Cran-Max®
Scientific Studies

Anti-Max®
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Bil-Max®
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Blue-Max®
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Cranberol™
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CRANBERRY PROBIOTIC

Elder-Max®
ELDERBERRY EXTRACT

Eye-Max®
EYE HEALTH BERRY EXTRACT

Saw-Max®
SAW PALMETTO EXTRACT

Proprietary Nutritionals Incorporated
Dean Mosca, President
519-647-2071
dean@pnibrands.com

Scientific Studies on the health benefits of Cran-Max® and cranberries.

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Forward

Welcome to Scientific Studies on the health benefits of Cran-Max® and cranberries. This booklet is intended as an overview of the various studies – both completed and underway – that support the position that the bioactives in cranberries inhibit the growth of E. Coli responsible for urinary tract infections (UTIs).

Moreover, these recent studies demonstrate that Cran-Max® with its unique Bio-Shield protection, is a superior way to deliver these bioactive so that the body can make the most of their powerful effect.

Consider these facts about Cran-Max®:

- **Cran-Max® is a clinically tested product that has been shown to have a positive effect on nutritionally supporting healthy urinary tract functions.**
- **It is made from 100% cranberry fruit solids, through a proprietary process that intensifies the natural benefits of the whole cranberry, without the use of any solvents, preservatives, sugars, water, flavorings or color.**
- **Cran-Max® is more powerful and works faster in addressing the symptoms of UTIs than any other cranberry product, with none of the side effects found in prescription drugs.**
- **Cran-Max® is the only cranberry preparation made using the patented Bio-Shield® Technology that protects the cranberry from destruction by gastric acide, delivering the nutrients to the lower gastrointestinal tract where they can be absorbed through a time-released mechanism.**
- **Cran-Max® is the only dosage-confirmed (500 mg) cranberry product available. It takes 34 pounds of whole fresh cranberries to product one pound of Cran-Max®, giving it 3 times greater antioxidant activity than cranberry juice and 25% more fiber, while maintaining a healthy urinary tract.**

You will notice that many of the studies are underway. As they become completed, we will share the final results with you. We are proud and excited by the findings to date and look to bring you more news about this amazing and natural supplement.

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TABLE OF CONTENTS:

Results of Completed Cran-Max® Studies:

A randomized double-blind study on the prevention of recurrent cystitis with GynDelta®.
Dr. Jean-Marc Bohbot, A. Fournier Institute Paris

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

The Effect of Prophylactic Administration of Cranberry Extract 7 (Swiss Cran-Max™ 7500 mg) on the Occurrence of Recurring Infections of the Urinary Tract.
L. Hejzlar, Urology Clinic of PPCHC, SANUS in Hradec Kralove; J. Poduska, Urology Clinic of UNV, Prague.

Initial Pilot Study. Jan Poduska, MD, Department of Urology, Central Military Hospital, Prague, Czech Republic, 1999

Dr. Ronald Wheeler Cran-Max® Study. Outcome Study, Dr. Ronald Wheeler

Development and characterization of novel nutraceuticals with spray drying technology

Preliminary Results and Abstracts of Cran-Max® Studies Under Way:

Preventive Treatment With Cranberry Extract Of Vesico-Ureteral Reflux (VUR) in Children - Preliminary Report.
Yosef Binyamini, Yuval Bar-Yosef, Mario Sofer, Haim Matzkin and Yaakov Ben Haim.; Children's Urology Unit, Urologic Department, Tel Aviv Medical Center

Effectiveness of cranberry extracts as primary prevention of urinary tract infections and evaluation of cost-effectiveness, amongst female soldiers.; Abstract of the trial procedure

Evaluation of Cran-Max for the Prevention of UTI in Spinal Cord Injured Patients with Neurogenic Bladders. Veteran Affairs, Boston Healthcare System.

Can Cran-Max® Be Used To Treat Current Urinary Tract Infections? McMaster University.
Dr. Anil Kapoor. Treatment of urinary tract infection.

Independent Laboratory Results for BioShield®:

Proposed Mechanism of BioShield bound Anthocyanins, Integrated Biomolecule Corporation. Tucson, Arizona

Controlled Delivery of Components from CranMax-an In vitro Study, Doddabele Madhavi, Ph.D, BioActives, Inc., Worcester, MA

Background Cran-Max® Q&A Document:

- *Cran-Max® Frequently Asked Questions. Dr. Anil Kapoor*

Appendix

- *Bibliography of Cranberry Studies*

Proprietary Nutritionals Incorporated
Dean Mosca, President
519-647-2071
dean@pnibrands.com

Results of Completed Cran-Max® Studies

LA REVUE DU PRATICIEN
GYNECOLOGIE & OBSTETRIQUE

THE GYNAECOLOGIST'S AND OBSTETRICIAN'S JOURNAL

Monthly Continuing Medical Training Journal

Prevention of recurrent cystitis with GynDelta®

(500mg Cran-Max)

Results of a randomised, double-blind study

Results of a randomised, double-blind study on the prevention of recurrent cystitis with GynDelta®

Dr Jean-Marc BOHBOT, A. Fournier Institute, Paris.

ABSTRACT

• Study objective

To investigate the impact of consuming cranberry capsules in a single, post-coital dose on the onset of lower tract urinary infections in female patients presenting with recurrent urinary infections.

• Methodology, location and participants

A prospective, randomised, double-blind study conducted over a period of 45 days between May and August 2006, at the A. Fournier Institute, (Paris), in 120 female patients having had over 6 lower urinary tract infections during the last 12 months. The patients were randomly allocated to one of three groups.

• Procedure

In the 6 hours following intercourse, each patient had to take a single dose of:

- **Either 1 capsule infused with cranberry powder according to the Cran-Max Bioshield procedure, (GynDelta®);**
- **Or 1 capsule of dry cranberry extract containing 36 mg of pro-anthocyanidins A (PAC);**
- **Or 1 placebo capsule (magnesium stearate and red iron oxide).**

• Evaluation criterion

Number of patients presenting with a recurrent episode of lower urinary tract infection.

• Results

Over the study period, 10.8% of patients in the GynDelta® group suffered a recurrent bout of lower urinary tract infection compared with 18.9% of patients in the cranberry group containing 36 mg PAC and 43.2% of patients in the placebo group.

• Conclusion

GynDelta® proved its efficacy in the prevention of lower urinary tract infections after a single, post-coital dose with a greater level of statistical significance (p = 0.005) than cranberry containing 36 mg of PAC (p = 0.048) compared with the placebo.

Lower urinary tract infection (LUI) is considered to be the most prevalent bacterial infection [1]. One in three women contracts LUI warranting treatment with antibiotics, before 24 years of age, and virtually one in two women will be affected by LUI during her lifetime [1]. Some categories of the population are more prone to this condition than others: the elderly, children, pregnant women, medullary trauma patients, diabetics, patients with a urinary catheter, immunosuppressed patients and patients with anatomical urinary tract anomalies, etc. are particularly at risk. LUIs are also common in subjects with no clearly identified risk factors and have a non-negligible risk of recurrence.

The prevention of recurring LUI has, until now, been based on the prolonged administration of antibiotics (over several months) with the risks of side affects and the development of resistance.

Ever since the studies of Sobota, in 1984 [2], we know that the cranberry *(Vaccinium macrocarpon:* the wild bilberry of North America) is likely to inhibit the adherence of *Escherichia coli* to the urinary epithelium. This action appears to be related to the presence of tannins (pro-anthocyanidins and anthocyanidins [3]), which inhibit the synthesis of E. *coli* pili *[4]* and bind competitively to the bacterial receptors of the urinary epithelium [5]. Possessing marked, anti-radical properties, cranberry tannins could also exhibit anti-inflammatory activity [6] promoting good urethro-vesical, mucous trophicity [7].

Several clinical trials have confirmed the preventive role of the cranberry in the prophylaxis of recurrent, urinary infections. This efficacy was validated in 2004 by a Cochrane library journal [8], which, nevertheless, specified that:

- The optimal dosage had yet to be defined;
- Problems of long-term compliance were noted with cranberry juice.

The same year, Afssa (Agence française de sécurité sanitaire des aliments – the French Agency for the Safety of Foodstuffs) authorised a health allegation on the basis of studies conducted by Avorn *et al*. [9] and Kontiokari *et al*. [10] stating, outside the conclusion, that 36 mg of pro-anthocyanidins were measured in one of these studies (Avorn).

Although this last study was not selected by Cochrane, we wished to compare the efficacy of two types of cranberry capsules versus placebo. The first capsule contained 500 mg of powder infused according to a patented procedure (Bioshield), allowing the entire berry to be conserved (GynDelta® in France), and the second was an extract of *Vaccinium macrocarpon* containing 36 mg of pro-anthocyanidins (PAC). The second objective was to assess the efficacy of cranberry consumption in accordance with a protocol to promote optimal compliance.

Sexual relations are very often incriminated as one of the causes of recurrence. According to certain studies, episodes of cystitis associated with sexual relations account for 4% of all LUIs and 60% of cases of recurrent cystitis [11]. One study showed that the risk of developing LUI was 2.6 times greater in a 24 year-old woman who had sexual relations within a 3-day period than in a woman of the same age who had not had intercourse for 8 days [12]. Amongst a student population, Strom *et al.* found a correlation between the proximity of sexual intercourse and the onset of cystitis with an odds ratio (OR) of 58 if intercourse had taken place less than 48 hours previously, and an OR of 9.1 when intercourse had been between 3 and 7 days earlier [13]. In 1995, Foxman *et al.* showed that even protected intercourse over the previous 15 days increased the risk of developing cystitis by 53% [14]. We, therefore, opted to assess the efficacy of a single, post-coital dose of cranberry (within 6 hours of sexual intercourse) in patients at high risk of recurrence.

Patients and methods

Between May and August 2006, 120 female patients between 18 and 65 years of age were recruited for consultation at the Fournier Institute with a view to participating in this randomised, double-blind study.

Table 1 – Cardinal symptoms

	Number	Percentage
Female patients	116	
Patients presenting with at least one cardinal symptom	115	99.1
Pollakiuria	109	94.0
Burning sensation on micturition	114	98.3
Turbid urine	74	63.8
Malodorous urine	53	45.7
Sub-pelvic pain	43	37.1
Pruritus	18	15.5

Women who had had at least three episodes of LUI over the preceding 6 months and who had intercourse on more than one occasion every fortnight could be included in the study. After having given their written, informed consent, the patients were divided into three groups according to the randomisation table. For 45 days following their inclusion in the study, the patients had to take one capsule of either GynDelta® (group A), an extract of *Vaccinium macrocarpon* containing 36 mg of pro-anthocyanidin A (group B) or a placebo (group C) within 6 hours of sexual intercourse. The patients were reviewed after 45 days. The number of recurring episodes of cystitis, the length of time to onset of the first bout of cystitis after inclusion and product tolerability were evaluated. The evaluation was made on the basis of the patients' interview and the study of a calendar completed by the patient and listing the following information: details of sexual relations during this period, administration of the allotted treatment, any recurrence of cystitis, the possible consumption of antibiotics and side effects.

Statistical analysis

The case report forms and follow-up sheets were the subject of dual interactive input using Clintrial 4.4 software. The transfer and quality control were carried out using SAS software version 8.2.

Analysis of the length of time to onset of recurrence was carried out using the Kaplan Meyer method. The number of relapse patients was analysed according to the method of Holm, Hochberg, and Benjamini and Hochberg.

Results

Overall, out of the 120 patients entered into the trial, dossiers for 116 patients proved eligible for analysis: 38 in group A (GynDelta®), 39 in group B (36 mg of PAC) and 39 in the placebo group.

An average of 8 cases of cystitis per year

The average age of the patients was 35.7 years (group A: 37 years, group B: 33.1 years and group C: 36.9 years). Out of the 116 dossiers eligible for analysis, none of the women was pregnant, 6 were pre-menopausal (5.3%*)* and 17 were menopausal (14.9%*)*.

The average annual number of cases of cystitis in the patients' medical history was 8 episodes per year (group A: 8.1, group B: 8.4, group C: 7.4).

Table 1 shows the symptoms most frequently reported by patients during episodes of cystitis. There were over 100 symptoms since the patients described several related symptoms.

Thirteen patients (11.2%*)* presented with cystitis on the day of inclusion. Eleven received a single dose of fosfomycine trometamol and two were treated with oral norfloxacine for 4 or 8 days.

