

Prevalence of Different Serotypes of Uro-Pathogenic Escherichia Coli (UPEC) causing Recurrent Urinary Tract Infections and the Effect of Cranberry Extract on them

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Abstract

Objective: To determine the prevalence of different serotypes of Uro-Pathogenic Escherichia coli (UPEC) causing recurrent urinary tract infections and to assess the effect of Cranberry extract on them.

Material and Methods: It is cross sectional retrospective study conducted in Mayo Hospital Lahore. A total of 60 samples of urine were collected from patients admitted in from Urology Department with history of recurrent urinary tract infections. Urine studies were performed including: Urine microscopy, urine culture on CLED medium, biochemical isolation and serotyping of Uro-Pathogenic Escherichia coli. The patients were given Cranberry Extract x 500mg once daily for 3 months, after which a follow-up urine study was performed.

Results: A total of 60 urine samples were collected, out of which 15 strains of Uro-Pathogenic Escherichia coli were isolated. 53% of strains tested positive for E.Coli-26 serotype, and 47% tested positive for E.Coli-45 serotype. After taking Cranberry extract for 3 months, 67% of E.coli positive urine samples turned negative. Cranberry extract was 100% effective at eliminating E.Coli-45 serotype infection, but only 38% effective at eliminating E.Coli-26 serotype infection.

Conclusion: Findings of this study show promising results of Cranberry extract in mitigating the severity of recurrent urinary tract infections especially those caused by Uro-Pathogenic Escherichia coli-45 serotype.

Keywords: Uro-Pathogenic Escherichia coli, E. coli Serotypes, Recurrent Urinary tract infection, Cranberry extract

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Introduction

Urinary tract infections (UTI) are frequently acquired through community and hospitals. According to a Systematic Review done by American University of Beirut, Lebanon in 2021: Urinary infections are twice more likely to occur in females compared to males and its prevalence increases with increasing age. In young women, spermicide use and frequency of sexual intercourse are the main risk factors evidenced by increased

urethral and vaginal colonization. In contrast, older women's predisposing risk factors are high urinary residue, atrophic vaginitis, and cystocele.¹ Men can also get repeated attacks of UTIs due to enlarged prostate. Moreover, cancer, diabetes and stress are also common factors that increase the risk. Among the uropathogens, Escherichia coli is a major contributor agent of UTI in both indoor and outdoor patients, followed by Pseudomonas, Proteus, Klebsiella, Staphylococcus saprophyticus and Enterococcus species presenting clinically with symptoms of dysuria, frequency of micturition and/or urgency.² Most common serotypes of E.coli causing UTI are O4,O6,O7,O20,O25, O26,045 O50 and O51. Furthermore, in a recent study done by the Institute of Biotechnology, Brazil in 2022: Phylogenomic analyses have consistently demonstrated that the E. coli species is very complex and structured in eight distinct

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phylogroups, as follows: A, B1, B2, C, D, E, F, and the newly described G. The large majority of the UPEC isolates have been assigned into phylogroup B2, in addition to isolates observed in other *E. coli* phylogroups. Regarding somatic antigen (O) typing, which defines the *E. coli* serogroups the serogroups O6 (12.5%, 14/112) and O25 (8.9%, 10/112) were the most frequently detected.³

