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Effect of oral cranberry extract (standardized proanthocyanidin-A) in patients with recurrent UTI by pathogenic *E. coli*: a randomized placebo-controlled clinical research study

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Abstract

Purpose To evaluate the effect of cranberry extract (PAC-A ~ proanthocyanidin-A) on the in vitro bacterial properties of uropathogenic (*E. coli*) and its efficacy/tolerability in patients with subclinical or uncomplicated recurrent UTI (r-UTI).

Materials and methods After obtaining clearance from the ethics committee and administering a written informed consent, 72 patients with r-UTI were enrolled as per protocol (November 2011 to March 2013) in this prospective study, to randomly receive (PAC-A: group I, 36) or (placebo: group II, 36), for 12 weeks. Any change/reduction in the incidence of r-UTI at 12 weeks was construed to be the primary endpoint of this study.

Results After 12 weeks, bacterial adhesion scoring decreased (0.28)/(2.14) in group I/II ($p < 0.001$); 32/36 (88.8 %) and 2/36 (5.5 %) in groups I and II, respectively, turned MRHA negative ($p < 0.001$); biofilm ($p < 0.01$) and bacterial growth ($p < 0.001$) decreased in group I; microscopic pyuria score was 0.36/2.0 in group I/II ($p < 0.001$); r-UTI decreased to 33.33 versus 88.89 % in group I/II ($p < 0.001$); mean subjective dysuria score was 0.19 versus 1.47 in group I/II ($p < 0.001$), while mean urine pH was 5.88 versus 6.30 in group I/II ($p < 0.001$). No in vitro antibacterial activity of cranberry could be demonstrated, and no adverse events were noted.

Conclusions The overall efficacy and tolerability of standardized cranberry extract containing (PAC-A) as a food supplement were superior to placebo in terms of reduced bacterial adhesion; bacterial MRHA negativity; urine pH reduction; and in preventing r-UTI (dysuria, bacteriuria and pyuria). Larger randomized controlled trials are needed to elucidate the precise role, exact dose and optimal duration of PAC-A therapy in patients at risk of r-UTI.

Abbreviations

PAC-A	Proanthocyanidin-A
r-UTI	Recurrent urinary tract infection
MS	Mannose sensitive
MR	Mannose resistant
MRHA	Mannose-resistant hemagglutination assay
MPS	Microscopic pyuria score
MBA	Mean bacterial adhesion

Introduction

Recurrent urinary tract infection (r-UTI~ three episodes of UTI in the last 12 months or two episodes in the last 6 months) is common with more than 25 % of them recurring within 6 months [1]. The adhesin protein (pili/fimbriae) helps in adhesion of *E. coli* to uroepithelial cells causing UTI, and these proteins may be mannose resistant (MR)/mannose sensitive (MS) [2]. *E. coli* with MS type-1 pili that facilitate bacterial adhesion (inhibited by fructose in cranberries) are non-pathogenic, while r-UTI (p-fimbriae or pyelonephritis fimbriae ~MR) is due to more virulent

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strains of *E. coli* in which proanthocyanidins-A (PACs-A) help prophylactically by reducing *E. coli* adherence [2, 3] and r-UTI [4]. Prolonged antimicrobial prophylaxis in r-UTI may be associated with resistance/superinfection by bacteria like clostridium difficile [4]. Other non-pharmacological alternatives include immunotherapy, probiotics, urinary acidification and cranberry therapy though no direct comparative studies have been reported [1]. There appears to be lack of clarity in the published English literature on the efficacy of prophylactic cranberry therapy in patients with r-UTI, and this study was undertaken to explore the effect of prophylactic cranberry as an alternative to antimicrobials in patients prone to r-UTI; this formed the primary rationale for the current study.