Four times fewer recurring episodes with GynDelta®

Out of the 120 patients included in the study, 9 were lost to follow up including 4 dossiers, which were rejected as they were incomplete in terms of patient description. 111 women took the treatment allocated to them and could, therefore, be analysed.

Table 2 - Recurrent episodes of cystitis associated with sexual intercourse during the study

	GynDelta®	Group B	Placebo	Total
Number of female patients	37	37	37	111
Cystitis due to sexual relations n (%)				
No	33 (89.3)	30 (81.1)	21 (56.8)	84 (75.7)
Yes	4 (10.8)	7 (18.9)	16 (43.2)	27 (24.3)

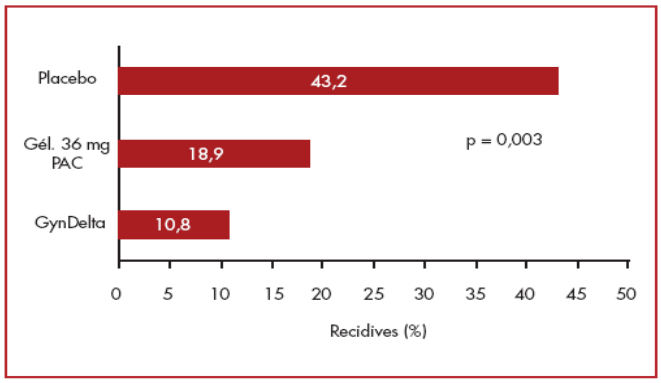

Schéma 1 - Pourcentage de femmes ayant une récidive de cystite au cours de l'étude.

Tolerance

Eleven female patients out of 116 (9.5%) reported an undesirable side effect during the study: 3 in the GynDelta® group (headaches, gastralgia), 8 in group B (gastralgia, nausea) and none in the placebo group. None of these side effects triggered premature treatment withdrawal. It should be noted that, two patients, one in the GynDelta® group and the other in the B group, developed a vaginal infection during treatment.

Table 2 shows the distribution of women who developed one or more episodes of cystitis triggered by sexual relations during the follow-up period.

Overall, almost one in 4 patients (24.3%) experienced a recurring episode of cystitis during the study with considerable variations depending on the treatment received. Women in the GynDelta® group, for instance, had four times fewer relapses than those in the placebo group (p = 0.005) and almost two times fewer relapses than those receiving 36 mg of PAC (group B) [diagram 1].

If the recurrence levels are statistically compared within the 3 treatment groups, a significant difference is evident in favour of GynDelta® treatment, regardless of the statistical method used (Table 3).

Diagram 2 shows the length of time to onset of recurring cystitis during treatment in the three groups.

The longest period to the reappearance of the first episode was recorded in the GynDelta® group (22 days vs. 8 days for group B and 4 days for the placebo group). The results are independent of the length of time to onset of the first sexual relation (2 days, on average, in each group) and the average number of sexual relations before the first reappearance of the symptoms (12.3 in the GynDelta® group; 8.4 in the B group; 11.5 in the placebo group).

The patient's clinical evaluation of the 3 treatments is listed in Table 4.

The product was assessed as good or very good by 88.9% of patients in the GynDelta® group compared with 80.6% in group B and 52.9% in the placebo group.

Diagram 1 - Percentage of women who experienced recurrent cystitis

Table 3 - Statistical evaluation of the results according to treatments

Statistical tests	p-value	Adjusted p-value		
	Chi^2	Holm method	Hochberg method	Benjamini and Hochberg method
GynDelta® versus placebo	0.002	0.005	0.005	0.005
Group B versus placebo	0.024	0.048	0.048	0.036

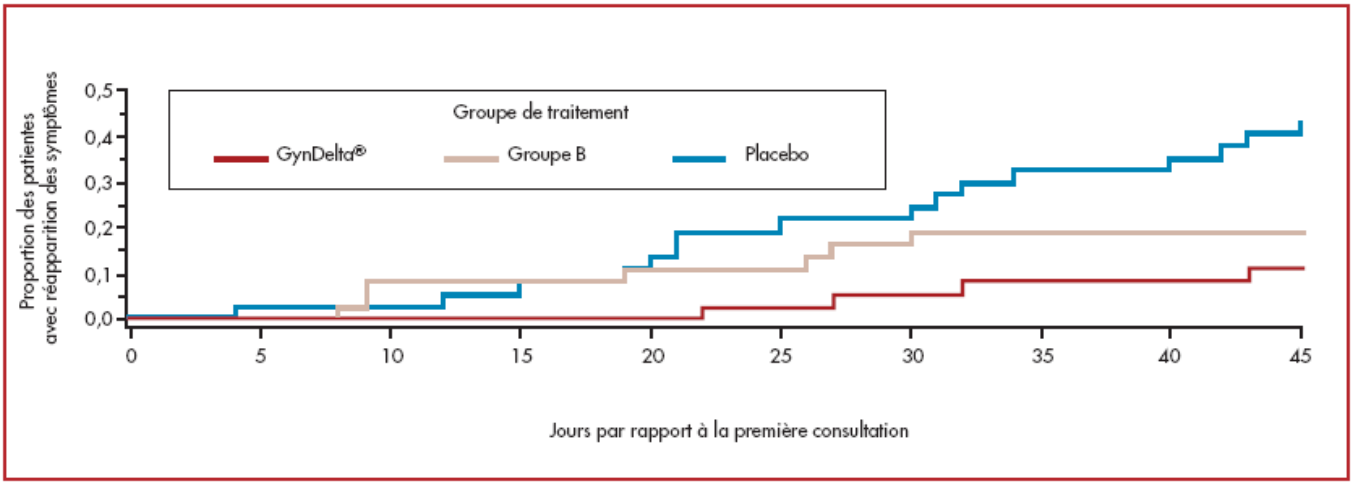

Schéma 2 - Délai de survenue de la réapparition des symptômes. Courbe de survie (méthode de Kaplan-Meier). Les réapparitions des symptomes répertoriés dans les fiches de suivi des trois patientes (004 et 025 du groupe B, 015 du groupe GynDelta®) ne sont pas prises en considération dans ce graphique. En effet, l'investigateur n'a pas reconnu ces symptômes comme étant des cystites.

No. of days with reference to the first consultation

Diagram 2 - Length of time to onset of the reappearance of symptoms. Survival curve (Kaplan-Meier method). The reappearance of the symptoms listed in the follow-up files of the three patients (004 and 025 in group B, 015 in the GynDelta® group) is not taken into account in this graph. In fact, the Investigator did not recognise these symptoms as being those of cystitis.

Table 4 - Patient's global assessment of treatment on completion of treatment

	GynDelta®	Group B	Placebo	Total
Number of female patients	36	36	34	106
Global treatment assessment n (%)				
Very good	29 (80.6)	18 (50.0)	18 (52.9)	65 (61.3)
Good	3 (8.3)	11 (30.6)	0 (0.0)	14 (13.2)
Moderate	2 (5.6)	2 (5.6)	7 (20.6)	11 (10.4)
Nil	2 (5.6)	5 (13.9)	9 (26.5)	16 (15.1)
Aggravation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Discussion

There is a high average number of cases of cystitis in the patients' medical history. This can be attributed to the fact that consultations at the Fournier Institute specialise in the management of recurrent uro-genital infections and treat patient who often experience numerous recurring episodes.

The symptoms most often listed by the patients are, unsurprisingly, pollakiuria and burning sensation on micturition.

The results obtained with GynDelta® highlight efficacy in the prevention of recurrent cystitis, both in the number of patients with recurring episodes of cystitis and in the length of time to onset of the first bout of recurrence. GynDelta® is clinically more effective than the capsules containing 36 mg of PAC as regards the number of patients experiencing a relapse, with a greater level of statistical significance compared with the placebo, even if the patients' global evaluation is comparable.

A non-negligible placebo effect can be observed with over 56% of patients not experiencing a relapse in this group. This result is certainly consistent with the duration of the study (45 days). A longer study period would, most certainly, have yielded less favourable results for the placebo group.

Side effects were seldom observed during the study and were of moderate intensity as they did not result in any study drop-outs.
Overall, the prevention of recurrent cystitis is a basic step for ensuring a patient's quality of life. Although long-term antibiotic treatment has proved effective up to a point, the impact of such treatments on the patients themselves and on the risk of developing mid-term resistance should be emphasised. Extracts of *Vaccinium macro-carpon* are considered as an effective alternative to long-term antibiotics by preventing the deleterious effects of the latter. The study conducted at the Fournier Institute prove that administration of a single GynDelta® capsule within 6 hours following intercourse has a genuine, protective effect as regards recurring bouts of cystitis. It also shows that the concentration of 36 mg pro-anthocyanidins A, sometimes considered as the lower limit of efficacy, must be reconsidered or that other substances contained in GynDelta® play an active role in preventing the recurrence of cystitis via antibacterial and/or anti-inflammatory action.

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A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women

Lynn Stothers, MD

Department of Surgery, Division of Urology, and Department of Health Care and Epidemiology
University of British Columbia, Vancouver, B.C., Canada

Stothers L. A randomized trail to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. The Canadian Journal of Urology. 2002; 9(3):1558-1562.

Purpose: To determine from a societal perspective, the effectiveness and cost effectiveness of concentrated cranberry tablets, versus cranberry juice, versus placebo used as prophylaxis against lower urinary tract infection (UTI) in adult women.

Material and methods: One hundred fifty sexually active women aged 21 through 72 years were randomized for one year to one of three groups of prophylaxis; placebo juice + placebo tablets versus placebo juice + cranberry tablets, versus cranberry juice + placebo tablets. Tablets were taken twice daily, juice 250 ml three times daily. Outcome measures were: (1) a >50% decrease in symptomatic UTI's per year (symptoms + ≥ =100,000 single organisms/ml) and (2) a >50% decrease in annual antibiotic consumption. Cost effectiveness was calculated as dollar cost per urinary tract infection prevented. Stochastic tree decision analytic modeling was used to identify specific clinical scenarios for cost savings.

Results: Both cranberry juice and cranberry tablets statistically significantly decreased the number of patients experiencing at least 1 symptomatic UTI/year (to 20% and 18% respectively) compared with placebo (to 32%) ($p<0.05$). The mean annual cost of prophylaxis was $624 and $1400 for cranberry tablets and juice respectively. Cost savings were greatest when patients experienced >2 symptomatic UTI's per year (assuming 3 days antibiotic coverage) and had >2 days of missed work or required protective undergarments for urgency incontinence. Total antibiotic consumption was less annually in both treatment groups compared with placebo. Cost effectiveness ratios demonstrated cranberry tablets were twice as cost effective as organic juice for prevention.

Conclusions: Cranberry tablets provided the most cost effective prevention for UTI.

Key Words: urinary tract infection, cost effectiveness

Introduction

Cranberries (Vaccinium macrocapon) and cranberry juice were used for centuries by Native Americans as a food source and for medicinal purposes including treatment of bladder and kidney disease. Once introduced to Europe, they were used in the treatment of stomach ailments, blood disorders, liver problems, fevers and scurvy. In the late 1800's and early 1900's, cranberries were used as a treatment for bladder gravel and “blood toxins”. Cranberries are commonly believed to be effective in preventing or treating urinary tract infections, and are one of the five most-commonly-used herbal remedies.1 However, the evidence supporting the use of cranberries in the prevention of UTI has not been strong.2

We conducted a study to evaluate the effectiveness and cost effectiveness of cranberry juice and cranberry extract tablets in the prevention of UTIs. We hypothesized that patients receiving tablets of cranberry extract would experience a mean of at least 50% fewer UTIs, defined as symptomatic, culture-positive infection with >/=100,000 single organisms per ml, compared with those in the placebo group. To test the hypothesis, we chose a pure, unsweetened organically-grown cranberry juice, and a tablet containing cranberry extracts and cranberry juice concentrate.

