CRANBERRY INTERVENTION IN PATIENTS WITH LOCALIZED PROSTATE CANCER PRIOR TO RADICAL PROSTATECTOMY

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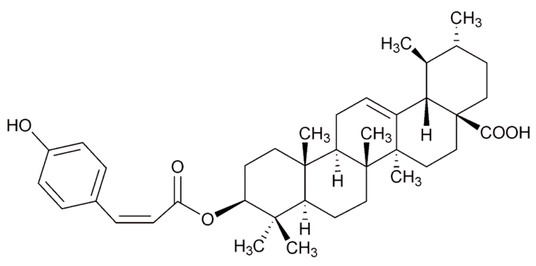
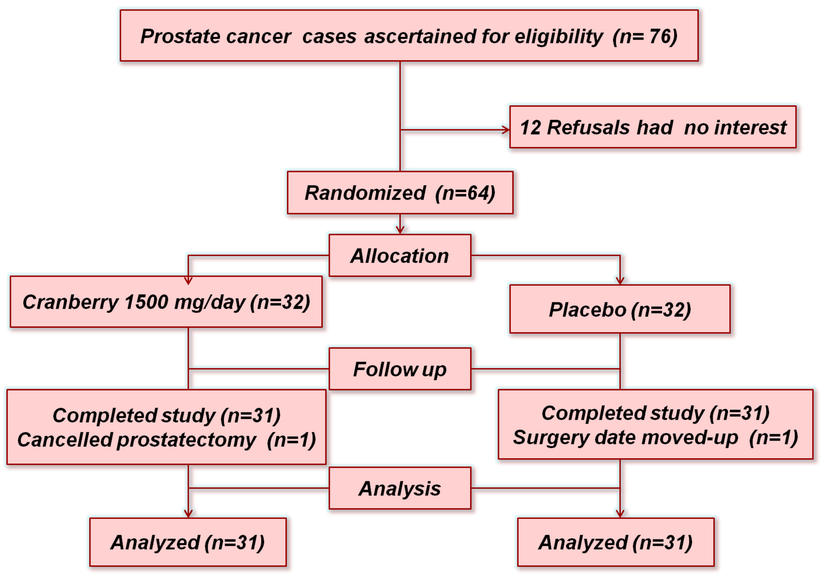
In this study, we evaluated, in a randomized, double-blind, placebo control trial the effects of cranberry fruit powder on blood, urine and prostate tissue markers in PCa patients. The dose of 500 mg three times a day (total 1500 mg/day) of cranberry fruit powder was given to men with PCa at least 21 days before radical prostatectomy (means were 31 ± 9 days in the cranberry group and 35 ± 8 days in placebo group). On the day of surgery, there was a decrease of 22.5 % in PSA level in the cranberry arm and an increase of 0.9 % in the placebo arm. The down-regulation of serum PSA may be related a trend to down-regulation of beta-microseminoprotein (MSMB). The significant increase of malondialdehyde levels in plasma and erythrocyte between start and end day in both groups can give evidence that cranberry consumption was not effective in inhibition of lipid peroxidation in PCa patients.

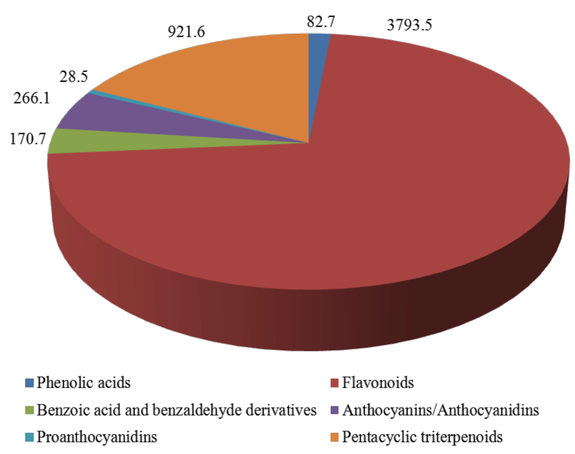
Whole cranberry powder (peel, juice, seeds)



Cis-hydroxycinnamoyl ester of ursolic acid from cranberry fruit
(Neto C C J. Nutr. 2007;137:186S-193S)



