REVIEW ARTICLE

Urinary Tract Infection: A Multimodal Approach to Management

Arif Ahmed Faruqui

Received on: 06 July 2024; *Accepted on*: 22 October 2024; *Published on*: 12 February 2025

Abstract

Urinary tract infections (UTIs) are highly prevalent, resulting in 7 million outpatient visits, 1 million emergency department visits, and 100,000 hospitalizations annually. They predominantly affect females aged 20–50. Antibiotics are the primary treatment, but about 30% of treated females experience recurrence (rUTI). Regular antibiotic use also increases the risk of antibiotic resistance and side effects. Moreover, antibiotics can cause dysbiosis of the intestinal and vaginal flora, increasing the risk of recurrence. Therefore, nonantibiotic treatments are worth considering reducing antibiotic use and side effects. Nonantibiotic options such as cranberry juice, D-mannose, probiotics, and potassium magnesium citrate can alleviate UTI symptoms and reduce recurrence risk. Studies indicate that combining these non-antibiotic treatments, which work through different mechanisms, leads to better clinical outcomes. This review explores the role of each non-antibiotic treatment, the rationale for their combination, and supports their effectiveness with clinical evidence. Thus, the combination of non-antibiotic treatments may provide a better outcome for patients with UTI and rUTI.

Keywords: Antibiotic, Cranberry, D-Mannose, Nonantibiotic, Probiotics, Recurrence.

Journal of Obstetric and Gynaecological Practices POGS (2025): 10.5005/jogyp-11012-0045

Introduction

Urinary tract infection (UTI) ranks as one of the most common infectious diseases worldwide.[1] Urinary tract infection symptoms are a frequent cause for primary care consultations, where the majority of suspected cases are addressed. Uncomplicated lower UTIs typically resolve rapidly, and many are self-limiting. Nevertheless, 11% of females have stated experiencing at least one UTI, while 3% have reported having three or more UTIs within the previous year.[2] Urinary tract infections are a major public health issue due to their high occurrence in both community and hospital settings. Symptomatic UTIs result in 7 million outpatient visits, 1 million emergency department visits, and 100,000 hospitalizations annually. With the rise of antimicrobial resistance, these infections not only cause significant morbidity and financial burden but also pose a risk of mortality, particularly among hospitalized patients. A study in India found that UTIs were prevalent in 73.57% of females in outpatient departments, compared to 35.14% in males.[3] Urinary tract infections are much more prevalent in females, especially those between the ages of 20 and 50, with a rate of incidence 50 times greater than in men.[2] Women have a higher susceptibility to UTIs compared to men because of their shorter urethra, lack of prostatic secretions, pregnancy, and the increased risk of urinary tract contamination by fecal bacteria.[1]

UTI Classification

Urinary tract infections are of two main types: Uncomplicated and complicated. Uncomplicated UTIs usually occur in people who are overall healthy and don't have any structural or neurological issues in their urinary tract. Uncomplicated UTIs are further divided into lower UTIs, known as cystitis, and upper UTIs, referred to as pyelonephritis.[4] The risk of developing cystitis is higher for women due to factors such as a history of UTIs, sexual activity, vaginal infections, diabetes, obesity, and genetic predisposition.[4–6] Complicated UTIs are associated with conditions that weaken the urinary tract or the body's immune system. The potential concerns could involve urinary blockage, buildup from neurological disorders, compromised immune function, kidney failure, kidney transplant, pregnancy, and the presence of stones, catheters, or other drainage devices.[4]

Department of Pharmacology, Clinical Pharmacology, Mumbai, Maharashtra, India

Corresponding Author: Arif Ahmed Faruqui, Department of Pharmacology, Clinical Pharmacology, Mumbai, Maharashtra, India, Phone: +91 9322429615, e-mail: drfaruqui@gmail.com

How to cite this article: Faruqui AA. Urinary Tract Infection: A Multimodal Approach to Management. J Obstet Gynaecol Pract POGS 2025;3(1):42–48.

Source of support: Nil

Conflict of interest: None

Clinical Presentation of UTI

Symptoms of uncomplicated UTIs include:[6]

- Pain while urinating (dysuria)
- The need to urinate often (frequency)
- Difficulty initiating urination (hesitancy)
- An immediate urgency to urinate (urgency)
- Pain or discomfort in the area above the pubic bone (suprapubic pain)
- Spasms in the bladder
- Blood in the urine (hematuria)

Etiology of UTIs

The usual microorganisms that lead to UTIs consist of both positive and negative gram bacteria; along with specific fungi.[4] The majority of uncomplicated UTI cases are acquired within the community and