Materials and methods

This study was a randomized double-blind controlled trail that was peer reviewed and approved by the institutional ethics review board. All patients had a complete history, physical examination, urinalysis and urine culture prior to enrolment in the study, Subjects invite to participate in the study had had at least two symptomatic, single-organism, culture-positive urinary tract infections in the prior calendar year, but were currently free of urinary tract infection on urinalysis and culture. Exclusion criteria were neurogenic bladder dysfunction, pregnancy, allergy to cranberry products, insulin-dependent diabetes, immunosuppressive disease, steroid use, or intermittent or indwelling catheterisation. Patients signed an informed consent that described the need for dietary restriction of additional cranberry products during the study and the fact that they might be randomized to the group that received a placebo treatment. Patients who provided informed consent were randomized in blocks of 10 to one of the 3 arms of the study:

1) Placebo arm: a placebo tablet twice daily and 250 ml of placebo juice (filtered water with food coloring plus 20 ml pineapple juice) three times per day.
2) Tablet arm: one tablet of concentrated cranberry juice (at least 1:30 parts concentrated juice) twice daily and 250 ml of placebo juice three times per day, and
3) Juice arm: 250 ml of pure unsweetened cranberry juice three times per day and one tablet of placebo twice daily. The volume of juice was selected to make the juice intake comparable to what was available in tablet formulations.

The pharmacy dispensed the prepared juices (placebo or cranberry juice) and tablet packages (placebo or cranberry extract tablets). The investigator was unaware of the arm to which patients were assigned

Patients remained on the protocol for 12 months. Symptoms of lower urinary tract infection were treated with a culture-directed prescription of antibiotics for 3 days and then prophylaxis was restarted. Compliance was monitored by a pill count and questioning regarding fluid intake. Side effects were monitored by questioning at routine visits every 8 weeks. A positive culture was defined as > or equal to 100 000 single organisms per milliliter.

Cost effectiveness was defined as dollar cost per UTI prevented. Patients' receipts, interviews and medical records provided data on patient costs. Direct patient cost included costs of cranberry juice or tablets or bottled water, antibiotics including dispensing fees, and costs of complications such as time lost from work and taxi/parking receipts for

doctors appointments. Indirect patient cost included lost wages. Time lost from work was valued at the group mean pre-study gross weekly income, which was #675 per week. Direct health sector costs included physician visits and investigations. Stochastic tree decision models were used to identify cost saving scenarios.

Statistical methods included ANOVA for statistical significance of the mean number of infections in each arm of the trial. Power was set at 80% and significance was defined as a p< or equal to 0.05.

Results

One hundred fifty sexually active women aged 21-72 years (mean 42 years) participated, with 50 randomized in blocks of 10 to each study arm. Fifty-two women were menopausal and 15 were non-insulin-dependent diabetics. One hundred seventeen worked outside of the home with a mean pre tax gross income of $35000 per year (range $15000 to $62000). The mean number of UTI's prior to the study was 2.8 (range 2 to 5) in the prior calendar year. Table 1 presents these data by group.

Compliance rates by each of the groups by month are shown in Figure 1.

The number experiencing at least one urinary tract infection during treatments was 16 (32%) in the placebo group, 10 (20%, p<0.05) in the juice group and 9 (18%, p<0.05) in the tablet group. The mean number of UTI's in a calendar year following treatment was 0.72 in the placebo group, 0.30 in the juice group (p<0.05) and 0.39 in the tablet group (p<0.05).

Complications reported by patients in the placebo group were headache (2 patients) and mild nausea (2 patients). None of these patients discontinued treatment. In the juice group symptoms of reflux were reported by 3 patients, 2 of whom dropped out of the study due to this problem. Complications reported in the tablet group were: mild nausea (4 patients) and increased frequency of bowel movements (1 patient). None of these complaints required discontinuation of treatment. Eight patients complained about the size of the tablets and two stated they were difficult to swallow.

The annual cost of prophylaxis was $624 with cranberry tablets (calculated as CDN$0.73 per capsule, 1 capsule twice daily, and 14% tax) and $1400 with cranberry juice (calculated as CDN$5.30 per litre, 250 ml taken three times per day, and no tax). Cost effectiveness ratio for juice was CDN$3333 per UTI prevented with 82% direct patient cost, 6% indirect patient costs and 11% direct health sector costs. The cost effectiveness ratio for tablets was CDN$1890 per UTI prevented with 73% direct patient costs, 5% indirect patient costs and 21% direct health sector costs.

Before the study, the mean number of days of antibiotic use in a calendar year by the 150 women was 6 (range 3 to 17). This decreased to a mean of 4.0 in the placebo group (range 0-9), 2.9 in the juice group and 2.1 in the tablet group. The mean annual cost of antibiotics used per patient was $18.60 (range $7.50-$90.00) prior to the study. During the study this was a mean of $7.30 (range $0 - $51.10) in the placebo group, $5.13 (range $0 - $42.00) in the juice group and $4.70 (range $0 - $42.25) in the tablet group.

TABLE 1. Comparison of characteristics (no significant differences between groups, >0.05)

	Placebo (N=50)	**Tablet (N=50)**	**Juice (N=50)**
Age (range and (mean))	21-72 (43)	23-68 (40)	21-70 (44)
Pre-Post menopause	34:16	30:20	37:13
Income ($mean annual)	40,000	34,500	37,800
UTI's in preceding year (range (mean))	2-5 (3.5)	2-4 (3.1)	2-5 (3.3)

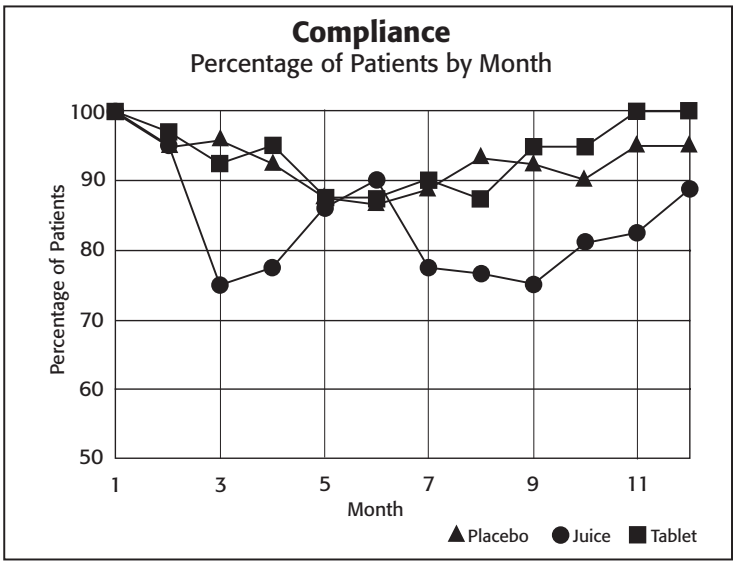

Figure 1. Compliance with treatment regimens showing that those in the cranberry juice group were less compliant that those in the placebo and tablet groups, with compliance dropping below 80% during 5 of 12 months.

Discussion

This study found that cranberries are an effective means of preventing urinary tract infections in women who experience recurrent UTIs. We found that 40% fewer women experienced UTIs when receiving cranberry products compared with placebo juice (19% versus 32%), and that on average, they experienced half the number of UTIs per year. There was also a decrease in UTIs in the placebo group compared with the previous year, which may be related to the increased volume of liquid consumed in the placebo juice.

\ A Cochrane systematic review of the literature in 2000 found six trials examining the effectiveness of cranberries for prevention of UTIs. Of the six, two were excluded because they did not have UTI as an outcome measure. None of the remaining four met the criteria for adequate randomization. Of the four studies, three were cross-over studies.[3-5] In two of these, the sample size was extremely small. In Foda's study, only 21 completed study,[4] and in Haverkorn's study, only seven subjects were included in the final analysis.[5] The fourth study was a parallel groups study,[6] but only 10 patients completed this study. Only two of the trials were double blind. The strongest study[3] demonstrated in a randomized double-blind study that drinking 300 ml of cranberry cocktail daily.

Women who experience recurrent UTIs are often prescribed low-level prophylactic antibiotic regiments, but increasingly, there are reports of antibiotic-resistant strains.[20] Thus, an agent such as cranberry juice that is not specific to a particular bacterial strain is desirable if it is effective.

Conclusions

Cranberry juice and cranberry tablets with increased fluid intake are more effective than fluid intake alone in preventing urinary tract infections in sexually active women with recurrent UTIs. Our results support the findings of other randomized studies involving adult women[9], that cranberry products should be offered as an option in the clinical management of recurrent UTI's. Ten to fifteen percent of women will experience fewer clinical lower urinary tract infections if cranberry products are added to the conservative measure of simply increasing fluid intake.

Further studies are required to determine the optimum amount, and the most cost-effective method of delivery.

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[Inserted from page 1]
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Address correspondence to Dr. Lynn Stothers. #590 - 1144 Burrand Street, Vancouver, BC V6Z 2A5 Canada

The Effect of prophylactic administration of cranberry extract (Swiss Cran-Max™ 7500mg) on the occurrence of recurring infections of the urinary tract

L. Hejzlar - Urology Clinic of PPCHC - SANUS in Hrodee Králové
J. Poduska - Urology Clinic of UNV in Prague

Introduction

SWISS CRAN MAX™ 7500mg (Vaccinum macrocarpon) is a standardized natural extract, equivalent to 7500mg of fresh Canadian cranberries. It is produced from pure cranberry fibre and concentrated cranberry juice.

The first historical reports of the medical use of cranberries originate in the 17th century from European settlers in North America who noted their healing utilization from native Indians. Later, cranberries were used in various forms on ships crossing the Atlantic Ocean as a prevention of scurvy. Their excellent effect on urinary infections was accidentally discovered at that time. The first serious studies of the therapeutic effects of cranberries (USA) date back to the twenties of the 20th century.

(diagram showing the structure of ellagic acid)

The exact operation mechanism of the effect is not known. Nevertheless, it is expected that there is a lowering of the ability of bacteria to adhere to the cell membrane of the bladder. The cranberry extract also functions as a strong antioxidant. A significant role in the operation mechanism is played by ellagic acid.

Methodology

The study objective was the monitoring of the effects of prophylactic administration of cranberry extract on the occurrences of recurring infections of the urinary tract.

		2x)	
Side effects of treatment by antibiotics and chemotherapeutics per patient during the 6 months of observation: (total in set: diarrhea 6x, colpitidum 4x, digestive difficulties 2x, skin reaction 2x)	0.68 (0-3)	Side effects of treatment:	None

Graph showing the results for groups A and B:

Legend: Control Set

CRAN-MAX™ group

x-axis labels: Clinical symptoms of urinary tract infection

Urine (chemical + sediment)

KBU

NU

Subjective evaluation of the treatment by the patients themselves:

significant improvement	37% (9 patients)
improvement	56% (14 patients)
no changes	7% (2 patients)
feeling worse	0%

Conclusions

Despite the relatively small number of patients, it was observed that the prophylactic administration of the preparation CRAN-MAX™7500mg resulted in the significant reduction of the number of clinical manifestations of urinary tract infections, as well as laboratory findings of the monitored individuals, i.e. approximately 6x. A considerably good effect was observed on patients with a neurogenous bladder

OBSERVATION SET: During the time period from March 1999 to October 1999, we administered 1 capsule of the preparation SWISS CRAN-MAX™7500mg per day to 25 patients (24 women and 1 man), suffering from an anamnesis of recurring infections of the urinary tract (3 times or more during the past year) for a time period of 6 months. Two patients had a neurogenous bladder with torpid infections of the urinary tract. The observation set consisted of patients without current symptoms of a urinary tract infection. The patients were monitored every two month after the initial examination. Subjective symptoms, such as the urinary chemistry and sediments, urinary bacteria counts and the appearance of side effects, were monitored. The average age of the patients was 43.2 years (16-75).