CONSORT trial diagram



The amount of selected constituents (mg) in 100 g cranberry fruit powder

Clinical trial design, study population and treatment dose

The study design was a single-center, randomized, placebo-controlled intervention trial consisting of two parallel treatment arms. The trial was conducted at the Department of Urology according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by the Ethics Committee of the University Hospital and Faculty of Medicine and Dentistry, Palacky University in Olomouc, Czech Republic (reference number 55/12). The enrollment began in May 2012 with follow-up complete in May 2013. We invited 76 patients aged 45 to 75 years who were scheduled to undergo radical prostatectomy as their primary treatment and at least 21 days from surgery. Twelve patients had no interest to take part in a trial. Written informed consent was obtained from all patients. To be eligible, the patient had to have a pathological diagnosis of adenocarcinoma of the prostate from prostate biopsy. Other inclusion criteria were BMI<37, normal liver function test, range of blood pressure and heart rate. The exclusion criteria were current antibiotic use (antibiotics reduce the intestinal microflora) or history of hormonal and radiation therapies or chemotherapy. Before study entry, patients had history and physical examination, complete blood count and clinical chemistry profile. The subjects (n=64) were randomly assigned to either cranberry supplementation, the daily dose 1500 mg dry cranberry powder (Pacran®, n=32) or placebo (n=32) at least 21 days before surgery. Suggested clinical dosing of cranberry powder was based on our study in men at risk of prostate disease with LUTS, elevated prostate-specific antigen, negative prostate biopsy and clinically confirmed chronic nonbacterial prostatitis (Vidlar et al. 2010). Patients were instructed not to consume food rich in color pigment (anthocyanin-containing fruit) or soy products or to make other dietary or lifestyle changes during the study. Blood and urine samples for clinical chemistry, hematology and urine analysis were collected on the first day at registration and after intervention immediately before surgery. The prostatectomy specimens were entirely embedded in paraffin, step-sectioned, and microscopically examined.

Patient baseline demographics and clinical characteristics.

Parameters	Units	Cranberry	Placebo
Number of patients		31	31
Age	Years	62.5/66.0/68.0	61.0/64.0/68.5
BMI		24.8/27.8/28.7	25.8/26.9/29.1
Initial PSA	mg/l	5.73/7.97/11.72	3.67/6.14/8.94#
Zinc	mg/l	0.981/1.174/1.438	1.034/1.225/1.577
Selenium	mg/l	97.1/120.1/131.0	102.7/120.1/142.7
Gleason sum at diagnosis		6/7/7	7/7/7
5	No. (%)	2 (6.45)	2 (6.45)
6	No. (%)	7 (22.58)	4 (12.90)
7	No. (%)	19 (61.29)	25 (80.65)
8	No. (%)	1 (3.23)	0
9	No. (%)	2 (6.45)	0

#Significant difference between Cranberry and Placebo groups by two-sample Wilcoxon test *P*<0.1

The content of selected components in Pacran®

Component			
Phenolic acids		**Anthocyanins/Anthocyanidins**	
benzoic acid	167.6 ± 19.4	cyanidin 3-O-arabinoside	62.7 ± 1.0
chlorogenic acid	14.8 ± 1.9	cyanidin 3-O-galactoside	42.4 ± 1.9
p-coumaric acid	86.5 ± 16.7	cyanidin	31.6 ± 1.3
p-hydroxybenzoic acid	2.6 ± 0.4	delphinidin 3-O-glucoside	2.7 ± 0.2
ferulic acid	8.4 ± 1.2	delphinidin	24.4 ± 0.8
protocatechuic acid	31.8 ± 4.8	malvidin 3-O-galactoside	5.4 ± 0.2
sinapic acid	4.7 ± 0.7	pelargonidin 3-O-glucoside	7.6 ± 0.2
Flavonoids		peonidin 3-O-glucoside	82.1 ± 1.3
apigenin	0.4 ± 0.0	peonidin 3-O-rutinoside	1.3 ± 0.2
catechin	2.7 ± 0.1	peonidin	13.5 ± 1.1
epicatechin	13.4 ± 0.1	**Proanthocyanidins**	
epigallocatechin	24.4 ± 0.2	procyanidin B1	0.8 ± 0.0
hesperidin	2.6 ± 0.1	procyanidin B2	4.8 ± 0.0
hyperoside	1 408.0 ± 36.7	procyanidin A2	22.9 ± 0.1
isorhamnetin	188.2 ± 22.4	**Pentacyclic triterpenoids**	
kaempferol	25.2 ± 4.6	ursolic acid	921.6 ± 74.2
myricetin	482.8 ± 21.7		
quercitrin	504.0 ± 149.0		
quercetin	1 138.8 ± 32.5		
rutin	3.0 ± 0.2		

Results are expressed as mean ± SD, n = 5, values are given in mg per 100 g of Pacran®.

