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Efficacy of Daily Intake of Dried Cranberry 500 mg in Women with Overactive Bladder: A Randomized, Double-Blind, Placebo Controlled Study

Ahra Cho, Andrew Eidelberg, Daniel J. Butler, David Danko, Ebrahim Afshinnekoo, Christopher E. Mason and Bilal Chughtai*,†

From the Department of Urology (AC, AE, BC), Weill Cornell Medical College-New York Presbyterian Hospital, New York, New York, Tri-Institutional Computational Biology & Medicine Program (DJB, DD, EA, CEM), Weill Cornell Medicine, New York, New York, Department of Physiology and Biophysics (DD), Weill Cornell Medicine, New York, New York, The HRH Prince Alwaleed Bin Talal Bin Abdulaziz Alsaud Institute for Computational Biomedicine (EA, CEM), Weill Cornell Medicine, New York, New York, WorldQuant Initiative for Quantitative Prediction (EA, CEM), Weill Cornell Medicine, New York, New York, and The Feil Family Brain and Mind Research Institute (CEM), Weill Cornell Medicine, New York, New York

Purpose: We sought to determine the efficacy of dried cranberry on reducing symptoms of overactive bladder in women.

Materials and Methods: Eligible women aged 18 or older with overactive bladder were randomized to either daily dried cranberry powder (500 mg) or placebo (500 mg) and followed for 24 weeks. Efficacy was measured by 3-day voiding diaries and Overactive Bladder Questionnaire Short Form, Patient Perception of Bladder Condition, Sexual Quality of Life-Female and Pelvic Floor Distress Inventory surveys. Statistical analyses were performed by BIOFORTIS using SAS® software version 9.4.

Results: Of the 98 women who were randomized 77 completed all the visits and 60 were included in the per protocol analysis. Compared to placebo using per protocol analysis the cranberry group showed a significant reduction of daily micturitions (−1.91, 95% CI −3.74−−0.88, p=0.0406), urgency episodes (−2.81, 95% CI −4.82−−0.80, p=0.0069), and Patient Perception of Bladder Condition scores (−0.66, 95% CI −1.23−0.08, p=0.0258) at 24 weeks of followup. Mean volume per micturition, nocturia and the remaining survey outcomes did not differ significantly between the groups (p >0.05).

Conclusions: Daily intake of dried cranberry powder reduced daily micturition by 16.4%, urgency episodes by 57.3% and patient perception of bladder condition by 39.7%. However, an intent-to-treat analysis showed no statistically significant difference between the groups for these measurements (p >0.05). Future larger studies with longer followup periods are needed to further determine the long-term effect of cranberry on overactive bladder.

Abbreviations and Acronyms

a.u. = arbitrary unit
CRADI-8 = Colorectal-Anal Distress Inventory
HRQL = health-related quality of life
LUTS = lower urinary tract symptoms
OAB = overactive bladder
OABQ-SF = Overactive Bladder Questionnaire Short Form
PFDI-20 = Pelvic Floor Disability Index 20
POPDI-6 = Pelvic Organ Prolapse Distress Inventory
PPBC = patient perception of bladder condition
SQOL-F = Sexual Quality of Life—Female
UDI-6 = Urinary Distress Inventory

Key Words: urinary bladder, overactive; Vaccinium macrocarpon; urination; urination disorders, perception

Overactive bladder is defined as urinary urgency often with frequency and nocturia with or without urgency incontinence.[1] More than 1 in 3 women experience OAB in their lifetime with higher prevalence with advancing age

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* Correspondence: Weill Cornell Medicine, Department of Urology, Department of Obstetrics and Gynecology, 425 East 61st Street, 12th Floor, New York, New York 10065 (telephone: 646-962-4811; FAX: 646-962-0140; email: bic9008@med.cornell.edu).
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after age 44.[2,3] Symptoms of OAB have been reported to be associated with social isolation, depression, embarrassment and stigmatization.[4,5] Cost of OAB management is estimated at $12 billion annually in the United States, with $9 billion incurred in the community.[6,7]