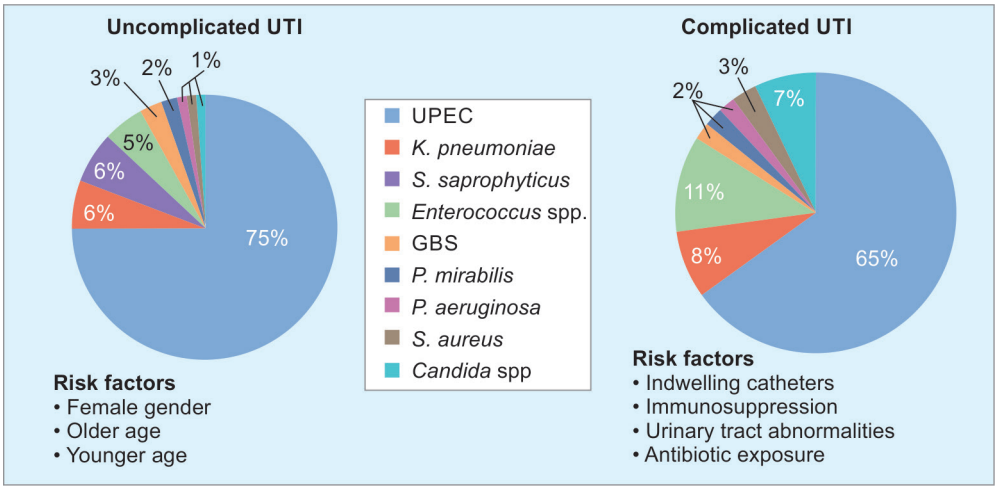

Fig. 1: Etiology of UTIs

Source: Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13(5):269–284. DOI: 10.1038/nrmicro3432

are mainly caused by uropathogenic *E. coli* (UPEC) and *Klebsiella* spp., accounting for approximately 75–95% of all cases. Other organisms such as *Proteus* spp., *Enterobacter* spp., *Pseudomonas* spp., *Enterococcus faecalis, Staphylococcus saprophyticus, Staphylococcus aureus, and Candida* spp. may also cause UTI, but their prevalence is lower (Fig. 1).[1,4]

General Management of Urinary Tract Infections

The cornerstone treatment for bacterial infections of any origin, including a UTI, is antimicrobial therapy. Given the high frequency of UTIs, especially in women, it is essential to initiate the controlled use of antibiotics for treatment.[7]

The most commonly used antimicrobial agents for uncomplicated UTIs are trimethoprim, trimethoprim-sulfamethoxazole, fluoroquinolones, β-lactams, fosfomycin tromethamine and nitrofurantoin. These medications are preferred due to their tolerability, effectiveness against uropathogens, and favorable pharmacokinetics. The resolution of bacteriuria in UTIs is associated with high concentrations of the antimicrobial agent in the urine rather than in the serum. All approved agents achieve urinary concentrations significantly higher than serum levels. Trimethoprim-sulfamethoxazole and fluoroquinolones are particularly effective for long-term treatment, as they target aerobic gram-negative flora while sparing vaginal and fecal anaerobic flora.[7]

Recurrence of Urinary Tract Infections

Recurrent urinary tract infections (rUTIs) are defined as a person having 2 acute bacterial cystitis occurrences with related symptoms in the last 6 months, or 3 occurrences in the past 12 months. These infections are commonly seen in women.[8] The majority of women who have UTIs experience positive results with antibiotic therapy, typically seeing symptom improvement within 2–4 days. Nevertheless, around 30% of females may encounter a recurrence within a span of 6 months.[6]

Pathophysiology of rUTIs

Recurrent urinary tract infections often occur due to new bacterial infections. If the infections persist even after treatment, it could be a sign of a urinary stone, or prostatitis or untreated source such as an abscess. Normally, bacteria from the rectum contaminate the periurethral area and then move up to the bladder. Studies have revealed an intricate connection between the intestinal, vaginal, and urinary microbiomes. Moreover, *E. coli* is the most common bacteria responsible for 75% of rUTIs.[8]

Distinguishing between rapid reinfection (new organism) and relapse (same organism not fully treated) is crucial. Relapse means the infection comes back within 2 weeks with the same germ, while reinfection happens when a new infection occurs more than 2 weeks after treatment.

Most recurring UTIs are new infections and usually don't need a urological check-up or imaging unless certain signs and symptoms are observed.[8]

Recurrent urinary tract infections can be attributed to various risk factors such as menopause, frequent sexual activity, atrophic vaginitis (untreated), and the use of diaphragms loaded with spermicide. These factors can disrupt the vaginal flora and introduce bacteria into the urethra. Genetic factors can increase the likelihood of recurring UTIs, particularly in cases with a family history of frequent UTIs.[8]

