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ORIGINAL ARTICLE

Cranberry fruit powder (Flowens™) improves lower urinary tract symptoms in men: a double-blind, randomized, placebo-controlled study

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Abstract
Background Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia increase with age. To date, several medications are available to treat LUTS, including herbal remedies which offer less side effects but lack robust efficacy studies.
Methods This 6-month, randomized, double-blind, placebo-controlled study aimed at evaluating the dose effect of 250 or 500 mg cranberry powder (Flowens™) on LUTS and uroflowmetry in men over the age of 45. A total of 124 volunteers with PSA levels <2.5 ng/mL and an international prostate symptoms score (IPSS) score ≥8 were recruited and randomized. The primary outcome measure was the IPSS, evaluated at 3 and 6 months. Secondary outcome measures included quality of life, bladder volume (Vol), maximum urinary flow rate (Q_{max}), average urinary flow rate (Q_{ave}), ultrasound-estimated post-void residual urine volume (PVR), serum prostate-specific antigen, selenium, interleukin 6, and C-reactive protein at 6 months.
Results After 6 months, subjects in both Flowens™ groups had a lower IPSS (−3.1 and −4.1 in the 250- and 500-mg groups, $p = 0.05$ and $p < 0.001$, respectively) versus the placebo group (−1.5), and a dose–response effect was observed. There were significant differences in Q_{max}, Q_{ave}, PVR, and Vol in the Flowens™ 500-mg group versus baseline ($p < 0.05$). A dose-dependent effect on Vol was observed, as well as on PVR, for participants with a nonzero PVR. There was no effect on clinical chemistry or hematology markers.
Conclusions Flowens™ showed a clinically relevant, dose-dependent, and significant reduction in LUTS in men over 45.

Keywords *Vaccinium macrocarpon* · Cranberry · Lower urinary tract symptoms · Benign prostatic hyperplasia · IPSS

Background

Lower urinary tract symptoms (LUTS) become increasingly bothersome as men age, with a prevalence of moderate-to-severe symptoms rising to nearly 50 % of men in their eighties [1]. LUTS may be related to benign prostatic hyperplasia (BPH) that occurs in 50 % of men in their 50 and 90 % of men in their eighties [1] or can arise from age-related bladder detrusor dysfunction and other sympathetic conditions [2]. LUTS are measured using the international prostate symptoms score (IPSS), a validated tool, widely used among the medical community [3].

Although LUTS are not a life-threatening condition, its impact on quality of life (QoL) can be significant and treatment is necessary in most cases to avoid complications [4] and in certain cases, surgery may be recommended. Upon diagnosis, watchful waiting is recommended in approximately 34 % of cases in the USA [1].

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Registered pharmacological treatments for LUTS may be responsible for a variety of side effects. Complementary medicine is increasingly being used by men who wish to reduce LUTS [5]. Current herbal remedies include stinging nettle (*Urtica doica*), saw palmetto (*Serenoa repens*), African plum (*Pygeum africanum*), rye pollen (*Secale cereale*), South African star grass (*Hypoxis rooperi*), pumpkin seeds (*Cucurbita pepo* L.), pine (*pinus*), spruce (*picea*), flaxseed, and beta-sitosterol, which may exert inhibition of 5α-reductase, as well as anti-estrogenic, anti-proliferative, and anti-inflammatory effects [5].

Cranberry fruit (*Vaccinium macrocarpon* Ait., Ericaceae) was used by Native Americans to treat kidney and urinary ailments [6]. Cranberry fruit is recognized as a rich source of organic and phenolic acids, flavonols, flavan-3-ols, anthocyanins, proanthocyanidins (PACs), and pentacyclic triterpenoids, including ursolic and oleanic acids [7]. Preventive use of cranberry ingredients for urinary tract infections has encouraged this research on LUTS in men.

A recent study reported that a 6-month daily intake of 1500 mg cranberry powder significantly reduced the IPSS by 4.48, increased the urinary flow rate, and reduced total prostate-specific antigens (PSA) and post-void residual volume (PVR) in men with LUTS [8]. The aim of this study was to evaluate the effect of a 6-month daily intake of 250 or 500 mg of cranberry powder (Flowens™) on lower urinary tract (LUT) parameters in men with moderate-to-severe LUTS with IPSS score ≥8 and a PSA <2.5 ng/mL.