First line management for OAB includes lifestyle and behavioral modifications, such as bladder training, pelvic floor muscle training and controlled fluid intake. However, if these measures do not lead to significant symptom reduction, pharmacological therapy with oral antimuscarinics or oral ß3-adrenoreceptor agonists is used as second line treatment.[8] Antimuscarinic agents are the most commonly prescribed, and have been shown to improve bladder filling and reduce urgency.[9,10] While effective, these medications are associated with undesired adverse effects such as sedation, dry mouth, constipation, impaired cognitive function, tachycardia and blurry vision.[10,11]

Complementary therapy using extracts of plant based bioactive compounds is becoming widely used for a variety of conditions, including lower urinary tract symptoms.[12] Cranberry fruit (*Vaccinium macrocarpon*) has been recognized in traditional medicines for its disease fighting ability.[13] The predominant bioactive ingredients found in cranberries are anthocyanins, flavonols, tannins, terpenes and phenolic acid derivatives.[13,14] Randomized clinical trials on the effect of a 6-month daily intake of dried cranberry powder demonstrated significant improvements on moderately symptomatic LUTS in men, specifically, a dose-response reduction in the International Prostate Symptom Score, bladder volume and postvoid volume residual, while an elevation in maximum and average urine flow.[15,16] However, to date there have been no clinical studies that examine the effect of dried cranberry on improving OAB. We sought to evaluate the efficacy of daily consumption of dried cranberry on women with OAB without incontinence.

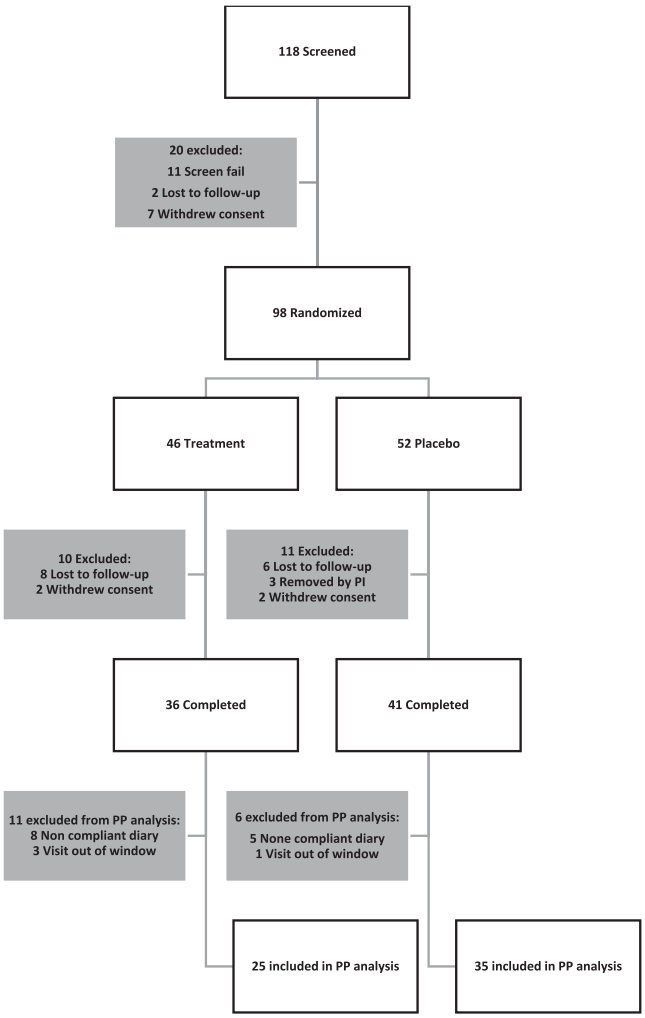
MATERIALS AND METHODS

Design

The study was a single-center, randomized, double-blind, placebo controlled trial in women aged 18 years or older with OAB at a tertiary care facility. The study was approved by the Weill Cornell Medical College Institutional Review Board (IRB No. 1506016303) for Human Studies and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent and all data are reported in accordance with the Health Insurance Portability and Accountability Act (HIPAA). The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The study was registered on ClinicalTrials.gov (NCT03017170).