Antibiotics Drawbacks and Need for New Alternatives in UTI Management

Antimicrobial agents are typically the initial treatment for UTIs. However, there is increasing concern about antibiotic resistance, making the decision to prescribe antibiotics more complex.[9] Antibiotics can lead to side effects such as rashes, dizziness, diarrhea, nausea, vomiting, headaches, and yeast infections. In rare cases, they can cause severe allergic reactions.[10] Prolonged use of nitrofurantoin can result in hypersensitivity pneumonitis.[11] Additionally, long-term antibiotic use can alter the microbiome, affecting both the gut and urinary tract flora and promoting resistance in uropathogens.[12,13] The rise of resistant strains like extended-spectrum beta-lactamases and carbapenem-resistant *E. coli* highlights the need for new agents with fewer side effects and better long-term efficacy.[13] This prompted the exploration of alternative treatments and preventive measures for UTIs.[14] Other alternatives to antibiotics are behavioral modifications, NSAIDs, phytotherapy (like Chinese herbal remedies and cranberry items),

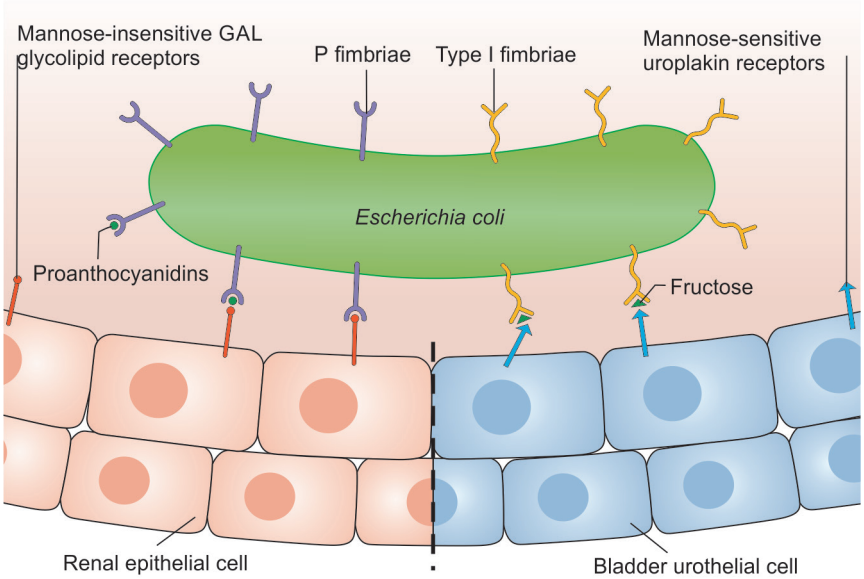

Fig. 2: Cranberry components and their mechanism of action for UTI prevention 14 fructose inhibits the binding of type I fimbriae to uroplakin receptors, while proanthocyanidins prevent the binding of P fimbriae to glycolipid receptors

Source: Sihra N, Goodman A, Zakri R, et al. Nonantibiotic prevention and management of recurrent urinary tract infection. Nat Rev Urol 2018;15(12):750–776. DOI: 10.1038/s41585-018-0106-x

D-mannose, probiotics, estrogens, methenamine hippurate, immunostimulants, intravesical glycosaminoglycans, vaccines and inoculation (less harmful bacterial organisms).[14] Using these agents combined could offer the best treatment for decreasing rUTIs, and it is essential to carry out trials in particular population segments to confirm their effectiveness.[14]

Phytotherapy in UTI Management

The history of using plants or their components for medical purposes dates back centuries. Chinese herbal medicine (CHM) and cranberry products have been extensively studied for their potential to prevent and treat UTIs.[14]

Cranberries and Cranberry-based Products

Cranberry, a plant belonging to the *Ericaceae* family, is known by the scientific names *Vaccinium macrocarpon, Vaccinium oxycoccos,* and *Vaccinium erythrocarpum*.[14] Cranberries have a high-water content of more than 80% and are comprised of 10% carbohydrates. Additionally, they contain various beneficial compounds like flavonoids, anthocyanins, catechin, triterpenoids, organic acids, and a small quantity of ascorbic acid. The main organic acids found in cranberries consist of citric, malic, and quinic acids, with lesser quantities of benzoic and glucuronic acids.[15] Anthocyanidins and proanthocyanidins, which are tannins (polyphenols), act as a natural defense mechanism in plants to combat microbial infections. These compounds have shown significant benefits in treating UTI infections in women.[14,15]

Proposed Mechanism of Cranberry in UTI

In vitro research highlights the significant role of proanthocyanidins, a key compound in cranberries, in preventing UTIs.[14] *E. coli* attaches to urothelial cells to cause UTIs with the help of adhesins like type I fimbriae and P fimbriae. These adhesins bind to carbohydrate receptors on the cells to facilitate the attachment process.[16,17] Most uropathogenic *E. coli* strains produce type I fimbriae that target mannose-like receptors, while highly pathogenic strains in recurring UTIs or pyelonephritis also express P fimbriae.[18]

