Cranberry fruit powder *(Vacccinium macrocarpon)* in the prevention of recurrent urinary tract infection in women

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AIMS: Cranberry (*Vaccinium macrocarpon*) is being increasingly studied for its use in the prevention of recurrent urinary tract infection (rUTI) where it affects the adhesion of pathogens notably *Escherichia coli,* to the uroepithelial cells. The key components are considered to be proanthocyanidins (PACs).
The aim of this 6 month, randomised, double-blind placebo-controlled intervention trial was to evaluate whether a daily dose of 500 mg Pacran®, a whole-cranberry powder standardised to at least 0.3% PACs could prevent rUTI in healthy sexually active women with a history of UTIs. The main outcome measure was the cumulative rate of first occurrence of a UTI. Secondary outcomes included the proportion of participants in each group experiencing a rUTI, the time to first UTI, the total number of rUTIs experienced, urinalysis and safety indices (haematology and clinical chemistry parameters) at baseline and at the end of the end of the 6-month study period.

CLINICAL TRIAL DESING: The study was carried out according to the Declaration of Helsinki and The Good Clinical Practice Guidelines of the European Medicines Agency and National Regulations on clinical trials. The study was approved by the Ethics Committee of the University Hospital and Faculty of Medicine and Dentistry, Palacky University in Olomouc, Czech Republic (reference 129/09). Written informed consent was obtained from all participants. The study was a 6-month, single-center, randomized, double-blind and placebo-controlled trial consisting of two parallel treatment arms. It was conducted between January 2010 and April 2011 at the Clinic of Urology of the University Hospital.
Sexually active women, aged 18 to 75 years , with a medical history of at least 2 symptomatic UTI in the previous 12 months were eligible to participate. Participations were randomly divided into two groups: Cranberry group (500 mg Pacran® ; two capsules containing 250 mg Pacran®) and Placebo groups (two capsules free of Pacran®). Blood samples for clinical chemistry and haematology, urine samples for an analysis of the urine and its sedimentation and vital signs (heart rate, systolic and diastolic blood pressure) were collected at baseline and at 3 and 6 months. If a UTI was confirmed [bacteriuria $\geq 10^5$ cfu/mL plus symptoms of a UTI (see *Urinalysis, microbial examination and clinical diagnosis of UTI*), the subject was treated with antibiotics (culture-directed antibiotic treatment for 1-3 days), and study treatment was halted. Once the course of antibiotics was completed, urine samples were collected to confirm that the UTI had resolved, and the subject was permitted to continue with their respective study product.

The content of selected phenolics in Pacran®

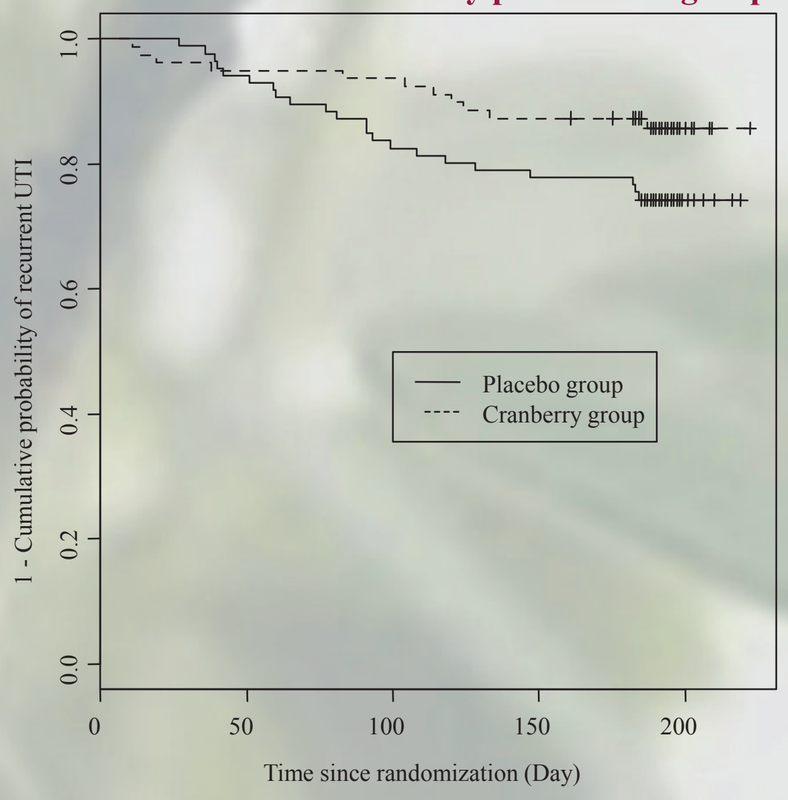
Compound	mg/100 g Pacran®
Benzoic acid	167.6
p-Hydroxybenzoic acid	2.6
Protocatechuic acid	31.8
p-Coumaric acid	86.5
Ferulic acid	8.4
Sinapic acid	4.7
Chlorogenic acid	14.8
Catechin	160
Quercetin	140.4
Total anthocyanins	107.2
Total proanthocyanidins	560

Subject characteristics at baseline

	Placebo (n=93)	Pacran® (n=83)	Difference (p value)
UTIs in the last 12 months	3.27±1.33	2.93±1.22	0.08
Age (years)	38.03±13.40	35.61±12.97	0.23
Height (cm)	167.7±6.03	166.3±6.73	0.14
Weight (kg)	66.44±10.79	64.18±12.52	0.20
Temperature (°C)	36.32±0.21	36.35±0.19	0.36
Pulse (beats per minute)	69.02±6.89	70.47±6.32	0.15
Systolic blood pressure (mmHg)	116.9±11.03	115.8±10.61	0.48
Diastolic blood pressure (mmHg)	77.31±7.39	76.87	0.68
Sedimentation (HPF)	Negative	Negative	NA
pH	5.76±0.76	5.83±0.67	0.64