Eligibility Assessment

The inclusion criteria included women of age 18 years or older who reported at least 8 micturitions per 24 hours without incontinence and at least 3 episodes of urgency per day on a 3-day voiding diary. Participants were excluded if they had greater than 3 incontinence episodes (in the month before screening), active urinary tract infection, chronic urological inflammatory conditions (interstitial cystitis, urethral syndrome, painful bladder syndrome), history of neurogenic bladder, cerebrovascular diseases, carcinoma of the urinary system, hepatic disorders, gastrointestinal obstruction, psychiatric disorders and diabetes. We excluded participants with concurrent bladder prolapse or incontinence to focus on those with dry OAB. Women of childbearing potential who were pregnant, planning to become pregnant or breastfeeding during the study were excluded. Women with an allergy to cranberry products or prescription of drug or nondrug treatments of OAB were excluded. Those on warfarin or any anticoagulant agent more potent than 81 mg of aspirin were excluded from the study as well.



CONSORT study design

Randomization and Intervention

Participants were randomized 1:1 to treatment group or placebo group using block of 4 generated by a computerized random number generator by Naturex-DBS, LLC (www.random.org). Each subject was assigned a number

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Table 1. *Baseline characteristics of the study population*

	Total Completed Study			Per Protocol Population		
	Treatment	Placebo	Total	Treatment	Placebo	Total
Total No.	41	36	77	25	35	60
Mean age (SD)	47.5 (13.2)	48.1 (16.4)	47.8 (14.9)	46.8 (14.2)	47.1 (16.8)	47.0 (15.7)
Mean weight, kg (SD)	69.8 (22.7)	78.8 (22.7)	71.9 (22.7)	71.1 (19.6)	72.4 (21.2)	71.9 (20.3)
Mean height, cm (SD)	161.2 (5.43)	163.2 (5.69)	162.3 (5.62)	160 (5.75)	162 (5.65)	161 (5.75)
No. race (%):						
Asian	2 (5.60)	2 (5.00)	4 (5.30)	2 (8.00)	2 (5.90)	4 (6.80)
Black	12 (33.3)	15 (37.5)	27 (35.5)	9 (36.0)	13 (38.2)	22 (37.3)
White	13 (36.1)	14 (35.0)	27 (35.5)	8 (32.0)	11 (32.4)	19 (32.2)
Hispanic	9 (25.0)	8 (20.0)	17 (22.4)	6 (24.0)	7 (20.6)	13 (22.0)
Other	0 (0.00)	1 (2.50)	1 (1.30)	0 (0.00)	1 (2.90)	1 (1.70)
Missing	0	1	1	0	1	1
Mean daily micturition episodes (SD)	12.0 (3.69)	11.3 (2.83)	11.6 (3.25)	11.9 (3.99)	11.2 (2.62)	11.5 (3.24)
Mean daily urgency episodes in grade 3 and 4 (SD)	8.13 (4.03)	7.72 (3.35)	7.91 (3.66)	7.51 (3.65)	7.65 (3.49)	7.59 (3.53)
Mean daily nocturia episodes (SD)	1.85 (1.42)	1.50 (1.19)	1.67 (1.30)	1.61 (1.22)	1.54 (1.20)	1.57 (1.20)
Mean volume in ml per micturition (SD)	160.3 (72.6)	171.4 (70.6)	166.2 (71.3)	165.9 (70.2)	177.4 (74.1)	172.6 (72.1)
Mean duration of OAB symptoms in years (SD)	2.1 (3.36)	1.7 (1.54)	1.9 (2.46)	2.4 (3.92)	1.6 (1.56)	1.9 (2.67)

corresponding to either the treatment or placebo group. The association between the number and the group was unknown to investigators and participants. Those in the treatment group were given 1 pill of dried cranberry powder or placebo per day. Dried cranberry powder pill contained 500 mg of proprietary full spectrum dried cranberry fruit (*V. macrocarpon*, Aiton) manufactured by Naturex-DBS, LLC (Sagamore, Massachusetts)/Virage Sante (Canada). Placebo pill contained 500 mg proprietary mixture of maltodextrin and food grade colors (Advanced Nutraceutical [Hackensack, New Jersey]/Virage Sante). The treatment and placebo pills were identical in appearance to ensure blinding of investigators and participants.

