature [12]. Firstly, analysis was by intention to treat. Secondly, it was the only trial other than Avorn's to have used a matching placebo beverage [1]. Thirdly, it targeted a previously unstudied group—elderly hospital patients—a group at high risk of UTI. Fourthly, it included male participants, a group in whom the effectiveness of cranberry juice has yet to be established. And finally, high adherence levels of around 90% were achieved by having the beverages prescribed in the ward drug kardex and so administered twice daily by nursing staff, who also documented the quantity unconsumed. This is a considerably more robust method than self-report which has been used in previous studies. The high number of withdrawals in previous cranberry juice trials has been raised as a concern, but the adverse events rate in our trial was low, and did not differ significantly between groups. Only 25/376 (6.6%) withdrew citing a dislike of the beverage as the reason.

This is the largest randomised trial yet to have examined the effect of cranberry juice ingestion on symptomatic UTI rates, and the only one to have participants of both sexes. The observed symptomatic infection rate was considerably lower than anticipated so the study was accordingly underpowered. Whilst inconclusive, the results are in keeping with other studies of cranberry juice in showing a 50% difference between groups in UTI incidence [1, 7, 8]. Although this study has confirmed the acceptability and tolerability of cranberry ingestion in older people, larger trials are now required to establish whether cranberry juice ingestion is effective in the prevention of UTI in elderly hospital patients.

Key points

- Cranberry juice is commonly given to older people in hospital to prevent UTI, although there is little evidence to support its use.
- Despite having the largest sample size of any clinical trial of cranberry juice to date, the actual UTI rate was lower than anticipated, making the study underpowered and inconclusive.
- Significantly fewer infections with *E. coli* occurred in the cranberry juice group, a finding compatible with an effect of the juice. However, this was a secondary outcome, so should be treated with caution.

Acknowledgements

The study was funded by project grant K/OPR/2/2/D398 from the Chief Scientist Office at the Scottish Executive Department of Health. The cranberry juice and matching placebo were supplied by Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA, USA. Thanks to the ward staff, the laboratory staff in medical microbiology and the study participants.

Conflict of interest

None declared.

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Received 28 May 2004; accepted in revised form 29 December 2004

Age and Ageing 2005; **34:** 261–267
doi:10.1093/ageing/afi057
Published electronically 11 March 2005

Cranberry for Prevention of Urinary Tract Infections

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Traditionally, cranberry has been used for the treatment and prophylaxis of urinary tract infections. Research suggests that its mechanism of action is preventing bacterial adherence to host cell surface membranes. Systematic reviews have concluded that no reliable evidence supports the use of cranberry in the treatment or prophylaxis of urinary tract infections; however, more recent, randomized controlled trials demonstrate evidence of cranberry's utility in urinary tract infection prophylaxis. Supporting studies in humans are lacking for other clinical uses of cranberry. Cranberry is a safe, well-tolerated herbal supplement that does not have significant drug interactions. (Am Fam Physician 2004;70:2175-77. Copyright© 2004 American Academy of Family Physicians.)

American cranberry (Vaccinium macrocarpon) is one of only three species of fruit native to North America. The other species are blueberry (Vaccinium angustifolia) and bilberry (Vaccinium myrtillus). Cranberry typically grows in bogs and is a member of the same family as blueberry and bilberry. Massachusetts and Wisconsin are the main areas of present-day commercial production of cranberry.[1] The ripe fruit was used medicinally by Native Americans for the treatment of bladder and kidney ailments. Pilgrims called the fruit "craneberry" because the stem and flower resembled the head, neck, and beak of a crane.[1] Therapeutic applications of cranberries documented during the 17th century included the relief of blood disorders, stomach ailments, liver problems, vomiting, appetite loss, scurvy, and cancer.[2] Before the advent of antibiotics, cranberry continued to be a popular treatment for urinary tract infections (UTIs).[3]

Pharmacology

The mechanism of action of cranberry has prompted much scientific discussion. It was first hypothesized that acidification of the urine contributed to an antibacterial effect. The current proposed mechanism of action focuses primarily on cranberry's ability to prevent bacterial binding to host cell surface membranes. In vitro studies have observed potent inhibition of bacterial adherence of *Escherichia coli*[4] and other gram-negative uropathogens.[5] Cranberry has been found to specifically inhibit hemagglutination of *E. coli* by expression of types 1 and P adhesin[6] through the component compounds fructose[7] and proanthocyanidins.[8]

Uses and Efficacy

URINARY TRACT INFECTION

In the United States, one of every five women has been reported to have a lifetime incidence of UTI.[9] Of these women, 3 percent experience recurrent disease.[9] Eleven million women receive medication for UTIs annually.[10] A recent Cochrane Database systematic review[11] found no randomized trials assessing the effectiveness of cranberry juice in the treatment of UTIs and concluded that there is no evidence to support its use. There is much greater evidence-based information available for the use of cranberry in UTI prophylaxis.

The first relatively large placebo-controlled studies[12,13] assessing efficacy were conducted in elderly women living in long-term care facilities. The findings of these studies[12,13] showed that cranberry significantly reduced the frequency of bacteriuria and pyuria, but these were not intention-to-treat analyses. A 1997 study, published as a letter in *The Jour-*

TABLE 1
Key Points About Cranberry

Efficacy	UTI prophylaxis: modest effect UTI treatment: evidence lacking
Adverse effects	May increase urinary oxalate levels
Interactions	No significant herb-drug reactions have been reported.
Dosage	Varies depending on preparation. Cranberry extract tablets: 1 tablet (300 to 400 mg) twice daily; unsweetened juice: 8 oz three times daily
Cost	Tablets: $10 to $15 for 30-day supply Unsweetened juice: varies, depending on brand
Bottom line	Safe botanical medicine; effective in UTI prophylaxis

UTI = urinary tract infection.

nal of Family Practice,[14] used a younger cohort of women and was the first study to use cranberry extract tablets rather than juice. Results showed that the cranberry concentrate was more effective than placebo in reducing the occurrence of UTIs.[14] However, only 10 women completed the study.[14] Another pair of studies[15,16] found cranberry ineffective in decreasing bacteriuria in children with neurogenic bladder requiring intermittent catheterization. A Cochrane Database systematic review,[17] citing small sample sizes and the poor quality of available trials, determined that there was no reliable evidence of effectiveness of cranberry in UTI prophylaxis.

However, since 2001, two good-quality studies have been published. The first trial[18] of 150 women consisted of three arms: (1) cranberry/lingonberry juice; (2) probiotic supplementation with Lactobacillus GG drink; and (3) no intervention for 12 months. Findings were a statistically significant 20 percent reduction in absolute risk of infection in women receiving cranberry (number needed to treat: 5) compared with no effect in the probiotic-supplementation and no-intervention groups.[18] Most recently, a randomized, placebo-controlled trial[19] of 150 women over a 12-month period found that cranberry juice and cranberry extract tablets significantly decreased the number of patients having at least one symptomatic UTI per year.

OTHER USES

A single experimental study[20] showed that the "high-molecular-weight constituent" of cranberry juice that inhibits the adherence of *E. coli* was effective in reversing and inhibiting the coaggregation of a large portion of dental plaque bacteria. Cranberry also has been recommended as an adjunctive treatment for Candida infections. In vitro studies[21,22] have shown that cranberry juice exerts fungistatic effects against dermatophytic and other fungi but has no effect against *Candida albicans*. There are no controlled trials in humans evaluating the effectiveness of cranberry in treating fungal infections.

Contraindications, Interactions, Adverse Effects

Cranberry has a record of safety, although specific long-term safety data are lacking. No significant herb-drug interactions have been reported. A single study[23] found that cranberry may increase the absorption of vitamin B_{12} in patients who also are taking proton pump inhibitors and that it may allow the kidneys to metabolize weakly alkaline drugs (such as antidepressants and opioids) more rapidly, thus reducing their effectiveness. A small study[24] found a significant rise in urinary oxalate levels, prompting a caution that regular use of cranberry may increase the risk of kidney stone formation in patients with a history of oxalate calculi.

Dosage

Each of the reviewed studies used different doses and formulations of cranberry, including unsweetened cranberry juice, cranberry juice cocktail, and cranberry extract tablets. The recommended dosing for UTI prophylaxis is based on the most recent positive randomized controlled trial[19] that used one tablet of concentrated cranberry extract (300 to 400 mg) twice daily, or 8 oz of pure unsweetened cranberry juice three times daily.

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Final Comment

Cranberry appears to be a safe, herbal choice for UTI prophylaxis and has relatively good tolerability. The most recent studies[18,19] have found that the use of cranberry for up to 12 months is safe and moderately effective. More evidence is necessary to recommend its use for clinical indications other than UTI prophylaxis. Care should be taken when recommending cranberry for long-term use in patients who are known urinary oxalate stone formers. No significant herb-drug reactions with cranberry have been reported. Reviews the efficacy, safety, and cost of cranberry.

The author indicates that he does not have any conflicts of interest. Sources of funding: none reported.

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Strength of Recommendations

Key clinical recommendation	Label	References
A recent Cochrane Database systematic review found no randomized trials assessing the effectiveness of cranberry juice in the treatment of UTIs and concluded that there is no evidence to support its use.	B	11
Most recently, a randomized, placebo-controlled trial of 150 women over a 12-month period found that cranberry juice and cranberry extract tablets significantly decreased the number of patients having at least one symptomatic UTI per year.	A	19

UTI = urinary tract infection.

Cranberry and adhesion inhibiting E.coli jama 2002

Cognitive Outcomes Following Cardiopulmonary Bypass

To the Editor: Dr Van Dijk and colleagues[1] found no difference in 12-month cognitive outcomes between patients who underwent either on-pump or off-pump coronary artery bypass grafting (CABG). Although the authors alluded to a possible role of microemboli, they did not provide an explanation for the disturbing frequency and permanency of memory loss and dementia following CABG.

It is possible that patients with extremely low hemoglobin levels may be at higher risk for cognitive deficits following CABG. The current practice of performing cardiac surgery on patients with hematocrits as low as 18% has not been adequately evaluated.[2] Preoperative transfusions to hematocrits as high as 33% may increase survival.[3] Valeri et al[4] estimated that as many as 40000 myocardial infarctions per million surgical procedures were caused by undertransfusion.

Patients who have coronary atherosclerosis are more likely to have similar lesions throughout the body, including in the carotid and cerebral vasculature. Oxygen delivery to tissue is directly related to the amount of red blood cells as a function of time. A patient with both anemia and stenosis has even higher risk of ischemia. It is not surprising that patients who undergo surgery with severe anemia and stenosed vessels are more likely to experience irreversible cell loss due to tissue anoxia.

There is a need for studies to assess whether the current practice of hemodilution in arteriosclerotic patients is a major factor in postoperative cerebral dysfunction. Other options, including use of erythropoietin, frozen blood storage, and hemoglobin substitutes, also require further study. It would be interesting to determine if the use of these substitutes, which would enable a normal perioperative hemoglobin level to be achieved, has a protective benefit.

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To the Editor: Dr Van Dijk and colleagues[1] demonstrated that patients who received their first CABG without cardiopulmonary bypass (CPB) had a small improvement in the cognitive outcome 3 months after the procedure, but the effects did not persist at 12 months. Cerebral microembolism and hypoperfusion, which are associated with CPB, are the main mechanisms of brain injury in patients undergoing CABG. Microembolic signals detected by transcranial Doppler ultrasound and echocardiography monitoring during CPB can be directly associated with aortic manipulations, but a large proportion of them are thought to represent air bubbles or microparticulate emboli generated from the pump circuit and not completely eliminated by the arterial line filters.[2] Off-pump CABG is associated with a marked reduction of the microembolic load during surgery and, therefore, is believed to reduce cognitive impairment in those patients.