The control set was formed by 24 female patients with the same initial criteria, i.e. infection of the urinary tract at least 3 times during the past year and no current urinary tract infection symptoms at the time of insertion into the study. The patients were monitored only during clinical urinary tract infection symptoms for urinary chemistry and sediments and urinary bacteria counts. They were treated using the standard methods, i.e. short-term cycles of antibiotics or chemotherapeutics. The side effects of the prescribed drugs were al monitored. The average age was 41.6 years (16-64)

Results

A. Control Set		**B. Observation Set SWISS CRAN-MAX™ 7500mg**	
The average number of clinical manifestations of a urinary tract infection per patient during the 6 months of observation:	2.3 (1-4)	The average number of clinical manifestations of a urinary tract infection per patient during the past 6 months of observation:	0.33 (0-2)
The average observations in the urine sediment (above 5 leukocytes in ZP) per patient:	2.3 (1-4)	Average observations in the urine sediment (above 5 leukocytes in ZP) per patient:	0.45 (0.2)
A positive observation of quantifiable bacteria (10 and more/ ml or urine) per patient during the 6 months of observation: (total in Set: E, Coli 36x, Enterococcus 8x, Proteus mir, 6x, Kleb. Pneu 5x)	2.1 (1-3)	A positive observation of quantifiable bacteria (10 and more/ml or urine) per patient during the 6 months of observation: (total in set: E. Coli 6x, Kleb. Pneu 5x, Acinetobacteria 2x, Enterobacteria 2x, Kleb. Oxytoc.	0.38 (0-2)

An important advantage in comparison with the treatment using antibiotics and chemotherapeutics is the absence of treatment side effects and the possibility of utilization by e.g. pregnant female patients. In addition to the sub-inhibition doses of antibiotics, chemotherapeutics and imunomodulatory preparations, this natural preparation represents additional possibilities in the profylation of recurring urinary tract infections.

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Initial Pilot Study

Jan Poduska, M.D.,
Department of Urology, Central Military Hospital, Prague, Czech Republic, 1999

Objective:

To study the safety and efficacy of Cran-Max® against recurrent UTI

Design:

24 female out-patients, with history of recurrent UTI (2 or more infections in previous year); average age 37

Upon positive culture diagnosis and in presence of symptoms the patients were divided into 2 Groups

- Group 1: Pertinent antibiotic and Cran-Max® 250 mg BID
- Group 2: Pertinent antibiotic only

Both Groups examined at one-month intervals

Results:

- Group 1 experienced one recurrence (E.Coli 1X)
- Group 2 experienced 1-4 infections with an average 2.3 (E.Coli 18X)

Tolerability:

- Group 1 - no side effects
- Group 2 - 7 events (3 diarrhea, 2 gynecological, 1 vomiting, 1 dermatological)

Conclusion:

Cran-Max® markedly lowers recurrences of lower UTI and ensures long term negative microbiological findings.

Dr. Ronald Wheeler Cran-Max® Study

Summary

Conducted by Dr. Ronald Wheeler

- 60 women with symptoms of chronic urinary tract infections recruited from private practice
- Each subject filled out a questionnaire (nine questions on a scale from 0-5) before and after taking Cran-Max 500 mg daily
- Over 90% of the subjects experienced significant improvement.

Outcome Study

Six month study following 60 women with symptoms of chronic urinary tract infections and urethritis while taking Cran-Max®

Dr. Ronald Wheeler conducted a pilot study, which included 60 women with symptoms of chronic urinary tract infections and urethritis, which he recruited from his practice. Each subject filled out a questionnaire (nine questions on a scale from 0-5) covering frequency of urination, sensation of not emptying, voiding in small amounts, intermittent urination, difficulty in holding, weakness in stream, straining and burning or stinging sensation.

The subjects were asked to fill out the questionnaire before and after going on 500mg of Cran-Max® per day.

Results:

Questions asked on scale of zero to five.
Percentage Decrease After taking Cran-Max®

How many times did you get up during the night to urinate? 44%

How often have you had the sensation of not emptying? 32%

How often have you had to urinate in less than two hours, after urinating? 45%

When you void in less than 2 hours, how often did you void in small amounts? 34%

How often have you stopped and started again several times when urinating? 85%

How often have you found it difficult to postpone urination? 60%

How often did you have a weak urinary stream? 39%

How often have you had to push or strain to begin urination? 100%

History of pain, burning or stinging on urination? 63%

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Development and characterisation of novel nutraceuticals with spray drying technology

D. Chiou *, T.A.G. Langrish

School of Chemical and Biomolecular Engineering, University of Sydney, Sydney NSW 2006, Australia

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Abstract

The introduction of natural fruit fibres as an encapsulating agent has demonstrated encouraging results as a replacement carrier for spray drying sticky materials. The combination of these fruit fibres and bioactives (*Hibiscus sabdariffa* L.) has created a novel nutraceutical product suitable for a variety of applications in functional food manufacturing. Through characterisation of the product, it appears that the material is appropriate in terms of its moisture content and encapsulation of the bioactive material. It also maintains a free-flowing form under appropriately controlled humidity conditions suitable for manufacturing purposes. The presence of the bioactive material in the fibres does not appear to affect the product size or shape significantly. An unusual moisture change phenomenon was observed during exposure of the spray-dried powder to ambient air. A rapid moisture sorption and gradual slow desorption pattern was seen and is believed to be associated with crystallisation behaviour.

Keywords: Amorphous; Bioactive; Crystallisation; Encapsulation; Fruit fibre; Spray drying

1. Introduction

Spray drying is a one-step processing operation for turning a liquid feed into a powder product, minimising handling while reducing the bulk weight and size of the powder, and also preserving the product by reducing the water activity required for bacterial degradation (Hayashi, 1989). Spray drying has also been used to micro-encapsulate material since the product may be encapsulated by a particular carrier used in the feed slurry by the phenomenon known as selective diffusion. Common carriers for these encapsulation processes include carbohydrates, gums and cellulose esters and ethers. Combinations of carriers are also used to provide efficient and stable agents for particular feed materials (Re, 1998). Natural food fibres such as waste fruit peels and skins are possible carriers that have not been thoroughly investigated.

The replacement of maltodextrins as carriers for the spray drying of sticky and sugar based bioactives is an important development for the food industry. The properties of maltodextrins, in terms of undesired taste alteration and also being an unnatural additive, mean that a suitable alternative carrier for spray drying needs to be found. This carrier needs to have appropriate encapsulation properties. It is possible that natural fibres may be able to fulfil this role, and this possibility has been investigated here.

Regular consumption of fibre in a balanced diet aids in maintaining a healthy digestive system. It has been known that eating insoluble fibre assists regular bowel movements and flushing the intestinal system of undesirable materials. The consumption of soluble fibres is also important in slowing down metabolism rates of sugars and forming a lining gel within the intestines (Beckmann, 1987).

Insoluble dietary fibres are complex carbohydrates and are known to have strong absorption properties. This property of the fibres makes them excellent carriers for the desired additive extract. Micro-encapsulation of the extract

* Corresponding author. Tel.: +61 2 9351 5661; fax: +61 2 9351 2854.
E-mail address: dchiou@chem.eng.usyd.edu.au (D. Chiou).

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by the fibres through adsorption can also occur, increasing the amount of extract carried by the fibres (Re, 1998).

Antioxidant extracts are produced from a variety of bio-waste or novel sources such as Hibiscus flowers (also known as sorrel and roselle), more specifically *H. sabdariffa* L. There has been much recent interest in this extract due to its popularity in alternative medicine and cultural drinks such as Sorrel in Nigeria (Andrade & Flores, 2004; Nnam & Onyeke, 2003). The main compound group in most foods with antioxidant properties is from the polyphenol group, and more specifically in *H. sabdariffa* L. the anthocyanin complexes. These compounds are present in fruit peels, seeds and other common bio-wastes (Larrauri, Ruperez, Bravo, & Saura-Calixto, 1996; Mazza & Miniati, 1993).

This encapsulation process combines two products that are beneficial to health (the edible fruit fibre and antioxidant hibiscus extract) into one multipurpose functional food. To determine if the micro-encapsulation process is successful, appropriate visualisation is needed to confirm the presence of the anthocyanin extracts within the fibres. Characterisation of powder properties is required to determine if successful development of the product is achieved. Measurements of moisture content, hygroscopicity, particle size and shape, stickiness and colour are all important considerations. Amorphous to crystalline behaviour has been observed in spray-dried materials (Jouppila & Roos, 1994). The behaviour is known to be linked to glass transition temperatures and environmental conditions (Bhandari & Howes, 1999).

Slurry mixtures of milled citrus fruit fibres and hibiscus extract were used as the novel nutraceutical and spray dried. Their properties were examined for appropriate characteristics as spray-dried food powders and interpretation of all these measurements has been carried out in this work, together with a discussion of the significance of the outcomes.

2. Materials and methods

2.1. Fibre and extract mixture

The ingredients used to form the slurry used in the spray-drying process consisted of fine milled citrus fibre, with characteristics to be discussed (Lang Technologies Pty Ltd.) and hibiscus extract (*H. sabdariffa* L., Vic Cherikoff Foods Pty Ltd). The slurry mixture was prepared using equal parts of the fibre to the solids content of extract by mass. The combined extract was diluted with water until the mixture had a solids concentration of 10%. Experimentation on the fruit fibres in higher concentrations showed that the fibre solids absorbed water and swelled to be too viscous for the peristatic pump. A magnetic stirrer bar, rotating at 1000 rpm, was used to keep the slurry homogenised.

2.2. Drying conditions

The slurry was fed into a Büchi B-290 mini spray dryer for drying. The operating conditions were as follows; aspirator rate 100% (0.0127 kg/s); drying air temperature 200 °C; pump rate 25% (8.8 mL/min); atomisation air rotameter 35 mm (to the bottom of the gauge ball) (~538 L/h) and the nozzle cleaner set to 9 (51 strikes/min). The system was kept running after the completion of the experiment runs with the heating element turned off until the air inlet temperature fell below 70 °C. The samples were then collected for measurements and characterisation. Separate runs using the same conditions and slurry preparation were sampled and labelled in order, R0 (Run 0), R0-1, R0-2 (Runs 0 repeat 1 and 2, respectively).

2.3. Visualisation techniques

To observe the encapsulation of the hibiscus extract, a fluorescence microscopy technique was used. The anthocyanin component of the extract exhibited fluorescent behaviour and was a suitable marker. The fluorescence response to high energy wavelengths has been utilized to visualise compounds and complexes containing conjugated bonds. However, it is difficult to determine if the compounds generating the fluorescent response are internal or external to the sample.

In order to address this challenge, confocal microscopy, which is an advanced form of fluorescent microscopy (Paddock, 1999), has been used to eliminate unfocused light problems. By processing a series of raster laser scans across the sample, slices of focussed images can be reconstructed to form three-dimensional images displaying the locations of the fluorescent-responsive complexes within the sample. This approach enables accurate visualisation to locate fluorescing compounds within samples.

2.4. Characterisation of products

2.4.1. Moisture content

Moisture contents were determined using a gravimetric measurement method with a fan forced drying oven (Thermoline TDF-150) over a period of 24 h. Equilibrium moisture content measurements were performed by using saturated salt solutions to give controlled relative humidity conditions in desiccators as seen in Table 1 (Winston & Bates, 1960). The samples were left in the desiccators for several weeks to allow equilibrium homeostasis before their moisture content was determined by oven drying.

Table 1
Saturated salt solutions for equilibrium moisture content measurements

Relative humidity (%)	Saturated salt solution
10.0	Zinc chloride
20.0	Potassium acetate
32.5	Magnesium chloride
51.0	Calcium nitrate
60.0	Iron chloride
75.0	Sodium chloride
89.0	Magnesium sulfate

The hygroscopic properties of the powders, particularly the rate of change for the moisture content, were measured gravimetrically after exposure to ambient humidity. The samples were originally equilibrated at 10% relative humidity in a desiccator before being exposed to the ambient air. The relative humidity of the ambient air was also measured using a wet and dry-bulb hygrometer (Livingstone Scientific) with a small fan to ensure adequate air velocity past the wetted wick.

2.4.2. Particle morphology and size

The particle size and shape were examined primarily using a laser diffraction device (Malvern Mastersizer S). A dry particle feeder connected to compressed air and vacuum supplies enabled samples of the powder to remain dry across the measurement section of the system (QSpec dry powder feeder). Using a mathematical transformation (Bushell, Yan, Woodfield, Raper, & Amal, 2002), the raw data from particle size measurements in terms of the intensities at the different diffraction rings were used to calculate fractal dimensions for all the samples using a macro program (Malvern, 2003).

2.4.3. Glass transition temperature and crystallinity

The glass transition temperature of the powders was determined by modulated differential scanning calorimetry (MDSC) (TA Instruments Modulated DSC 2920). The heating ramp rate was set to 5 °C/min from an equilibrium starting temperature of 32 °C with an oscillation of ±0.50 °C every 60 s. Hermetically sealed aluminium pans were used for the samples, while a 60 ml/min flow rate of nitrogen purge gas was also used. DSC for assessing the degree of crystallinity was not performed due to the samples charring and pyrolysing under high temperature conditions and the generation of internal pressure from moisture evaporation at high temperatures rupturing the sealed pans used.