Cranberries contain fructose, which inhibits the attachment of type I fimbriated *E. coli*, and proanthocyanidins, which prevent P fimbriated *E. coli* from adhering to urothelial cells (Fig. 2).[14,19,20] Proanthocyanidins, composed of flavan oligomers and polymers, possess antiadhesive properties that hinder various bacteria, including *Pseudomonas aeruginosa, E. coli*, and *Proteus mirabilis*.[19,20] Cranberries are unique due to their A-type linkage in proanthocyanidins, crucial for preventing *E. coli* adhesion.[21]

Although the exact mechanism is not fully understood, cranberry components may act as receptor analogs, and inhibits *E. coli* adhesion by binding to fimbrial tips competitively.[18] They can also alter bacterial cell surface properties, reducing fimbrial length and density, thus lowering adherence to urothelial cells.[18] Extended cranberry exposure can morphologically transform *E. coli*, making them more likely to be repelled by urothelial cells (Fig. 2).[22]

Additionally, ursolic acid in cranberries can synergize with proanthocyanidins to alter *E. coli* gene expression, preventing biofilm formation. Laboratory studies showed that 10 µg of ursolic acid significantly reduced *E. coli* biofilm formation, with DNA microarray analysis indicating that ursolic acid activates genes related to chemotaxis, mobility, and heat shock response, thereby hindering mature biofilm development.[23]

D-mannose in Urinary Tract Infections

D-mannose is crucial for the glycosylation of proteins, including monoclonal antibodies. It is quickly absorbed when taken orally and appears in the bloodstream within 30 minutes, eventually being excreted through the urinary system.[24] Research has demonstrated that D-mannose has the potential to be an effective preventive treatment for rUTIs.[25]

Proposed Mechanism of Action for D-mannose

Type I fimbriae, or pili, are protein projections in enteric bacteria like *E. coli* that are essential for attachment.[26] They are composed of Fim proteins, with the FimH adhesion molecule at the tip, which binds to mannosylated host proteins on the urinary tract, such as uroplakin 1a, Tamm-Horsfall glycoprotein, and beta-1 and alpha-3 integrins. FimH is crucial for the development of UTIs caused by *E. coli*, making it a potential target for UTI treatments.[27,28] D-mannose, which resembles the binding sites of urothelial glycoprotein receptors, can saturate FimH adhesins in the urine, preventing bacterial attachment. An *in vitro* study showed that D-mannose completely prevented adherence in 42% of *E. coli* strains and reduced adherence by at least 50% in 18% of strains from clinical isolates.[29]

Thus, D-mannose combats UTIs caused by *E. coli* mainly by resembling urothelial glycoprotein receptors such as uroplakin. This resemblance enables D-mannose to saturate FimH adhesins on type I pili, which are essential for bacterial attachment to the urinary tract lining. Consequently, D-mannose hinders *E. coli* from binding to host receptors, leading to decreased adherence and potentially lessening the severity of UTIs.

Probiotics

Probiotics, living organisms ingested for health benefits, play a crucial role in maintaining the normal bacterial flora in humans. This flora acts as a vital defense mechanism against infections. Consequently, replenishing the vaginal and intestinal flora with probiotics is an attractive approach for preventing infections. In healthy women, the balanced vaginal ecosystem is safeguarded by normal flora, which aids in repelling pathogenic bacteria that may cause UTIs. Among these, *Lactobacilli* species are especially significant in preserving the healthy vaginal flora and in hindering the attachment and movement of pathogens to the bladder and urothelium.[30] Lower levels of *Lactobacilli* in the vagina have been associated with increased colonization of *E. coli*. Various factors, including sexual activity, the use of spermicides in post-menopausal women, and frequent antibiotic use, contribute to the decrease in vaginal *Lactobacilli* levels.[14]

Proposed Mechanism of Action for Probiotics

Lactobacilli spp. produces multifaceted approach to preventing UTI. *Lactobacilli*, a beneficial bacterial species, employs following mechanisms to help prevent UTIs:

- Competitive inhibition of uropathogen adhesion
  Lactobacilli compete with uropathogens (bacteria that can cause UTIs) for adhesion receptors present on epithelial cells in the vagina. *Lactobacillus* in the vagina prevents uropathogens from successfully colonizing through exclusion, competition, and displacement mechanisms. *Lactobacilli* take up binding sites, compete for adhesion receptors, and can displace uropathogens already attached to vaginal cells, thus preventing their establishment.[31]
- Production of antimicrobial compounds
  Lactobacilli generate a range of antimicrobial compounds, such as hydrogen peroxide, lactic acid, and bacteriocins which are antimicrobial proteins. These compounds create an acidic environment that is inhospitable for uropathogens.[32]
- Inhibition of biofilm formation
  When *lactobacilli* coaggregate or cluster with uropathogens, it concentrates the antimicrobial compounds near the uropathogens. This hinders the uropathogens' capacity to create defensive biofilms-clusters of bacteria surrounded by a self-generated extracellular matrix. Biofilms make infections more difficult to treat.[33,34]
- Downregulation of inflammation
  The concentrated antimicrobials also suppress the production of certain proinflammatory cytokines, such as IL-6, IL-8, IL-10 and tumor necrosis factor. This helps reduce the inflammatory response that can accompany UTIs.[34,35]