Methods

Flowens™ and placebo capsules

Flowens™ (dry cranberry powder, Batch No. 120906) supplied by NATUREX-DBS LLC., USA, was used. Capsules consisted of either 500 mg of Flowens™ or a combination of 250 mg of Flowens™ and 250 mg of placebo or 500 mg of placebo (low-density STAR-DRI® 1015A maltodextrin, canola oil, Red 40 Lake, sodium aluminum silicate, and Blue 1 Lake). The capsules were indistinguishable in appearance. All capsules were provided in identical plastic boxes with safe seal.

Study design and participants

The study was a 6-month, single-center, randomized, double-blind, placebo-controlled trial, consisting of three parallel treatment arms. The study was conducted at the Department of Urology at the university hospital in Olomouc in the Czech Republic, 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 55/12). Enrollment began in October 2012 with follow-up completed in July 2013. Inclusion criteria comprised IPSS score ≥8 and PSA values <2.5 ng/mL. Exclusion criteria included food allergies, prostatitis, chronic liver or kidney diseases, neurological, gastrointestinal or metabolic disorder, or any other chronic health condition. Subjects were also ineligible if they had prior invasive treatment for BPH or recent treatment with α-blockers (within 1 month) or 5α-reductase inhibitors (within 6 months) or phytotherapy (within 3 months). The primary endpoint of this study was the evaluation of LUTS using IPSS, evaluated at baseline, 3, and 6 months. Secondary endpoints included quality of life (QoL) at baseline, 3, and 6 months, as well as bladder voided volume (Vol), maximum urinary flow rate (Q_{max}), average urinary flow rate (Q_{ave}), ultrasound-estimated PVR, serum PSA, selenium, interleukin-6 (IL-6), and C-reactive protein (CRP), at baseline and 6 months.

Intervention and randomization

Written informed consent was obtained from the eligible participants. They were instructed not to make dietary or lifestyle changes during the study. Participants were randomly assigned to consume daily 500, 250 mg of Flowens™ or placebo for 6 months. The randomization plan was generated with online software QuickCalcs (GraphPad Software Inc., USA, last accessed on July 2, 2014) and carried out by clinical staff not directly involved in the study.

Participants were observed at baseline and 6 months for: (1) detailed medical history, (2) assessment of all concurrent medical drugs and therapies, (3) dietary habits, (4) completion of the IPSS questionnaire, including a question on QoL, (5) urinalysis, (6) uroflowmetry, (7) kidney and bladder ultrasound, and (8) blood laboratory analysis including PSA. At 3 months, only the physical examination and IPSS score were performed. The Flowens™ bottles were collected at 3 months and at the end of study. Compliance was assessed by performing remaining capsule counts.

Uroflowmetry

Q_{max} and Q_{ave} were measured using FlowMic (Medkonsult, Czech Republic). The Q_{max} and Q_{ave} were calculated by measuring the Vol per unit of time. PVR was assessed within 10 min of voiding using an ultrasound device BK Medical Viking 2400 with abdominal probe 3–7 MHz. Vol, and PVR were calculated using the formula for a prolate ellipsoid (width × length × height × 0.523).

Table 1 Summary of baseline characteristics and LUT measures

	Placebo ($n = 41$)	Flowens™ 250 mg ($n = 43$)	Flowens™ 500 mg ($n = 38$)
Age (years)	54.0 ± 5.1	53.3 ± 5.2	52.5 ± 5.4
Weight (kg)	89.3 ± 11.9	91.2 ± 11.9	90.1 ± 8.0
Height (cm)	178.5 ± 6.6	180.6 ± 6.6	180.7 ± 6.2
Body Mass Index	28.1 ± 3.8	27.9 ± 2.9	27.7 ± 3.0
Systolic blood pressure (mmHg)	131.1 ± 12.1	130.6 ± 10.1	132.1 ± 11.5
Diastolic blood pressure (mmHg)	80.1 ± 7.3	80.5 ± 7.2	80.9 ± 7.4
Heart beat (bpm)	68.9 ± 3.5	67.8 ± 4.6	68.1 ± 4.4
IPSS (score)	9.1 ± 2.0	9.7 ± 3.1	9.4 ± 2.0
PVR (mL)	15.0 ± 19.2	15.9 ± 23.2	17.8 ± 21.0
Q_{max} (mL/s)	22.0 ± 7.8	20.5 ± 7.1	19.5 ± 7.5
Q_{ave} (mL/s)	14.3 ± 5.2	12.5 ± 4.6	12.5 ± 5.5
Bladder volume (mL)	408.5 ± 117.9	339.9 ± 114.4	339.0 ± 118.9

Results are presented as mean ± standard deviation (SD)

Clinical chemistry and hematology

Basic biochemical and hematological parameters were determined in all samples using a HITACHI Modular Evo P analyzer (Hitachi, Japan). Serum PSA was determined using an Architect-type LEIA analyzer (Abbott Laboratories, Abbott Park, IL, USA). CRP was determined by a Quikread 101 and IL-6 by the system Modular® Analytics <E176>. Selenium in plasma was estimated by atomic absorption spectrometry using the AA6300 instrument (Shimadzu, Japan). Hemoglobin (Hb), hematocrit (Htc), erythrocytes (RBC), thrombocytes (PLT), and leukocytes (WBC) were measured in Na_2EDTA blood.