2.4.4. Visualisation of product

Visualisation of the extract was performed through fluorescent microscopy (Nikon E800) and confocal microscopy (Bio-Rad MRC600). This enabled the confirmation of extract absorption or adsorption into the fibres through bright signal sight markers in the imaged samples.

3. Results

Table 2 summarises the characteristics of the powders produced in these experiments.

3.1. Moisture content and hygroscopic behaviour

The moisture contents from the powders were measured to be in the range of 8–10%. These moisture contents can be compared with the equilibrium values taken from the desiccators with the saturated salt samples, as shown in Fig. 1. These moisture contents from the samples that were taken directly out of the dryer correspond to an ambient humidity of 20%. If the samples were exposed to a typical ambient humidity of 64–70% (as measured here), then the sorption isotherm indicates that the moisture content would be around 20–25%. There appears to be no significant difference between the sorption isotherms of the powders from the three different experiments. The difference between the highest and the lowest moisture contents at each relative humidity for the three experiments was divided by the average moisture content at each relative humidity. The resulting differences were between 3% and 10% of the average values, 6.3% on average. Since these differences are comparable to the size of the graph symbols on Fig. 1, error bars have not been plotted on this figure.

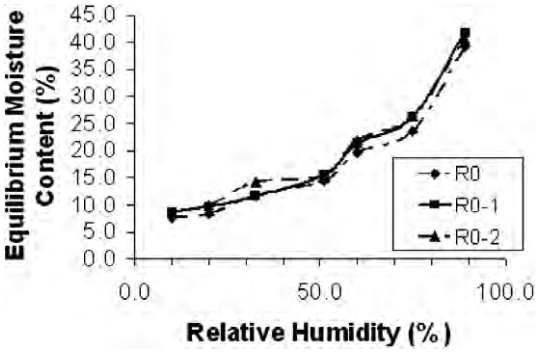

Fig. 1. Equilibrium moisture content as a function of relative humidity.

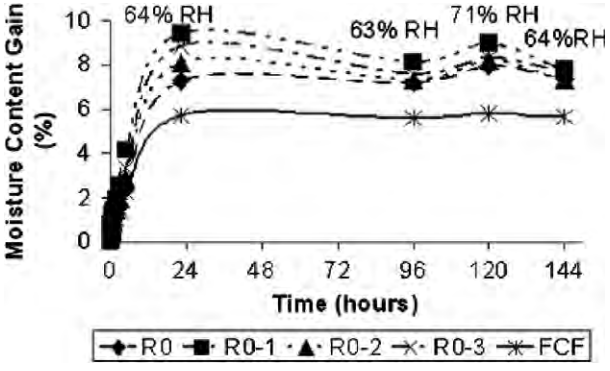

Fig. 2. Moisture gain as a function of time, illustrating the hygroscopic adsorption rate in a static layer.

Table 2
Characteristics of produced powders

Sample Number	Moisture content (%)	Mean size (μm)	Glass transition temperature (°C)	Fractal dimension (–)
R0-0	8.3	16.4	63	2.0
R0-1	8.1	15.5	68	2.2
R0-2	10.7	23.0	57	2.2

Sorption measurements were plotted as a function of time, as shown in Fig. 2. The majority of adsorption from atmospheric moisture content seems to occur within the first 24 h of exposure. Slight variations in ambient humidity have a small impact on the moisture content, but the powder returns to its equilibrium moisture content quickly and consistently. It was also observed that there was a small decrease in moisture content after the initial adsorption period that could not be attributed to the effect of ambient humidity, since the moisture content was lower even at a similar relative humidity.

3.2. Particle shape and size

The particle size measurements produced from the laser diffraction method gave a range of average sizes from 16 to 23 μm ($d[4,3]$). Fractal dimensions from the light diffraction measurements give an indication of the particle shapes. The values obtained here for the fractal dimensions, from 2.0 to 2.3, indicate rounded disc/sheet like objects (1 = single line, 2 = flat sheet, 3 = sphere).

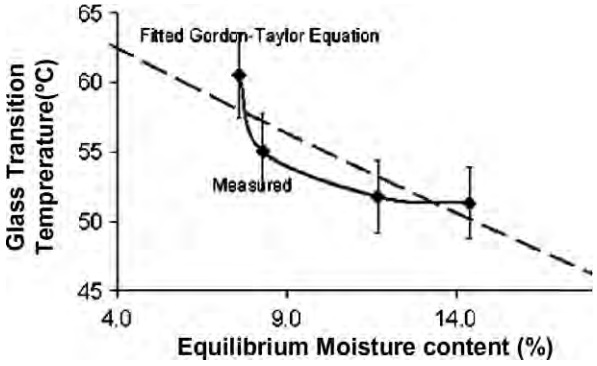

Fig. 3. Measured glass transition temperature as a function of equilibrium moisture contents for sample R0 and Gordon–Taylor fitted glass transition temperature as a function of equilibrium moisture content. Error bars of 5% marked.

3.3. Glass transition temperature

The glass transition temperatures for the powders produced directly from the dryer were 57–68 °C, depending on the moisture contents. There was no measurable glass transition when fruit fibres were tested without adding any extract. The glass transition temperature was also measured for R0-0 (the first set of fibre and extract) samples after being placed in controlled humidity conditions, as shown in Fig. 3.

3.4. Visualisation of product

The visualisation of the powders produced a series of images demonstrating the autofluorescence properties of the citrus fibres, and the fluorescent properties of the citrus fibre-hibiscus extract combination, as shown in Figs. 4 and 5. The images taken from the MRC600 confocal system also display the sites showing where the polyphenol complexes from the hibiscus extract are located inside the fibres.

4. Discussion

4.1. Effect of sorption properties and water activity

The sorption properties are important for storage considerations. The powder appears to quickly reach moisture contents in equilibrium with ambient conditions within a 24 h period. The increase of moisture content is undesired after spraying since it causes some dissolution of the dried bioactive or change in its state, resulting in caking. The rearrangement from high energy, amorphous, to low energy, crystalline, states also occurs more quickly with

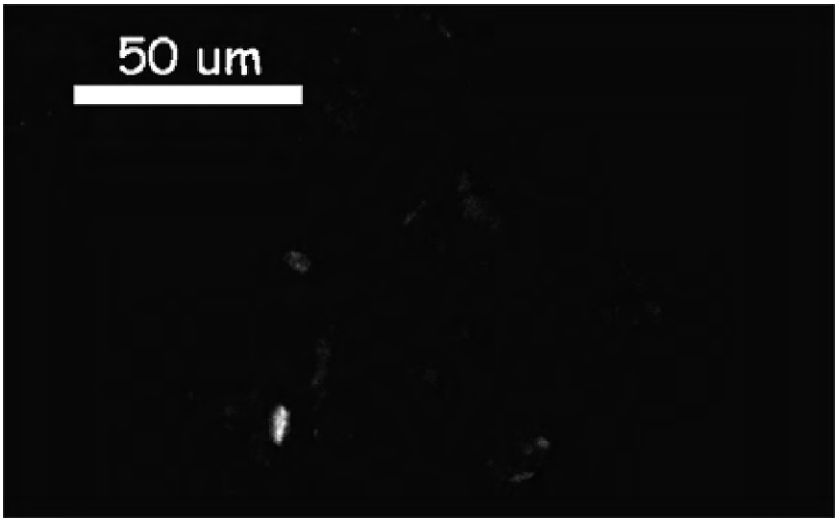

Fig. 4. Fibre only control from the MRC 600 confocal system. The absence of a visible fluorescent response means no bioactive is present.

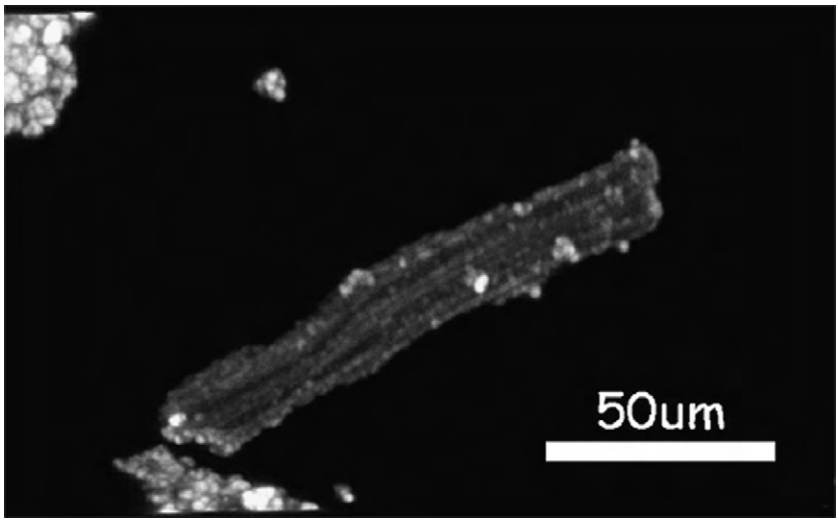

Fig. 5. Fibre with bioactive, from the same system as fig. 4. Response signals are of bioactive fluorescence.

increasing moisture content after spraying, creating large lumps that are not suitable for free-flowing powders.

Another concern related to storage conditions is the water activity of the powder. Since the powder is designed for human consumption, there are regulations regarding the moisture content of the material. Materials with too high a moisture content allow the growth and development of harmful molds, bacteria and other micro-organisms. Any product developed with a water activity lower than 0.6 is considered to be safe for general storage (Fontana, 1998).

By comparison, the powder produced with a moisture content range of 8–10% has a water activity of 0.15–0.20. In order to be at a water activity of 0.6, the moisture content of the powders would have to reach 20–22%. When the powder was left at an ambient relative humidity of 50%, the moisture content of the powders reached 15%. Given this consideration, the product powder must be stored at a relative humidity under 50% to prevent micro-organisms from developing.

4.2. Crystallisation of amorphous powders

In this section, the moisture sorption behaviour observed in Fig. 2 is examined in more detail. The

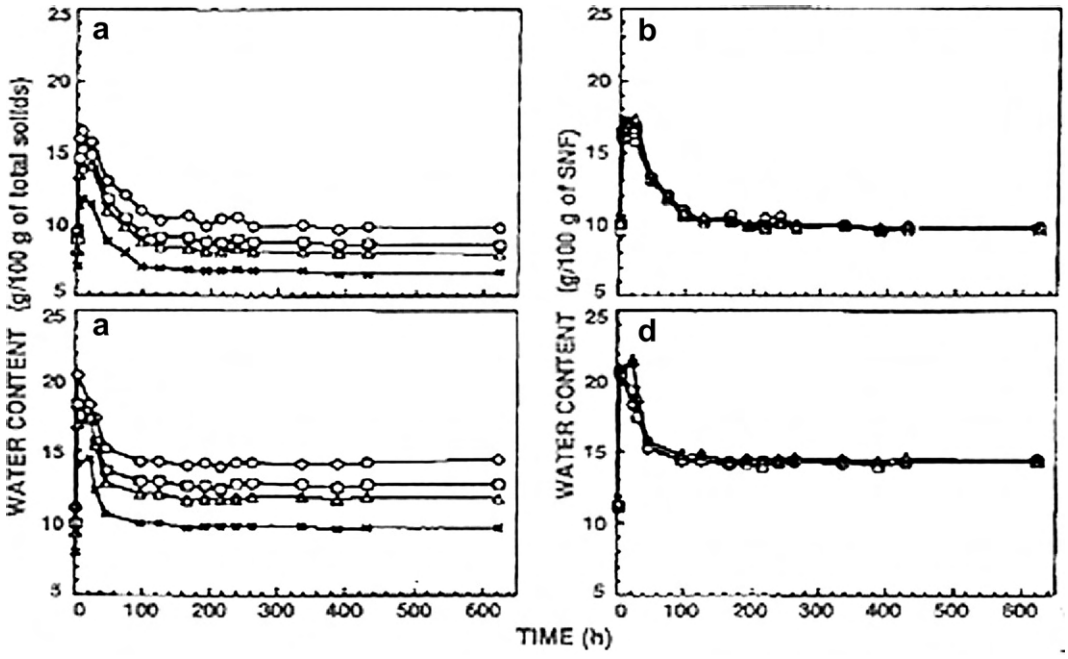

Fig. 6. "Water sorption of milk powders containing lactose at relative humidity of 66.2: total solids (a) and SNF basis (b) and 76.4% total solids (c) and SNF basis (d) at 24 °C. Experimental water contents are shown for dehydrated skim milk (○), low fat milk with 1% (□) and 1.9% fat (Δ), and whole milk (x). The amount of fat affected the rate of loss of adsorbed water caused by lactose crystallisation." (Quote and figure taken directly from Fig. 5, Jouppila and Roos (1994)).

approach taken compares the sorption behaviour of the fruit fibres with timber fibres to support the idea of the fruit fibres being in a crystalline state.