Our center has been performing routine CABG without CPB for the past 2 decades.[3] In 1995, we reported[4] a prospective study comparing 48 patients undergoing CABG with CPB and 33 patients operated without CPB. At that time, we did not find significant differences in early neurologic and neuropsychologic examinations between the 2 groups. In addition, we could not observe differences in early neurologic outcome in a small series of patients with similar risk factors randomized to CABG with and without CPB.[2] The much lower number of microembolic signals detected by intraoperative transcranial Doppler ultrasound monitoring in the patients operated without CPB suggests that the constitution and the nature of the emboli, rather than their number, could be associated with neurologic outcome. Moreover, the changes in flow velocity and pulsatility index might be another potential mechanism of brain injury in patients who do not undergo CPB.[2]

Despite the methodological limitations, these studies suggest a multifactorial genesis of cerebral injury in CABG and re-

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

emphasize the need for large randomized trials to further elucidate these complex interactions.

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1. Van Dijk D, Jansen EWL, Hijman R, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. *JAMA*. 2002; 287:1405-1412.
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To the Editor: Dr Van Dijk and colleagues[1] reported little difference in the cognitive function of patients 12 months after either off-pump or on-pump CABG. This outcome was unexpected since on-pump procedures are associated with aortic cannulation and prolonged extracorporeal perfusion, both of which may shower the brain with emboli. One explanation for this finding, which the authors did not discuss, might be that patients in need of CABG have a high baseline rate of 12-month cognitive decline with or without surgery. This is a testable hypothesis: control groups of patients who are managed without surgery (eg, with drugs only or with drugs and angioplasty) could be assembled and followed up for a year and subjected to the same tests of cognitive function as the intervention groups in this study. Then we might better learn if CABG or some other aspect of these patients' illness is responsible for their cognitive decline over time.

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1. Van Dijk D, Jansen EWL, Hijman R, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. *JAMA*. 2002; 287:1405-1412.

To the Editor: The results of Dr Van Dijk and colleagues[1] do not appear to have resolved the conflicting conclusions drawn from the 2 prior randomized trials that have found that off-pump CABG reduced the postoperative cognitive dysfunction.[2,3] One potential limitation of all these studies is the adequacy of management of the patient during CPB. Relevant variables would include maintaining an appropriate hematocrit, high flow rate, and mean perfusion pressure while on bypass, and having a blood filter on the arterial limb of the bypass circuit. These differences could greatly influence cerebral morbidity.

In addition to psychometric evaluation of the cerebral injury in patients with CPB procedures, a high incidence of abnormalities was found on magnetic resonance imaging (MRI) obtained before and after the CPB procedure. The ischemic lesions demonstrated by MRI typically are localized at the gray/white junction and the watershed area suggesting that embolic phenomena and hypoperfusion, respectively, are likely the underlying causes of the cerebral injury. Based on our experience with preoperative and postoperative (3-7 days) MRI imaging, the CPB procedures performed with strict in-line filtration and relatively high perfusion rate demonstrated no MRI or neurological evidence of ischemic injury in any of our patients.[4] Such findings further support the notion that the variation in CPB procedure can influence the neurological outcome in patients undergoing any type of surgery requiring CPB procedure. Therefore, the efficacy of off-pump CABG surgery cannot be adequately assessed without standardized CPB procedure and quality control.

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1. Van Dijk D, Jansen EWL, Hijman R, et al. Cognitive outcome after off-pump and on-pump coronal artery bypass graft surgery: a randomized trial. *JAMA*. 2002; 287:1405-1412.
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In Reply: We agree with Drs Fouad-Tarazi and Feldschuh that while moderate hemodilution may improve rheology and maintain oxygen delivery, severe hemodilution combined with stenosis of cerebral arteries may contribute to negative cerebral outcomes. However, this hypothesis needs to be formally evaluated. This could be accomplished in a retrospective study investigating the relationship between perioperative hematocrit and stroke, in a design comparable with the study of Wu et al,[1] which assessed the association between hematocrit and mortality in patients with myocardial infarction. If a negative impact of severe hemodilution during CABG were confirmed, a formal trial of a more aggressive transfusion regimen would be warranted, in which the effect on subtle cognitive decline could be evaluated.

Dr Malheiros and colleagues have a large experience in off-pump surgery and were one of the first groups to describe a large series of off-pump procedures.[2] The results of their studies are in accordance with ours; avoiding CPB does not lead to a large or easily detectable improvement of cognitive or neurologic outcome.[2,3] The shower of microemboli to the brain is only one of the postulated mechanisms of cognitive decline following CABG. A subsample of the patients in our study also underwent intraoperative transcranial Doppler ultrasound examination. Like Malheiros et al, we found more emboli in on-pump patients than in off-pump patients (unpublished results). We agree that the composition rather than the number of the emboli probably determines the clinical effect. A trial larger with more statistical power than ours may help to establish whether

there is a smaller beneficial effect of off-pump surgery on cognitive outcome. However, the design of a randomized trial is not appropriate to elucidate the complex interactions between patient and surgical variables and cognitive outcome or to study the multifactorial genesis of cerebral injury in CABG.

We agree with Dr Venes that an extra control group may help to put the findings of our trial into perspective. The perfect control group, as Venes suggests, would consist of patients who are eligible for CABG but would receive a different treatment. Such a control group obviously does not exist. Patients receiving drug treatment or coronary angioplasty usually have less advanced arterial disease and therefore form a less comparable control group. Moreover, patients undergoing coronary angioplasty are also at risk for cerebral complications.[4] We therefore added a nonsurgical, nonangioplasty control group of 110 age-matched volunteers to our study. The results of repeated neuropsychologic testing in these subjects are currently under review.

We agree with Dr Yuh and colleagues that CPB probably influences cognitive outcome. It is conceivable that modern CPB, with the use of membrane oxygenators, α-stat pH management, arterial line filters, mild rather than moderate hypothermia, relatively slow rewarming rates, and prevention of postoperative hyperthermia, has reduced the incidence of cognitive decline after on-pump CABG.[5-7] Such CPB management was applied to the on-pump patients included in our study and may be another explanation for the small difference in cognitive outcome that was found between the patients randomized to off-pump and on-pump CABG.

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When Should Perioperative β-Blockers Be Discontinued?

To the Editor: In their review of perioperative β-blockade for noncardiac surgery, Drs Auerbach and Goldman[1] may have created some confusion about the potential for complications of withdrawal of β-blockade. They summarize an article by Shammash et al[2] as follows: "A recent prospective observational study noted that patients who were not receiving β-blockers long-term but who discontinued perioperative use immediately after surgery had an increased risk for postoperative myocardial infarction."

In fact, this article reports a retrospective review of medical records of patients who received β-blockers before surgery. Patients whose β-blockade was continued into the postoperative period were compared with patients whose β-blockade was not reinstituted. Most of the regimens described to date for perioperative β-blockade extend significantly into the postoperative period.[3,4] Although there is the potential for a rebound reaction following the institution of perioperative β-blockade, the literature reviewed does not address that situation. In particular, it remains unclear whether the problem is a true withdrawal phenomenon or whether the simple lack of therapy with β-blockers increases morbidity and mortality.

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In Reply: In response to Drs Silverstein and Tagliente, because Shammash et al[1] did not separate patients who had long-term β-blockers discontinued from those who had perioperative β-blockers discontinued, it is indeed unclear what led to mortality in their findings. For example, it is possible that the excess mortality they observed was a result of so-called rebound from β-blockers, removal of the protective effect of perioperatively administered β-blockers, or withdrawal of the protective effect of chronically administered β-blockers.

Although we agree that these results could be interpreted in more than one manner, we believe that evidence from this study and others supports the practice of continuing β-blockers throughout hospitalization, thereby avoiding even a theoretical risk of β-blocker withdrawal when postoperative patients may be most prone to ischemia.[2]

Inadvertent discontinuation of medications in the perioperative period can lead to adverse outcomes,[3] and effective use of perioperative β-blockers requires that chronic β-blockade not be inappropriately discontinued after surgery. In fact, it is likely that many patients who are eligible for β-blockers perioperatively are also candidates for them over the long term. Although managing long-term medications may be a challenge in the perioperative period, when numerous physicians are in-

volved and coordination of care can be complex, this time also represents an opportunity for improving the quality of short- and long-term care.

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Emergency Treatment for Commotio Cordis

To the Editor: Dr Maron and colleagues[1] reported that ventricular tachycardia/fibrillation was identified in 36 of 82 cases of commotio cordis and that most were successfully resuscitated by an external defibrillator.

Time is of the essence in treating this lethal tachyarrhythmia, and external defibrillators are often unavailable. Thumpversion,[2] or a manual thump to the precordium, has been shown to be effective in terminating both ventricular tachycardia and ventricular fibrillation.[3] It might seem to be a paradox to treat commotio cordis, which is caused by a chest blow, by a second precordial thump. Caldwell et al,[4] however, reported that thumpversion was efficacious in a prospective study of 5000 medical-surgical patients. Therefore, a chest blow is apparently a double-edged sword: it can cause sudden ventricular arrhythmias but also terminate them.

A similar prospective study of thumpversion in commotio cordis would thus be an important study because thumpversion could be applied instantaneously and easily by any trained rescuer at the scene when no external defibrillator is immediately available.

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In Reply: Dr Cheng raises the interesting and provocative question of whether the precordial thump[1] could be an effective measure in resuscitating individuals in whom a chest blow induced ventricular tachycardia/fibrillation (known as commotio cordis).[2,3] Cheng suggests that precordial blows may serve as a cause of sudden cardiac arrest as well as a means of mechanical defibrillation. Indeed, we are aware of 2 instances of survival from commotio cordis events that were associated with a precordial thump. Although the American Heart Association Advanced Life Support Guidelines[4] do not address precordial thump, a thump remains an accepted optional practice for health professionals in a witnessed arrest, as long as it does not delay electrical defibrillation.[5] Although precordial thump is not an unreasonable intervention if a defibrillator is not immediately available, in practice it appears to have low efficacy.[6] Unfortunately, a prospective study testing the efficacy of the precordial thump, as suggested by Cheng, would be virtually impossible given the very low event rate and unpredictable occurrence of commotio cordis.

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α-Methylacyl Coenzyme A Racemase as a Marker for Prostate Cancer

To the Editor: Dr Rubin and colleagues suggested that α-methylacyl coenzyme A racemase (AMACR) may be a tissue biomarker for prostate cancer.[1] We agree that AMACR is a promising diagnostic marker for prostate cancer and recently reported that AMACR has high sensitivity for the detection of prostate cancer on needle biopsy.[2] However, it is important to recognize the limitations of this marker. In our study of atypical adenomatous hyperplasia of the prostate, a benign condition that mimics prostate cancer, AMACR immunoreactivity was found in a small subset of cases (17.5%).[3] Therefore, caution should be exercised in interpretation of AMACR immunostaining.

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In Reply: In response to Dr Jiang and colleagues, 3 independent groups have now reported that AMACR is expressed in prostate cancer.[1-3] However, as we reported, some precursor lesions, such as high-grade prostatic intraepithelial neoplasia and atrophic lesions, also express AMACR. Jiang et al note that still another putative precursor lesion, adenosis, may also express AMACR. Like all putative biomarkers, AMACR may not be specific to a single disease and should be used with caution as a tool for diagnosis. For diagnostic purposes, AMACR should be used in combination with a basal cell marker, as pointed out by all 3 groups.[1-3] We also have observed AMACR expression in other tumor types, including colon, breast, and melanoma.[4] Therefore, AMACR appears to be a marker for early neoplastic change but requires other markers to help distinguish the tissue of origin.

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RESEARCH LETTERS

Plasma Lysophosphatidic Acid Concentration and Ovarian Cancer

To the Editor: Xu et al[1] previously reported that lysophosphatidic acid (LPA) levels are increased in the plasma of patients with ovarian cancer, and they proposed that LPA may be a useful early marker of ovarian cancer. Other studies have also reported that LPA levels are increased in malignant effusions in patients with cancer,[2,3] particularly of the ovaries.[4] To assess the utility of LPA as a marker of ovarian cancer, we measured the amount of LPA in plasma from patients with ovarian cancer and from healthy control subjects, as well as LPA levels in fluid from malignant effusions.