Materials and methods

Patients with subclinical asymptomatic bacteriuria and/or r-UTI, not responding to antimicrobials, and patients prone to r-UTI with entry/exit criteria as per registered protocol CTRI/2014/08/004864 were enrolled in this study. The working definition of r-UTI was as described earlier in the EUA guidelines [1]. After approval by IEC-HR dt-03.12.2011 and administering a written informed consent, eligible patients were screened for inclusion and randomized as per www.radomization.com (seed 18151, created on september 17, 2011, 10:14:1). Group I patients received a standardized oral preparation of cranberry as Cranpac™ (containing PAC-A 60 mg per capsule), one capsule twice a day as nutritional supplement for 12 weeks, while group II patients received lactobacillus (containing 400 million lactobacillus acidophilus per capsule), 1 capsule twice a day as placebo for 12 weeks. Follow-up was done at three (2nd visit), six (3rd visit) and 12 weeks (4th visit) with compliance visits scheduled once a week until the completion of therapy, at which patients were contacted to produce the consumed empty strips. Patients were assessed for efficacy, side/adverse events and compliance. Urine routine microscopy, pH (dipstick) and culture, patient's subjective well-being scoring (excellent to poor) and objective scoring were done by adding points given to evaluated efficacy parameters at the primary endpoint; however, a primary change in the occurrence of r-UTI at 12 weeks after therapy with interventional/comparator agent was treated as the final primary endpoint of the current study. The study flow diagram of the protocol for this study is depicted in Fig. 1.

Sample size computation

'PASS 2008' software was used to calculate the sample size. Considering a power factor of 80 and 5 % level of significance and considering 30 % change in mean, a
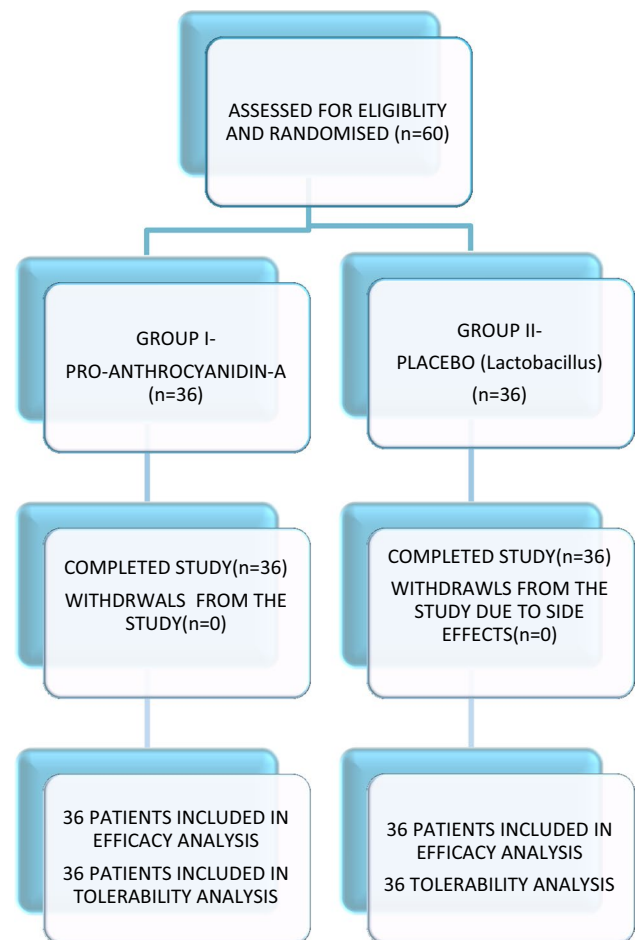

Fig. 1 Study flow diagram (registered protocol CTRI/2014/08/004864)

minimum sample size of 60 (30 in each group) was considered necessary. After compensating for 20 % as a follow-up loss, 36 subjects per group were required for this study.

Method of studying bacterial adhesion

Centrifuged urine/cells were washed in phosphate-buffered saline pH 7.1 and air-dried with Gram-stained slides analyzed under oil immersion for cytoadherence. The mean number of bacteria adherent per uroepithelial cell was expressed as number of bacteria/cell in the manner as described by Reid et al. [5] after randomly viewing at least 50 cells in high-power field.