One of the most noteworthy features of Fig. 2, for the moisture adsorption behaviour of spray-dried citrus fibre and hibiscus extract (Chiou & Langrish, 2005), is that some similar features are seen in Fig. 6, which shows the adsorption behaviour of milk powders containing lactose. The adsorption behaviour of Fig. 6 is typical of water-induced crystallisation where a rapid moisture sorption is observed. This allows a molecular re-arrangement with water as a 'lubricant', so that amorphous to crystalline state change can occur. Following this re-arrangement, a moisture desorption is seen due to the crystalline structures being more compact and orderly than the original amorphous state.

In Fig. 2, the fibre-only sample shows almost no initial peak, which is consistent with this solid fibre sample staying almost purely crystalline throughout the spray drying process. In contrast, the samples of spray-dried mixtures of both fibre and extract show peaks in the plots of moisture content as a function of time, which is similar to the adsorption behaviour of milk powders containing lactose. Since the extract is a liquid, it is likely to form an amorphous solid on drying, so the spray-dried mixtures of fibre and extract are likely to contain both crystalline fibre and amorphous extract. Hence the amorphous extract part of the sample may crystallise with increasing time, giving the peaks seen in the plots of moisture content as a function of time in Fig. 2.

Since the powder has two main components (fibre and extract), it is important to consider if the moisture sorption behaviour is an effect of one or both components. Examination of the fruit fibre sorption behaviour compared with timber fibres gives possible insights about the behaviours of the components. In separate equilibrium experiments, the fibres were shown to have equilibrium moisture contents that were up to half their dry mass (Langrish, 2005). The behaviour of the fruit fibre has been compared with the sorption properties of timber, which contains cellulose, using the BET and GAB isotherms as seen in Fig. 7. The curve in Fig. 2, with only fruit fibre, can be compared with Fig. 7 for the equilibrium moisture contents of timber at a known relative humidity. From the data, the moisture content for the fruit fibre after spray drying was 4.4% and, with the addition of 5.6% moisture due to sorption at the plateau shown in Fig. 2, the value of the final moisture content at the plateau is 10%. Using Fig. 7, the equilibrium moisture content for the fruit fibre is approximately 9.4% at a relative humidity of 50%. This agreement between Figs. 2 and 7 is good for the equilibrium moisture content of the fine fruit fibres.

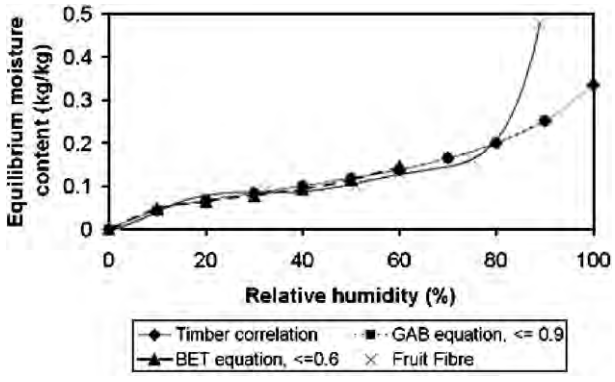

Fig. 7. BET and GAB isotherm fitting for fruit fibre comparison with timber.

In Fig. 7, the fruit fibres show similar sorption behaviour to the timber isotherm at lower relative humidities than 80%. Since timber is mainly cellulosic, the increase in the equilibrium moisture content above a relative humidity of 80% is consistent with the behaviour of hemicellulose. This behaviour was seen in a study of water sorption in hemicellulose from timber where the moisture content increases more rapidly than for timber alone at these high humidities (Christensen & Kelsey, 1958). This similarity suggests that the moisture adsorption of a spray-dried citrus fibre behaves in a similar way to a mainly hemicellulose fibre and suggests that the fibre is already in a crystalline-like state. This means no further crystallisation of the fibre is possible and should have no effects on the crystallisation of the extract.

The combination of fibre and hibiscus extract is then showing the crystallisation of amorphous material for the hibiscus extract only. This behaviour has been noted before in previous reports of solid-phase crystallisation for materials including lactose (Jouppila & Roos, 1994). This work has shown some evidence for this process occurring for hibiscus extract. It is therefore suggested that the nature of the crystallisation process from spray-dried amorphous products may be universal, and that this process may occur, to some extent, in spray dryers themselves.

4.3. Effects of moisture content on glass transition temperature

Significant features of the powders are their sorption and glass transition properties. These properties have implications regarding the operating conditions for producing the powders and for the associated storage conditions, in that moisture content and temperature are linked to the operating conditions through the occurrence of stickiness, since the greater the level of stickiness, the lower the product yield due to sticky deposits on equipment surfaces, and the more difficult the product is to store and use. A 1:1 fibre:extract ratio gave a yield of 38%, a 10:1 fibre:extract ratio gave a yield of 40%, and a 100:1 fibre:extract ratio gave a yield of 45%.

One factor that is important regarding stickiness is the glass transition temperature. It is known that spray drying produces largely amorphous products (Bhandari, Datta, & Howes, 1997). If amorphous products are heated above the

glass transition temperature, then they become rubbery and potentially sticky. This transformation generally occurs 20 °C above the glass transition temperature (Bhandari et al., 1997). With the measured glass transition temperature being around 57–68 °C and a measured outlet air temperature of 131 °C, it is likely that the product would be sticky at these outlet conditions.

Moisture acts as a plasticiser in materials. Increased moisture content in the sample reduces the glass transition temperature (water has a glass transition temperature of −137 °C (Bhandari et al., 1997)). It would be desirable to remove moisture and hence raise the glass transition temperature for most particles above the temperatures throughout most of the dryer. Spray dryers are commonly operated at temperatures below the sticky point temperature, which is related to the glass transition temperature. This situation is intended to give fewer wall deposits in the spray dryer, and a higher yield. Increasing the relative humidity gives higher moisture contents, as seen in Fig. 1 for all the samples, giving lower glass transition temperatures, as seen in Fig. 3, so it is important that inlet air is appropriately conditioned to remove excessive moisture if a high humidity environment is present.

Fitting the measured glass transition temperatures to the Gordon–Taylor equation (using a least squares method) shows that the equation does not fit the experimental data perfectly. This may be due to non-ideal mixing effects between water (the moisture content), the fibres, and the extract. This non-ideality is consistent with adsorption behaviour between water and the fibres, and the extract and fibres, in the sense that ideal mixing would be expected to result from very weak adsorption. The fitted values are compared with the measured values for sample R0 in Fig. 3. Glass transition temperatures have onset and termination values, and often glass transition temperatures are stated as the middle value of the temperature range between onset and termination (Bhandari & Howes, 1999). With an uncertainty in the glass transition temperature of ±5% applied to the experimental data in Fig. 3, the fitted values from the Gordon–Taylor equation are within the error bars, suggesting that the degree of non-linearity may not be very large, even though the mixing effects may still be present.

4.4. Product size and shape

The particle shape and size measurements affect the flowability of powders. Compared with spray-dried fibre only, the particle size of the fibres and extracts together is not significantly different, indicating that the presence of bioactive materials in the fibres does not affect the particle size significantly. This result also indicates that any separate bioactive particles are too small to affect the laser diffraction measurements. The shape of the fibres also stays the same, which allows them to be relatively free-flowing. Visual observations also demonstrated that powders began to cake in relative humidities above 50%.

This work, particularly from Figs. 4 and 5, demonstrates the incorporation of the bioactive material by the fibres. These results show that there is some form of physical protection being offered by the fibres having bioactive material within them.

5. Conclusions

The main characteristics of the powder have been examined with a variety of techniques. The situation indicates a well-formed powder with moisture content suitable for storage and consumption. The desired bioactive has also been detected to be present within the fibre carriers, thus demonstrating the fibre encapsulation extract as a potential replacement for maltodextrin-type carriers. If the storage conditions can be maintained under a relative humidity of 50%, then the powder is unlikely to cake. The presence of the bioactive material does not appear to alter the particle size or shape significantly. Crystallisation behaviour was monitored and may be universal for all amorphous spray-dried powders.

Acknowledgements

Thanks are due to Lang Technologies P/L for the fine milled citrus fibres and Vic Cherikoff Foods for the hibiscus extract. Financial support from the Australian Research Council under the Linkage Grants Program and Lang Technologies P/L is gratefully acknowledged. Thanks also to Ellie Kable and Louise Cole from the Electron Microscope Unit at the University of Sydney for their assistance in Fluorescence and Confocal Microscopy.

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Preliminary Results and Abstracts of Cran-Max® Studies Under Way

Preventative treatment with cranberry extract of vesico-ureteral reflux (VUR) in children—preliminary report

Yosef Binyamini, Yuval Bar-Yosef, Mario Sofer, Haim Matzkin and Yaakov Ben Haim.

Children's Urology Unit, Urologic Department, Tel Aviv Medical Center

Introduction:

Recurrent infections of the urinal tract, often associated with fever, are common in children suffering from reflux of urine from the bladder to the urether (VUR). Such infections may also leave scars in the kidney parenchyma and cause irreversible damage to kidney functions. In these cases preventive long-range antibiotic treatment is therefore recommended, then waiting for the reflux complaint to eventually pass away spontaneously. Several studies were published demonstrating the efficacy of cranberry treatment for prevention of recurrent infections in the urinary tract in adults, but to the best of our knowledge such treatment has not yet been tested on children with VUR.

Materials and methods:

During a period of 18 months 35 children were collected of average age 37 months (range 12-120 months). They included 6 males and 29 females, all suffering from reflux. Three children had reflux degree 1, eleven children degree 2, 16 children degree 2, 16 children degree 3, 4 degree 4 and one child had degree 5. 34 of them had received preventive antibiotic treatment and were switched to preventive treatment with a cranberry preparation—**Cran-Life**, containing 250 mg cranberry extract and 60 mg vitamin C. Patients aged up to 7 years were given one capsule and those over 7 years of age 2 capsules per day. The children were invited for medical examination once in three months to obtain result of urine sample culture and general urine examination. At that time the children returned the remaining capsules which serve as index of the take up of the preparation.

Results:

Average follow-up 7.3 months (range 1-15 months). Six children dropped out of the study: 2 because of inflammation which necessitated switch over to antibiotic treatment and 4 on account of lack of cooperation by the family. The remaining 29 children are still being treated with cranberry **and do not suffer from any infection**.

Summing up:

From the preliminary results of this study it may be concluded that the cranberry preventive treatment is effective in hindering urinary tract inflammations and pyelonephritis in children suffering from VUR. These results are preliminary and the children will be followed up for two years from the day of start of study.

(398)

Effectiveness of cranberry extracts as primary prevention of urinary tract infections and evaluation of cost-effectiveness, amongst female soldiers

Abstract of the trial procedure

Background:

Urinary tract infections (UTI) among female soldiers are quite common, in particular in trainees and those engaged in intensive physical exercise. The risk causes include: "complex" hygenic conditions (profuse perspiration, habitual prolonged restraint, use of public toilets), dehydration, girls at an age of starting sexual activity, etc. In Training Base 1, for example, the reported incidence of UTI among trainees (in a 10 week course) is around 9%, and there is no doubt that this is an underestimate. In the course of 10 weeks of training, one out of 10 girls will report UTI whereby each trainee is given 0.4 B sick leave and 0.2 C sick leave on average. These are mostly cases of uncomplicated cystitis but sometimes this develops into complicated UTI. The systemic problem is of course the damage to health, but also the loss of training and working days.