Methods. Using liquid chromotography/mass spectroscopy,[5] we measured plasma concentrations of 5 individual LPA acyl species (LPA 16:0, 18:2, 18:1, 18:0, and 20:4, which comprise more than 90% of total plasma LPA) in 32 patients with ovarian cancer and 32 healthy control subjects (mean [SD] age, 53 [13] and 42 [12] years, respectively). We also determined LPA concentrations in samples of ascites and pleural fluid from patients with malignant effusions related to their ovarian cancer, as part of a previous study.[2] All patients provided informed consent in accordance with the policies of our institutional review board.

For each LPA species obtained from malignant effusions, 1-way analyses of variance, with site of the tumor as the main effect, were used to analyze log-transformed data. For plasma, data from the 5 fatty LPA acyl species were considered simultaneously; site of tumor and type of LPA acyl species were considered as main effects, with patients nested by tumor type. Power analysis indicated that sample sizes ranging from 9 to 49 were significantly large to detect differences of 1.5 to 0.6 SDs.

Results. The plasma concentrations of neither individual LPA species nor total LPA differed between ovarian cancer patients and control subjects (TABLE). Likewise, plasma LPA levels were not increased in patients with other gynecologic malignancies (data not shown). Patients with ovarian cancer had somewhat higher total plasma LPA levels than did control subjects, but this difference was not statistically significant. The ranges for all individual LPA species, as well as total LPA, overlapped significantly between the 2 groups. However, LPA levels in malignant effusions, including ovarian cancer, were significantly increased compared with those in control subjects. Furthermore, the rank order of individual LPA species differed between LPA in plasma and malignant effusions among patients with ovarian cancer.

Comment. Unlike prior studies,[1,6] we did not find increased plasma LPA levels in patients with ovarian cancer. One possible explanation is that we used a different centrifugation process to isolate plasma than did Xu et al.[1,6] This is important because LPA is generated by activated platelets.[7] Thus, we made every effort to remove platelets from plasma samples prior to analysis. Our protocol comprised a 2-step process, first using low-speed (1000*g*) and then high-speed (10000*g*) centrifugation to generate platelet-poor plasma. In separate experiments, we found no difference in mean (SD) total plasma LPA levels from healthy volunteers (n=5) when plasma was centrifuged only at low or at both at low and high speeds (0.40 [0.06] vs 0.42 [0.07] μmol/L, respectively). Likewise, there was no difference in total plasma LPA levels in patients with ovarian cancer (n=10) when plasma was centrifuged only at low or at both at low and high speeds (0.26 [0.07] vs 0.31 [0.09] μmol/L, respectively). Moreover, the total plasma LPA level in the control group was 0.70 (0.24) μmol/L, which agreed with the value of 0.60 (0.19) μmol/L that Xu et al[1] previously reported, as well as with our previous report in healthy women (0.74 [0.17] μmol/L).[5]

Table. Quantitative Analysis of LPA Levels in Plasma and Malignant Effusion Samples From Control Subjects and Patients With Ovarian Cancer*

	Plasma LPA, Mean (SD), µmol/L			Malignant Effusion LPA, Mean (SD), µmol/L		
LPA Species	Control (n = 32)	Ovarian Cancer (n = 49)	*P* Value	Nonmalignant (n = 22)	Ovarian Cancer (n = 10)	*P* Value
16:0	0.10 (0.05)	0.13 (0.11)	.65	0.57 (0.49)	3.70 (1.81)	<.001
18:2	0.31 (0.11)	0.34 (0.32)	.87	0.56 (0.47)	2.37 (1.58)	<.001
18:1	0.10 (0.04)	0.13 (0.10)	.96	0.39 (0.32)	1.78 (1.24)	<.001
18:0	0.06 (0.04)	0.05 (0.03)	.62	0.14 (0.10)	0.59 (0.28)	<.001
20:4	0.14 (0.07)	0.18 (0.19)	.98	0.16 (0.13)	1.33 (0.73)	<.001
Total	0.70 (0.24)	0.82 (0.67)	.91	1.83 (1.45)	9.77 (4.79)	<.001

*LPA indicates lysophosphatidic acid.

Using a previously validated stable-isotope dilution liquid chromotography/mass spectroscopy assay, we were unable to distinguish patients with ovarian cancer from healthy control subjects through determination of plasma LPA levels. Furthermore, the rank order of LPA molecular species in plasma and malignant effusions was different, suggesting that these LPA pools are distinct. These results raise questions about the utility of plasma LPA levels for early detection of ovarian cancer.

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Cranberry Juice and Adhesion of Antibiotic-Resistant Uropathogens

To the Editor: Urinary tract infections (UTIs) account for more than 11 million physician visits annually in the United States and have become increasingly resistant to first-line antibiotic therapy.[1] Recent evidence suggests that consumption of cranberry juice beverages is effective at preventing UTIs,[2,3] although further studies are needed to validate potential treatment effects. While early research focused on a mechanism of urinary acidification, the largest clinical trial to date found no evidence to support this.[2] Recent studies suggest that cranberry proanthocyanidins (condensed tannins) may inhibit P-fimbriated *Escherichia coli* from adhering to uroepithelial cells,[4] the initial step in development of UTI. The effectiveness of cranberry proanthocyanidins and cranberry beverages against antibiotic-resistant *E coli*, however, has not been previously tested. We assessed whether consumption of cranberry juice cocktail prevents adhesion of antibiotic-resistant uropathogenic P-fimbriated *E coli* to the uroepithelium.

Methods. Thirty-nine uropathogenic P-fimbriated *E coli* isolates were obtained from women aged 18 to 39 years with clinically diagnosed, culture-confirmed UTIs. Isolates were incubated for 20 minutes in urine collected over a 12-hour period from healthy women before and after consumption of 240 mL of commercial cranberry juice cocktail, and in cranberry proanthocyanidin extract (pH 6.5) (2-fold dilution series). Isolates tested were a subset of those previously screened for resistance; 24 (62%) of those selected were resistant to trimethoprim-sulfamethoxazole.[5] These bacteria were then harvested and screened for ability to adhere to isolated uroepithelial cells, agglutinate human red blood cells (A^1, Rh^+), and resin beads coated with isolated P-receptor oligosaccharides.

Results. Urine after cranberry juice cocktail consumption (average pH 6.2) prevented adhesion of 31 (80%) of the 39 iso-

lates and 19 (79%) of the 24 antibiotic-resistant isolates in all bioassays, while preconsumption urine (average pH 6.2) failed to prevent adhesion in any of the samples. Antiadhesion activity was evident in the urine within 2 hours and persisted for up to 10 hours following cranberry juice cocktail ingestion. The extracted proanthocyanidins inhibited adhesion of all isolates at concentrations ranging from 6 to 375 µg/mL, demonstrating potent in vitro antiadhesion activity against these antibiotic-resistant strains.

Conclusions. These data suggest that consumption of cranberry juice cocktail may offer protection against both sensitive and resistant strains of P-fimbriated *E coli* by a mechanism that is not likely to increase selective pressures associated with antibiotic resistance. In light of the evidence that antibiotic usage is a contributing factor in development of trimethoprim-sulfamethoxazole–resistant uropathogenic *E coli*,[5] further trials are warranted to explore the use of cranberry juice as an alternative strategy to prevent UTIs and potentially reduce the rate of antibiotic resistance.

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Funding/Support: Isolate collection was supported by National Institutes of Health grant R01 DK35368, and bacterial antiadhesion work was supported by Ocean Spray Cranberries, Inc. Ocean Spray provided monetary support only and did not participate in the design, analysis, or interpretation of the data.

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CORRECTION

Incorrect Wording: There was incorrect wording in the Editorial entitled "Placebo in Clinical Trials for Depression: Complexity and Necessity" published in the April 10, 2002, issue of THE JOURNAL (2002;287:1853-1854). The last 3 sentences in the fourth paragraph should read as follows: From this 8-week clinical trial, the authors conclude that neither sertraline nor hypericum was significantly different from placebo on either of the primary outcome measures: change in total Hamilton Depression Scale (HAM-D) score and full response defined by combined cutoff scores on both the HAM-D and the Clinical Global Impression Scale (CGI-I). However, sertraline was significantly better than placebo ($P = .02$) on the CGI-I alone, which was a secondary outcome measure in this study. The overall response rates (including partial and full response) were 38.1% for hypericum, 43.1% for placebo, and 48.6% for sertraline.

SAFETY AND EFFICACY OF CRANBERRY (*Vaccinium Macrocarpon*) DURING PREGNANCY AND LACTATION

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ABSTRACT

Background
There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for herbs commonly used during pregnancy and lactation.

Objectives
To systematically review the literature for evidence on the use, safety and pharmacology of cranberry, focusing on issues pertaining to pregnancy and lactation.

Methods
We searched 7 electronic databases and compiled data according to the grade of evidence found.

Results
There is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. Indirectly, there is good scientific evidence that cranberry may be of minimal risk, where a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of cranberry is unknown.

Conclusions
Women experience urinary tract infections with greater frequency during pregnancy. Given the evidence to support the use of cranberry for urinary tract infections (UTIs) and its safety profile, cranberry supplementation as fruit or fruit juice may be a valuable therapeutic choice in the treatment of UTIs during pregnancy.

Key words: *Cranberry, vaccinium macrocarpon, pregnancy, lactation, breastfeeding, systematic review*

American cranberry (*Vaccinium macrocarpon)* is one of the few fruits native to Eastern North America. It is also found in Northern Europe. Traditional medicinal use of cranberry fruit by Native Americans was primarily for the treatment of bladder and kidney ailments.[1]There has also been a relatively long history of scientific research on this herbal remedy, dating back to its chemical characterization in the late 19th century.[2] Cranberry's principal therapeutic value today continues to be for the treatment and prevention of urinary tract infections.[3] It was originally thought that cranberry's biological activity was due to an acidifying effect on urine, however, this theory has been largely disproved.[1] The currently accepted mechanism of action in treating and

preventing urinary tract infections is through disabling *Escherischia coli*'s capacity to adhere to the urethra.[2,4] The fruit contains two compounds, fructose and a proanthocyanidin, that adhere to proteins on the fimbriae of *E. coli,* effectively inhibiting the bacteria from sticking to the epithelial cell lining of the urethra.[2,4] Without the ability to establish a strong foothold via adherence, the infection is either attenuated or prevented at the outset.

The pregnant woman, along with a number of other issues, has to deal with an increased frequency of urinary tract infections.[5,6] Given the recognised safety of cranberry juice and its efficacy in the treatment of urinary tract infections[2,7], it is of no surprise that this therapy is widely used by pregnant women. A survey of 400 women from Norway found that cranberry fruit juice was the most commonly used herbal therapy during pregnancy.[8] The popular use of this herb during pregnancy calls for an in-depth understanding of its efficacy and potential for harm during pregnancy and lactation. We endeavoured to address these issues in a systematic review of the literature.

Synonyms/Common Names/Related Substances
American cranberry, arandano Americano, arandano trepador, cranberries, European cranberry, grosse moosbeere, kranbeere, canneberge, large cranberry, moosebeere, mossberry, ronce d'Amerique, small cranberry, trailing swamp cranberry, tsuru-kokemomo, vaccinium, *vaccinium macrocarpon*[9]

Constituents
Proanthocyanidins, triterpenoids, lectins, catechins, ascorbic acid, benzoic acid, quinic acid, oxalic acid, citric acid and malic acid[10]

Part Used
Fruit[9]

METHODS

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant scientific medical literature that provided information as to the safety, efficacy and pharmacology of cranberry in pregnancy and lactation. We searched the following databases from inception to June 2006: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database and Natural Standard. The common and Latin names of the herb were used as the key words along with "pregnancy", "lactation" and "breastfeeding". In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in the final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm is rated as displayed in Table 2.