Measurement

Participants completed a 3-day voiding diary before each clinic visit: screening visit (Visit 1), baseline visit (Visit 2), and followup visits at 12 weeks (Visit 3) and 24 weeks (Visit 4). The 3-day voiding diary was used to assess the primary outcome of treatment success, defined as an average of 1 or more void reduction per day, the number and degree of urinary incontinence episodes, urge severity, presence of nocturia and fluid intake. Secondary clinical signs and symptoms were assessed by changes in the mean volumes voided per micturition, Overactive Bladder Questionnaire Short Form, Patient Perception of Bladder Condition, Sexual Quality of Life-Female and Pelvic Floor Disability Index 20. Secondary outcome of treatment success was defined as at least a 5-point decrease in the OABQ-SF score from baseline compared to 24 weeks.

Adverse events were assessed from baseline to the final followup visit (Visit 4) and recorded by Clavien–Dindo Grading System. Participants were interviewed and observed for any negative change in the health of the participants. Physical exam was conducted at the baseline and vital signs were recorded at each visit.

Sample Size Calculations

A power calculation predicted that a sample of 58 patients with equal allocation to active and placebo treatments was needed. Assuming an attrition rate of 20%, a total of 76 patients were planned to be recruited to provide 80% power to detect a real difference with the 2-tailed t-test and an α of 0.05. For this calculation the mean number of daily micturition was expected to change from baseline by −3.50 for the treatment group and −2.00 for placebo group, representing a difference of −1.50, and the SD in the number of daily micturitions of 2.00.

Statistical Analyses

Statistical analyses were performed by BIOFORTIS using SAS® software version 9.4 (SAS Institute Inc., Cary, North Carolina). Statistical significance was set at $p < 0.05$ a priori. Participant characteristics were determined using descriptive analyses (mean, standard deviation, percentages and frequencies). Continuous variables were analyzed by using 1-way analysis of variance, and categorical variables were evaluated by chi-square tests. We conducted a per protocol analysis to account for the considerable number of subjects lost to follow up in our evaluation of the effect of treatment and adverse events in patients based on dosage and completed questionnaires.

RESULTS

Baseline Characteristics of Participants

In total, 98 women were randomized to cranberry (46) and placebo (52; see figure). Of the participants 77 (mean age 47.8 years, SD 14.9) completed all the visits (36 in cranberry, 41 in placebo) (table 1). Seventeen participants were noncompliant (11 in cranberry, 6 in placebo) because one of the visits was out of the compliance window, or they completed the voiding diary incorrectly. The remaining 60 participants comprised the per protocol population. The reported mean duration of OAB symptoms was 1.9 years (SD 2.67). The patient reported symptom scores reported at baseline, 12-week and 24-week followup are found in table 2.

Study Outcomes

We found that daily intake of dried cranberry powder significantly improved the mean daily number of

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Table 2. *Three-day voiding diary and other urinary symptoms*

