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Antibiotic susceptibility of urinary isolates in nursing home residents consuming cranberry capsules versus placebo

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Abstract

Antimicrobial susceptibility of urinary isolates is compared amongst nursing home participants from a randomized controlled trial of cranberry capsules versus placebo. We hypothesized that cranberry spares non-*Escherichia coli* *Enterobacteriaceae*, which tend to be less susceptible to oral antibiotics. Analyses showed no differences in susceptibility or proportions of non-*E. coli* *Enterobacteriaceae*.

Introduction

Urinary tract infection (UTI) is the most common infection in nursing home residents and the microorganisms prevalent in this setting pose significant challenges for treatment.¹

Cranberries (*Vaccinium macrocarpon* Aiton) are thought to reduce UTIs; this view is supported by a placebo-controlled trial showing lower rates of bacteriuria plus pyuria with daily ingestion of 300 mL of cranberry juice cocktail (15.0% versus 28.1% in controls); however, subsequent studies of cranberries for prevention of UTI, including a large Cochrane meta-analysis, have shown mixed results.^{2,3}

Various mechanisms of the bacteriologic effect of cranberries are postulated; however, inhibition of P fimbriae-mediated adhesion of *E. coli* by proanthocyanidin (PAC) remains the leading theory.⁴

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We sought to compare antibiotic susceptibility and proportions of non-*E. coli* *Enterobacteriaceae* amongst gram-negative urinary isolates from participants randomized to cranberry capsules compared to placebo.

Methods

Data were gathered from a double-blind, randomized, placebo-controlled trial of residents from 11 nursing homes in Connecticut.⁵ Since the parent study had Yale University Human Investigation Committee (HIC) approval, this analysis was not considered human subjects research and did not require additional HIC review. Inclusion criteria included female, history of UTI, age 65 years or older, long-term residence in the nursing home, and English-speaking. Exclusion criteria were total incontinence, warfarin therapy, <4 weeks residence, chronic indwelling catheter, terminal prognosis, antibiotic therapy, nephrolithiasis, dialysis, cranberry therapy, or cranberry allergy. 0, 1, 2, and 3 capsules daily (containing 0, 36, 72, and 108 mg of PAC respectively) were compared over one month with 4 weekly urine collections (320 scheduled urine cultures). Of 80 participants enrolled, 20 were randomized to receive placebo and 60 to receive varying doses of cranberry (20 participants in each active treatment group).

Of 302 urine cultures collected, those reported as 'no growth' (n=19), less than 10,000 colony forming units (CFUs) with no specific microorganism identified (n=8), 'mixed flora' (n=111), and gram-positive isolates (n=14) were not included. Of 150 cultures with identified gram-negative bacteria, 19 had growth of second isolates that were included. A total of 169 isolates were divided into those taking cranberry (42 participants, 118 isolates) and placebo (15 participants, 51 isolates).

The primary outcome, antibiotic susceptibility, was quantified using counts and percentages of susceptible isolates to each of six antibiotics. Ampicillin, ampicillin/sulbactam, trimethoprim/sulfamethoxazole, ceftriaxone, ciprofloxacin, and nitrofurantoin were chosen to represent classes of orally available antibiotics used to treat UTI. In addition, percentages of *E. coli* and non-*E. coli* were compared according to treatment group.

Rao-Scott chi-square tests accounting for the clustering of repeated isolates within individuals were used as a measure of association. A multivariable generalized estimating equations (GEE) model was used to test the association of treatment group with the total count of antibiotics to which isolates were susceptible.

Results

The smallest p-value comparing antibiotic susceptibility between the cranberry and placebo groups was for ceftriaxone (91.0% susceptible in participants receiving cranberry versus 80.4% receiving placebo); however, the difference was not statistically significant ($p=0.28$) (see Table 1). Lowest susceptibility rates were seen for ampicillin (<45% in both groups). Relative proportions of *E. coli* to non-*E. coli* gram-negatives were not statistically different between cranberry and placebo groups (71.2% *E. coli* in cranberry group versus 72.5% *E. coli* in placebo, $p=0.90$). Finally, the GEE model did not show an adjusted association

between treatment group and the total count of antibiotics reported as susceptible (adjusted means: cranberry 4.16 and placebo 4.20, $p = 0.91$).

Discussion

A pilot study conducted in nursing home residents to establish the optimal dose of cranberry capsules in females demonstrated a dose-dependent trend towards decreased bacteriuria plus pyuria.⁵ This effect was seen amongst *E. coli* isolates but not with non-*E. coli* *Enterobacteriaceae*, consistent with the purported *E. coli*-specific mechanism of PAC.

Non-*E. coli* urinary isolates are susceptible to fewer antibiotics compared to *E. coli* among nursing home residents in the greater New Haven area.⁶ We hypothesized that overall bacterial susceptibility to oral antibiotics would be decreased due to an increased proportion of non-*E. coli* *Enterobacteriaceae* in the cranberry group compared to placebo. These results do not suggest that cranberry affects antibiotic susceptibility or the proportion of non-*E. coli* gram-negatives.

One potential explanation for these findings is that proportions of non-*E. coli* compared to *E. coli* isolates were similar in both groups suggesting cranberry may not act through an *E. coli*-specific mechanism. Although P fimbriae are typically associated with *E. coli*, P fimbriae and P fimbriae-like proteins have been identified in other *Enterobacteriaceae* including *Klebsiella*, *Proteus*, and *Enterobacter*.⁷ Moreover, cranberry has been shown to act through fimbriae-independent mechanisms by modifying bacterial gene expression, disrupting quorum sensing, and altering virulence factor production.^{8,9}

Strengths of this study include its relevant nursing home population known for high rates of UTI and bacterial resistance, in addition to being a setting where broad introduction of prophylactic measures is possible. However, there are limitations to this study. In this secondary data analysis, the benefits of randomization are diminished. Small sample size and a short observation period limited the ability to detect subtle or long-term, but potentially important, effects on antibiotic susceptibility.

Although these data are encouraging to suggest cranberry does not foster antibiotic resistance, larger studies must be done to confirm efficacy as well as investigate the effect on antibiotic resistance over a longer period of time and in different patient populations.

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Table 1

Frequency of antibiotic susceptibility in cranberry capsule versus placebo treatment groups.

Antibiotic	Cranberry		Placebo		p-value
	n	n (%) Susceptible	n	n (%) Susceptible	
Ampicillin ^a (n = 163)	112	50 (44.6%)	51	22 (43.1%)	.91
Ampicillin/Sulbactam (n = 156)	107	73 (68.2%)	49	33 (67.4%)	.94
Trimethoprim/Sulfamethoxazole (n = 168)	117	103 (88.0%)	51	45 (88.2%)	.98
Ceftriaxone (n = 163)	112	102 (91.0%)	51	41 (80.4%)	.28
Ciprofloxacin (n = 169)	118	74 (62.7%)	51	38 (74.5%)	.38
Nitrofurantoin (n = 168)	117	81 (69.2%)	51	33 (64.7%)	.70

Note. N-values indicate the numbers of gram-negative isolates for which antibiotic susceptibility testing was available.

^a Antibiotic susceptibility data for all six antibiotics was not available for all 169 isolates based on laboratory protocol.