Method of studying mannose-resistant hemagglutination assay (MRHA) [6]

Bacterial antiadhesion activity was evaluated with MRHA by direct bacterial hemagglutination test (DBHT) by noting clumping of erythrocytes by *E. coli* fimbriae in the presence

of D-mannose, and *E. coli* strains were inoculated in 1 % nutrient broth and incubated at 37 °C for 48 h for full fimbriation. A panel of red blood cells (RBC) was selected by obtaining human blood group 'O.' The RBCs were washed thrice in normal saline and prepared as a stock 3 % suspension in fresh saline to be used immediately within a week stored at 3–5 °C. DBHT was done on multiple concavity slides by adding a drop of RBC suspension to a drop of broth culture, and slide was rocked to and fro at room temperature for 5 min; presence of clumping was taken as positive for hemagglutination. Mannose-sensitive hemagglutination was detected by the absence of hemagglutination in a parallel test in which a drop of 2 % w/v D-mannose was added to RBC and a drop of broth culture. MRHA was detected by the presence of hemagglutination of 3 % 'O' group human RBC in the presence of 2 % D-mannose as described by Vagarali et al. [6].

Demonstration of antibacterial activity of proanthocyanidin-A

Cranpac™ extract was too viscous to allow disk diffusion; hence, to demonstrate bactericidal activity of PAC-A, broth microdilution method was used as per 'Clinical Laboratory Standards Institute (CLSI)' guidelines [7]. Since CLSI does not define breakpoints for PAC-A, a stock solution was made in dimethylsulfoxide (DMSO) [an organic solvent non-toxic for bacteria used to dissolve oil-based drugs]. Serial doubling dilutions were made ranging from 2048 to 16 μg/ml in microdilution plates to test in vitro efficacy of PAC-A against wild strains obtained from PAC group in their initial visit. Control strains from American Type Culture Collection [*E. coli* (ATCC 25922) and *S. aureus* (ATCC 29213)] were used; due to its opaque nature the visual minimum inhibitory concentration (MIC) of the bacterial isolates could not be read; therefore, subcultures made from wells containing mixture of bacteria/PAC-A on Mueller–Hinton Agar to determine the minimum bactericidal concentration [8].

Method of detecting biofilm formation on urinary catheters

Biofilm on catheter tips was detected by serial roll-plate technique; proximal 2 inches of the catheter tip was cut with a sterile blade and was rolled over a blood agar plate one and half times to check for bacterial growth and biofilm formation. The plates were incubated in ambient air for 24 h at 35 °C for bacterial colony count [9].

Efficacy (outcome) parameters

The efficacy outcome measures included improved clinical symptoms, decreased pyuria/bacterial count in urine culture and/or conversion of positive urine culture to sterile, microscopic decreased bacterial adherence to uroepithelial cells, bactericidal activity and MRHA. The endpoints (objective outcome measures) at 3, 6 and 12 weeks (final endpoint) were scored, and change/reduction in the incidence of r-UTI at 12 weeks was construed to be the primary endpoint in this study. *Tolerability (outcome) parameters:* Adverse events/side effects/compliance to therapy was recorded. *Statistical analysis:* Data were statistically analyzed for efficacy/tolerability of cranberry extract over the placebo using Chi-square test, repeated-measure ANOVA test and Fisher's exact *t* test.

Observations and results

The salient demographic characteristics of the two patient groups are described in Table 1. The baseline mean [age, urinary pH, dysuria score, pyuria score, bacterial growth, bacterial adhesion score, biofilm and MRHA(+)] was 41.6/35.8 years, 6.28/6.19, 1.42/1.08, 2.28/1.5, 33/36, 2.11/1.81, 8/6 and 33/35 in groups I/II, respectively (see Table 1). Group I/II were compared and found to be similar. With regard to our patient types, in group I of the 8 catheterized patients, 4 were on intermittent catheterization, 2 had BPH, 1 had neurogenic bladder and 1 had supra-pubic cystostomy (SPC), while in group II of the 6 catheterized patients 3 were on intermittent catheterization, 1 had SPC and 2 had BPH. No patient had diabetes mellitus in either of the groups. A significant reduction in the mean bacterial adhesion score, significant increase in MRHA negativity and a significant reduction in biofilm were observed in patients of group I. In group I, there was a significant decrease (18, 72 and 75 %) in the number of patients with bacterial growth at 3, 6 and 12 weeks of therapy, respectively. Microscopic pyuria score (MPS) decreased by 41, 70 and 84 % (group I) and increased by 8, 20 and 25 % (group II) after 3, 6 and 12 weeks of therapy, respectively; thus, PAC-A was significantly effective in lowering the MPS ($p < 0.001$). There was a significant decrease in mean burning micturition score in group 1 ($p < 0.001$), and it appeared that cranberry therapy was associated with a more acidic urine ($p < 0.001$) (see Table 1).