In the Pacran® group, the proportion of women experiencing at least one UTI was significantly lower than in the placebo group [9/83; 10.8% vs. 24/93; 25.8%, respectively, p=0.04, with age-standardized 12 month UTI history (p=0.01), age (p=0.73), and age-squared (p=0.05) included in the model]. There was a similar finding when risk of an *E. coli* UTI was assessed (p=0.03). When the Kaplan-Meier survival curves were compared, women in the Pacran® group experienced a longer time to first UTI relative to the placebo group (p=0.04). The average number of UTIs per subject was significantly lower in the Pacran® group relative to placebo group (p=0.03). This corresponds to a relative risk reduction of 58% in the Pacran® group relative to the placebo group. The cumulative rate of UTI over 6 months for a women with average duration of observation, average age, and average UTI history, was 0.085 (8.5%) in the Pacran® group and 0.194 (19%) in the placebo group (p=0.04). The proportion of women experiencing at least 1 UTI caused specifically by *E coli*, was 7/83 women (8.43%) in the Pacran® group and 22/ 93 women (23.66%) in the placebo group (p = 0.03 vs placebo), with age-adjusted prior 12-month UTI history (p=0.007), age (p=0.74) and age-squared (p=0.12) included in the model.

Kaplan-Meier curves of survival to UTI recurrence for the cranberry placebo and groups



Haematology and clinical chemistry markers in the placebo and cranberry groups at 0 and 6 months

Parameter	Placebo (n=86)			Pacran® (n=73)		
	Day 0	Day 180	Change from baseline	Day 0	Day 180	Change from baseline
Haemoglobin (g/L)	131.30±9.80	133.98±8.99*	2.67±6.42	132.96±9.07	134.37±7.94	1.41±6.28
Erythrocytes (10^{12}/L)	4.40±0.32	4.41±0.34	0.01±0.24	4.48±0.35	4.46±0.30	-0.02±0.24
Leukocytes (10^9/L)	6.06±1.58	6.11±1.64	0.05±1.40	6.10±1.59	6.19±1.76	0.08±1.42
Hematocrit (L/L)	0.84±4.16	0.40±0.03	-0.44±4.17	0.39±0.03	0.40±0.03	0.01±0.03
Platelets (10^9/L)	245.18±58.41	253.44±57.26	8.26±54.19	263.82±64.97	268.23±61.74	4.41±36.14
Urea (mmol/L)	4.42±1.19	4.26±1.23	-0.16±0.94	4.45±1.35	4.43±1.12	-0.03±1.02
Creatinine (µmol/L)	67.88±12.02	67.38±10.64	-0.50±10.11	69.25±14.30	68.10±12.55	-1.15±7.56
Bilirubin (µmol/L)	7.97±3.60	8.97±4.18*	1.00±3.61	9.18±4.93	8.64±4.72	-0.53±3.98[b]
ALT (µkat/L)	0.37±0.32	0.37±0.29	-0.01±0.15	0.35±0.24	0.36±0.40	0.01±0.40
AST (µkat/L)	0.44±0.14	0.44±0.23	0.01±0.20	0.40±0.08	0.39±0.10[a]	-0.01±0.09
GGT (µkat/L)	0.31±0.24	0.39±0.61	0.08±0.49	0.33±0.18	0.34±0.28	0.01±0.17
CRP (mg/L)	2.59±4.40	2.59±3.75	0.00±5.23	3.21±4.24	3.24±4.43	0.03±5.29
Total cholesterol (mmol/L)	4.97±0.99	5.18±1.02*	0.21±0.72	5.11±1.09	5.31±1.04*	0.20±0.88[a]
TAG (mmol/L)	1.31±0.94	1.19±0.60	-0.12±0.79	1.23±0.55	1.21±0.50	-0.02±0.45
HDL cholesterol (mmol/L)	1.63±0.35	1.77±0.77	0.14±0.69	1.69±0.38	1.71±0.35	0.02±0.26
Total cholesterol/HDL	3.16±1.03	3.18±0.89	0.02±0.55	3.22±0.88	3.18±0.92	-0.04±0.46
LDL cholesterol (mmol/L)	2.78±0.87	2.95±0.89*	0.17±0.63	2.97±0.94	3.06±1.01	0.10±0.50
Glucose (mmol/L)	4.92±0.69	4.89±0.69	-0.03±0.77	4.97±0.76	5.02±0.82	0.05±0.94
oxLDL (mmol/L)	53.88±22.27	61.71±23.24*	7.83±22.44	53.34±21.26	63.13±20.03	10.07±21.30

CONCLUSION: A daily dose of 500 mg Pacran® proved effective in reducing the risk of symptomatic UTI in women with a history of rUTIs. Pacran® was well-tolerated, with no adverse effects reported.

Acknowledgements: Financial support from the Czech Ministry of Education, Youth, and Sport (Grant No. MSM 6198959216) and the Institutional Support of Palacky University in Olomouc is gratefully acknowledged.. The cranberry fruit powder (PACRAN®) was supplied by NATUREX-Decas Botanical Synergies, Carver, MA 02330, USA.