	Treatment (SD)	Placebo (SD)	Per Protocol (SD)
Total No.	25	35	60
Mean daily micturition episodes:			
V2 (Baseline)	11.9 (3.99)	11.2 (2.62)	11.5 (3.24)
V3 (Week 12)	10.3 (3.31)	10.9 (4.79)	10.6 (4.22)
V4 (Week 24)	9.95 (4.18)	10.6 (4.22)	10.7 (4.58)
V3-V2	−1.60 (3.66)	0.3 (2.99)	−0.90 (3.32)
V4-V2	−1.95 (4.07)	0.0 (3.49)	−0.80 (3.84)
Mean daily urgency episodes in grade 3 and 4:			
V2 (Baseline)	7.51 (3.652)	7.65 (3.487)	7.59 (3.526)
V3 (Week 12)	4.03 (3.172)	6.75 (6.180)	5.62 (5.286)
V4 (Week 24)	3.21 (2.256)	6.15 (5.837)	4.92 (4.881)
V3-V2	−3.48 (3.530)	−0.90 (3.768)	−1.97 (3.861)
V4-V2	−4.30 (4.145)	−1.50 (3.924)	−2.67 (4.217)
Mean daily number of nocturia:			
V2 (Baseline)	1.61 (1.216)	1.54 (1.197)	1.57 (1.195)
V3 (Week 12)	1.32 (1.230)	1.31 (1.041)	1.32 (1.114)
V4 (Week 24)	1.00 (0.918)	1.39 (1.585)	1.23 (1.352)
V3-V2	−0.29 (1.237)	−0.23 (0.839)	−0.26 (1.015)
V4-V2	−0.61 (1.204)	−0.15 (1.170)	−0.34 (1.196)
Mean volume in ml per micturition:			
V2 (Baseline)	165.9 (70.22)	177.4 (74.13)	172.6 (72.14)
V3 (Week 12)	180.3 (82.69)	179.0 (82.18)	179.5 (81.69)
V4 (Week 24)	176 (74.55)	175.1 (70.27)	175.5 (71.46)
V3-V2	14.1 (50.31)	1.60 (61.65)	6.90 (57.10)
V4-V2	10.2 (35.48)	−2.2 (48.95)	2.90 (43.95)
OABQ-SF symptom severity subscore (a.u., 0—36):			
V2 (Baseline)	15.8 (4.84)	16.3 (4.79)	
V3 (Week 12)	12.1 (3.92)	14.2 (4.74)	13.3 (4.51)
V4 (Week 24)	11.7 (5.15)	13.2 (4.91)	12.6 (5.03)
V3-V2	−4.00 (5.08)	−2.50 (4.92)	−3.10 (5.00)
V4-V2	−4.20 (5.04)	−3.50 (4.71)	−3.80 (4.82)
OABQ-SF HRQL subscore (a.u., 0—78):			
V2 (Baseline)	33.8 (12.91)	35.2 (13.86)	34.6 (13.37)
V3 (Week 12)	24.1 (11.87)	30.3 (15.14)	27.8 (14.13)
V4 (Week 24)	22.2 (12.44)	26.3 (13.81)	24.6 (13.30)
V3-V2 (24 pts)	−10.3 (13.44)	−4.90 (8.26)	−7.10 (10.90)
V4-V2	−11.6 (12.17)	−8.90 (8.11)	−10.1 (10.00)
PPBC score (a.u., 1—6):			
V2 (Baseline)	3.70 (0.75)	3.60 (0.77)	3.70 (0.76)
V3 (Week 12)	2.80 (1.01)	3.10 (1.18)	3.00 (1.12)
V4 (Week 24)	2.23 (1.22)	2.79 (1.22)	2.60 (1.25)
V3-V2	−0.90 (0.95)	−0.50 (1.17)	−0.70 (1.10)
V4-V2	−1.47 (1.29)	−0.81 (1.16)	−1.10 (1.25)
SQOL-F score (a.u., 0—108):			
V2 (Baseline)	70.4 (12.80), 24 pts	74.4 (12.10), 34 pts	72.7 (12.44), 58 pts
V3 (Week 12)	72.1 (13.43), 22 pts	75.4 (15.77), 32 pts	74.0 (14.82), 54 pts
V4 (Week 24)	71.0 (16.15), 23 pts	76.7 (12.44), 31 pts	74.3 (14.82), 54 pts
V3-V2	(8.34), 22 pts	1.40 (12.84), 32 pts	1.20 (11.14), 54 pts
V4-V2	0.70 (10.64), 23 pts	2.30 (10.98), 31 pts	1.60 (10.76), 54 pts
PFDI-20 score (a.u., 0—80):			
V2 (Baseline)	28.6 (4.73)	29.5 (5.88)	29.1 (5.41)
V3 (Week 12)	26.1 (5.09)	27.2 (6.70)	26.8 (6.06)
V4 (Week 24)	25.8 (5.51)	27.1 (6.67)	26.5 (6.20)
V3-V2	−2.50 (3.44)	−2.30 (5.22)	−2.40 (4.53)
V4-V2	−2.80 (4.03)	−2.50 (5.29)	−2.60 (4.77)
PFDI-20 POPDI-6 subscore (a.u., 0—24):			
V2 (Baseline)	7.90 (1.66)	8.30 (2.27)	8.10 (2.03)
V3 (Week 12)	7.40 (1.67), 23 pts	7.50 (2.13)	7.40 (1.95), 58 pts
V4 (Week 24)	7.40 (1.67), 23 pts	7.30 (2.04)	7.40 (1.96), 58 pts
V3-V2	−0.60 (1.41), 23 pts	−0.80 (2.35)	−0.70 (2.02), 58 pts
V4-V2	−0.70 (1.19), 23 pts	−0.90 (2.15)	−0.80 (1.83), 58 pts
PFDI-20 CRADI-8 subscore (a.u., 0—32):			
V2 (Baseline)	11.0 (2.75)	11.2 (2.75)	11.1 (2.73)
V3 (Week 12)	10.0 (2.60), 23 pts	10.9 (3.49)	10.6 (3.17), 58 pts
V4 (Week 24)	9.70 (2.29), 23 pts	10.8 (3.85)	10.4 (3.35), 58 pts
V3-V2	−1.00 (2.34), 23 pts	−0.20 (2.51)	−0.50 (2.45), 58 pts
V4-V2	−1.30 (2.78), 23 pts	−0.30 (2.60)	−0.70 (2.69), 58 pts
PFDI-20 UDI-6 subscore (a.u., 0—24):			
V2 (Baseline)	9.60 (2.04)	10.1 (2.35)	9.90 (2.22)
V3 (Week 12)	8.80 (1.70), 23 pts	8.80 (2.06)	8.80 (1.91), 58 pts