Statistical methods

The primary and secondary analyses were based on the per-protocol population that included all eligible participants who were treated during the entire length of the study. A Mann–Whitney *U* test was used to compare both treatment dose and placebo data. Differences versus baseline measures were performed using the Wilcoxon matched pairs test. *P* values <0.05 were considered to be significant.

An analysis of covariance was used to test whether there was an effect of the dose on the outcome measure at the end of treatment. The volume of urine among participants with PVR was modeled using a truncated Poisson distribution. A two-stage model was fit using the *hurdle* function in the 'pscl' package (Developed by Achim Zeileis and Simon Jackman, Stanford University) running on R version 3.0.0. Dose/250 mg, baseline PVR, and baseline IPSS were entered into this model.

Results

A total of 148 men were pre-screened for the study. A total of 124 men were randomized, 41 to the placebo group, 43 to the Flowens™ 250-mg group, and 40 to the Flowens™ 500-mg group. In the Flowens™ 500-mg group, two participants were lost to follow-up and were not included in the per-protocol analysis. Table 1 presents a summary of baseline characteristics and LUT function measures across the three groups of the analysis. Adherence with scheduled visits was 98.4 %. Compliance to the treatment was 100 %.

IPSS data with voiding and storage symptom subscore and QoL data during the 6-month treatment period are presented in Table 2. Uroflowmetry data are presented in Table 2.

At 6 months, mean difference and corresponding 95 % confidence interval (CI) were −1.5 (−2.2, −0.89) for the placebo group, −3.1 (−4.0, −2.2) for the Flowens™ 250-mg group, and −4.1 (−4.7, −3.5) for the Flowens™ 500-mg group (Fig. 1).

Analysis of covariance for IPSS at 6 months with baseline IPSS entered as a covariate showed a significant dose effect ($t_{119} = -4.8$, $p < 0.0001$) and a significant effect of baseline score ($t_{119} = 8.3$, $p < 0.0001$). In the Flowens™ 500-mg group, a significant reduction in voiding symptoms was observed at both visits ($p = 0.03$ and $p < 0.001$, respectively); as well as storage symptoms at 6 months ($p = 0.018$) (Table 2). At 6 months, analysis of covariance of Q_{max} and Q_{ave} found a statistically indeterminate effect of dose. 59, 49, and 50 % of the participants in the placebo, 250, and 500 mg Flowens™ groups reported a nonzero PVR, respectively, which represented a significant dose-dependent reduction in PVR of 0.09 (95 % CI 0.03–0.14)

Table 2 Participants IPSS score, voiding and storage symptom score, quality of life score, and uroflowmetry at baseline, 3, and 6 months after placebo, Flowens™ at 250- or 500-mg intake