Specific markers in ex vivo prostate tissue

Parameters	Units	Cranberry	Placebo
Ki67	% of positivity	3.0/5.0/10.0	3.0/7.5/10.0
Chromogranin A[a]	% of positivity	0.0/0.0/0.5	0.0/0.0/0.0
PSMA[b]		1.00/2.00/3.00	1.00/2.00/2.75
AR[c]		90/150/150	90/100/150
p65 NF-kB[c]		100/150/200	150/175/200
COX-2[c]		150/200/200	150/200/200

[a]Percentage of positivity above 5% was present only in two patients from cranberry group.
[b]PSMA was evaluated as follows: 0, absent; 1, weak positivity in some glands; 2, medium positivity in less than half of glands; 3, strong positivity in more than half of glands or medium positivity in majority of glands.
[c] Histoscore; % of positivity multiplied by staining intensity (0, absent; 1, weak; 2, moderate; and 3, strong), resulting in histoscore from 0 to 300

Markers of clinical chemistry

		Cranberry		Placebo	
Parameters	**Units**	**Start Day**	**End Day**	**Start Day**	**End Day**
ALT	mkat/l	0.37/0.43/0.49	0.39/0.44/0.55	0.35/0.45/0.49	0.37/0.45/0.53
GGT	mkat/l	0.41/0.47/0.77	0.37/0.45/0.76*	0.37/0.58/0.72	0.39/0.49/0.84
Creatinine	mmol/l	78.5/83.0/89.5	76.5/86.0/90.0	74.5/81.0/87.0	77.5/82.0/88.0
BUN	mmol/l	4.8/5.1/5.8	4.8/5.4/5.8	4.6/5.2/5.7	4/4.9/5.6
Glucose	mmol/l	5.2/5.7/6.4	5.1/5.5/6.2	5.1/5.6/6.4	5.3/5.7/6.7
TAG	mmol/l	1.05/1.38/1.66	1.028/1.29/1.69	1.315/1.67/2.51	1.235/1.65/2.19
Cholesterol	mmol/l	4.32/4.95/5.90	4.23/4.92/5.94	4.67/5.22/6.01	4.64/5.26/6.29
LDL	mmol/l	2.25/2.69/3.82	2.24/2.84/3.78	2.55/3.01/3.66	2.46/3.07/3.81
HDL	mmol/l	1.21/1.39/1.79	1.26/1.41/1.63	1.08/1.28/1.34	1.17/1.23/1.47
CRP	mg/l	0.75/1.20/2.20	0.70/1.00/1.60	0.60/1.10/2.75	0.38/1.05/2.55
Il-6	ng/l	1.5/2.9/3.95	2/2.9/3.75	1.525/2.6/3.8	1.5/2.7/3.65
IGF-1	mg/l	105/137/161	113/149/174*	113/138/170	121/142/164
IGFP	mg/l	2089/2590/2855	2148/2568/2853	2342/2581/2879	2337/2541/3090
TST	nmol/l	11.92/15.39/21.57	11.26/15.17/17.68	11.34/14.58/18.79	11.86/14.81/17.03
fTST	nmol/l	24.63/30.55/39.75	19.75/27.75/36.10	25.00/31.30/35.70	24.25/28.50/36.20*
PSA	mg/l	6.23/8.83/13.59	4.54/6.84/13.03**	3.68/5.38/9.33	3.62/5.43/9.05**

*Significant difference between value of Start day by one-sample Wilcoxon test *P<0.1*
**Significant difference between value of Start day by one-sample Wilcoxon test *P<0.05*
*one-sample Wilcoxon test, *P<0.1*; **one-sample Wilcoxon test, *P<0.05*