(continued)

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Table 2. (*continued*)

	Treatment (SD)	Placebo (SD)	Per Protocol (SD)
V4 (Week 24)	8.90 (2.73), 23 pts	8.90 (1.98)	8.90 (2.28), 58 pts
V3-V2	−0.90 (2.28), 23 pts	−1.30 (1.84)	−1.10 (2.02), 58 pts
V4-V2	−0.90 (2.33), 23 pts	−1.20 (2.77)	−1.10 (2.59), 58 pts

micturition by 16.4%, urgency episodes by 57.3% and patient reported bladder condition by 39.7% compared to baseline at the end of the study period of 24 weeks (table 2). There was statistically significant difference between the treatment and placebo groups in these parameters ($p < 0.05$). The intent-to-treat analysis showed a mean difference of −1.04 in the number of micturitions ($p = 0.20$) and −1.46 in the number of urgency episodes ($p = 0.08$) between treatment and placebo group (tables 3 and 4).

Number of Daily Micturitions and Mean Volume per Micturition

The mean daily number of micturitions decreased significantly by 1.95 in the treatment group (95% CI −3.34−−0.55) from baseline to 24-week followup (tables 3 and 4), equivalent to a 16.4% reduction. There was no statistically significant change in the placebo group (−0.04; 95% CI −1.21−1.14). The mean difference between the treatment and placebo groups was −1.91 micturitions per day (95% CI −3.74−−0.08, $p = 0.0406$). The mean volume per micturition did not show a statistically significant change in either group (treatment 9.01, 95% CI −10.76−28.78 vs placebo −1.39, 95% CI −18.09−15.32). The mean difference in variation between these groups was 10.39 (95% CI −15.52−36.30, $p = 0.4275$).

Daily Number of Urgency Episodes and Nocturia

The mean daily number of urgency episodes in grade 3 and 4 decreased significantly in both groups (treatment −4.30, 95% CI −5.84−−2.77 vs placebo −1.50, 95% CI −2.79−0.20) from baseline to 24-weeks followup. The change in the treatment group is equivalent to a 57.3% reduction (baseline 7.51 vs 24-weeks 3.21; table 2). The mean difference in daily urgency episodes between the groups was −2.81 episodes (95% CI −4.82−−0.80, $p = 0.0069$). The mean daily number of nocturia decreased significantly by 0.60 in the treatment group (95% CI −1.00−−0.20) and by 0.16 in the placebo group (95% CI −0.50−0.17). However, the mean difference between the two groups was not statistically significant, at −0.43 (95% CI −0.96−0.09, $p = 0.1036$).

Questionnaire Scores

PPBC score (a.u., 1−6) was significantly reduced by 1.47 in the treatment group (95% CI −1.91−−1.03) and by 0.81 in the placebo group (95% CI −1.18−−0.44) from baseline to 24-week followup. The change in the treatment group is equivalent to a 39.7% reduction (baseline 3.70 vs 24 weeks 2.23; table 2). Mean difference between the groups was −0.66 points (95% CI −1.23−0.08, $p = 0.0258$) compared to placebo. Other mean questionnaire scores did not differ significantly between the groups. OABQ-SF severity score differed by −1.12 (95% CI −3.31−1.08, $p = 0.3152$), OABQ-SF Health-Related Quality of Life subscore by −3.11 (95% CI −8.14−1.92, $p = 0.2223$) and SQOL-F by −2.16 (95% CI −8.15−3.82, $p = 0.4732$). Changes in PFDI-20 score and its subscores between the groups did not vary significantly as well. PFDI-20 differed by −0.01 (95% CI −0.04−0.03, $p = 0.5968$), PFDI-6 subscore by 0.01 (95% CI −0.03−0.06, $p = 0.6188$), CRADI subscore by −0.03 (95% CI −0.08−0.01, $p = 0.1611$) and UDI-6 subscore by 0.00 (95% CI −0.05−0.05, $p = 0.9483$).