Cranberrys (vaccinium macrocarpon) were known as an ancient popular remedy as early as the 17th century, mainly as treatment of urinary tract diseases but also for other complaints. There are offered today as a preventive and treatment for urinary tract infections - in the form of cranberry juice or as tablets containing cranberry extract. On the one hand this is a food supplement with high safety and almost devoid of known side-effects. On the other hand, proof of the efficacy of cranberries is not yet impressive. A review published in 2004 (Cochrane Database systemic review, by Jepson et al.) shows that few quality investigations have been carried out. No study was found which deals with primary prevention in a homogeneous group such as female soldiers.

Purpose of the trial:

1. Primary prevention and reduction of incidence of urinary tract infections among female soldiers, by use of cranberry extract.
2. Cost effectiveness of the use of cranberry extract to prevent urinary tract infections among female soldiers in a training course.

Detailed description of the trial:

Prospective double-blind study with cross-over, to take place during a course of female officers at the training base, comprising 4 contingents.

After being given a lecture and explanation concerning the trial, the trainee will be asked to sign an agreement to join in the trial - without any promise/advantage or disadvantage accruing to those who participate or who do not participate.

The participants will fill a short questionnaire on general health issues and questions concerning UTI in particular. Every participant will also give a urine sample for culture at the beginning of the trial.

The trial tablets will be provided unstamped and only marked A and B - for the cranberry extract tablets and the placebo tablets in blind manner.

The participants will be randomly divided into two groups. Tablets will be given to each participant once a week. In the middle of the training period, i.e. after 5 weeks, each participant will again fill a brief questionnaire and will again give a urine sample for culture. Cross-over will be carried out between the groups (tablets A < -- > B interchange) until the end of the training period. At the end of training—after 10 weeks, again a brief medical questionnaire will be filled and urine sample given.

In the course of training, the participants will update the medical team concerning urinary complaints and in such cases a urine culture will be taken and treatment given by decision of the physician in charge.

Age:
the age group of participants in female officers course (18-30).

Sex:
women only.

Medical supervision in the course of trial:
As aforesaid, apart from intervention at the beginning, in the middle and at the end of the participation period, with continued routine medical supervision of trainees. In case of urinary complaints, greater emphasis will be placed on giving a urine culture for documentation. The conventional empirical treatment will be given as usual and only in case growth of a treatment-resistant bacterium is detected, will the treatment be changed to the conventional one. Extra attention will be given to possible side-effects and effects not yet reported.

Duration of treatment for each participant:
For the duration of the female officers course (0-10 weeks).

Duration of the medical trial:
4 female officers course contingents—6 months.

Evaluation of Cran-Max® for the Prevention of UTI in Spinal Cord Injured Patients with Neurogenic Bladders

Veteran Affairs,
Boston Healthcare System.

Design:

150 subjects; randomized, double-blind, placebo controlled, crossover study, 2 years duration

Completed; awaiting statistical analysis

Preliminary Data

- Cran-Max® evaluated in over 100 patients at dosage of 500 to 1000 mg once to twice daily over 3 years
- Positive findings led to clinical review of a sample of 12 patients
- UTI history and symptom questionnaire
- Urinalysis performed before and after Cran-Max® usage (urinary pH, leucocyte esterase and bacteriuria)
- Results: significant reduction in frequency of UTI after the initiation of prophylaxis
- No significant change in urinary pH or the incidence of leukocyte esterase

Can Cran-Max® Be Used To Treat Current Urinary Tract Infections?

Anil Kapoor, M.D., Ivan Kai-Hsiang Hsia
2003 McMaster University

Study Summary

- Pilot Study To Determine Effectiveness of Cran-Max as a prescribed method of treatment for current Urinary Tract Infections.
- Study site: McMaster University, Hamilton, Ontario, Canada; Dr. Anil Kapoor, Urologist
- 30 Women, 3 Groups:
  - Norfloxacin BID for five days
  - 500mg Cran-Max once daily for five days
  - 500mg of Cran-Max twice a day for five days

Preliminary Findings

- 6 women with uncomplicated UTI given Cran-Max 500mg twice daily for 3 days
- 4 women required antibiotic therapy after 2-3 days
- 2 women improved with Cran-Max alone and did not require antibiotics
- Preliminary results suggest Cran-Max may have utility in treating select patients with uncomplicated UTI

CIHR Research Proposal:

Treatment of Uncomplicated Urinary Tract Infections with Cranberry Extract

Urinary tract infections (UTIs) are a prevalent and disruptive disease. North American data of the prevalence of UTIs was estimated at approximately 3.5% of the population.[i] They account for 1.2% of all office visits by women and 0.6% of all office visits by men.[ii] In present day medical practice, antibiotic therapy is the treatment of choice for UTIs. Our better understanding of urinary tract pathogens and our development of new antibiotics have made this treatment modality effective. Unfortunately, decades of antibiotic use has given rise to antibiotic resistance. Canadian data shows that E. Coli, the most common pathogen causing UTIs, has resistance rates of 41.1% to ampicillin, 18.9% to trimethoprim-sulfamethoxazole, 7.4% to mecillinam, and 1.2% ciprofloxacin.[iii] [iv] There are limitations to even our best antibiotic family, the fluoroquinolones, which include ciprofloxacin and norfloxacin. “Administration of the fluoroquinolones to immature animals has caused damage to the developing cartilage, and, therefore, these agents are currently contraindicated in children, adolescents, and pregnant or nursing women.”[v] Therefore, it would be a prudent course of action to investigate alternative treatments for UTIs. The first documented use of Cranberry as a medicine was in the 17th century, by the European settlers who observed these medical practices in the Native Indian community. Recent studies have shown prophylactic usefulness of Cranberry Extract

against UTIs. It was once believed that this was a direct result of increased urinary acidity, but now there is evidence that Cranberry Extract inhibits the binding of the bacterial pathogens to the urothelium. Decreased binding ability has been demonstrated in E. coli, Proteus, Klebsiella, Enterobacter and Pseudomonas.[vi] [vii] To date there is no useful evidence regarding Cranberry Extract's effectiveness as a treatment for UTIs. A meta-analysis looking for such data was performed for the Cochrane Database of Systematic Reviews and in its conclusion it stated that, "After a thorough search, no randomized trials which assessed the effectiveness of cranberry juice for the treatment of urinary tract infections were found. Therefore, at the present time, there is no good quality evidence to suggest that it is effective for the treatment of urinary tract infections."[viii]

Therefore, I propose to investigate and generate data regarding Cranberry Extract as a treatment for uncomplicated UTIs. Uncomplicated UTIs, for the purposes of our investigation, will be defined as an afebrile, local infection in a patient with a structurally and functionally normal urinary tract. This will be a comparative study between norfloxacin and two different doses of Cranberry Extract working under the null-hypothesis that norfloxacin is more effective than Cranberry Extract in the treatment of UTIs. In the initial study, we propose to randomize 30 patients, which meet our criteria, into 3 branches.

UTI Pilot Protocol

3 arms of the study, 10 patients each

5 days norfloxacin 400mg PO BID (control group)
5 days Cran Maxä 500mg PO OD
5 days Cran Maxä 500mg PO BID

Initial Visit (Day 1)

Data: Urinalysis, Culture and Sensitivity, CBC, History and Physical (including patient data: age, sex, etc.) Symptom score (Validated O'leary-Sant questionnaire)

Day 2

Data: Urinalysis, Culture and Sensitivity, Symptom score (if patient is on Cran-Max® and symptoms worsen or there is development of a fever then treatment is changed to antibiotics.) (otherwise continue course)

Day 5

Data: Urinalysis, Culture and Sensitivity (if previous Culture positive for growth then change to antibiotics), Symptom score

Optional day 5 extension if Urinalysis positive, but the patient feels much better (physician's decision)

The results will be entered into an Excel database and a subsequent analysis using SPSS statistics program will be performed with the completed data. Appropriate parametric and non-parametric statistical tests will be run to compare between group data, i.e. control versus treatment arms, and within group data. Examples of analytical tests include a Chi-Squared test looking for differences in positive/negative cultures between control and treatment arms, an ANOVA analysis for comparison of between group symptom scores, and a repeated measures ANOVA to see if there are day to day improvements within each treatment regiment. After the analysis, we will have data that will let us draw conclusions, on how effective, if at all, Cranberry Extract is in treatment of uncomplicated UTIs. We will also have data on the time course of each treatment arm, including information on when bacterial levels drop in the urine and when patients start to feel better. The study will produce data by which evidence-based decisions, regarding the usage of Cranberry Extract as a treatment for UTIs, can be made.

Cystitis Symptoms Index

Please circle the number that best describes your answer to the following questions:

During the past few days, how often have you felt the strong need to urinate with little or no warning?

0. not at all
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

During the past few days, have you had to urinate less than 2 hours after you finished urinating?

0. not at all
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

During the past few days, how often did you most typically get up at night to urinate?

0. not at all
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

During the past few days, have you experienced pain or burning in your bladder?

0. not at all
1. less than 1 time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

Interstitial Cystitis Problem Index:
During the past few days, how much has each of the following been a problem for you?

Frequent urination during the day?

0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

Getting up at night to urinate?

0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

Need to urinate with little warning?

0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

Burning, pain, discomfort, or pressure in your bladder?

0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

Independent Laboratory Results for BioShield

Proposed Mechanism of BioShield® bound Anthocyanins

Integrated Biomolecule Corporation
9030 South Rita Road, #100, Tucson, AZ 85747-9102

Anthocyanins are the glycosolated (sugar bound) analogs of anthocyanidins. The anthocyanidins are purportedly the species that are actually active in the body at the site of action; In a study by Youdim, KA et al they investigated the potential antioxidant properties of blueberry polyphenolics in vitro and vivo, using red blood cell (RBC) resistance to reactive oxygen species (ROS) as the model. In vitro incubation with anthocyanins or hydroxycinnamic acids (HCA) was found to enhance significantly RBC resistance to peroxid induced ROS production. This protection was also observed in vivo following oral supplementation to rats. However, only anthocyanins were found to afford protection at a significant level, this at 6 and 24 h post supplementation. This protection was consistent with the measured plasma levels of anthocyanins. The difference in absorption between anthocyanins and HCA is likely to have contributed to the observed difference in their abilities to afford protection to RBC. This protection represents a positive role following dietary consumption of intact anthocyanins allowing for conversion to anthocyanidins in vivo, however as the anthocyanidins are insoluble in water they, therefore, cannot be easily absorbed by the body if ingested in their active non-glycosolated state. Thus it is necessary to absorb anthocyanins and allow the body to convert these to the anthocyanidins at the site of use.

The anthocyanins possessing the bound sugar renders them water soluble and thus easily absorbed by the body. This has been demonstrated by Tsuda, T et al, in order to clarify the mechanism of action of Cyanidin 3-O-beta-D-glucoside, they investigated the absorption and metabolism of Cyanidin 3-O-beta-Dglucoside in rats. Cyanidin 3-O-beta-D-glucoside appeared in the plasma after the oral administration of enterically coated Cyanidin 3-O-beta-D-glucoside. Protocatechuic acid, which is produced by the degradation of a glycon of Cyanidin 3-O-beta-Dglucoside (cyanidin), was not present in the plasma. In a similar study the same authors have further clarified how Cyanidin 3-O-beta -D-glucoside is absorbed and metabolized in vivo. Although Cyanidin 3-O-beta -D-glucoside rapidly appeared in the plasma, Cyanidin was not detected, although it was present in the jejunum. It should be noted however the chemical linkage between the anthocyanidin and the sugar group is highly fragile in acid environments. Thus when intact anthocyanins are ingested orally they are rapidly degraded by the acidic environment of the upper gastrointestinal tract to the sugar group and the now insoluble, unabsorbable anthocyanidin.

The key benefit of the Bio-Shield® matrix is to maintain the integrity of the anthocyanidin to glucose bond thereby allowing intact anthocyanins to be passed into the lower gastrointestinal tract where they may be readily absorbed from an aqueous medium.

In a study by Paganga, G there is described evidence for the absorption of flavonoids and their presence in human plasma in the glycosylated form by HPLC analysis with photodiode array detection, Rutin and other quercetin glycosides, phloridzin, as well as other anthocyanins are detected simultaneously. In addition, a compound eluting with the spectral properties of the aurone family is identified. The results reveal that phloretin and quercetin are absorbed from the diet as glycosides.