By employing this multifaceted approach inhibiting uropathogen adhesion, producing antimicrobials, disrupting biofilms, and dampening inflammation, *lactobacilli* play a key role in preventing and managing UTIs. In addition to their mechanisms for preventing UTIs, research has demonstrated that *lactobacilli* can also exhibit antimicrobial effects against certain problematic bacterial strains. *Lactobacilli* exhibit antimicrobial activity against resistant pathogens. *Lactobacilli*, particularly *L. plantarum* and *L. fermentum*, have demonstrated inhibitory activity against extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and multidrug-resistant organisms. These two specific species of *lactobacilli* have exhibited the most pronounced antimicrobial effects, suggesting their potential as natural alternatives or adjuncts to conventional antibiotics in combating the growing threat of antibiotic resistance. The inhibitory properties of these *lactobacilli* may be attributed to their ability to produce antimicrobial compounds, compete for nutrients and adhesion sites, and modulate the host immune response, making them promising candidates for further research and development in the field of antimicrobial therapy.[36,37]

Limited research has been conducted on the use of oral probiotics in adults with recurrent UTI compared to studies in children. In a randomized trial with postmenopausal females ($n = 252$) with recurrent UTIs, received either oral probiotics or antibiotic prophylaxis. The study found that probiotics reduced UTI recurrence from 6.8% to 3.3% over one year but did not meet the non-inferiority criteria compared to antibiotics. Notably, the probiotic group did not develop antibiotic resistance, while the antibiotic group had a 95% resistance rate after just 30 days.[38] These results indicate that oral probiotics may be a more favorable choice than antibiotics for many patients with UTI.

Potassium Magnesium Citrate

Dysuria, a common symptom of UTI, is referred as painful or uncomfortable sensation while urinating.[39] Dysuria in women may indicate the simultaneous presence of urinary tract inflammation and infection. Pain experienced at the onset or during urination is indicative of the existence of infection and inflammation.[40] Urinary alkalizing agents are commonly utilized in certain regions for the symptomatic control of uncomplicated UTIs, and they are endorsed in specific national drug formularies.[41] Potassium citrate is recommended for alleviating the symptoms of dysuria linked to minor UTIs, particularly cystitis.[42] This medication functions by alkalizing the urine, thereby decreasing irritation during urination.[42]

Rationale for Combination

Urinary tract infections are widespread, causing significant patient suffering, resulting in substantial financial burdens on healthcare systems, and are a leading cause of antibiotic consumption globally. The increasing challenge of antimicrobial resistance underscores the urgent need to explore non-antibiotic options for managing and preventing UTIs. Possible alternatives to antibiotics for UTI treatment and prevention encompass cranberry juice, D-mannose, probiotics, and alkalizing agents.[14,43]

It may be necessary to conduct trials in specific population groups in order to determine the most effective treatment for reducing recurrent UTI, which could involve a combination of these agents.[14]

Cranberry proanthocyanidins have the ability to prevent the attachment of P-fimbriated *E. coli* to bladder and vaginal epithelial cells, in a manner that is dependent on the dosage. P-fimbriae are responsible for enabling bacteria to adhere to the urinary tract, especially the kidneys.[43,44] Cranberry proanthocyanidins blocks the P-type fimbriae on bacteria, which prevents the bacteria from sticking to the cells of the urinary tract.[43,44] Although the search results do not explicitly state the binding of D-mannose to type-I fimbriae, certain research studies have indicated that D-mannose could potentially exhibit antiadhesive properties against uropathogenic *E. coli* through its interference with type-I fimbriae.[14] This accelerates removal of uropathogens through urine.

Proanthocyanidins (type A) found in cranberries are known for their powerful ability to inhibit mannose-resistant adhesins. Cranberries can also lead to the detachment of bacteria that are adhering to uroepithelial cells. D-mannose works by saturating FimH adhesins on type I pili, which in turn prevents *E. coli* from binding to host receptors, reducing adherence and potentially lessening the severity of UTIs.[44]

Probiotics produce a multifaceted approach to preventing UTI. *Lactobacilli*, a beneficial bacterial species, prevent UTIs through competitive inhibition of uropathogen adhesion, production of antimicrobial compounds, inhibition of biofilm formation, and downregulation of inflammation.[14] Potassium magnesium citrate can help make the urine less acidic, thereby reducing irritation during urination. Thus, a combination of cranberries, D-mannose, probiotics, and potassium citrate will be well tolerated and result in significant control of urinary infections and their recurrence.[43]