A total of 12/36 (33 %) and 32/36 (89 %) patients developed (r-UTI) over 12 weeks in group I/II, respectively; thus, PAC-A was significantly effective in lowering the episodes of UTI ($p < 0.001$). Cranberry failed to demonstrate any in vitro antibacterial activity in any patient. There were no adverse events noted apart from one patient in each group reporting self-limiting constipation. There was no withdrawal from therapy in any patient.

Table 1 Comparison of efficacy parameters in both groups

Parameters	Baseline			3 week		6 week		12 week		
	G (I)	G (II)	p	G (I)	G (II)	G (I)	G (II)	G (I)	G (II)	p
Showing that all baseline data were similar/comparable apart from pyuria score										
Age	41.6 (15–76)	35.8 (18–70)	0.13	–	–	–	–	–	–	–
Mean urinary pH	6.28	6.19	0.03	6.1	6.24	5.97	6.18	*5.88*	*6.30*	xx
Burning micturition score*	1.42	1.08	0.07	0.83	1.36	0.47	1.5	*0.19*	*1.47*	xx
Micro. pyuria score**	2.28	1.5	<0.001	1.33	1.64	0.67	1.89	*0.36*	*2.0*	xx
Bacterial growth nos. (%)	33/36	36/36	0.24	27	36	9	32	*8*	*35*	<0.001
Bacterial adhesion***	2.11	1.81	0.10	1.22	1.89	0.42	1.72	*0.28*	*2.14*	<0.001
Biofilm formation (no.)	8 ($n = 8$)	6 ($n = 6$)	1	5	5	1	6	*3*	*6*	0.018
MRHA (no. of patients)	33/36	35/36	0.61	17	35	3	32	*1*	*33*	<0.001

Patients with r-UTI (>2 episodes) who had culture-positive UTI and had taken multiple antimicrobial courses in the past 1-year desiring alternative therapy were given the option of entering into this randomized controlled clinical study

Values in bolditalics indicate the primary end point at 12 weeks in groups I and II

* Burning micturition score (0—mild, 2—moderate and 3—severe); ** microscopic pyuria score (0 = <5 pus cells/hpf; 1 = 5–10 pus cells/hpf; 2 = 10–20 pus cells/hpf; >20 pus cells/hpf = 3); *** bacterial adhesion score— (<5 bacteria/urothelial cell = 0; 5–10 bacteria/urothelial cell = 1; 10–20 bacteria/urothelial cell = 2; >20 bacteria/urothelial cell = 3); MRHA—mannose-resistant hemagglutination assay

Discussion

PAC-A was probably effective in decreasing the mean bacterial adhesion scoring versus placebo (see Table 1). Various studies comparing the effect of cranberry/different PAC concentrations on bacterial adhesions in patients of UTI are depicted in Table 2a.