Pathogenic *E. coli* strains causing UTI are due to a range of virulent determinants which include adhesins (Type I fimbriae–P fimbriae and EPEC adherence factor), motility/chemotaxis factors (Flagella) and toxins (LPS and cytotoxins). Indeed, according to Khauli R. et al: One of the main bacterial virulence features is the binding of the uropathogen to the mucosal cellular layer. It has been well studied that *Escherichia coli* type 1 fimbria is heavily associated with cystitis, and other pathogenic-fimbriated strains are associated with pyelonephritis. Furthermore, these pathogenic fimbriae are associated with persistent colonization of the urothelium and eliciting an inflammatory response. It has been also theorized that these bacteria can mature into biofilms in the urothelial barrier to cause recurrence of infections and elude the host immune system.¹ In the current strategy of treating UTI, For acute uncomplicated UTI, the Infectious Diseases Society of America (IDSA) advocates the use of nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX), or fosfomycin for 3–5 days.¹ However, in the case of recurrent or chronic UTI, according to Dr. Ron Golan and his team at Columbia University Medical Center, New York in an article published in 2020: “Patients who present with repeat infections may also be initially treated as per their previous urine culture results until new cultures are available. Imaging to identify a source of infection, such as an abscess or stone, should be done with relapsing infections that involve the same organisms. Patients who presented initially with hematuria should be checked for urinary blood again after the infection has been successfully treated.”⁴ In other words, if patient is suffering from repeated attacks of UTI, as clinicians we should focus on reversing the cause while treating the UTI. On another note, with regards to CAUTI or Catheter-associated urinary tract infection, a study done in 2017 at Weill Cornell shows that Cranberry was effective in reducing the number of symptomatic CA-UTIs in all patients (n=22). Resistance to antibiotics was reduced by 28%. Furthermore, colony counts were reduced by 58.65%. No subjects had adverse events while taking cranberry.¹¹ As can be seen, cranberry plays a promising role in UTI

treatment without harboring any ill effects. Furthermore, according to a study published in 2019, it is important to note that “Increasing antimicrobial resistance with its expenditure and health consequences has raised interest in applying different non-antibiotic ways of preventing and treating uncomplicated lower UTIs.⁵ As we know from history that antimicrobial resistance adversely affects the normal flora and may cause super infection with *Clostridium difficile* or Fungi. Therefore, safe and effective non-antimicrobial strategies are needed. Cranberry has been used in both food and medicine industries for centuries. It contains Anthocyanidins and Proanthocyanidins (PAC) which inhibit lectin mediated adherence of type I fimbriated (mannose specific receptors) and type P fimbriated (α and β -D-Gal specific receptors) of *E. coli* to uroepithelial cells.⁵ In order to expand on this, the purpose of this study is to determine which serotypes of *E. coli* are prevalent among patients with recurrent UTI from Urology Department, Mayo Hospital, and to provide a cheaper and safer option like Cranberry extract in prophylaxis of recurrent UTI caused by *Escherichia coli*. This is important in order to avoid the serious hazards of imprudent usage of antibiotics especially in a developing country like Pakistan.

Material and Methods

It is cross sectional retrospective study conducted in Mayo Hospital Lahore. A total of 60 samples of urine were collected from patients admitted in Urology Department with history of recurrent urinary tract infections. Urine studies were performed including: Urine microscopy, urine culture on Cystine Lactose Electrolyte Deficient (CLED) medium, biochemical isolation and serotyping of Uro-Pathogenic *Escherichia coli*. The patients were given Cranberry Extract x 500mg once daily for 3 months, after which a follow-up urine study was performed.

Results

A total of 60 urine samples were collected from patients with history of repeating urinary tract infections, out of which 15 strains of Uro-Pathogenic *E. coli* were isolated. 53% of strains tested positive for *E. coli*-26 serotype, and 47% tested positive for *E. coli*-45 serotype. After taking Cranberry extract for 3 months, 67% of *E. coli* positive urine samples turned negative due to the prevention of bacterial adhesion to the uroepithelium, but not necessarily due to killing of bacteria. Cranberry extract was 100% effective at eliminating *E. coli*-45

serotype, but only 38% effective at eliminating E.Coli-26 serotype.

Table 1: UPEC Serotype frequencies

Sero Types	Frequency	Percent
E.Coli-26 serotype	8	53%
E.Coli-45 serotype	7	47%
Total	15	100

Table 2: 3-month Cranberry effect on different UPEC serotypes

3-Month Cranberry Effect	Positive Urine Culture	Negative Urine Culture	Total
E.Coli-26 serotype	5 (62%)	3 (38%)	100%
E.Coli-45 serotype	0 (0%)	7 (100%)	100%
Total	5	10	15