	Group	Baseline, Mean ± SD (*p* value)		3 months, Mean ± SD (*p* value)		6 months, Mean ± SD (*p* value)		Relative change at 6 months (% change vs placebo)
Total IPSS score	Placebo	9.1 ± 2.0		7.4 ± 2.0		7.6 ± 2.6		−1.5 ± 2.1
	Flowens™ 250 mg	9.7 ± 3.1	(NS)	7.6 ± 3.7	(NS)	6.6 ± 3.4	0.05	−3.1 ± 3.0
	Flowens™ 500 mg	9.4 ± 2.0	(NS)	6.5 ± 2.6	(NS)	5.3 ± 2.5	<0.001*	−4.1 ± 1.9
Voiding/obstructive symptoms score	Placebo	4.9 ± 1.8		3.7 ± 1.6		3.9 ± 2.3		−1.0 ± 1.9
	Flowens™ 250 mg	5.1 ± 2.4	(NS)	3.6 ± 2.7	(NS)	3.4 ± 2.8	(NS)	−1.8 ± 2.1
	Flowens™ 500 mg	4.6 ± 1.8	(NS)	2.9 ± 1.7	0.03*	2.3 ± 1.4	<0.001*	−2.3 ± 1.8
Storage/irritative symptoms score	Placebo	4.2 ± 1.3		3.7 ± 1.4		3.7 ± 1.4		−0.5 ± 1.2
	Flowens™ 250 mg	4.6 ± 1.5	(NS)	3.8 ± 1.8	(NS)	3.3 ± 1.5	(NS)	−1.3 ± 1.6
	Flowens™ 500 mg	4.8 ± 1.6	(NS)	3.6 ± 2.0	(NS)	3.0 ± 1.9	0.018*	−1.8 ± 1.4
Quality of life	Placebo	2.4 ± 0.9		2.1 ± 0.8		2.0 ± 0.7		−0.4 ± 0.81
	Flowens™ 250 mg	2.3 ± 0.8	(NS)	2.2 ± 0.9	(NS)	2.0 ± 0.7	(NS)	−0.3 ± 0.7
	Flowens™ 500 mg	2.1 ± 0.6	(NS)	2.0 ± 0.7	(NS)	1.9 ± 0.5	(NS)	−0.2 ± 0.6
Q_{max} (mL/s)	Placebo	22.0 ± 7.8	–	–	–	21.9 ± 8.6	(NS)	−0.1 ± 5.2
	Flowens™ 250 mg	20.5 ± 7.1	–	–	–	21.4 ± 6.7	(NS)	+0.9 ± 5.0
	Flowens™ 500 mg	19.5 ± 7.5	–	–	–	21.7 ± 8.9	0.018§	+2.2 ± 5.8
Q_{ave} (mL/s)	Placebo	14.3 ± 5.2	–	–	–	14.2 ± 5.1	(NS)	−0.1 ± 2.8
	Flowens™ 250 mg	12.5 ± 4.6	–	–	–	13.2 ± 4.0	(NS)	+0.7 ± 3.4
	Flowens™ 500 mg	12.5 ± 5.4	–	–	–	13.8 ± 5.7	0.040§	+1.3 ± 3.9
PVR (mL)	Placebo	15.0 ± 19.2	–	–	–	14.4 ± 18.3	(NS)	−0.6 ± 24.5
	Flowens™ 250 mg	15.9 ± 23.2	–	–	–	13.6 ± 18.1	(NS)	−2.3 ± 26.3
	Flowens™ 500 mg	17.8 ± 21.0	–	–	–	9.9 ± 13.6	0.027§	−7.9 ± 21.4
Vol (mL)	Placebo	408.5 ± 117.9	–	–	–	364.3 ± 112.5	(NS)	−44.2 ± 92.0
	Flowens™ 250 mg	339.9 ± 114.4	–	–	–	368.6 ± 104.6	(NS)	+28.7 ± 112.6
	Flowens™ 500 mg	339.0 ± 118.9	–	–	–	393.0 ± 134.0	0.014§	+54.0 ± 122.5

Results are presented as mean ± SD

NS not significant

* Denotes a significant difference versus placebo using the Mann–Whitney *U* test

§ Denotes a significant difference versus baseline using the Wilcoxon matched pairs test

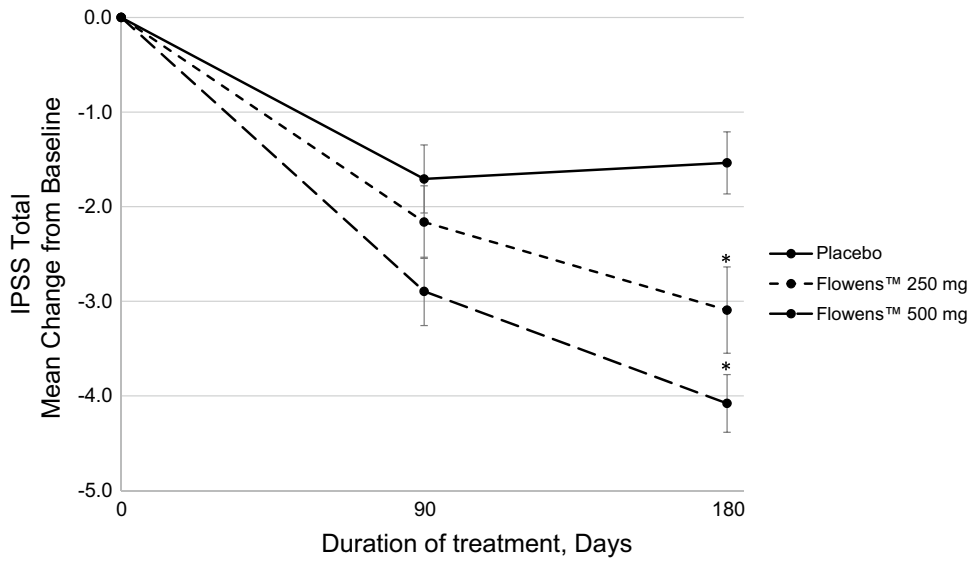

Fig. 1 Mean change in total IPSS score from baseline. Data represent the mean change ± the standard error of the mean. *$p < 0.05$ versus placebo based on analysis of covariance at the end of treatment