In a study by Risco et al. [10], the mean bacterial adhesion (MBA) was 36 at PAC level of 0 mg/ml and 23 at PAC level of 75 mg/ml showing 34.5 % decrease ($p < 0.05$); the authors concluded that PAC demonstrated significant inhibition of *E. coli* adherence to uroepithelial cells. In a study by Reid et al. [5], the MBA was 5.40 at day 0 and 1.18 after 15 days (78 % decrease, $p < 0.05$). Di Martino et al. [11] demonstrated a MBA of 76 and 3 in the placebo versus cranberry group (62 % decrease, $p < 0.05$) and concluded that cranberry had significant antiadherence activity against *E. coli*. Gupta et al. [12] demonstrated that the MBA was 2.5×10^5 at PAC level of 0 mg/ml and 0.9×10^5 at PAC level of 50 mg/ml (70 % decrease, $p < 0.05$), concluding thereby that PAC may be considered as an inhibitory agent for drug-resistant strains of *E. coli*. Howel et al. [7] also showed a 56 % decrease in MBA (22.3 vs. 9.9 in placebo versus cranberry, $p < 0.05$) and concluded that PAC may be protective against bacterial adhesion in the urinary tract. Gupta et al. [13] in an experimental study demonstrated a MBA of 6.9 and 1.6/cell (PAC level of 0 and 75 mg/ml) with a 77 % decrease ($p < 0.001$) in *E. coli* adherence.

In the present study, most of our MRHA(+) strains turned MRHA(−) with PAC-A therapy in group I.

Comparison with other studies on MRHA is summarized in Table 2b. Gupta et al. [12] in a study comparing the effect of PAC (150-750 μg/μl) on MRHA demonstrated that PAC exhibited significant antiadhesion activity on *E. coli* by rendering them MRHA (−). Howel et al. [7] and Gupta et al. [13] independently showed a dose-dependent effect of PAC-A therapy on MRHA activity propounding its protective efficacy against bacterial adhesion. In our study, it appeared that PAC-A therapy reduced biofilm formation significantly in our catheterized patients, and other similar studies depicting the effect of cranberry are compared in Table 2c. Reid et al. [5] and LaPlente et al. [14] demonstrated major reduction in biofilm-producing *E. coli* after consuming cranberry. PAC-A did not demonstrate any in vitro antibacterial activity in this study. Monroy-Torres et al. [15] showed that cranberry was not associated with any bacteriostatic properties, while Lee Y et al. [16] in a pilot study showed that 7/20 (35 %) patients on cranberry had antibacterial activity against *E. coli*. In this study, PAC-A therapy was associated with decreased bacterial growth (see Table 1), and other studies depicting the effect of cranberry on bacterial growth are summarized in Table 2d. Other researchers like Reid et al. [5] and Bailey et al[17] independently demonstrated no bacterial growth, while some like McMurdo et al. [17] demonstrated fewer *E. coli* infections, after cranberry therapy, with both concluding that PAC may prevent r-UTIs. However, Barbosa-Cesnik et al. [18], Beerepoot et al. [19], Waites et al. [20] and Linsenmeyer et al. [21] in four independent studies failed to show any beneficial effect of cranberry on r-UTI.

Table 2 Comparison of different studies on (a) bacterial adhesion on uroepithelial cells; (b) MRHA; (c) cranberry extracts on biofilm formation; and (d) effect on bacterial growth