Discussion

As can be seen by the findings of our study, Cranberry extract given in patients suffering from chronic UTI helps to decrease the severity and symptoms of UTI, mainly due to the prevention of bacterial adhesion to uroepithelium but not necessarily due to killing of bacteria. As there are minimal studies in Pakistan which have tested the sole effect of Cranberry in patients with chronic UTI, this study provides a very helpful insight into safe and affordable treatment options for a very common but life-threatening illness. Chronic UTI is life-threatening because if it becomes complicated, meaning: urinary tract infections in immune compromised patients, males, and those associated with fevers, stones, sepsis, urinary obstruction, catheters, or involving the kidneys⁶ this may lead to a fatal condition called florid urosepsis, in which if the urine accumulates in the urinary tract and is not expelled due to post-renal obstruction, this can cause local bacterial overgrowth, which may enter the bloodstream directly or via lymphatics causing septic shock, MODS (Multi-organ dysfunction syndrome), and eventually death.⁷ According to a 2021 epidemiological report from Critical Care Department of Aga Khan University, Karachi, mortality rate from septic shock was around 22.8%, with one of the major causes being renal disease.⁸ As can be seen, much attention needs to be paid to make sure we as clinicians do test every avenue in preventing and treating chronic UTI which unfortunately may lead to the loss of life. In a study from Quebec, Canada done by Roussel et.al in 2022: We demonstrated that PAC (Proanthocyanidin)-rich cran-

berry extract microbial metabolites significantly blunt activation of UPEC virulence genes at an early stage in the gut reservoir. We also showed that altered virulence in the gut affects infectivity on the urothelium in a microbiota-dependent manner. Among the possible mechanisms, we surmise that specific microbial PAC metabolites may attenuate UPEC virulence, thereby explaining the preventative, yet contentious properties of cranberry against UTI.⁹ Cranberry plays a vital role in prevention of bacterial adhesion to uroepithelium, this can reduce symptoms and/or prevent attack of recurrent UTI. In a Systematic Review done by Gonzalez et. al at the Institute of Food Science Research, Madrid, Spain in 2020, it is stated that: “At present, cranberry supplementation can safely be suggested as complementary therapy in women with recurrent UTIs.”¹⁰ In addition, in a 2017 Meta-Analysis conducted at Tufts University School Of Medicine, Boston, it was shown that; Results of the meta-analysis showed that cranberry reduced the risk of UTI by 26% in otherwise healthy women.¹² With regards to the findings in this study, similar results have been obtained through conducting urine studies on 60 patients suffering from recurrent urinary tract infections admitted in Urology Department of Mayo Hospital Lahore. Of the 60, 15 samples tested positive for Uro-Pathogenic E.coli, of which 7(47%) were E.coli Serotype-45, and 8 (53%) were E.coli Serotype-26, after 3-month intake of Cranberry extract, 10 (67%) out of 15 Uro-Pathogenic E.coli positive urine cultures became negative. Of the 10 (67%), 7 (70%) were E.coli Serotype-45, and only 3 (30%) were E.coli Serotype-26. As can be seen by our data, cranberry extract was less than half as effective at eliminating UTI caused by E.coli Serotype-26. This indicates that even though cranberry extract plays an important role in the reduction of recurrent attacks of UTI and the severity of its symptoms, more studies are needed to be carried out to consider its role as a prophylactic or therapeutic measure. This is especially important since cranberry provides a safer and cheaper option compared to antibiotics whose misuse can cause grave side effects in a developing country like Pakistan.

Conclusion

Results of this study show promising results of Cranberry extract in mitigating the severity of recurrent urinary tract infections especially those caused by Uro-Pathogenic Escherichia coli-45 serotype; however, further studies need to be done to assess the role of Cranberry extract as a prophylactic and/or therapeutic measure in patients with recurrent urinary tract infections.

Conflict of Interest

None

Funding Source

None

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Authors Contribution

ZZ: Conceptualization of Project

ZZ: Data Collection

ZZ, SM: Literature Search

ZZ, SM: Statistical Analysis

SM, FS: Drafting, Revision

ZZ, SM: Writing of Manuscript