Markers of oxidative stress in blood

		Cranberry		Placebo	
Parameters	**Units**	**Start Day**	**End Day**	**Start Day**	**End Day**
MDA	nmol/g[a]	18.51/20.67/23.62	23.66/26.72/29.71**	18.65/20.98/25.28	23.18/27.41/32.45**
GSH	mmol/g[a]	6.97/7.85/8.92	6.93/8.01/9.03	6.97/8.04/8.58	7.01/7.84/9.07
PMDA	nmol/g[b]	82.8/103.5/119.8	81.2/115.1/151.8**	70.9/105.0/132.7	84.3/113.6/135.9**
TSHG	mmol/g[b]	6.50/7.24/8.12	6.99/7.69/8.56**	6.47/6.79/8.49	6.88/7.48/8.42*
PON1	mkat/l	0.83/1.50/2.00	0.79/1.31/2.14	0.75/1.23/2.29	0.70/1.43/2.43*
8-OHdG	mg/l	7.57/9.03/11.20	8.55/9.87/11.95	6.90/8.74/11.02	6.66/9.19/11.18
Catalase	mkat/g[a]	1.12/1.19/1.43	1.17/1.30/1.46**	1.07/1.32/1.49	1.11/1.39/1.47
GSX	mkat/g[a]	1.54/2.17/2.92	1.40/1.87/2.37*	1.86/2.25/2.84	1.18/1.69/2.19**
GSR	mkat/g[a]	0.21/0.25/0.29	0.22/0.25/0.28	0.20/0.23/0.28	0.21/0.24/0.31*
SOD	U/g[a]	3.09/3.28/3.51	3.00/3.41/3.65	3.10/3.34/3.62	3.17/3.39/3.83

[a] g of hemoglobin; [b] g of protein
*Significant difference between value of Start day by one-sample Wilcoxon test *P<0.1*
**Significant difference between value of Start day by one-sample Wilcoxon test *P<0.05*
*one-sample Wilcoxon test, *P<0.1*; **one-sample Wilcoxon test, *P<0.05*

Markers of hematology

		Cranberry		Placebo	
Parameters	**Units**	**Start Day**	**End Day**	**Start Day**	**End Day**
Htc		0.43/0.44/0.46	0.42/0.44/0.46**,##	0.43/0.44/0.46	0.43/0.45/0.46##
Hgb	g/l	145.5/151.0/155.0	142.5/149.0/156.0	143.0/150.0/156.0	145.0/149.0/157.5
PLT	x10(9) l	187.5/232.0/257.0	184.0/207.0/249.0	189.5/223.0/266.5	190.0/233.0/258.5
RBC	x10(12) l	4.71/4.91/5.20	4.64/4.88/5.17	4.74/4.92/5.11	4.70/4.91/5.21
WBC	x10(9) l	5.54/6.40/7.25	5.32/6.20/7.03	5.90/6.49/7.62	5.80/7.42/7.85

**Significant difference between value of Start day by one-sample Wilcoxon test *P<0.05*
##Significant difference between value of Cranberry and Placebo group by two-sample Wilcoxon test *P<0.05*
** one-sample Wilcoxon test, *P<0.05*; ## two-sample Wilcoxon test, *P<0.05*
Abbreviations used: Hct (hematocrit), Hgb (hemoglobin), PLT (platelet test), RBC (red blood cells), WBC (white blood cells).

RNA urine markers

		Cranberry		Placebo	
Parameters	**Units**	**Start Day**	**End Day**	**Start Day**	**End Day**
RNA	ng/ml	8.23/17.46/37.23	5.16/10.55/15.22*	7.37/17.19/42.52	7.48/13.70/33.25
Ct PSA	dCt	32.30/34.21/35.61	30.79/34.17/35.85	31.41/34.02/35.83	32.70/34.66/36.97
AMACR	-dCt	-4.21/-1.90/-0.79	-4.25/-2.61/-0.87	-3.47/-2.19/-0.60	-3.45/-2.35/-1.12
PCA3	-dCt	-5.41/-4.44/-3.34	-4.26/-3.30/-2.71**	-5.27/-3.08/-2.68	-3.87/-3.26/-2.58
TRPM8	-dCt	-4.58/-3.98/-3.59	-4.31/-4.03/-3.03	-4.92/-4.41/-3.69	-5.09/-4.56/-4.33
MSMB	-dCt	-0.55/0.29/0.70	-0.72/-0.18/0.76*,#	-0.56/-0.27/0.51	-0.74/-0.13/0.53#
EZH2	-dCt	-2.16/0.81/1.93	-1.73/-0.20/1.13	-1.40/0.04/2.19	-2.52/0.46/1.92

*Significant difference value of Start day by one-sample Wilcoxon test *P*<0.1;
**Significantly different value of Start day by one-sample Wilcoxon test *P*<0.05; #Significant difference value of cranberry and placebo group by two-sample Wilcoxon test *P*<0.1
* one-sample Wilcoxon test, *P*<0.1; ** one-sample Wilcoxon test, *P*<0.05; # two-sample Wilcoxon test, *P*<0.1

Conclusion:

Our results show that the commercial cranberry powder used in this study may contain constituents that regulate the expression of androgen-responsive genes. These data support further studies to evaluate cranberry as a prophylactic against the biochemical recurence of prostate cancer in patients after surgery.

Acknowledgements:

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