RESULTS

Indications for Use

	Evidence Grade
Prevention of urinary tract infections[11]	A
Prevention of stomach ulcers[12,13]	E
Prevention of periodontal disease[14-16]	E
Influenza prevention[17]	E

Use and Safety during Pregnancy

	Level of evidence for potential harm
Commonly used without evidence of harm[8,18]	3a
Minimal risk (taken as food)[19]	5

A survey was conducted on 400 Norwegian postpartum women.[8] The authors reported that cranberry was one of the most commonly used herbs during pregnancy.[8] A herbal compendium reported that cranberry is of minimal risk during pregnancy when consumed in food quantities.[19] There are no clinical studies in the evidence-based medicine literature of cranberry being either safe or contraindicated during pregnancy.

Use and Safety during Lactation

	Level of evidence for potential harm
Unknown	6

There are no reports in the evidence-based medicine literature of cranberry being either safe or contraindicated during lactation.

Toxicity and Adverse Effects

Cranberries have been consumed as a food throughout recorded history and have proven safe as a food item. This track record of safety does not necessarily imply, however, that the fruit (processed or not) is entirely safe in all populations or at high levels of consumption. One possible area of concern is patients at risk of kidney stones. In a study of healthy volunteers consuming cranberry tablets for one week at the manufactures recommended dose, urinary oxalates were found to have increased significantly.[20] While consumption of up to 4L/day of cranberry juice has been shown to be non-toxic in healthy individuals[21], people with nephrolithiasis may be at increased risk for stone formation if consuming large amounts of cranberries or cranberry juice. In infants and young children, gastrointestinal distress, including diarrhea, has been reported when consuming more than 3L/day of cranberry juice.[22-24]

Pharmacology

The proanthocyanidins present in cranberry fruit interfere with bacterial adherence to the urinary tract epithelial cells.[25-33] The fructose in cranberries has also been shown to contribute to the antibacterial activity of cranberry.[31,34,35] In the case of *Escherichia coli* (*E. coli*), the cause of most urinary tract infections, proanthocyanidins have been shown to wrap around these bacteria and prevent their adherence to the urinary tract wall.[13,34,36,37] Cranberry juice cocktail was shown to inhibit adherence in 77 clinical isolates of *Escherichia coli* obtained from patients with diagnosed urinary tract infections.[36] It has been demonstrated, however, that cranberry does not appear to be able to dislodge bacteria that have already adhered to the urinary tract epithelial cells.[38]

Cranberry juice has antibacterial activity against *E. coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Proteus mirabilis.*[30,34,36] Cranberry has been shown to have antiviral action against the poliovirus type 1[39]; and has been found to prevent the adherence of *Helicobacter pylori* (*H. pylori*) in the stomach.[12,13] Cranberry may also prevent adhesion of plaque bacteria that cause periodontal disease.[14-16] Recent findings indicate that cranberry may even reduce adhesion and infectivity of the influenza virus.[17] Cranberry has significant levels of antioxidant and has demonstrated anticarcinogenic activity.[40,41]

Drug Interactions

Anecdotal reports of interaction with warfarin have been made[42-44], however, in a clinical study of 14 healthy individuals, no alteration of CYP2C9, the enzyme responsible for metabolizing warfarin, was evident.[45] One laboratory study indicates that cranberry juice may inhibit enteric CYP3A4[46], yet, a clinical study found no evidence of altered levels of cyclosporine, a CYP3A4 substrate, due to consumption of cranberry juice.[47]

DISCUSSION

There is extensive research on the constituents and potential therapeutic properties of cranberry fruit and juice. The predominant theme of the research to date, both clinical and preclinical, involves the exploration of cranberry fruit's ability to reduce the risk of infection, particularly of the urinary tract, by a process of directly inhibiting a pathogen's ability for tissue and host cell adherence. Evidence suggests that not only is this possible for bacteria, but also for viruses as well.

There is very strong evidence supporting the use of cranberry in the prevention of urinary tract infections. A Cochrane database systematic review investigating the use of cranberry for the prevention of urinary tract infections, concluded that cranberry juice may effectively prevent the frequency of urinary tract infections.[11] While evidence regarding other uses of this fruit is nowhere near as rigorous, there are some promising *in vitro* evidence related to oral hygiene, *H. pylori* induced stomach ulceration, and even possibly in the prevention of influenza.

There is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. As reported above, a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of

cranberry is unknown. Its common usage, low toxicity and the fact that cranberries are eaten as a food, however, does support the hypothesis of safety in pregnancy and lactation when consumed in food amounts. At higher dosages, however, the safety or harm cannot be confirmed without further high quality clinical studies.

In the situation where a woman is predisposed to nephrolithiasis, however, caution is warranted in the consumption of foods containing high amounts of oxalic acid, cranberries included. Increased risks to the fetus either from radiographic diagnosis, treatment and even stone passage make the formation of kidney stones even more problematic and potentially risky for the pregnant woman.[48] It should be noted, however, that pregnant women are not generally at increased risk for stone formation.[49]

Overall, cranberry appears to be a useful therapeutic agent for the prevention of urinary tract infections in women who are either pregnant or breastfeeding. Promising evidence regarding other anti-infective properties of cranberry need to be further pursued, including improved oral hygiene, stomach ulceration and the prevention of influenza. It is encouraging that there is a nutritious natural health product available that, in most cases, may safely prevent a common and debilitating complaint in pregnant woman.

TABLE 1 Levels of Evidence for Efficacy

GRADE	LEVEL OF EVIDENCE
A	**VERY STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.
B1	**STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).
B2	**GOOD SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.
C	**WEAK SCIENTIFIC EVIDENCE** Statistically significant evidence of benefit from one or more cohort studies OR case control studies.
D	**VERY WEAK SCIENTIFIC EVIDENCE** Evidence from case series OR case reports.
E	**INDIRECT EVIDENCE** Expert opinion OR laboratory studies.
F	**HISTORICAL OR TRADITIONAL EVIDENCE** Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.

TABLE 2 Levels of Evidence for Harm

LEVEL	EVIDENCE
1	**STRONG SCIENTIFIC EVIDENCE** Statistically significant evidence from one or more systematic reviews or RCTs.
2	**ACCEPTABLE SCIENTIFIC EVIDENCE** Statistically significant evidence from one or more well designed cohort studies OR case control studies.
3a	**WEAK SCIENTIFIC EVIDENCE** Evidence from one or more case series.
3b	**VERY WEAK SCIENTIFIC EVIDENCE** Evidence based on case reports.
4	**INDIRECT SCIENTIFIC EVIDENCE** Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.
5	**THEORETICAL EVIDENCE** Evidence based on scientific theory OR expert opinion.
6	**UNKNOWN** No available information.

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Journal of Antimicrobial Chemotherapy (2009) **63**, 389–395
doi:10.1093/jac/dkn489
Advance Access publication 28 November 2008

JAC

Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women

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Received 22 July 2008; returned 30 October 2008; revised 5 November 2008; accepted 5 November 2008

***Objectives*: To compare the effectiveness of cranberry extract with low-dose trimethoprim in the prevention of recurrent urinary tract infections (UTIs) in older women.**

***Patients and methods*: One hundred and thirty-seven women with two or more antibiotic-treated UTIs in the previous 12 months were randomized to receive either 500 mg of cranberry extract or 100 mg of trimethoprim for 6 months. Trial registration: ISRCTN80031108.**

***Results*: Thirty-nine of 137 participants (28%) had an antibiotic-treated UTI (25 in the cranberry group and 14 in the trimethoprim group); difference in proportions relative risk 1.616 (95% CI: 0.93, 2.79) $P = 0.084$. The time to first recurrence of UTI was not significantly different between the groups ($P = 0.100$). The median time to recurrence of UTI was 84.5 days for the cranberry group and 91 days for the trimethoprim group ($U = 166$, $P = 0.479$). There were 17/137 (12%) withdrawals from the study, 6/69 (9%) from the cranberry group and 11/68 (16%) from the trimethoprim group ($P = 0.205$), with a relative risk of withdrawal from the cranberry group of 0.54 (95% CI: 0.19, 1.37).**

***Conclusions*: Trimethoprim had a very limited advantage over cranberry extract in the prevention of recurrent UTIs in older women and had more adverse effects. Our findings will allow older women with recurrent UTIs to weigh up with their clinicians the inherent attractions of a cheap, natural product like cranberry extract whose use does not carry the risk of antimicrobial resistance or super-infection with *Clostridium difficile* or fungi.**

Keywords: urinary infections, UTIs, antibiotics

Introduction

Urinary infection is the most common bacterial infection in older people and recurrent urinary tract infection (UTI) is particularly common in older women. The current management of recurrent UTI involves either repeated courses of antibiotics or low-dose long-term antibiotic prophylaxis.[1] The evidence in support of antibiotic prophylaxis is strong, with 11 placebo controlled trials of which 10 show a significant treatment benefit.[1] In these trials, antibiotic prophylaxis was highly effective: number needed to treat (NNT) to prevent one recurrence was 1.85, but side effects severe enough to stop treatment were equally common (NNT for severe side effects was 1.58). The main side effects measured in the trial were fungal super-infection (oral or vaginal thrush) and gastrointestinal infections. However, a growing reluctance to prescribe antibiotics is emerging because of concerns about antimicrobial resistance and other adverse effects on the normal bacterial flora, such as super-infection with *Clostridium difficile*. At the same time, there has been a resurgence of interest in the role of cranberry products, stimulated by the conclusion of a Cochrane review that 'there is some evidence from two good quality RCTs that

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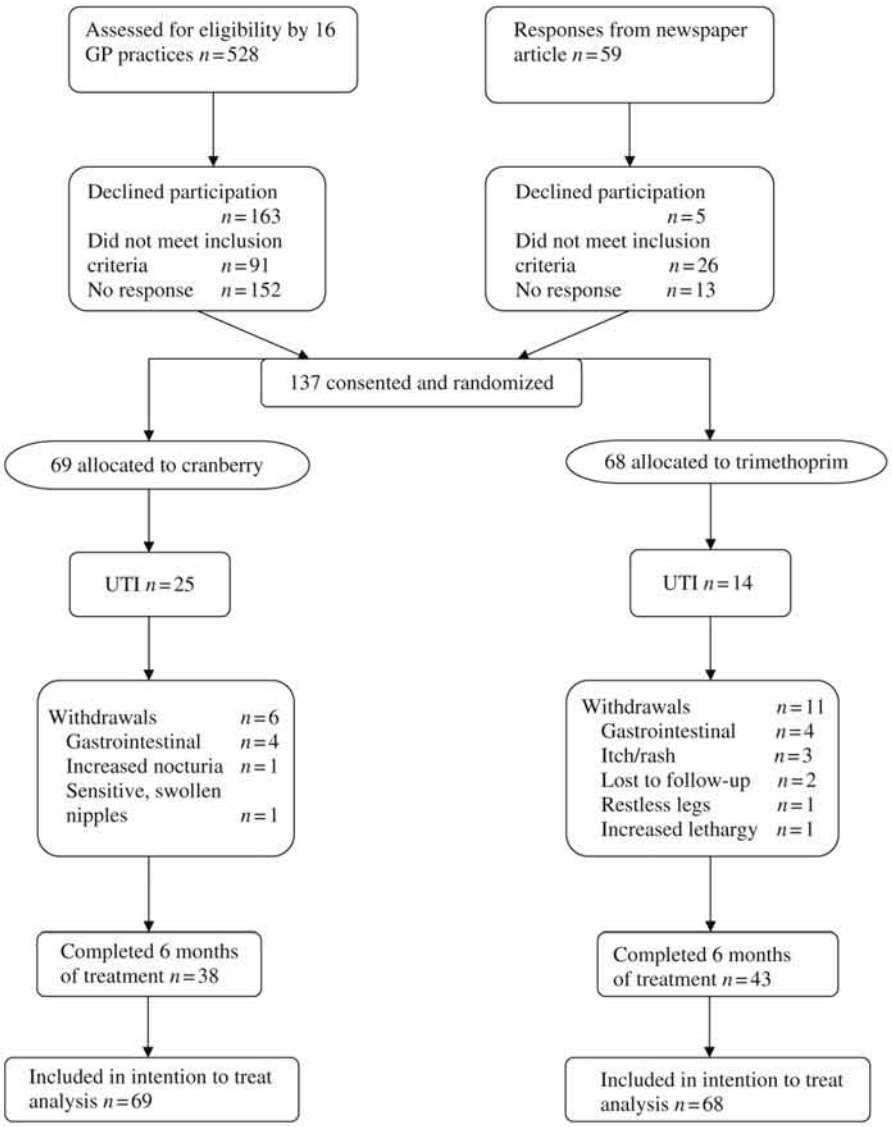

Figure 1. CONSORT flow chart.