per 250-mg dose, for a given baseline PVR and IPSS ($z = -3.0$, $p = 0.003$). Vol measurements, with baseline Vol entered as a covariate, found a significant linear effect of dose ($t_{119} = 2.8$, $p = 0.005$).

All clinical hematology parameters were within normal range at the beginning and at the end of the study, thereby demonstrating the safety of the intervention product (data not shown).

Discussion

This double-blind, randomized, placebo-controlled study demonstrated the efficacy and the safety of the daily intake of Flowens™ at 250 or 500 mg in men with LUTS for 6 months. At 6 months, the decrease in IPSS score was significant and dose dependent (−3.1 and −4.1 in the 250 and 500-mg groups, $p = 0.05$ and $p < 0.001$, respectively) versus the placebo group (−1.5), while no side effects were observed. This decrease in IPSS score was >3 versus baseline for both doses, which is considered clinically meaningful by the American Urological Association [3]. In the 500-mg group, voiding symptoms were significantly reduced at 3 and 6 months versus placebo, and storage symptoms were significantly reduced versus placebo at 6 months. In addition, all parameters (Q_{max}, Q_{ave}, Vol, and PVR) were significantly improved versus baseline at the end of treatment ($p < 0.05$). However, urinary flow rate measures tend to suffer from some inaccuracy due to the natural variation in urinary flow with the same individual from test to test and to training effect. Urinary flow rate also decreases as men age, and a clinical cutoff value of 15 mL/s has been defined to identify those with higher risk of having bladder outlet obstruction [9], defining the current cohort as being moderately symptomatic. A PVR superior to 100 mL suggests abnormality and could require further tests [10]. Although a strong relationship has been found between PVR and prostate volume [11], PVR lacks precise clinical or urodynamic meaning [12], limiting direct conclusions linking PVR with the beneficial effect of Flowens™ on LUTS. Bladder volume was also significantly increased with Flowens™ dose, which may be related to an improvement in bladder detrusor activity [2, 13].

The results obtained with Flowens™ were superior to those observed with most other botanicals. For instance, *Serenoa repens* (Saw palmetto) was not superior to placebo at any dose after a 72-week trial [14]. In addition, only few *Serenoa repens* studies used validated symptom scores, and most were-short duration studies [15]. Purified beta-sitosterol, on the other hand, significantly improved IPSS score to an extent similar to that of Flowens™; a −4.9 weighted mean difference was observed in two different 6-month studies [16]; however, these studies were conducted in the early 1990s, and no additional trial has confirmed these results, except for a few open studies on stinging nettle [17, 18]. A Concord grape juice was overall not effective at reducing LUTS in men over 45 years old, albeit an improvement in Q_{max}. These results might be due the length of the study, as well as a low concentration in antioxidant compounds [19].

Potential mechanism of action may involve effects on the bladder detrusor contraction and relaxation (through muscarinic receptor agonist or α-blockers) or on dynamic and static prostatic components of voiding (through α-blockers, 5α-reductase inhibition, or phosphodiesterase-5 inhibition), modulation of micturition reflex, or reduction in inflammation [2, 20–24].

Conclusions

In this double-blind, randomized, placebo-controlled intervention study, 250 or 500 mg of Flowens™ taken once daily showed significant, clinically meaningful and dose-dependent reduction in LUTS, as demonstrated by a reduction in IPSS score of >3 after a 6-month period. Larger, multi-centric clinical studies with a longer follow-up period and side effects reporting may be warranted to confirm these data in order to recommend Flowens™ as a possible alternative in reducing LUTS for moderately symptomatic men.

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Conflict of interest MR and EF are employed by NATUREX and NATUREX-DBS, respectively.

Ethical standard Ethics Committee of the University Hospital and Faculty of Medicine and Dentistry, Palacky University in Olomouc, Czech Republic (reference 55/12).

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