No.	Author	Design	Nos.	Intervention	Results*
(a) comparison of bacterial adhesion with other studies					
1.	Risco et al. [10]	In vitro and in vivo expt. study	–	Tablets containing 0–75 mg of PAC	34.5 % ↓
2.	Reid et al. [5]	Pilot study NR	15	250 ml of water and 250 ml of CE/ juice	78.1 % ↓
3.	Martino et al. [11]	Double-blind RPCC-COS	20	Placebo beverage—750 ml, CE juice—750 ml	62 % ↓
4.	Gupta et al. [12]	In vitro experimental study	–	PAC (0–50 μg/ml) isolated from CE/juice	70 % ↓
5.	Howel et al. [7]	Double-blind RS	32	Placebo cap and cap CE ~72 mg PAC	55.60 % ↓
6.	Gupta et al. [13]	Experimental study	–	300 mg CE cap ~2.7 mg PAC/ capsule	76.8 % ↓
7.	Present study	RPCCT	72	Placebo—lactobacillus cap 1 b.i.d. (60 mg PAC-A) 1 capsule b.i.d.	86.72 % ↓
(b) comparison of MRHA with other studies					
1.	Gupta et al. [12]	In vitro experimental. study	–	PAC (0 μg/ml to 50 μg/ml) isolated from CE**juice	At low/no PAC—highly + MRHA, at high PAC—weakly ± MRHA
2.	Howel et al. [7]	Double-blind RS	32	Placebo cap and cap ~72 mg PAC	Placebo-MRHA negative-0 % 72 mg PAC-MRHA negative-50 % 36 mg PAC-MRHA negative-100 %
3.	Gupta et al. [13]	Experimental study	–	300 mg CE** capsule ~2.7 mg PAC/cap	25 μg/ml PAC-MRHA negative-50 % 72 μg/ml PAC-MRHA negative-100 %
4.	Present study	RPCCT	72	Placebo—lactobacillus cap 1 b.i.d. CE** (60 mg PAC-A) 1 cap b.i.d.	Placebo-MRHA negative-5.71 % PAC-A-MRHA negative-97 %
(c) various studies showing effect of cranberry on biofilm formation					
1.	Reid et al. [5]	Pilot study NR	15	250 ml of water and 250 ml of CE**/juice	78.1 % ↓
2.	Laplente et al. [14]	In vitro study	–	Standardized CE	↓Biofilm formation
3.	Present study	RPCCT	14	Placebo—lactobacillus capsule 1 b.d. CE** (60 mg PAC-A) 1 cap b.d.	62.5 % ↓
(d) Comparison of various studies showing effect on bacterial growth					
1.	Reid et al. [5]	Pilot study NR	15	250 ml water and 250 ml CE/juice	27.27 % reduction
2.	Bailey et al. [23]	Pilot study NR	12	200 mg of CE cap (30 % PAC)	100 % reduction
3.	McMurdo et al. [17]	Double-blind RPCT	376	300 mg CE/juice/placebo	Placebo-14/189 (7.4 %) Cranberry-7/184 (3.8 %)
4.	Barbosa-Cesnik et al. [18]	RPCT	319	240 ml CE/juice/placebo	Placebo-23/164 (14 %) Cranberry-31/155 (20 %)
5.	Beerepoot et al. [19]	Double-blind RCT	221	500 mg cranberry capsules and 480 mg of TMP-SMX	Cranberry-47.1 % TMP-SMX-46.71 %
6.	Waites et al. [20]	Double-blind PS	48	CE/juice capsules 2 g &placebo	No difference
7.	Linsenmeyer et al. [21]	Double-blind COS	21	Standardized 400 mg cranberry tablet and placebo	No difference
8.	Present study	RPCT	72	Placebo—Lactobacillus cap. 1 b.i.d. CE (60 mg PAC-A) 1 cap b.i.d.	Placebo-1/36, PAC-A-8/33 (↓bacterial growth in 75.75 % patients)

* Denotes (% reduction in bacterial adherence)

MRHA: denotes mannose-resistant hemagglutination assay status

** CE: denotes cranberry extract; ~: denotes containing

NR non-randomized, *RPCT* randomized placebo-controlled clinical trial, *PS* parallel study, *COS* crossover study and *RNPCT* randomized non-placebo clinical trial