Results

A total of 137 women were randomized, 69 to cranberry and 68 to trimethoprim (Figure 1).

There were no significant differences between the groups at baseline (Table 1).

Primary outcome

A total of 39/137 (28%) of participants had a symptomatic antibiotic-treated UTI (25 in the cranberry group and 14 in the trimethoprim group); the difference in proportions was relative risk 1.616 (95% CI: 0.93, 2.79) $P = 0.084$.

The time to first recurrence of UTI was not significantly different between the groups [log-rank test: $\Delta = 2.7$, χ^2 (2.7, 1) $P = 0.100$].

The median time to recurrence of UTI was 84.5 days for the cranberry group and 91 days for the trimethoprim group ($U = 166$, $P = 0.479$).

Secondary outcomes

Withdrawals. There were 17/137 (12%) withdrawals from the study, 6/69 (9%) from the cranberry group and 11/68 (16%) from the trimethoprim group ($P = 0.205$), with a relative risk of withdrawal from the cranberry group of 0.54 (95% CI: 0.19, 1.37).

The reasons were as follows: for the cranberry group, gastrointestinal upset $n = 4$; increased nocturia $n = 1$; sensitive swollen nipples $n = 1$ and the trimethoprim group, gastrointestinal upset $n = 4$; itch/rash $n = 3$; lost to follow-up $n = 2$; restless legs $n = 1$; increased lethargy $n = 1$. While gastrointestinal upsets were equally common in both groups, itch/rash and loss to follow-up occurred more commonly in the trimethoprim group.

Other adverse events. Other adverse events were similar between the groups (Table 2).

Adherence. Adherence was good in both groups. Median (range) adherence was 99 (25–149)% and 100 (66–112)% in the cranberry and trimethoprim groups, respectively.

Table 1. Baseline characteristics

Variables	Cranberry ($n = 69$)	Trimethoprim ($n = 68$)
Age (years)		
mean (SD)	62.6 (10.8)	63.3 (10.1)
range	45–93	46–88
Living circumstances		
living alone	12	18
sheltered housing	1	7
Number of medications		
median (range)	3 (0–13)	4 (0–11)
Length of history of UTIs (years)		
median (range)	11 (1–50)	18 (1–53)
Number of self-reported UTIs in past 12 months		
median (range)	3 (2–15)	3 (2–8)
Number of antibiotic-treated UTIs in past 12 months[a]		
median (range)	3 (2–15)	2 (2–8)
Bacteriuria at baseline	5/69 (7.2%)	7/68 (10.3%)
E. coli	2	6
K. pneumoniae	1	0
Streptococcus B	1	1
E. faecalis	1	0

[a]Mann–Whitney *U*-test ($P = 0.72$).

Table 2. Adverse events other than those resulting in withdrawal

	n (%)	
Adverse event	cranberry ($n = 69$)	trimethoprim ($n = 68$)
Non-UTI urinary symptoms	12 (17)	9 (13)
Gastrointestinal upset	9 (13)	13 (19)
Thrush	3 (4)	3 (4)
Colds/flu	4 (6)	4 (6)
Difficulty swallowing capsules/aftertaste/dry mouth	4 (6)	1 (1)
Exacerbation of back pain	4 (6)	2 (3)
Tiredness/lethargy	2 (3)	3 (4)
Itch/rash	2 (3)	2 (3)
Abdominal abscess	1 (1)	0
Breast carcinoma	1 (1)	0
Deterioration in bilateral vision	1 (1)	0
Vaginal dryness/atrophy	1 (1)	2 (3)
Falls	1 (1)	4 (6)
Shingles	0	1 (1)
Excessive thirst	0	1 (1)
Type II diabetes	0	1 (1)
Routine surgery	0	4 (6)
Migraine	0	1 (1)

Antibiotic use. A total of 15/69 (22%) participants in the cranberry group and 17/68 (25%) in the trimethoprim group were prescribed antibiotics for indications other than UTI during their period of participation.

Causative organisms. For the 39 women who developed a symptomatic UTI during the trial, the urine culture results were as follows: *E. coli*, 16 (9 in the cranberry group and 7 in the trimethoprim group); *Klebsiella pneumoniae*, 3 (2 in

the cranberry group and 1 in the trimethoprim group); no growth, 4 (2 in each group); mixed growth, 1 (in the cranberry group); no significant bacteriuria, 6 (4 in the cranberry group and 2 in the trimethoprim group). No urine specimen was obtained in 9 (7 in the cranberry group and 2 in the trimethoprim group).

Antibiotic resistance patterns. At baseline testing, 12 women had positive urine cultures with $\geq 10^4$ cfu/mL. Of these, 8 were *E. coli* (6 susceptible to trimethoprim), 2 group B *Streptococcus* (not tested against trimethoprim) and one each of *K. pneumoniae* (trimethoprim-susceptible) and *Enterococcus faecalis* (trimethoprim-resistant). Overall, therefore, 7/9 (78%) subjects bacteriuric at baseline with Gram-negative bacteria had trimethoprim-susceptible organisms.

Nineteen out of 39 (49%) women had symptomatic recurrences with positive urine cultures of $\geq 10^4$ cfu/mL. All were Gram-negative isolates. Of those with *E. coli* cultures, 11/16 were trimethoprim-susceptible, and of those with *K. pneumoniae*, 2/3 were trimethoprim-susceptible isolates. Thus, 13/19 of this subgroup of participants had trimethoprim-susceptible isolates.

Discussion

Our head-to-head trial has shown that for older women with recurrent urinary infections, the 6 month risk of developing a UTI on cranberry products is only 60% greater than that on low-dose trimethoprim; this difference was not statistically significant. Compared with cranberry extract, treatment with trimethoprim conferred fewer than 7 additional UTI-free days. Our primary endpoint was symptomatic UTI treated by the GP. However, recurrence rates for microbiologically confirmed symptomatic UTI were also similar (16% for cranberry versus 12% for trimethoprim).

Validity of the trial

Our target of 120 participants for the trial was set to have 80% power to detect a difference in effectiveness of 15% in risk of recurrence between trimethoprim and cranberry, and assumed a 15% dropout rate. In fact we recruited 137 participants, of whom 17 (12%) withdrew but only two (1.5%) were lost to follow-up. The remaining withdrawals were because of side effects, which was one of the secondary outcomes for the trial. The participants represented 29% of the 470 people who were screened and met the inclusion criteria. Most participants were recruited by screening patient records from 16 GP practices, which is 20% of all the practices in Tayside. The primary outcome was objective (first recurrence of clinical UTI treated by the GP) and could not be influenced by the investigators. Moreover, participants and investigators were unaware of the participants' treatment group until the statistical analysis had been completed. Adherence to treatment in our study was very good in both groups, which together with the modest withdrawal rate lends further support to the acceptability of encapsulated cranberry extracts.[2]

The internal validity of the trial therefore seems good and we also believe that the results should be applicable to other primary care populations. Nonetheless, the trial result was not what we expected. The literature had led us to predict that trimethoprim would prove considerably more effective, but only at

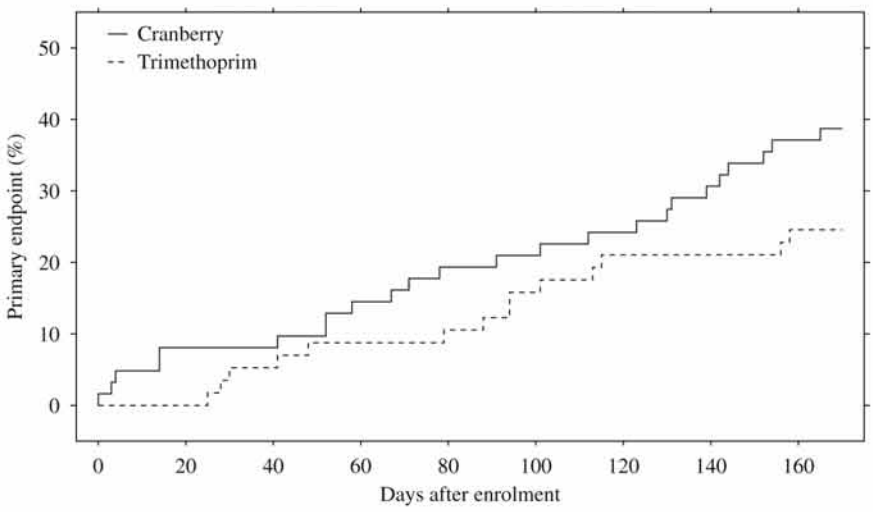

Figure 2. Time to first recurrence of UTI.

cranberry juice may decrease the number of symptomatic UTIs over a 12 month period in younger women' (mean ages 32 and 43 years).[2]

The Cochrane review of antibiotic prophylaxis and SIGN guideline 88 stated that a head-to-head trial of cranberry versus low-dose antibiotic in the prevention of recurrent UTI was required because previous placebo controlled trials had demonstrated effectiveness for both, with the effectiveness of antibiotic therapy being considerably superior.[2,3] While cranberry juice has been studied in an underpowered trial of UTI prevention in 376 hospitalized older people,[4] there is a dearth of evidence concerning its effectiveness in recurrent urinary infections in old age. This is a surprising gap in the literature, given that UTI occurs more frequently in old age than at any other time of life. In contrast, the literature on antibiotic prophylaxis does suggest that this is likely to be effective in older women. Of the 11 trials identified in the Cochrane review of antibiotic prophylaxis for recurrent UTI, eight included post-menopausal women.[1] We therefore designed a trial to compare the effectiveness and acceptability of low-dose trimethoprim with cranberry products in the prevention of recurrent UTI in older women. Trial registration: ISRCTN80031108.

Methods

Study population

Inclusions: community dwelling women aged $\geq$45 years with at least two antibiotic-treated UTIs or episodes of cystitis in the previous 12 months confirmed by their general practitioner (GP) but not necessarily confirmed by microbiological culture. Participants were recruited predominantly through the eastern node of the Scottish Primary Care Research Network and also from responses to an article in a local newspaper featuring the study.

Exclusions: previous urological surgery, stones or anatomical abnormalities of the urinary tract; urinary catheter; diabetes mellitus; immunocompromised; pyelonephritis; severe renal impairment; blood dyscrasias; symptomatic UTI at baseline; cognitive impairment precluding informed consent; resident in institutional care; on long-term antibiotic therapy; on warfarin therapy; regular cranberry consumers; child bearing potential; unwilling to participate.

As a number of potential participants were occasional cranberry consumers, it was decided that such individuals could participate provided that there was a 2 week washout period prior to commencing the study.

Written informed consent was obtained from participants and the study was approved by the Tayside Committee on Medical Research Ethics (06/S1402/23) and the MHRA (Eudract no: 2006-001313-15).