Reported adverse effects in the study included 1 patient with headache, 1 patient with skin rash and 1 patient with mild constipation.

Table 3. *Change of mean daily number of micturitions between week 24 and baseline*

	Treatment (95% CI)	Placebo (95% CI)	Mean Difference in Variation between Treatment and Placebo (95% CI)	p Value
Mean daily micturitions	−1.95 (−3.34−−0.55)	−0.04 (−1.21−1.14)	−1.91 (−3.74−−0.08)	0.0406
Mean daily urgency episodes in grades 3 and 4	−4.30 (−5.84−−2.77)	−1.50 (−2.79−0.20)	−2.81 (−4.82−−0.80)	0.0069
Mean daily nocturia	−0.60 (−1.00−−0.20)	−0.16 (−0.50−0.17)	−0.43 (−0.96−0.09)	0.1036
Mean volume in ml per micturition	9.01 (−10.76−28.78)	−1.39 (−18.09−15.32)	10.39 (−15.52−36.30)	0.4275
OABQ-SF symptom severity subscore (a.u., 0−36)	−4.45 (−6.12−−2.77)	−3.33 (−4.75−−1.91)	−1.12 (−3.31−1.08)	0.3152
OABQ-SF HRQL subscore (a.u., 0−78)	−11.89 (−15.73−−8.05)	−8.79 (−12.03−−5.54)	−3.11 (−8.14−1.92)	0.2223
PPBC score (a.u., 1−6)	−1.47 (−1.91−−1.03)	−0.81 (−1.18−−0.44)	−0.66 (−1.23−−0.08)	0.0258
SQOL-F score (a.u., 0−108)	0.19 (−4.34−4.73)	2.36 (−1.51−6.22)	−2.16 (−8.15−3.82)	0.4732
PFDI-20 score (a.u., 0−80) after log transformation	−0.05 (−0.08−−0.02)	−0.04 (−0.06−−0.02)	−0.01 (−0.04−0.03)	0.5968
PFDI-20 POPDI-6 subscore (a.u., 0−24)	−0.04 (−0.07−−0.00)	−0.05 (−0.08−−0.02)	0.01 (−0.03−0.06)	0.6188
PFDI-20 CRADI-8 subscore (a.u., 0−32)	−0.05 (−0.09−−0.02)	−0.02 (−0.05−0.01)	−0.03 (−0.08−0.01)	0.1611
PFDI-20 UDI-6 subscore (a.u., 0−24)	−0.05 (−0.09−−0.01)	−0.05 (−0.08−−0.02)	0.00 (−0.05−0.05)	0.9483

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Table 4. *Intent-to-treat analysis*

	Mean Difference in Variation between Treatment and Placebo	p Value
Mean daily micturitions	−1.04	0.20
Mean daily urgency episodes in grades 3 and 4	−1.46	0.08
Mean PPBC score	−0.3	0.29

DISCUSSION

Overall, we found that dried cranberry powder reduced the mean number of daily micturitions by 1.91 (p=0.0406) compared to placebo at 24 weeks (table 5). The reduction of mean micturitions resulting from antimuscarinic agents such as solifenacin 5 mg (−0.78, p=0.0018), solifenacin 10 mg (−1.22, p=0.0001)[17] and tolterodine (−0.54, p=0.026)[18] were at the expense of adverse events such as dry mouth, constipation, sedation, impaired cognitive function, tachycardia, urinary retention and visual disturbance that led almost two-thirds of users to discontinue use.[10,19] These adverse events account for the small fraction (1 in 5) of patients with OAB symptoms to be on pharmacotherapy.[20] Large randomized placebo controlled clinical trials have reported high safety profile of beta-3 adrenoceptor agonists that led to the approval from the U.S Food and Drug Administration in June 2012 for the treatment of OAB. Compared to placebo, mirabegron reduced the mean micturitions by 0.47 (p=0.007) and 0.42 (p=0.015) for 25 mg and 50 mg, respectively.[21] Compared to placebo, vibegron reduced the mean daily number of micturitions by 0.64 (p=0.007) and 0.91 (p <0.001) for 50 mg and 100 mg, respectively.[18] However, beta-3 agonists are associated with common adverse effects including headache, nasopharyngitis, diarrhea and nausea.[22]