Bio-Shield® being composed of natural plant fibers is considerably tolerant to acid environments, especially since the Bio-Shield matrix is made from the Cranberry fruit. Under acidic conditions the Bio-Shield® matrix offers protection from surrounding acids against degradation of anthocyanins, as it would in nature. This effect is thought to be due to a contraction of lignin-cellulose fibers in the presence of acids, thereby decreasing the permeability of the matrix to the aqueous acidic environment, and thus limiting the degradation of the anthocyanins that have been absorbed onto the Bio-Shield® matrix.

Once in the duodenum the environment surrounding this Bio-Shield® matrix returns to a neutral state, the Bio-Shield® matrix can relax and allow absorbed anthocyanins to solvate into the aqueous environment. The protected anthocyanins can be shown to exist in an unmodified state by experiments similar to those carried out by Lapidot, T, whereby they determined the potential bioavailability, in human, of several anthocyanins from red wine. Volunteers, having a polyphenois-free diet, drank 300 mL of water every hour for 12h and collected urine. Several weeks later, the same volunteers repeated the same procedure but replaced the water of the fourth drinking dose with white wine. Two weeks later, they repeated the procedure with red instead of white wine. In the 300 mL dose of red wine, the subjects received 218 mg of anthocyanins, which were detected in their urine by HPLC analysis with a photodiode array detector.

The Bio-Shield® matrix can be considered as a natural enteric coating that can be used to facilitate the absorption of intact bioavailable anthocyanins, and further to prolong the stability of anthocyanins, in a study by Fossen, T, it has been shown that variation over the pH range 1-9 during 60 days of storage, that was conducted on petunidin

3-[6-O-(4-O-E-p-coumaroyl- O-alpha-L-rhamnopyranosyl)- beta-D-glucopyranoside]-5-O-beta-D glucopyranoside (petanin) and Cyanidin 10 and 23 °C, demonstrated that petanin afforded higher color intensity and higher or similar stability throughout the whole pH range. At pH 4.0, 84% of petanin was intact after 60 days storage at 10 °C, while the corresponding solution of Cyanidin was totally degraded. At pH 8.1 the color intensity of petanin was even higher than at the lowest pH values. The natural matrix structure of the Bio-Shield® could be considered as a buffer to acidic environments, as would be in the case of the natural fruit from where it was derived, and thus limits the rate of natural degradation of the anthocyanins. ■

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These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.

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Controlled Delivery of Components from CranMax-an In vitro Study

Doddabele Madhavi, Ph.D, BioActives, Inc., Worcester, MA

The objective of this study was to determine the efficacy of CranMax matrix in reducing/inhibiting the release of the polyphenols and anthocyanins in the gastric milieu. The delayed release ensures the transfer of intact compounds to the absorption sites in the gastrointestinal tract. The bioactivity of the cranberry juice has been attributed to higher molecular weight polyphenols such as proanthocyanidin trimers (Yeap Foo et al., 2000). It is also reported that the polyphenols are sensitive to the acidic environment in the gastric lumen and are hydrolyzed to mixtures of small molecular weight components (Spencer et al., 2000).

The release of polyphenols was determined in an in vitro system using simulated gastric fluid. The in vitro system has been extensively used to determine the controlled delivery of pharmaceuticals and in dissolution studies (Bernkop-Schurch et al., 1999; Ofoefule and Chukwu, 1999; Cole et al., 2002).

Materials and Methods

CranMax was compared with cranberry juice powder and CranActin, a commercially available cranberry concentrate.

Methods

Simulated gastric fluid containing per liter, 2g NaCl, 7ml HCl and 3.2g pepsin (Sigma) was prepared according to the United States Pharamacopea (USP 25). A 10% suspension of the samples was incubated in the gastric fluid at 37oC on a shaker at 95rpm for 1hr simulating the residence time in the gastric lumen. The suspension was cooled to room temperature and centrifuged. The clear supernatant was used to determine the total anthocyanins and polyphenols. One ml of the solution was diluted to 5ml with methanol containing 1.5N HCl. The absorbance was measured at 535nm for total anthocyanin determination. Total polyphenols were determined by the Folin's method. Gallic acid (Sigma) was used as the standard. The control values were determined after extraction of the samples with 50% methanol. The samples (0.25g) were repeatedly extracted with 50% methanol and the volume was made up to 50ml. The solution after centrifugation was used for analysis as before.

Results

Figures 1 and 2 present the comparison of the percentage of total anthocyanins and polyphenols released in the in vitro system by the samples. The CranMax-gastric fluid showed the lowest percentage of anthocyanins and polyphenols as compared to CranActin and the juice powder. The CranActin-gastric fluid sample showed nearly twice the amount of release of active components as compared to CranMax.

Conclusions

The results clearly indicate that the CranMax matrix functions as a natural controlled release delivery system as compared to CranActin or the cranberry juice.

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Figure 1. A Comparison of the Release of Anthocyanins In Vitro

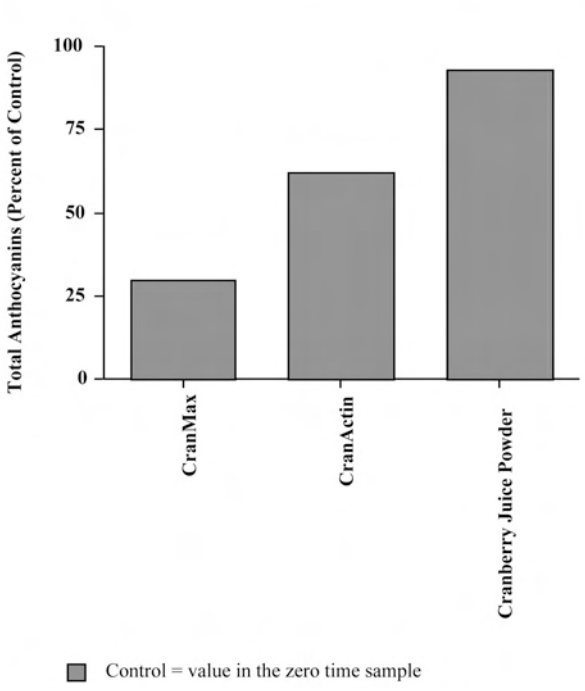
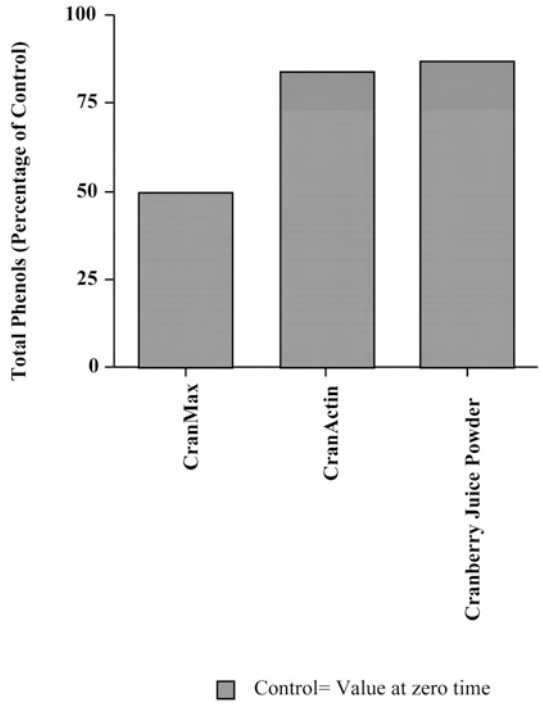


Figure 2. A Comparison of the Release of Total Polyphenols In Vitro



Background
Cran-Max®
Q&A Document

Cran-Max® Frequently Asked Questions

Anil Kapoor, M.D., F.R.C.S (C) (Urology),
is Assistant Professor of Surgery (Urology) at McMaster University/ St. Joseph's Hospital in Hamilton, Ontario, Canada

Q: What is a Urinary Tract Infection (UTI)?

A: UTI is typically characterized by the sudden onset of frequent, painful, and urgent urination. Lower abdominal pain or lower back pain may also be present. The urine is often foul smelling and cloudy.

Q: How prevalent are Urinary Tract Infections (UTIs)?

A: Eighty per cent of all women will experience a UTI in their lifetime; approximately 20% of women will have a UTI each year. One in seven visits to the doctor are urinary related, totaling 9.6 million visits annually.

Q: What causes UTI?

Many kinds of bacteria normally grow in the vagina and bowel. However, urine is normally bacteria free (sterile). So when bacteria enter the bladder from the normal vaginal and bowel flora, a bladder infection can develop.

Q: What are some of the risk factors for developing a UTI?

A: Women are at increased risk of developing a UTI for several reasons: 1) Anatomy - close proximity between the urethra and the rectal and vaginal area allows bacteria easier access into the bladder. 2) Sexual Activity - sexually active females are at higher risk for developing UTIs due to the close proximity of the vagina to the urethra. It is important to know that bacteria causing bladder infections are not passed between partners. 3) Pregnancy - a growing baby can put pressure on the bladder so that it cannot empty completely. When the urine is left to stagnate the risk of UTI increases. 4) Menopause - thinning of the uro-vaginal area makes it more likely for bacteria to break through and cause infection.

Q: Do UTIs occur more frequently during certain months of the year?

A: UTIs are more common in hotter months because we tend to be outdoors and more active. Perspiration and fluid loss lead to more concentrated urine, which creates the perfect environment for bacteria to thrive and develop a UTI.

Q: How is a UTI diagnosed?

A: In a woman with typical symptoms, a UTI is diagnosed by examination of a mid-stream urine sample (urinalysis and urine culture).

Q: How is a UTI traditionally treated?

Some cases of UTI may resolve without medication. Usually a short course of antibiotics is prescribed by your doctor.

Q: How do Cranberries prevent UTIs?

A: Research indicates that cranberries contain specific compounds, “condensed tannins,” and “proanthocyanidins,” which prevent the adherence of E. Coli bacteria (the primary cause of urinary tract infections) to the walls of the urinary tract. Thus, the bacteria (such as E. Coli) simply wash away in the normal cleansing process of the urinary tract.

Q: Cranberry juice vs. cranberry extract - what's the difference?

A: Although several clinical studies have found cranberry juice to be beneficial in preventing UTIs, the amount which must be consumed to be effective is considerable.

Cran-Max® cranberry extract is more potent than cranberry juice because it contains all the vital parts of the cranberry - fruit, seeds, skin and juice. A study published in the Canadian Journal of Urology, 2002, showed that Cran-Max® provided more effective and cost-effective treatment of UTI's when compared to cranberry juice.1 In addition, most juices contain about 27 to 33 per cent cranberry juice, with the remainder consisting of sugar and water. Drinking cranberry juice for bladder health can be expensive and increase one's calorie count. Cran-Max® does not contain any preservatives, carriers, solvents, sugars, water, flavorings or added color. It takes 34 lbs of cranberries to produce one pound of Cran-Max®.

Q: How does Cran-Max® work?

A: Cran-Max® features a patented technology, called Bio-Shield, which protects the bioactive components of the cranberry from being degraded by digestive fluids in the stomach, enabling it to provide a sustained release of its powerful cran factor to sites of action in the urinary tract.

Q: Have there been any clinical studies performed with Cran-Max®?

A: Cran-Max® is the only cranberry extract supported by scientific studies. Clinical studies performed in Prague, Czech Republic, and Canada show that Cran-Max® reduces the occurrence of urinary tract infections, and is more cost-effective than cranberry juice.1, 2, 3 In the Canadian study, subjects who took Cran-Max® tablets had 44% less incidences of urinary tract infections than those on placebo.1

Q: What is the role of blueberries in urinary health?

A: Blueberries provide a very potent source of antioxidant flavonoids called anthocyanins, which are also present in cranberries. These anthocyanins work to combat free radical damage, improve the strength of our capillaries and ward off urinary tract infections.

Q: What is the recommended dosage of Cran-Max® to obtain ideal benefits?

A: One 500 mg. capsule of Cran-Max® per day is recommended for urinary tract health.

Q: How safe is Cran-Max®?

A: No negative side effects have been reported from use of cranberry or Cran-Max®.

Q: What else can be done to prevent UTI?

A: In addition to Cran-Max®, you should drink plenty of fluids and void on a regular basis and especially after sex. Wipe yourself from front to back after urination to avoid spreading bacteria. Avoid the use of diaphragms and spermicides and clean cotton underwear is also recommended.

Q: When should you see your doctor?

A: You should see your doctor if you have frequent UTI, bloody urine, fevers, vomiting, flank pain, or UTI symptoms that continue treatment. ■

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