Randomization

Participants were randomized to receive either one capsule of 500 mg of cranberry extract (Cran-Max^{TM}; Buckton Scott Health Products Ltd, UK) taken at bedtime for 6 months or one capsule of 100 mg of trimethoprim. Randomization was performed off-site by DHP *pharma* in Powys, UK, which is an MHRA-approved manufacturing site. Randomization was performed in blocks of four using Prisym PFW clin software to generate random numbers. Participants were given a study number sequentially by the research nurses. A copy of the treatment code was held by the Clinical Trials Pharmacist in Ninewells Hospital, Dundee.

Cranberry product and trimethoprim preparation

DHP *pharma* over-encapsulated 100 mg trimethoprim tablets into red size 00 capsules, and filled red size 00 capsules with 500 mg of cranberry extract (Cran-Max^{TM}). Both sets of capsules were identical in appearance.

Urine culture methods

A urine specimen was obtained at baseline from all participants and cultured in the Medical Microbiology Laboratory using standard protocols. Identification and susceptibility testing on positive cultures were performed by Vitek I (bioMérieux) or Stokes' susceptibility testing and chromogenic agar for speciation of *Escherichia coli*. Baseline results were not reported to clinical or research staff. Specimens from participants who developed symptoms of UTI during the trial were processed in the same way.

Outcome measures

Primary outcome

This was the proportion of participants in each group experiencing a recurrence of an antibiotic-treated UTI and the time to first recurrence.

Participants were censored (i.e. withdrawn from study participation) after their first UTI. UTI was defined as clinical symptoms of dysuria and frequency in the absence of vaginal discharge with or without microbiological confirmation.

Secondary outcomes

Adherence. The participants were provided with two sealed tubs at baseline each with 200 capsules containing either 100 mg of trimethoprim or 500 mg of cranberry extract. Adherence was assessed by capsule counting at 3 and 6 months and expressed as the number of capsules consumed divided by the number of capsules that should have been consumed during the duration of each individual's period of study participation.

Adverse events and follow-up. After the baseline visit, further home visits occurred at 3 and 6 months to re-check study eligibility, record adverse events, check adherence and to note the courses of antibiotics that had been prescribed for any indications. Participants were telephoned at 1, 2, 4 and 5 months to encourage participation and adherence, and to record any adverse events.

Statistical methods

Sample size. Based on the available literature, it was predicted that a final sample of 102 participants would be required to have 80% power at $P = 0.05$ of detecting a reduction in occurrences of urinary infection from 16% in the cranberry group to 1% in the trimethoprim group.[5,6] In anticipation of a dropout rate of 15%, we intended to recruit at least 120 participants.

Statistical analysis. Data were entered onto an Excel database and then analysed using a Statistical Calculator v.2.06 (Mole Software, Alpes de Haute-Provence 04230, France). Full statistical analysis was completed prior to breaking the treatment code. Analysis was by intention to treat. Time to first recurrence of infection is presented as a Kaplan–Meier curve and differences between the groups were assessed using the log-rank test.

the expense of more adverse events. Withdrawals were indeed higher in the trimethoprim group, but other adverse event rates turned out to be low and remarkably similar between the groups.

Possible explanations

We have considered the possibility that neither treatment was effective. At the design stage, we considered the inclusion of a placebo group but rejected this option because Cochrane systematic reviews have concluded that both antibiotics and cranberry products are effective in preventing UTIs.[1,2] There is uncertainty about how effective both treatments are in older women, especially for cranberry but we did not consider that this was sufficient justification for inclusion of a placebo group. Moreover our eligibility criteria required two or more antibiotic-treated UTIs in the previous 12 months so it was reasonable to expect that without prophylaxis most women would experience a recurrence within 6 months. It is therefore unlikely that totally ineffective prophylaxis would have allowed 81 (59%) of the 137 participants to have completed 6 months of treatment free of UTI recurrence.

We selected trimethoprim for antibiotic prophylaxis because it is as effective as co-trimoxazole for treatment of UTI but has fewer side effects.[7] Trimethoprim was included in one of the placebo controlled clinical trials of antibiotic prophylaxis for UTI and proved as effective as co-trimoxazole and nitrofurantoin.[6] Resistance to trimethoprim in bacteria causing UTIs has increased in Northern European and American countries from 10% to 15% in the 1970s to 15% to 20% in the 1980s.[8] The prevalence of trimethoprim resistance in the *E. coli* isolates from our patients was 29%, which is only slightly higher than the average resistance for all primary care isolates from midstream urines in our laboratory (excluding catheter urine samples) of 24% in 2004. Resistance has yet to reach a level that should markedly reduce the effectiveness of trimethoprim in lower UTI. The recurrence rate after treatment of symptomatic lower UTI has been estimated for different levels of resistance to co-trimoxazole.[9] At a resistance rate of zero, the recurrence rate was estimated to be 5%, rising to 12% at 20% resistance and 15% at 30% resistance.[9] These calculations assumed that 60% of women would respond to co-trimoxazole if their infection was caused by a resistant organism. In a recent UK study, 61% of women with lower UTI caused by trimethoprim-resistant bacteria were symptom-free 1 week after trimethoprim treatment and 58% were free of bacteriuria 1 month after treatment.[10] We believe that trimethoprim prophylaxis should be effective at the levels of resistance observed in our study and in the Tayside population. It is possible that nitrofurantoin might have proved more effective as resistance is less common; however, the evidence suggests that it has more side effects.[1]

We selected cranberry extract in preference to juice for our study because previous work has shown equivalent efficacy between cranberry capsules (containing at least 1:30 parts concentrated juice) and cranberry juice.[11] Furthermore, cranberry capsules have potential advantages over juice; capsules are more convenient, cheaper (costs for 1 year of treatment are from £42 to £125 for cranberry tablets or capsules versus £175 to £257 for cranberry juice) and may overcome compliance issues for some individuals.[12] The high rates of withdrawal from some previous studies suggest that cranberry juice may not be an acceptable therapy over a long period of time.

Our power calculation estimated the difference in effect size to be 15%. In our trial, the difference in effect size was 15% (40% for cranberry versus 25% for trimethoprim), which was not statistically significant because the efficacy of both treatments was lower than we had predicted. We estimated that recurrence with cranberry would be 16% to 20% and 1% to 5% with antibiotics.[1,5,11] Our data regarding time to first recurrence suggest that the added benefit to patients from antibiotics is likely to be modest (Figure 2) and therefore that the value of information from a larger trial in older women is unlikely to justify the cost.[13]

Conclusions

Our trial is the first to evaluate cranberry in the prevention of recurrent UTIs specifically in older women, and the first head-to-head double-blind comparison of cranberry versus antibiotic prophylaxis.

Trimethoprim had a very limited advantage over cranberry extract in the prevention of recurrent UTIs in older women and had more adverse effects. Our findings will allow older women with recurrent UTIs to weigh up with their clinicians the inherent attractions of a cheap, natural product like cranberry extract whose use does not carry the risk of antimicrobial resistance or super-infection with *C. difficile* or fungi.

Further research is now required to discover if our findings might apply to younger individuals with recurrent urinary infections.

Funding

Moulton Charitable Foundation. Buckton Scott Health Products Ltd, UK supplied the Cran-Max™ free of charge. Neither the funder nor the supplier had any role in the concept, design, running, analysis, interpretation or reporting of the study.

Transparency declarations

No conflicts of interest to declare.

Contributions: M. E. T. M., P. D. and G. P. participated in study design, I. A. participated in recruitment and data collection, F. D. participated in the analysis, and all participated in the interpretation of the data, drafting and revising the paper and approving the final version. M. E. T. M. is the guarantor for the paper.

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eCAM Advance Access published October 25, 2007

eCAM 2007;Page 1 of 7
doi:10.1093/ecam/nem141

Original Article

Orthosiphon Versus Placebo in Nephrolithiasis with Multiple Chronic Complaints: A Randomized Control Trial

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Nephrolithiasis in the communities of Northeast Thailand frequently presents with multiple chronic health complaints, i.e. myofascial pain, back pain, dyspepsia, arthralgia, headache, fatigue, frank paresthesia, dysuria and any of these aggravated by purine-rich food (PRF). We assessed the efficacy of Orthosiphon in treating subjects with at least two active symptoms and negative for urine white blood cells. Subjects were randomly allocated to two groups. Crude extract of Orthosiphon given in a capsule (equivalent to 1.6–1.8 g of dried leaves of Orthosiphon) two times a day to Group 1 ($n = 36$) and a placebo to Group 2 ($n = 40$) for 14 days. The medication for each subject was packed and its code kept secret until the data analysis. Both groups were asked not to consume any of 25 purine-rich foods (PRFs) during treatment. The primary measure was the reduced sum of active severity symptoms as recorded using the visual analog scale before and after therapy (i.e. on day 7 and 14). The data on 76 subjects were processed. The mean of the total scores (95% CI) of the symptoms in each group were decreased significantly ($P < 0.001$); 185.6 (153.3, 218.0) to 94.7 (58.2, 131.2) in the Orthosiphon group and 196.1 (164.4, 227.8) to 89.6 (62.8, 116.5) in the placebo group. When comparing between groups, no statistically significant difference was found. The mean consumption in PRFs was significantly decreased ($P < 0.001$) in both groups; however, Orthosiphon did not have additional benefit over placebo at 7 and 14 days of treatment during which they reduced these foods.

Keywords: chronic fatigue – dyspepsia – myofascial pain – purine rich – renal stone

Introduction

Nephrolithiasis is a common health problem among the rural dwellers of Northeast Thailand. The prevalence of stone cases varies between reports according to the instruments used (range 0.38–16%) (1,2). Besides having kidney stones, affected persons have multiple chronic health complaints (MCHCs): (i) myofascial pain; (ii) back pain; (iii) dyspepsia; (iv) arthralgia; (v) headaches; (vi) fatigue; (vii) frank paresthesia; (viii) dysuria and, (ix) any of these symptoms are aggravated by drinking alcoholic beverages or eating fermented or purine-rich foods (PRFs) (3). These complaints (i.e. dyspepsia, myofascial pain, back pain, arthralgia) are among the common complaints in the out-patient departments (OPDs) of the sub-district health centers and community hospitals. Due to limited resources, patients are treated according to their symptoms and thus likely to revisit, leading to overcrowded OPDs.

A recent survey showed that 93.4% of rural dwellers consumed bamboo shoots or some PRF at least once a week and the prevalence of aggravated symptoms by PRF was 43.3% (4). Searching for an effective treatment

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of MCHC is essential for the patient as well as for reducing the workload at health centers. In another study, patients with kidney stones with MCHC, positive for white blood cells in the urine, were treated with antibiotics for 2 months plus *Orthosiphon grandiflorus* (OG) or sodium potassium citrate according to the treatment groups. More than 90% of both groups reported a dramatic reduction in symptoms (i.e. myofascial pain, arthralgia, dyspepsia and fatigue) without other pharmaceutical products (3). Similarly, Nirdnoy and Muangman (5) observed that drinking an infusion (tea) made from OG caused an increase in urinary pH and the tendency to increase excretions of both K and citrate. They questioned whether the outcome was the effect of the antibiotic or the OG via a correction of K and citrate which are depleted in Northeast Thais suffering from nephrolithiasis (6).

Plant-based systems continue to play an essential role in the primary healthcare of 80% of the world's population. Several of the effective anticancer agents in current use are derived from nature. The search for novel antitumor agents from natural sources is ongoing with botanists, marine biologists and microbiologists teaming up with chemists, pharmacologists, toxicologists and clinicians in the investigation of coral reefs, rainforests for novel bioactive compounds. Over 50% of the anticancer drugs approved by the United States Food and Drug Administration since 1960 originally derived from natural resources, especially from terrestrial plants (7).