Clinical Evidences of Combination

Lower UTIs are prevalent among women and can be easily treated, but the use of antibiotics for treatment and prevention of recurrence has disadvantages, such as contributing to antimicrobial resistance and intestinal imbalance. As a result, researchers are investigating alternative therapies.[45] Combining cranberry extract with D-mannose may be an effective method for managing acute UTIs. In a pilot study with 93 healthy, non-pregnant women, participants received either a recommended antibiotic alone or with cranberry extract plus D-mannose, followed by a clinical examination on day 7. Those who improved or were cured entered a double-blind phase, and received the combination product or a placebo for more 21 days before the next examination. The combination product resulted in higher cure rates at day 7 (91.6% vs 84.4%) and significantly improved cure rates for antibiotic-resistant strains (88.8% vs 37.5%, $p < 0.0001$). This suggests that cranberry extract in combination with D-mannose is promising for managing acute UTIs, especially in resistant cases.[45]

In addition, utilizing a combination of non-antibiotic methods may lead to improved results compared to the use of a single treatment approach. A recent small-scale trial involving 33 premenopausal women demonstrated that the administration of d-Mannose, cranberry extract, and *lactobacilli* in powder form effectively managed symptoms of acute uncomplicated cystitis and UTI. Throughout the study, participants received two doses of the combination daily for the initial month, followed by one sachet per day until the 60th day. By the conclusion of the trial, all subjects tested negative for nitrites and leukocyte esterase in their urine dipstick examination.[46]

Another study was conducted to assess the efficacy of a novel blend of D-mannose, pomegranate plant extract, prebiotics, and probiotics in relieving symptoms in women with acute, uncomplicated cystitis. The research took place at Villa Stuart Private Hospital from September to November 2018. Participants took the combination of cranberry extract and D-mannose twice daily for 5 days, then once daily for 10 days, along with increased fluid intake. Antibiotics were reserved for cases of symptom exacerbation. Thirty-three women with an average age of 38.1 $\pm$ 11.2 years completed the study. Results indicated a notable improvement in symptoms: 30.3% of women were symptom-free by day 15, rising to 90.9% by day 30. Symptoms persisted in 48.5% of women at day 15 and 9.1% at day 30, with no deterioration by the end of the study period. Both the acute cystitis symptom score (ACSS) and quality of life (QoL) assessments displayed significant enhancements. Six patients required antibiotics, and there were no reported adverse events. The findings suggest that this combination effectively alleviates acute cystitis symptoms in the majority of cases without the need for antibiotics, although the absence of microbiological evaluation, a control group, and potential confounding factors related to increased fluid intake are acknowledged as study limitations.[47]

Conclusion

The key approach to managing rUTI is to disrupt the cycle of infection and address any reversible factors. While antibiotics are a common treatment, they can lead to the development of bacterial resistance. Approximately one in four women experience recurring UTIs and are more susceptible to such infections. Non-antibiotic therapies, such as cranberry products, D-mannose, and probiotics, offer alternative options for treating and preventing UTIs. These therapies can help prevent bacterial adhesion to uroepithelial cells, slow down bacterial metabolism, and create an unfavorable environment for pathogens. By combining cranberry, D-mannose, and probiotics, individuals can reduce the risk of UTI recurrence and maintain a healthy urinary tract. This comprehensive approach, as suggested by recent reviews, is a promising alternative to antibiotic treatment for managing UTIs.

References

1. Mohapatra S, Panigrahy R, Tak V, et al. Prevalence and resistance pattern of uropathogens from community settings of different regions: An experience from India. Access Microbiol 2022;4(2):000321. DOI: 10.1099/acmi.0.000321.
2. Pujades-Rodriguez M, West RM, Wilcox MH, et al. Lower urinary tract infections: Management, outcomes and risk factors for antibiotic