Table 3 Comparison of various studies on recurrent UTI with present study

No.	Study	Design	No.	Intervention	Results (r-UTI)
1.	Kontiokari et al. [22]	RCT	150	50 ml cranberry juice/day and 100 ml of lactobacillus drink	Placebo-19/50 Cranberry-8/50 (**22 % ↓**)
2.	Bailey et al. [23]	Pilot study NR	12	200 mg of cranberry extract capsule (30 % PAC)	(**100 % ↓**)
3.	McMurdo et al. [17]	Placebo DB-RCT	376	300 mg cranberry juice versus placebo	Placebo-14/189 (7.4 %) Cranberry-7/184 (3.8 %) (**4 % ↓**)
4.	Barbosa-Cesnik et al. [18]	Placebo RCT	319	240 ml cranberry juice versus placebo	Placebo-23/164 (14 %) Cranberry-31/155 (20 %) (**6 % ↓**)
5.	McMurdo et al. [24]	Parallel RCT	137	500 mg cranberry tab. versus 100 mg TMP tab.	TMP-14/68 (20 %) Cranberry-25/69 (36 %). (**16 % ↓**)
6.	Beerepoot et al. [19]	Randomized DBT	221	500 mg cranberry capsules and 480 mg of TMP-SMX	Cranberry-47.1 % TMP-SMX-46.71 %
7.	Waites et al. [20]	Double-blind parallel study	48	Cranberry juice capsules 2 g and placebo capsules	No difference
8.	Linsenmeyer et al. [21]	Double-blind crossover	21	Standardized 400 mg cranberry tablet and placebo tablet	No difference
9.	Hess MJ et al. [25]	Crossover RCT	47	500 mg cranberry tab. b.i.d. and placebo tablet	Placebo-1.0 episode/year Cranberry-0.3 episode/year
10	Takahashi S et al. [30]	Placebo DB-RCT	118	Cranberry versus placebo	Cranberry-29.1 % versus placebo 49 % (**20 % ↓**)
11	Foxman et al. [32]	Placebo DB-RCT	160	Cranberry versus placebo × 6 weeks	Placebo-15/80 (19 %) Cranberry-30/80 (38 %) (**50 % ↓**)
12	Leda et al. [33]	Pilot placebo NR	22	Cranberry versus placebo × 8 weeks	Placebo-11/22 (50 %) Cranberry-02/22 (9.1 %) (**50 % ↓**)
13	Present Study	Placebo RCT	72	Placebo—lactobacillus capsule 1 b.i.d versus cranberry extract (60 mg PAC-A) 1 capsule b.i.d. × 12 weeks	Placebo-32/36 (88.89 %) Cranberry-12/36 (33.33 %) (**55 % ↓**)

Bold values indicate % reduction in the rate of recurrent UTI or r-UTI

↓: Denotes reduction in r-UTI

As depicted in Table 3, in our study UTI had recurred in 12/36 (33 %) versus 32/36 (89 %) in groups I and II, respectively, and PAC-A had decreased r-UTI by about 55 % at the end of the 12-week observation period. Other studies on the effect of cranberry in r-UTI are also summarized in Table 3. Kontiokari et al. [22] demonstrated 22 % reduction in r-UTI episodes with cranberry. Bailey et al. [23] found no patient developed UTI within the 12 weeks with cranberry therapy concluding that cranberry may prevent r-UTI in women. McMurdo et al. [17] also concluded that cranberry was acceptable in reducing symptomatic UTIs in their older patients. Barbosa-Cesnik et al. [18] showed that 31/155 patients (20 %) in the cranberry group versus 23/164 patients (14 %) who developed UTI in the placebo group concluded that cranberry did not lower the incidence of second UTI. McMurdo et al. [24] concluded that trimethoprim had a little advantage over cranberry in the prevention of r-UTIs in older women with 25/69 (36.23 %) and 14/68 (20.59 %) developing UTI ($p = 0.084$) in cranberry versus trimethoprim group.

Beerepoot et al. [19] concluded that trimethoprim-sulfamethoxazole was more effective than cranberry (500 mg daily) in preventing r-UTIs. Waites et al. [20] and Linsemeyer et al. [21] in separate studies found no difference in the episodes of UTIs in the patients with neurogenic bladder and concluded that cranberry was ineffective in reducing pyuria/UTIs in their patients. Hess et al. [25] demonstrated a reduction in UTI in the cranberry versus placebo group in 47 spinal cord-injured patients with neurogenic bladder after 6-month cranberry therapy, and they concluded that cranberry should be considered for preventing UTIs in the patients with neurogenic bladder. In a meta-analysis by Beerepoot et al. [26], the authors found that cranberries decreased r-UTI.