Recently, much attention has been directed toward extracts and biologically active compounds extracted from popular plant species. The aqueous extract of leaves of *Indigofera suffruticosa* obtained by infusion showed strong inhibitory activity against *Staphylococcus aureus*, *Trichophyton rubrum and Microsporum canis*. This study suggests that the aqueous extracts of leaves can be used in the treatment of skin diseases caused by dermatophytes (8). An *in vitro* study showed that an aqueous extract of *Orthosiphon aristatus* has an antibacterial activity against two serotypes of *Streptococcus mutans* (MIC 7.8–23.4 mg/ml) (9). Another study revealed that *Orthosiphon stamineus* extract inhibited spore-germination in six of nine fungal species tested (viz. *Saccharomyces pastorianus*, *Candida albicans*, *Rhizopus nigricans*, *Penicillium digitatum*, *Fusarium oxysporum* and *Trichophyton mentagrophytes*) (10).

Orthosiphon is found throughout Southeast Asia. It is called 'java tea' in Indonesia and 'Yha Nhuard Maw' (cat's whiskers) in Thailand. It grows to about 1 m in height and produces white to light-violet flowers. Orthosiphon has been used as herbal tea for centuries in Southeast Asian countries. Traditionally, it is used to treat gout, rheumatism, diabetes, hypertension and renal stones.

Side effects of Orthosiphon are rare. According to the Thai traditional medicine, the people believe that the Orthosiphon infusion may have high concentration of potassium and should not be used in the patients with concurrent cardiac diseases.

This study aimed to evaluate the effect of OG versus a placebo for the treatment of nephrolithiasis in patients suffering from MCHC and testing negative for white blood cell in the urine.

Materials and Methods

Trial Design, Funding and Ethics Approval

Our study was a prospective, concealed, randomized, controlled trial conducted over a 2-week period. The research was supported by Khon Kaen University and the protocol was approved by the Ethics Committee of Khon Kaen University (HE 471224). Written, informed consent was obtained from the patients who met the inclusion criteria.

Patients

Free, ultrasound checks for renal stones were announced through local health workers and village headmen in 15 villages. Participants joining the study were interviewed for their chronic health complaints, received an ultrasound examination and underwent urinalysis (using a urine strip). All of the subjects were asked about the presence of nine chronic symptoms: (i) multiple myofascial pain; (ii) back pain or lower abdominal pain; (iii) dyspepsia; (iv) poly-arthralgia; (v) single-side headache; (vi) fatigue; (vii) frank paresthesia; (viii) dysuria at least once a year and, (ix) any of these symptoms were aggravated by PRF.

The inclusion criteria comprised: (i) patients with renal stones or having a hyperechoic focus suspected of being a stone; (ii) having five or more of the nine variables of MCHC; (iii) having at least two active symptoms and, (iv) being between 20 and 65 years of age. Subjects were excluded if they had: (i) a stone obstruction; (ii) heart disease; (iii) known chronic renal failure; (iv) were pregnant or, (v) had any other severe illness. Patients with white blood cells in the urine, using a strip read by a portable urine analyzer (UriluxS, Roche, Basel, Switzerland), were also excluded from this study but entered into another.

Randomization

Subjects were stratified by the number of their active symptoms: those with two–four symptoms were assigned to Group A, and those with more than four symptoms to Group B. In each group, running numbers were listed according to the time sequence, viz. A01, A02, A03, . . . , A50 in Group A and B01, B02, B03, . . . ,B50 in Group B.

Within each group, patients were allocated to G1 (the OG group) or G2 (the placebo group) by block of six. For example, every six consecutive participants were enrolled in each group (A, B), three subjects by coin toss to the OG group and three to the placebo group. Thus, each running number in each subgroup belonged to the code of either OG or placebo. The medication was prepared according to the code. Thereafter, the codes were concealed and not opened until the data analysis phase.

Treatment

The placebo and OG extract were filled into identical-looking capsules. The placebo contained the dried ground vegetable Ipomoea Aquatica Forsk. To prepare the OG extract, dried leaves of OG were ground in a mechanical mill and put in hot water (kept at 70–80°C for 20 min. The infusion was separated in a container and put on a water bath. The temperature of the infusion was kept at 70–80°C for 36 h until it nearly dried then it was mixed with a prepared mixture, and left in the chamber for 48–72 h at 40–50°C until dried. This dried mixture was ground and capsules filled with it. Each capsule of OG extract equaled 1.6–1.8 g of the dried leaves.

Therapies consisted of 20 minute health education for the MCHC and encouraged them to stop consuming the 25 PRF items during the trial period. Group 1 took one capsule of OG two times a day while Group 2 took the placebo.

The Adverse Effects of Treatments

Adverse effects in this study were defined as: any new symptoms that occurred during treatment, or old, inactive symptoms which became active during treatment.

The Purine-Rich Foods

PRFs in this study included: bamboo shoot (*Gigantochloa albociliata*, *Bambusa sp.*, *Thysostachys siamensis Gamble*), tops of *Calamus rotang Linn*; leaf shoot of coconut (*Cocos nucifera Linn*); young leaves of *Acacia pennata*; common local mushrooms [*Pleurotus sajor-caju* (*Fr.*) *Singer*, *Lentinus squarrosulus Mont.*, *Volvariella volvaceae*, *Termitomyces fuliginosus Heim*]; fermented boiled flour in noodle form; all kinds of fermented fruits or vegetables; alcoholic beverage; grasshoppers [*Locusta migratoria manilensis* (*Meyen*), *Patanga succincta* (*Linnaeus*)]; queen or larva of red ant (*Oecophylla smaragdina*); silk worm (*Philoamia ricini Boisd*); all kinds of crickets (*Acheta testacea, Acheta bimaculatus De Geer*, *Bracytrupes portentosus Licht.*); beef or buffalo meat (*Swamp buffalo*); a local small freshwater fish (*Rasbora tornieri*); shellfish (*Sinotaia ingallsiana*, *Pila polita*); cuttlefish (*Sepia pharaonis*); squid (*Loligo peali*); chicken (*G.gallus domesticus*); duck (*Anseriformes anatidae*); adult, small /larva of frog (*Rana tigerina*) and ricefield rat (*Rattus argentiventer*).

Measurements

The main outcome measure was the sum of score of each patient's active symptoms on the visual analog scale (VAS). Each symptom had a maximum score of 100 and a minimum score of 0. The VAS was performed by each patient under supervision at the beginning (on day 0) and upon follow up (at day 7 and 14). The second outcome was the score on the general feeling of illness. Data on daily PRF intake were collected, retrospectively, through interviews on days 0, 7 and 14.

Data Analysis

Data were expressed as means and 95% confidence intervals (95% CI), medians and inter-quartile ranges (IQRs). A comparison of results between groups was performed using unpaired *t*-tests for normal distributions or the Mann–Whitney U-test for skewed distributions. Before and after within groups analyses were done using the paired *t*-test or the Wilcoxon signed ranks test (WSRT) for normal or skewed distributions, respectively. A probability of $P < 0.05$ was considered statistically significant.

Results

Eighty-seven subjects agreed to participate in the study, of whom six in the OG and five in the placebo group were lost. Four subjects in the OG declined to join because of the adverse effects: dizziness, myofascial pain, fatigue and palpitation. Two subjects from the OG group and three from the placebo group felt unchanged and quit in the second week. Two subjects in the placebo group moved out of province and we lost contact with them. Seventy-six subjects had complete data portfolios and were analyzed, on an intention to treat basis. (Fig. 1).

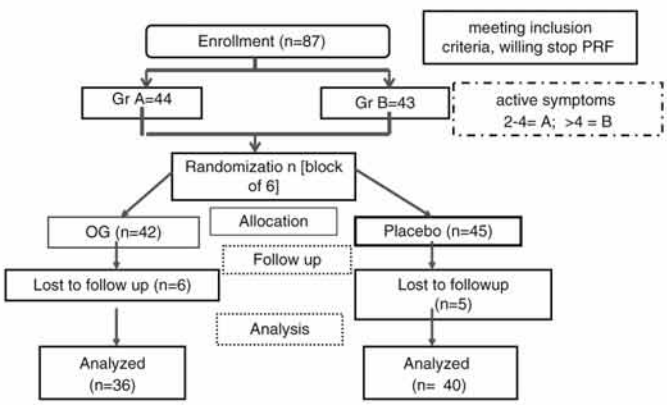

Figure 1. Details of MCHC patients enrolled in the study.

Table 1. Baseline characteristics and mean scores by VAS scale for 76 patients

Characteristic	OG[a] gr. ($n = 36$)	Placebo ($n = 40$)	*P*-value
Age (>45)	29 (80.0%)	32 (80.0%)	0.95[†]
Sex (female)	22 (64.5%)	27 (67.5%)	0.56[†]
Renal stone positive	22 (71.0%)	29 (80.6%)	0.36[†]
Urine red blood cell positive	9 (25.7%)	7 (17.5%)	0.39[†]
Aggravated by PRF[b]	27 (79.1%)	36 (94.7%)	0.08[†]
No. of MCHC[c] *mean(95%CI)*	6.7 (6.1,7.9)	7.5 (6.7,7.3)	0.22[‡]
No. of Active sym. *mean (95%CI)*	3.8 (3.3,4.2)	4.1 (3.6,4.7)	0.31[‡]
Gen feeling *mean (95%CI) of VAS*	52.6 (47.2,58.0)	50.3 (42.5,58.1)	0.71[‡]
MCHC[d] *mean (95%CI) of VAS*	185.6 (154.4,216.8)	196.1 (163.7,228.5)	0.64[‡]

[a]*Orthosiphon grandiflorus*; [b]Purine rich food; [c]Multiple chronic health complaint; [d]Sum of VAS scores of MCHC.
[†]Chi-square tests.
[‡]Mann–Whitney test U.

Table 2. VAS scores of general feeling of illness for 76 patients by treatments

Group	VAS score of general feeling of illness			
		Day 0	Day 7	Day 14
OG[a] ($n = 36$)	Median (IQR[b])	50 (12.8)	34 (20.8)*	27 (37.5)*
	Mean (SD)	52.1 (16.4)	35.5 (18.9)	31.3 (24.5)
	95% CI	46.5,57.5	29.1,41.9	22.9,39.5
Placebo	Median (IQR)	50.0 (35.0)	32.0 (44.0)*	15 (38.0)*
($n = 40$)	Mean (SD)	50.3 (24.1)	36.5 (24.1)	26.2 (24.4)
	95% CI	42.5,58.2	28.7,44.3	18.3,34.1
P-value[§]		0.779	0.928	0.374

[a]*Orthosiphon grandiflorus*; [b]Inter-quartile range.
*$P < 0.001$ compare before and after by Wilcoxon Signed Ranks.
[§]Compared between groups by Mann-Whitney U.

Table 3. Total VAS scores of MCHC for 76 patients by treatments

Group	Total VAS scores			
		Day 0	Day 7	Day 14
OG	Median (IQR[a])	166.5 (130.8)	109.5 (114.3)*	68.0 (125.8)*
($n = 36$)	Mean (SD)	185.6 (95.6)	119.0 (90.7)	94.7 (107.9)
	95% CI	153.3,218.0	88.3,149.7	58.2,131.2
Placebo	Median (IQR)	186.5 (104.5)	101.5 (119.0)*	79.5 (94.7)*
($n = 40$)	Mean (SD)	196.1 (99.2)	129.6 (92.7)	89.6 (83.9)
	95% CI	164.4–(227.8)	100.0–159.3	62.8–116.5
P-value[†]		0.747	0.689	0.791

[a]Interquartile range.
*$P < 0.001$, comparing before and after by Wilcoxon Signed Ranks.
[†]Compared between groups by Mann–Whitney U.

