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Pilot Randomized Controlled Dosing Study of Cranberry Capsules for Reduction of Bacteriuria Plus Pyuria in Female Nursing Home Residents

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To the Editor

Cranberry products represent a non-antimicrobial method for prevention of urinary tract infection (UTI). Cranberry proanthocyanidin (PAC), a type of condensed tannin, is the active ingredient in cranberry that inhibits adherence of P-fimbriated *Escherichia coli (E.coli)* to uroepithelial cells.[1, 2] Previous cranberry studies for UTI prevention yielded conflicting results, likely because of variability of PAC dose and clinical populations studied.[3, 4] In a clinical trial of 300ml of cranberry juice beverage daily (36mg PAC), older women (mean age 78.5 years) had a 58% reduction in the odds of having bacteriuria plus pyuria compared to controls.[5] However, nursing home residents have difficulty ingesting the volume of juice that is necessary to prevent bacteriuria. Cranberry capsules are feasible to administer to nursing home residents, but their efficacy has not been demonstrated.[6] In vitro, 36 to 108mg of PAC is efficacious at inhibiting bacterial adherence to uroepithelial cells,[7] but the most efficacious dose among older nursing home residents has not been identified. The goal of this study was to identify the optimal dose of cranberry capsules that reduced the incidence of bacteriuria plus pyuria over one month.

METHODS

This study was a pilot double-blind, randomized, placebo-controlled trial of 3 cranberry capsules daily (108mg PAC), 2 cranberry plus one placebo capsule daily (72mg PAC), 1 cranberry plus two placebo capsules daily (36mg PAC), and 3 placebo capsules daily for 30 days. The primary outcome was episodes of bacteriuria plus pyuria at 7, 14, 21, and 28 days of cranberry capsule treatment. Participants were stratified by presence or absence of baseline bacteriuria with 20 participants randomized by strata to each arm of the study.

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Author Contributions:
MJM was involved in study concept and design, analysis and interpretation of data, andpreparation of manuscript. LB, EP, and VT were involved in acquisition of subjects and/or data and preparation of manuscript. PVN was involved with analysis and interpretation of data and preparation of manuscript.

All authors have no potential conflicts of interest.

Conflict of Interest
This work was supported by the National Institute on Aging at the National Institutes of Health [Claude D. Pepper Older Americans Independence Center at Yale University School of Medicine P30AG021342 and 1K23AG028691 to MJM] and the National Center for Research Resources at the National Institutes of Health [CTSA Grant Number UL1 RR024139].

Cranberry and placebo capsules were donated by the manufacturer. Urine cultures and urinalyses were collected at baseline and then on a weekly basis for 4 weeks (total = 5 specimens). No additional follow-up was performed after the completion of cranberry capsule treatment. Bacteriuria was defined as >100,000 colony forming units per milliliter (cfu/ml) of any bacteria. Pyuria was defined as any white blood cells seen on microscopic urinalysis.[5] Inclusion criteria were: 1)female; 2)history of UTI; 3)age≥65 years; 4)long term residence; 5)English speaking. Exclusion criteria included: 1)total incontinence; 2)warfarin therapy;[8] 3)<4 weeks residence; 4)chronic indwelling catheter; 5)terminal prognosis; 6)antibiotic therapy; 7)kidney stones; 8)dialysis; 9)cranberry therapy; and 10)cranberry allergy. This study was approved by the Yale Human Investigation Committee. Eligible residents or surrogates provided written consent. SAS 9.22 (SAS Institute, Cary NC, 2009) statistical software was used to analyze the data.

RESULTS

In 11 homes, 1929 residents were screened; 1381 residents did not meet inclusion criteria (no history of UTI n=665[48.2%], male n=479[34.7%], short-term rehabilitation n=163[11.8%], non-English speaking n=38[2.8%], age < 65 years n=36[2.6%]). Of 548 remaining residents, 308 residents met exclusion criteria (totally incontinent n=104[33.8%], warfarin use n=72[23.4%], residence < 4 weeks n=31[10.1%], chronic indwelling catheter n=23[7.5%], discharged n=20[6.5%], terminal n=16[5.2%], antibiotic therapy n=14[4.5%], kidney stones n=9[2.9%], cranberry therapy n=7[2.3%], administrative decision n=6[1.9%], dialysis n=5[1.6%], cranberry allergy n=1[0.3%]) and 240 residents were eligible; 90 residents consented (37.5% consent rate), and 80 residents enrolled (10 participants met an exclusion criterion prior to enrollment). Demographics of the 80 participants included: 98% white(n=78), mean age 89.2 years(S.D., 7 years), and mean number of comorbidities 4.1(S.D., 1.7). Most participants were totally dependent in bathing(54%) and had some bowel(67%) and bladder(76%) incontinence. Of 80 baseline urine cultures, 1 had no growth, 8 had ≤100,000 cfu/ml, 41 had >100,000 cfu/ml, and 30 had mixed flora (3 or more organisms). The placebo, one, and three capsule groups each had 10 of 20 participants with >100,000 cfu/ml; the two capsule group had 11 of 20 participants with >100,000 cfu/ml on baseline urine culture. Of 80 baseline urinalyses requested, 73 were obtained: 11 had no pyuria and 62 had pyuria. Of 320 urine specimens that should have been collected, 302(94%) urine cultures and 294(92%) urinalyses were obtained. Results of bacteriuria plus pyuria by cranberry capsule group are provided in Table 1. These results represent 4 weekly follow-up urines obtained per participant while consuming cranberry capsules.