re-prescription in primary care. EClinicalMedicine 2019;14:23–31. DOI: 10.1016/j.eclinm.2019.07.012.
3. Walter Bushnell Healthcare Foundation. Resistance Pattern in UTI: Indian and International Perspectives. [online] Available from: https://wbhf.walterbushnell.com/publications/bush-beats/item/67-resistance-pattern-in-uti-indian-and-international-perspectives#. [Last accessed November, 2024].
4. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13(5):269–284. DOI: 10.1038/nrmicro3432.
5. Hannan TJ, Totsika M, Mansfield KJ, et al. Host-pathogen checkpoints and population bottlenecks in persistent and intracellular uropathogenic Escherichia coli bladder infection. FEMS Microbiol Rev 2012;36(3):616–648. DOI: 10.1111/j.1574-6976.2012.00339.x.
6. Abou Heidar NF, Degheili JA, Yacoubian AA, et al. Management of urinary tract infection in women: A practical approach for everyday practice. Urol Ann 2019;11(4):339–346. DOI: 10.4103/UA.UA_104_19.
7. Jancel T, Dudas V. Management of uncomplicated urinary tract infections. West J Med 2002;176(1):51–55. DOI: 10.1136/ewjm.176.1.51.
8. Aggarwal N, Leslie SW, Lotfollahzadeh S. Recurrent Urinary Tract Infections. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [online] Available from: https://www.ncbi.nlm.nih.gov/books/NBK557479/. [Last accessed November, 2024].
9. Amawi HA, U'wais HT, Nusair MB, et al. Management of urinary tract infections and antibiotic susceptibility patterns of bacterial isolates. Int J Clin Pract 2021;75(10):e14475. DOI: 10.1111/ijcp.14475.
10. WebMD. Antibiotics for UTI Treatment. [online] Available from: https://www.webmd.com/a-to-z-guides/what-are-antibiotics-for-uti. [Last accessed November, 2024].
11. Sabih A, Leslie SW. Complicated Urinary Tract Infections. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [online] Available from: https://www.ncbi.nlm.nih.gov/books/NBK436013/. [Last accessed November, 2024].
12. Kenneally C, Murphy CP, Sleator RD, et al. The urinary microbiome and biological therapeutics: Novel therapies for urinary tract infections. Microbiol Res 2022;259:127010. DOI: 10.1016/j.micres.2022.127010.
13. Gupta V, Nag D, Garg P. Recurrent urinary tract infections in women: How promising is the use of probiotics?. Indian J Med Microbiol 2017;35(3):347–354. DOI: 10.4103/ijmm.IJMM_16_292.
14. Sihra N, Goodman A, Zakri R, et al. Nonantibiotic prevention and management of recurrent urinary tract infection. Nat Rev Urol 2018;15(12):750–776. DOI: 10.1038/s41585-018-0106-x.
15. Raz R, Chazan B, Dan M. Cranberry juice and urinary tract infection. Harefuah 143(12):891–894, 909. PMID: 15666710.
16. Lynch DM. Cranberry for prevention of urinary tract infections. Am Fam Physician 2004;70(11):2175–2177. PMID: 15606066.
17. Ofek I, Beachey EH. Mannose binding and epithelial cell adherence of Escherichia coli. Infect Immun 1978;22(1):247–254. DOI: 10.1128/iai.22.1.247-254.1978.
18. Hisano M, Bruschini H, Nicodemo AC, et al. Cranberries and lower urinary tract infection prevention. Clinics (Sao Paulo) 2012;67(6):661–668. DOI: 10.6061/clinics/2012(06)18.
19. Hidalgo G, Chan M, Tufenkji N. Inhibition of Escherichia coli CFT073 fliC expression and motility by cranberry materials. Appl Environ Microbiol 2011;77(19):6852–6857. DOI: 10.1128/AEM.05561-11.
20. O'May C, Tufenkji N. The swarming motility of Pseudomonas aeruginosa is blocked by cranberry proanthocyanidins and other tannin-containing materials. Appl Environ Microbiol 2011;77(9):3061–3067. DOI: 10.1128/AEM.02677-10.
21. Howell AB, Reed JD, Krueger CG, et al. A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. Phytochemistry 2005;66(18):2281–2291. DOI: 10.1016/j.phytochem.2005.05.022.
22. Liu Y, Black MA, Caron L, et al. Role of cranberry juice on molecular-scale surface characteristics and adhesion behavior of Escherichia coli. Biotechnol Bioeng 2006;93(2):297–305. DOI: 10.1002/bit.20675.
23. Ren D, Zuo R, González Barrios AF, et al. Differential gene expression for investigation of Escherichia coli biofilm inhibition by plant extract ursolic acid. Appl Environ Microbiol 2005;71(7):4022–4034. DOI: 10.1128/AEM.71.7.4022-4034.2005.
24. Davis JA, Freeze HH. Studies of mannose metabolism and effects of long-term mannose ingestion in the mouse. Biochim Biophys Acta 2001;1528(2–3):116–126. DOI: 10.1016/s0304-4165(01)00183-0.
25. Fettweis JM, Brooks JP, Serrano MG, et al. Differences in vaginal microbiome in African American women versus women of European ancestry. Microbiology (Reading) 2014;160(Pt 10):2272–2282. DOI: 10.1099/mic.0.081034-0.
26. Fronzes R, Remaut H, Waksman G. Architectures and biogenesis of non-flagellar protein appendages in Gram-negative bacteria. EMBO J 2008;27(17):2271–2280. DOI: 10.1038/emboj.2008.155.
27. Mydock-McGrane LK, Cusumano ZT, Janetka JW. Mannose-derived FimH antagonists: A promising anti-virulence therapeutic strategy for urinary tract infections and Crohn's disease. Expert Opin Ther Pat 2016;26(2):175–197. DOI: 10.1517/13543776.2016.1131266.
28. Michaels EK, Chmiel JS, Plotkin BJ, et al. Effect of D-mannose and D-glucose on Escherichia coli bacteriuria in rats. Urol Res 1983;11(2):97–102. DOI: 10.1007/BF00256954.
29. Schaeffer AJ, Chmiel JS, Duncan JL, et al. Mannose-sensitive adherence of Escherichia coli to epithelial cells from women with recurrent urinary tract infections. J Urol 1984;131(5):906–910. DOI: 10.1016/s0022-5347(17)50706-5.
30. Velraeds MM, van der Mei HC, Reid G, et al. Inhibition of initial adhesion of uropathogenic Enterococcus faecalis by biosurfactants from Lactobacillus isolates. Appl Environ Microbiol 1996;62(6):1958–1963. DOI: 10.1128/aem.62.6.1958-1963.1996.
31. Andreu A, Stapleton AE, Fennell CL, et al. Hemagglutination, adherence, and surface properties of vaginal Lactobacillus species. J Infect Dis 1995;171(5):1237–1243. DOI: 10.1093/infdis/171.5.1237.
32. Osset J, Bartolomé RM, García E, etal. Assessment of the capacity of Lactobacillus to inhibit the growth of uropathogens and block their adhesion to vaginal epithelial cells. J Infect Dis 2001;183(3):485–491. DOI: 10.1086/318070.
33. Mastromarino P, Brigidi P, Macchia S, et al. Characterization and selection of vaginal Lactobacillus strains for the preparation of vaginal tablets. J Appl Microbiol 2002;93(5):884–893. DOI: 10.1046/j.1365-2672.2002.01759.x.
34. Barrons R, Tassone D. Use of lactobacillus probiotics for bacterial genitourinary infections in women: A review. Clin Ther 2008;30(3):453–468. DOI: 10.1016/j.clinthera.2008.03.013.
35. Zárate G, Nader-Macias ME. Influence of probiotic vaginal *lactobacilli* on in vitro adhesion of urogenital pathogens to vaginal epithelial cells. Lett Appl Microbiol 2006;43(2):174–180. DOI: 10.1111/j.1472-765X.2006.01934.x.
36. Manzoor A, Ul-Haq I, Baig S, et al. Efficacy of locally isolated lactic acid bacteria against antibiotic-resistant uropathogens. Jundishapur J Microbiol 2016;9(1):e18952. DOI: 10.5812/jjm.18952.
37. Shim YH, Lee SJ, Lee JW. Antimicrobial activity of lactobacillus strains against uropathogens. Pediatr Int 2016;58(10):1009–1013. DOI: 10.1111/ped.12949.
38. Beerepoot MA, ter Riet G, Nys S, et al. *Lactobacilli* vs antibiotics to prevent urinary tract infections: A randomized, double-blind, noninferiority trial in postmenopausal women. Arch Intern Med 2012;172(9):704–712. DOI: 10.1001/archinternmed.2012.777.
39. Mehta P, Leslie SW, Reddivari AKR. Dysuria. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [online] Available from: https://www.ncbi.nlm.nih.gov/books/NBK549918/. [Last accessed November, 2024].