In this study, dried cranberry powder reduced the mean number of urgency episodes by 2.81 (p=0.0069) at 24 weeks compared to placebo, which is an improvement to the reported effects of vibegron 50 mg (−0.76, p=0.024) and 100 mg (−1.24, p <0.001),[18] tolterodine (−0.94, p=0.007),[18] solifenacin succinate 5 mg (−0.86, p=0.003) and 10 mg (−0.92, p=0.0002),[17] mirabegron 25 mg (−0.33, p=0.13) and 50 mg (−0.59, p=0.007), all compared to placebo (table 5).[21] In addition, cranberry powder improved the patients' perception of their bladder condition as reflected by −0.66 points on PPBC questionnaire (p=0.0258) compared to placebo. This positive outcome in PPBC score was not observed in a large randomized controlled trial on mirabegron 25 mg (−0.1, p=0.49) and 50 mg (−0.0, p=0.64).[18]

Dried cranberry powder reduced the number of daily micturitions, urgency episodes and patient perception of bladder condition. None of the reported adverse effects were found to be significant enough to lead to withdrawal from the study.

Limitations of this study include subjects with dry OAB only. However, the reported prevalence rates of dry OAB (11.7% to 66%) is considerably higher than that of wet OAB (2% to 33%),[23–25] which in turn allows the study to be applicable to a larger population of patients with OAB. Some of the questions on the OABQ-SF and UDI-6 focus on incontinence episodes, which may have inadvertently suppressed the degree of improvement observed on these questionnaire scores compared to the significantly reduced micturition frequency on bladder diaries. Longer-term, multicenter studies are needed to further understand the role of cranberry in OAB. Other limitations of the study are that it did not have a run-in period to help alleviate some of the placebo effect like many other OAB studies, and the study was 6 months unlike many trials for OAB that follow up for 12 months,[26] which limits the comparability to other studies on OAB medications. A subsequent study with a followup of 12 months or longer can adjust for this limitation. Despite these limitations, the strengths of our study are that this was a randomized, double-blind, placebo controlled study that was adequately powered to demonstrate statistically significant changes in the mean number of daily voids, urgency episodes and patient perception of OAB. These significant outcomes make our findings both novel and clinically meaningful. Intake of dried cranberry for a longer duration may lead to significant changes in other variables that were observed as statistically nonsignificant during the followup of this study, such as mean daily number

Table 5. *Comparison of cranberry powder 500 mg to medications*

Intervention	Micturition Mean Difference	p Value	Urgency Mean Difference vs Placebo	p Value	Reference
Cranberry 500 mg	−1.91	0.0406	−2.81	0.0069	
Virabegron 50 mg	−0.64	0.007	−0.76	0.024	Mitcheson et al[18]
Virabegron 100 mg	−0.91	<0.001	−1.24	<0.001	Mitcheson et al[18]
Mirabegron 25 mg	−0.47	0.007	−0.33	0.13	Herschorn et al[21]
Mirabegron 50 mg	−0.42	0.015	−0.59	0.007	Herschorn et al[21]
Tolterodine	−0.54	0.026	−0.94	0.007	Mitcheson et al[18]
Solifenacin 5 mg	−0.78	0.0018	−0.86	0.003	Cardozo et al[17]
Solifenacin 10 mg	−1.22	0.0001	−0.92	0.002	Cardozo et al[17]

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of nocturia ($p=0.1036$), OABQ-SF severity score ($p=0.3152$), OABQ-SF HRQL subscore ($p=0.2223$), SQOL-F ($p=0.4732$), PFDI-20 ($p=0.5968$), POPDI-6 subscore ($p=0.6188$, CRADI subscore ($p=0.1611$) and UDI-6 subscore ($p=0.9483$).

CONCLUSIONS

Daily intake of dried cranberry powder improved daily micturition, urgency episodes and patient reported bladder condition, supporting its use as a safe treatment for OAB.

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