Micali et al. [27] and Burleigh et al. [28] in a review of clinical studies on the evaluation of cranberry efficacy in the prevention of UTIs approved the use of cranberry in prophylaxis of r-UTI in women. Takahashi [29] in a double-blind placebo-controlled RCT demonstrated a 20 % reduction in r-UTI in women after 5 months of cranberry

therapy in 118 women at risk of r-UTI. In a major review by Vasileiou et al. [30], the authors concluded that the beneficial effects of cranberry against UTIs were probably prophylactic, though their effectiveness in those at higher risk of r-UTIs was low. While cranberries (PAC-A) may inhibit adherence of p-fimbriated *E. coli* to the uroepithelial cells and also decrease r-UTI in about 30–40 % in premenopausal women with r-UTIs, its precise efficacy and optimal dosage remain unresolved [31].

Foxamn et al. [32] in a double-blind, placebo-controlled RCT explored the therapeutic efficacy of administering cranberry juice capsules in preventing UTI in 160 patients undergoing elective benign gynecological surgery entailing urinary catheterization in which the authors demonstrated a significant reduction in the rate of UTI by half ($p < 0.008$) without any significant difference in the incidence of adverse events.

Ledda et al. [33] in a pilot field-practice setting study independently demonstrated a negative urine in 20/22 (90.9 %) and 11/22 (50.0 %) in the cranberry versus control ($p < 0.005$) group without any adverse events, reiterating the effectiveness and safety of oral nutritional supplementation with a well-standardized cranberry preparation in the prevention of r-UTI.

There were no major side effects/adverse events/reactions (apart from one patient in each group with self-limiting constipation) in this study. Beerepoot et al. [19] in a randomized double-blind trial of cranberry versus trimethoprim-sulfamethoxazole on 221 patients demonstrated a 48.6 % (53/109 patients—cranberry group) incidence of adverse drug reactions consisting of rash, urticaria, nausea, vomiting, diarrhea, constipation (10 %) vaginal complaints and other adverse drug reactions. Lee et al. [16], Kontiokari et al. [22] and Bailey et al. [23] also did not observe any adverse drug reaction with the use of cranberry; however, Murdo et al. [17, 24] noted some adverse drug reactions which were probably related to trimethoprim and not due to cranberry.

Limitations of the present study

The 1st author was blinded to the data at the time of analysis, the second author collected relevant patient data and randomized the administered therapy, this blinding was not ideal, and a larger head-to-head trial for a longer duration could have increased the strength of the present study. Randomized comparison with antimicrobials and use of urinary bladder epithelial cell lines were omitted due to protocol limitations. The placebo (lactobacillus) used here may not have been ideal, as some reports [31] suggest that some lactobacilli strains may affect the adherence and growth of uropathogenic bacteria. Though the two patient groups were comparable, it is admitted that these patients were not entirely homogenous due to the coexisting urological disorders. Lifestyle advice measures like personal hygiene and fluid intake which could have partly contributed in amelioration of r-UTI could not be entirely excluded. This study attempted to explore the prophylactic benefit of PAC on those at risk of uncomplicated r-UTI only and not on the actual therapy of UTI due to *E. coli*. Further, we did not evaluate the effect of PAC-A on UTI due to organisms other than *E. coli*.

Conclusions

The overall efficacy and tolerability of standardized cranberry extract containing (PAC-A) were superior to placebo in terms of reduced bacterial adhesion; bacterial MRHA negativity; urine pH reduction; and in preventing recurrent UTI (dysuria, bacteriuria and pyuria). Larger randomized controlled trials are needed to elucidate the precise role, exact dose and duration of PAC-A therapy in patients at risk of recurrent UTI. Despite these limitations, the results of the present study appear to suggest a beneficial effect of cranberry when used prophylactically as a food supplement in selected patients with recurrent uncomplicated UTI.

Compliance with ethical standards

Conflict of interest The authors further declare that they have nothing to disclose and have no direct or indirect commercial and/or financial incentive associated with this research.

Ethical statement The authors declare that the above manuscript is in compliance with ethical standards for research in human participants and the authors have no potential sources of conflict of interest associated with its publication.

Informed consent The authors also certify that informed consent was obtained from all the human participants in this study as per its protocol registered with the Clinical Trials Registry of India.

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