40. Wrenn K. Dysuria, Frequency, and Urgency. In: Walker HK, Hall WD, Hurst JW (Eds). Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. [online] Chapter 181. Available from: https://www.ncbi.nlm.nih.gov/books/NBK291/. [Last accessed November, 2024].
41. O'Kane DB, Dave SK, Gore N, et al. Urinary alkalisation for symptomatic uncomplicated urinary tract infection in women. Cochrane Database Syst Rev 2016;4(4):CD010745. DOI: 10.1002/14651858.CD010745.pub2.
42. EMC. Potassium citrate mixture. [online] Available from: https://www.medicines.org.uk/emc/landing?status=1#gref. [Last accessed November, 2024].
43. 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(6):2357–2360. DOI: 10.1016/j.juro.2007.01.114.
44. 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(15):1085–1086. DOI: 10.1056/NEJM199810083391516.
45. Rădulescu D, David C, Turcu FL, et al. Combination of cranberry extract and D-mannose – possible enhancer of uropathogen sensitivity to antibiotics in acute therapy of urinary tract infections: Results of a pilot study. Exp Ther Med 2020;20(4):3399–3406. DOI: 10.3892/etm.2020.8970.
46. Vicariotto F. Effectiveness of an association of a cranberry dry extract, D-mannose, and the two microorganisms Lactobacillus plantarum LP01 and Lactobacillus paracasei LPC09 in women affected by cystitis: A pilot study. J Clin Gastroenterol 2014;48 Suppl 1:S96–S101. DOI: 10.1097/MCG.0000000000000224.
47. Pugliese D, Acampora A, Porreca A, et al. Effectiveness of a novel oral combination of D-Mannose, pomegranate extract, prebiotics and probiotics in the treatment of acute cystitis in women. Arch Ital Urol Androl 2020;92(1):34–38. DOI: 10.4081/aiua.2020.1.34.