DISCUSSION

This study showed a dose-dependent trend toward decrease in bacteriuria plus pyuria, particularly with *E.coli,* among female nursing home residents ingesting cranberry capsules over one month. Previous studies in older patients were conducted using cranberry juice,[5, 9] and studies of cranberry capsules are lacking. In this study, *E.coli* bacteriuria was reduced and is consistent with the mechanism of PAC, [7] but bacteriuria with other pathogens did not show this same pattern of results. *E.coli* accounts for about 50% of uropathogens in nursing home residents,[10] and reduction in bacteriuria may reduce treatment for UTI. Since the effect of two and three capsules was comparable and to reduce capsule burden, further investigation of two cranberry capsules daily in nursing home residents is warranted to determine if the reduction of *E.coli* bacteriuria is sustained over a longer period of time and whether it impacts clinical outcomes related to UTI (e.g., hospitalization, antibiotic therapy for UTI).

Acknowledgments

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All funding agencies and Pharmatoka had no role in the design, methods, subject recruitment, data collections, analysis, or preparation of the manuscript.

References

1. Gupta K, Chou MY, Howell A, et al. Cranberry products inhibit adherence of p-fimbriated Escherichia coli to primary cultured bladder and vaginal epithelial cells. J Urol. 2007; 177:2357–2360. [PubMed: 17509358]
2. Howell AB, Vorsa N, Der Marderosian A, et al. Inhibition of the adherence of P-fimbriated Escherichia coli to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. N Engl J Med. 1998; 339:1085–1086. [PubMed: 9767006]
3. Raz R, Chazan B, Dan M. Cranberry juice and urinary tract infection. Clin Infect Dis. 2004; 38:1413–1419. [PubMed: 15156480]
4. Barbosa-Cesnik C, Brown MB, Buxton M, et al. Cranberry juice fails to prevent recurrent urinary tract infection: Results from a randomized placebo-controlled trial. Clin Infect Dis. 2011; 52:23–30. [PubMed: 21148516]
5. Avorn J, Monane M, Gurwitz JH, et al. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA. 1994; 271:751–754. [PubMed: 8093138]
6. Juthani-Mehta M, Perley L, Chen S, et al. Feasibility of cranberry capsule administration and clean-catch urine collection in long-term care residents. J Am Geriatr Soc. 2010; 58:2028–2030. [PubMed: 20929476]
7. Lavigne JP, Bourg G, Combescure C, et al. In-vitro and in-vivo evidence of dose-dependent decrease of uropathogenic Escherichia coli virulence after consumption of commercial Vaccinium macrocarpon (cranberry) capsules. Clin Microbiol Infect. 2008; 14:350–355. [PubMed: 18190583]
8. Suvarna R, Pirmohamed M, Henderson L. Possible interaction between warfarin and cranberry juice. BMJ. 2003; 327:1454. [PubMed: 14684645]
9. McMurdo ME, Bissett LY, Price RJ, et al. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. Age Ageing. 2005; 34:256–261. [PubMed: 15863410]
10. Das R, Perrelli E, Towle V, et al. Antimicrobial susceptibility of bacteria isolated from urine samples obtained from nursing home residents. Infect Control Hosp Epidemiol. 2009; 30:1116–1169. [PubMed: 19785518]

Table 1

Cross-classification of cranberry capsule dose and presence of bacteriuria plus pyuria

Treatment Group	*E.coli* bacteriuria plus pyuria	Other bacteriuria plus pyuria[a]	Not growth[b]	Total
No cranberry capsules	33 (43.4%)	5 (6.6%)	38 (50.0%)	76
One cranberry capsule	29 (40.3%)	4 (5.6%)	39 (54.2%)	72
Two cranberry capsules	23 (29.9%)	10 (13.0%)	44 (57.1%)	77
Three cranberry capsules	25 (34.3%)	12 (16.4%)	36 (49.3%)	73
Total	110	31	157	298[c]

[a] Other bacteriuria plus any WBCs is >100,000 cfu/ml of a pathogen other than *E.coli* plus any WBCs. For no cranberry capsules, 3 were Proteus and 2 were Klebsiella species. For one cranberry capsule, 1 was Proteus and 3 were Klebsiella species. For two cranberry capsules, 2 were Proteus species, 1 Enterococcus, 4 beta-hemolytic Streptococci, 2 viridans Streptococci, and 1 Morganella morganii. For three cranberry capsules, 4 were Klebsiella, 3 Enterococcus, 4 Citrobacter freundii, and 1 coagulase negative Staphylococci.

[b] Not growth includes no growth, growth < 100,000, growth >100,000 but no WBCs, and mixed flora. Of 157 not growth, 19 were no growth, 23 were <100,000, 4 were growth >100,000 but no WBCs, and 111 were mixed flora.

[c] There were 22 missing either urine culture or urinalysis of the 320 total expected samples.

Abbreviation: WBC (white blood cell)