Baseline Patient Characteristics

The mean age of the 76 participants was 53.7 years (55.6 for OG and 53.8 for placebo); 36 were in the OG group and the 40 in placebo group. Table 1 shows the patients' baseline characteristics by treatment groups, which were similar. Most of the participants were women (64.5 and 67.5%) over 45 years of age (80.0 and 80.0%, respectively). In the OG and placebo groups, the respective mean (95% CI) of the MCHC variables was 6.7 (6.1, 7.9) and 7.5 (6.7, 7.3), and of active symptoms (95%CI) 3.8 (3.3, 4.2) and 4.1 (3.6, 4.7). For the OG and placebo groups, respective renal stone detection was 71.0 and 80.6% and for red blood cells (RBCs) in the urine 25.7 and 17.5%. The positive history for symptoms aggravated by PRF was 79.1 and 94.7%, respectively. The mean (95% CI) VAS score for general feeling of illness between the OG and placebo groups was 52.6 (47.2, 58.0) and 50.3 (42.5, 58.1), respectively. For total MCHC symptoms, the respective mean (95%CI) VAS score for the OG and placebo groups was 185.6 (154.4, 216.8) and 196.1 (163.7, 228.5) points.

Main Outcomes: Sum of VAS Scores of MCHC

In the OG group, the median (IQR) of the sum of VAS scores of the MCHC symptoms was 109.5 (114.3) at day 7 and 68.0 (125.8) at day 14, which were significantly decreased (*P*-value < 0.001, WSRT) from the value on day 0 [166.5 (130.8)] (Table 2). The respective mean (95% CI) sum of VAS scores on day 7 and 14 was 119.0 (88.3, 149.7) and 94.7 (58.2, 131.2), which was 64.1 and 51% of the value on day 0 [185.6 (153.3, 218.0)].

In the placebo group, the median (IQR) of the sum of VAS scores for MCHC symptoms was 101.5 (119.0) on day 7 and 79.5 (94.7) on day 14, significantly decreased (*P*-value < 0.001, WSRT) from the beginning [186.5 (104.5)] (Table 3). The respective mean (95% CI) of the sum of VAS scores on day 7 and 14 was 129.6 (100.0, 159.3) and 89.6 (62.8, 116.5), which was 66.1 and 45.7% of the value before treatment.

There was no statistically significant difference for the OG versus placebo groups for the beginning, day 7 and day 14 of treatment (Table 3). Instead, in both groups, each symptom of the MCHC, as a VAS score, at day 7 and 14 was significantly decreased (*P*-value < 0.05, WSRT) from day 0. Figure 2 illustrated the VAS scores at day 0, 7 and 14 for myofascial pain, arthralgia, dyspepsia and back pain.

The General Feeling of Illness

In the OG group, the median (IQR) of the VAS scores for the general feeling of illness was 34 (20.8) at day 7 and 27 (37.5) at day 14, both significantly decreased

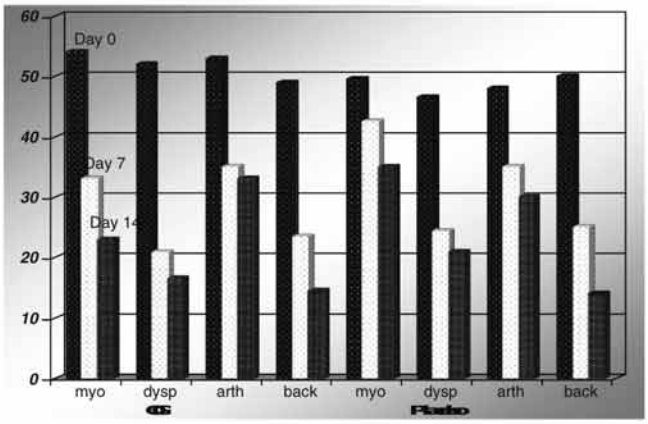

Figure 2. VAS scores of myofascial pain dyspepsia arthralgia back pain of OG, placebo group on day 0, 7 and 14 of treatment.

(P-value < 0.001, WSRT) from day 0 [50 (12.8)] (Table 2). The respective mean (95% CI) of the VAS scores for the general feeling of illness on day 7 and 14 was 35.5 (29.1, 41.9) and 31.3 (22.9, 39.5), which was 68.1 and 60.1% of the value in day 0 [52.1 (46.5, 57.5)].

In the placebo group, the median (IQR) of the sum of VAS scores of the general feeling of illness was 32.0 (44.0) on day 7 and 15 (38.0) on day 14, both significantly decreased (P-value < 0.001, WSRT) from the beginning [50.0 (35)] (Table 3). The respective mean (95% CI) of the sum of VAS scores of the general feeling of illness on day 7 and 14 was 36.5 (28.7, 44.3) and 26.2 (18.3, 34.1), which was 72.6% and 52.1% of the value before treatment [50.3 (42.5, 58.2)]. There was no significant difference between groups in the VAS scores on the general feeling of illness on days 7 and 14 of treatment.

Adverse Effects

The adverse effects in the first and second week of treatments were 27.8 and 2.8% for the first and the second week in the OG group, and 17.5 and 17.5% in the placebo group for the first and the second week, respectively (Table 4). There was a significantly difference ($P = 0.03$, Fisher exact Chi-Squared) when compared between groups in the second week. When compared within the same group at the first and second week, the reported adverse effects were reduced significantly in the OG group ($P < 0.01$, WSRT). The adverse effects reported during the treatments included myofascial, fatigue, back pain, abdominal pain, arthritis, gastrointestinal disturbance and headache; most of which are the symptoms included in the MCHC variables, but were inactive in the pretreatment period.

Purine Rich Foods

The frequencies of PRF consumptions over the seven previous days were reviewed retrospectively at the beginning of the trial and when the subjects came to follow up on day 7 and 14. Table 5 shows the median (IQR) and mean (95%CI) of PRF consumption the week before treatment and during the first and the second week of treatment.

In the OG group, the mean frequency of consumption of bamboo shoot and of the 25 kinds of PRF before treatment was 3.9 and 14.2 times/person/week but this dropped to 0.1 and 1.3 times 0.1 and 1.3 times/person/week during the first and second weeks, respectively.

For the placebo group, the respective mean frequency of eating bamboo shoots and the other kinds of PRFs was 3.6 and 11.4 times/person/week in the week before treatment and 0.4 and 0.9 times and 0.1 and 0.7 times/person/week during the first and second week, respectively.

Both groups significantly ($P < 0.001$, WSRT) reduced the intake of PRFs during the first and second week to < 10% of the frequencies before treatment. There was no significant difference in the frequencies of PRF consumptions between groups during the first and second weeks of treatment (Table 5).

Table 4. Reported adverse effects in the first and second week of treatments

Adverse effect and details	OG[a] gr. ($n = 36$)		Placebo gr.($n = 40$)	
	Day 0–7	Day 8–14	Day 0–7	Day 8–14
Reported adverse effects	10 (27.8%)**	1 (2.8)*	7 (17.5)	7 (17.5)*
Details[b] Myofascial	3	1	4	1
Fatigue	4	0	2	1
Back/abdominal pain	2	1	0	2
Arthritis	1	0	1	0
Sleep problem	2	0	1	0
Gastrointestinal disturbance	1	0	1	3
Headache	0	0	1	0
Others[c]	0	0	0	3

[a]Orthosiphon grandiflorus; [b]A subject had ≥ 1 symptoms; [c]Paresthesia, urticaria, and dizziness.
*$P = 0.03$ by Fisher exact Chi-Square.
**$P < 0.01$ compared within group by Wilcoxon Signed Ranks Test.

Discussion

This study was a double blind, randomized control trial with strict concealment, and it was the first to reveal a method of treating MCHC as a syndrome, the common presentation among the rural dwellers of Northeast Thailand. These groups of patients had renal stones (mostly small) or suspected of having stones, detected as hyperechoic foci on ultrasonography. All of the participants were negative for white blood cells in the urine.

Table 5. Mean (95%CI) of purine-rich foods consumption per week in 76 patients

Type of PRF	Period	OG[a] gr. (n = 36)		Placebo gr. (n = 40)		p-value[c]
		Median (IQR[b])	Mean (95%CI)	Median (IQR)	Mean (95%CI)	
Meat/chicken *(times/wk)*	Before	5.0 (6.0)	6.0 (3.8,8.2)	3.0 (5.0)	4.0 (2.8,5.2)	0.26
	Week1	0.0 (0.0)*	0.3 (0,0.7)	0.0 (0.0)*	0.3 (−0.1,0.7)	0.70
	Week2	0.0 (0.0)*	0.3 (0,0.5)	0.0 (0.0)*	0.2 (0.1,0.4)	0.76
Bamboo shoot *(times/wk)*	Before	3.0 (3.75)	3.9 (2.7,5.2)	3.0 (2.0)	3.6 (2.7,4.6)	0.88
	Week1	0.0 (0.0)*	0.1 (−0.4,0.2)	0.0 (0.0)*	0.4 (−0.2,1.0)	0.68
	Week2	0.0 (0.0)*	0.1 (0,0.2)	0.0 (0.0)*	0.1 (0,0.3)	0.93
All PRF[d] (times/wk)	Before	9.5 (12.8)	14.2 (9.7,18.7)	9.0 (8.0)	11.4 (8.1,14.7)	0.49
	Week1	0.0 (1.0)*	1.3 (0,02.6)	0.0 (0.0)*	0.9 (0.2,2.0)	0.29
	Week2	0.0 (1.0)*	1.3 (−0.3,2.9)	0.0 (1.0)*	0.7 (0.3,1.0)	0.56

[a]*Orthosiphon grandiflorus*; [b]inter-quartile range; [c]compared between groups by Mann-Whitney U; [d]Purine rich foods.
*$P < 0.001$ compared before and after by Wilcoxon Signed Ranks Test.

The study revealed that the PRF reduction can lessen the severity of the symptoms to approximately one-half by the end of the second week of treatment. When PRF consumption was restricted, the OG (3.2–3.6 g/day) did not have any additional benefit over placebo in the treatment of MCHC symptoms at day 7 or 14 after treatment. This suggests that when the rate of uric acid, or other waste compound, production was low, OG did not have additional benefit over placebo for the excretion.

People suffering from joint pains and myofascial pain feel better when they use Orthosiphon, even when they do not restrict any particular kinds of food. Accounts of this experience are anecdotal but have been reported in many countries for a long time. One study (3) indicated that when the authors did not ask for PRF restrictions, both OG plus antibiotic and sodium potassium citrate plus antibiotic dramatically reduced the MCHC symptoms associated with nephrolithiasis among patients positive for urine white blood cells. This information plus the data from our present study suggests: (i) Orthosiphon can reduce the symptoms even when there are no restrictions on the types of food eaten and, (ii) when consumption of PRFs are restricted, Orthosiphon does not have any additional effect over placebo.

Some foods (i.e. grasshoppers, red ant larvae, silk-worms, crickets, bamboo shoots, frogs and their larvae and ricefield rats) are unfamiliar to people in other parts of the world, but for the rural, subsistence dwellers of Northeast Thailand, these foods are common. Data from a random survey in the rural communities in Khon Kaen revealed that during 1 week, more than 9 out of 10 persons consumed at least once of the following PRF: bamboo shoot, fermented food, meat or insects; and 4 out of 10 reported having their symptoms aggravated by these foods (4). Most of the 25 kinds of restricted foods in the study, PRFs as well as the fermented foods and alcoholic beverages, usually cause pain in patients diagnosed as gout.

Restriction of the foods over our 2-week research period was practicable for the 76 participants, but it would not be easy to maintain compliance for much longer (and certainly not lifelong) without repeated education and public health information. Nevertheless, the study indicates that MCHC patients could relieve their own problems if they decided to restrict particular kinds of foods.

In order to create effective management guidelines for MCHC patients, further research should focus on: (i) will the symptoms completely disappear if the PRF restrictions are prolonged? (ii) Can the OG significantly relieve MCHC symptoms more than the placebo in patients who do not restrict PRF intake? (iii) What is the precise mechanism relating this effect to MCHC variables? (iv) What is the regional variation in the prevalence of MCHC and its association with PRF intake in communities with a different prevalence of renal stones?

Acknowledgments

This study was supported by Khon Kaen University. The authors thank Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

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Received January 18, 2007; accepted July 25, 2007

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