International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 11 | Nov - 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Cranberry and Other Non-Antibiotic Approaches for the Prevention of Recurrent Urinary Tract Infections

Jyotiraditya.B.Pawar*, Miss.kiran.Langhe[1], Vaishnavi Vijay Jambhulkar[2], Shraddha Dadabhau Bhor[3]

Sahakar Maharshi Kisanrao Varal Patil College Of Pharmacy Nighoj (414306)

Abstract:

Urinary tract infection (UTI) is one of the most common bacterial infections worldwide, especially among women. It is defined by the presence of clinical signs and symptoms involving the genitourinary tract, together with a significant bacterial load in the urine, typically $\geq 10^2$–10^3 colony-forming units per milliliter. UTIs may involve the bladder (cystitis), kidney parenchyma (pyelonephritis), or prostate gland (prostatitis). Recurrent UTIs are common, affecting up to one-third of women after a first episode, and are defined as two or more infections within six months or three or more within one year For decades, low-dose daily or post-coital antimicrobial prophylaxis has been the cornerstone of preventing recurrent UTIs. However, concerns about antimicrobial resistance and adverse effects have driven interest in non-antibiotic alternatives such as probiotics, vaccines, oligosaccharide inhibitors of bacterial adhesion, immunoreactive Escherichia coli extracts, local estrogen therapy, and cranberry products. Cranberry, long investigated as a prophylactic agent, inhibits adhesion of P- and type I-fimbriated uropathogenic E. coli to the uroepithelium. Evidence suggests that proanthocyanidins (PACs) are the principal active compounds. Clinical findings remain inconsistent due to heterogeneity in product standardization, dosing, and trial design. Meta-analyses show a modest (~35%) reduction in recurrence among young and middle-aged women, with uncertain benefit in other populations. High dropout rates, gastrointestinal intolerance, excess caloric intake from juices, and potential drug interactions limit long-term adherence.While cranberry remains a promising adjunct in UTI prophylaxis, current data do not support its routine clinical use. Further well-designed, standardized clinical trials are necessary.

Keywords:

urinary tract infection, recurrent UTI, cranberry, proanthocyanidins, non-antibiotic prophylaxis.

Introduction:

Scientific name: Vaccinium macrocarpon Aiton

Family: Ericaceae

Part used: Fruit (berry)

Synonyms : Large Cranberry , American Cranberry , Bearberry (common name in some regions)

Botanical synonym: Oxycoccus macrocarpus

Biological Source:

Cranberries are the dried or fresh ripe fruits of Vaccinium macrocarpon Aiton, belonging to the family Ericaceae.

Geographical Source

Native to North America

Also cultivated in Canada, USA, and Europe (cool, acidic bogs and wetlands)

Chemical Constituents

Flavonoids: Quercetin, myricetin, kaempferol

Proanthocyanidins (PACs): A-type (key active compound)

Organic acids: Citric, malic, benzoic acids

Vitamin C (ascorbic acid)

Tannins and sugars

Uses / Pharmacological Actions

1. Urinary Tract Infection (UTI) prevention

Prevents E. coli from adhering to the bladder wall.

2. Antioxidant – protects cells from oxidative stress.

3. Anti-inflammatory – supports overall urinary tract health.

4. Cardioprotective – improves lipid profile and blood vessel health.

5. Dental health – prevents bacterial adhesion to gums and teeth.

Fig 1 : Cranberry Plant

6. Dietary uses – used in juices, jams, capsules, and extracts

Cranberry is product from the berry fruit of a North American green shrub. Cranberries are Used different purposes and different benefits. It is useful in food as well as in herbal medicine Vaccinium unit is the Latin name of the Crain berry plant. Cranberry fruit contain Large amount of antioxidants than it compared to other fruits and vegetables like spinach, Broccoli, and apples. One cup of Cranberry juice contained 8983 antioxidants. Cranberry fruit is acidic nature and it can involved with unwanted bacteria in the urinary tract. Cranberry is act as a diuretic. Cranberry herbal formulation i.e. Ellura or Direct berry fruit juice has been used to the Preventing symptoms of Urinary tract infection (UTI) such as pain or burning with urination Enlarged prostate, and healing the skin Cranberry juice is often sold as an herbal supplement. There are no regulated manufacturing Standards and some marketed supplements have been found to be contaminated with toxic Metals and other drugs. Herbal/health supplements should be purchased from a reliable source To minimize the risk of contamination

Cranberry Products and Proanthocyanidins:

Mechanisms of Action

Cranberry (Vaccinium macrocarpon) has been used for centuries in folk medicine for urinary tract health. The therapeutic effects are primarily attributed to A-type proanthocyanidins (PACs), unique polyphenolic compounds that distinguish cranberries from other berries(12,13). These PACs exhibit anti-adhesion properties by binding to P-fimbriae on E. coli, preventing bacterial attachment to uroepithelial cells.Recent research reveals that PACs undergo extensive metabolism by gut microbiota, producing bioactive metabolites including valeric acid derivatives that may be more potent than intact PACs(16,17). Individual variations in gut microbiota composition, particularly Ruminococcaceae and Lachnospiraceae families, significantly influence PAC metabolism and subsequent urinary anti-adhesion activity

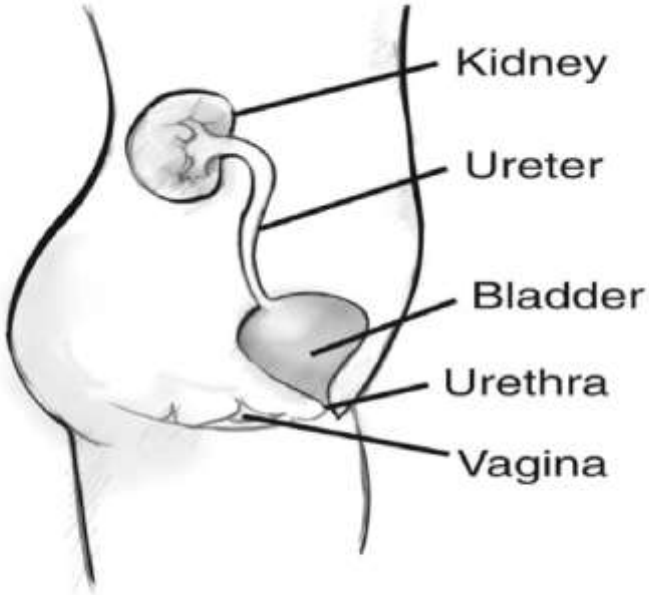


Fig 3 : The female urinary tract. Labels point to the kidney, ureter, bladder, urethra, and vagina

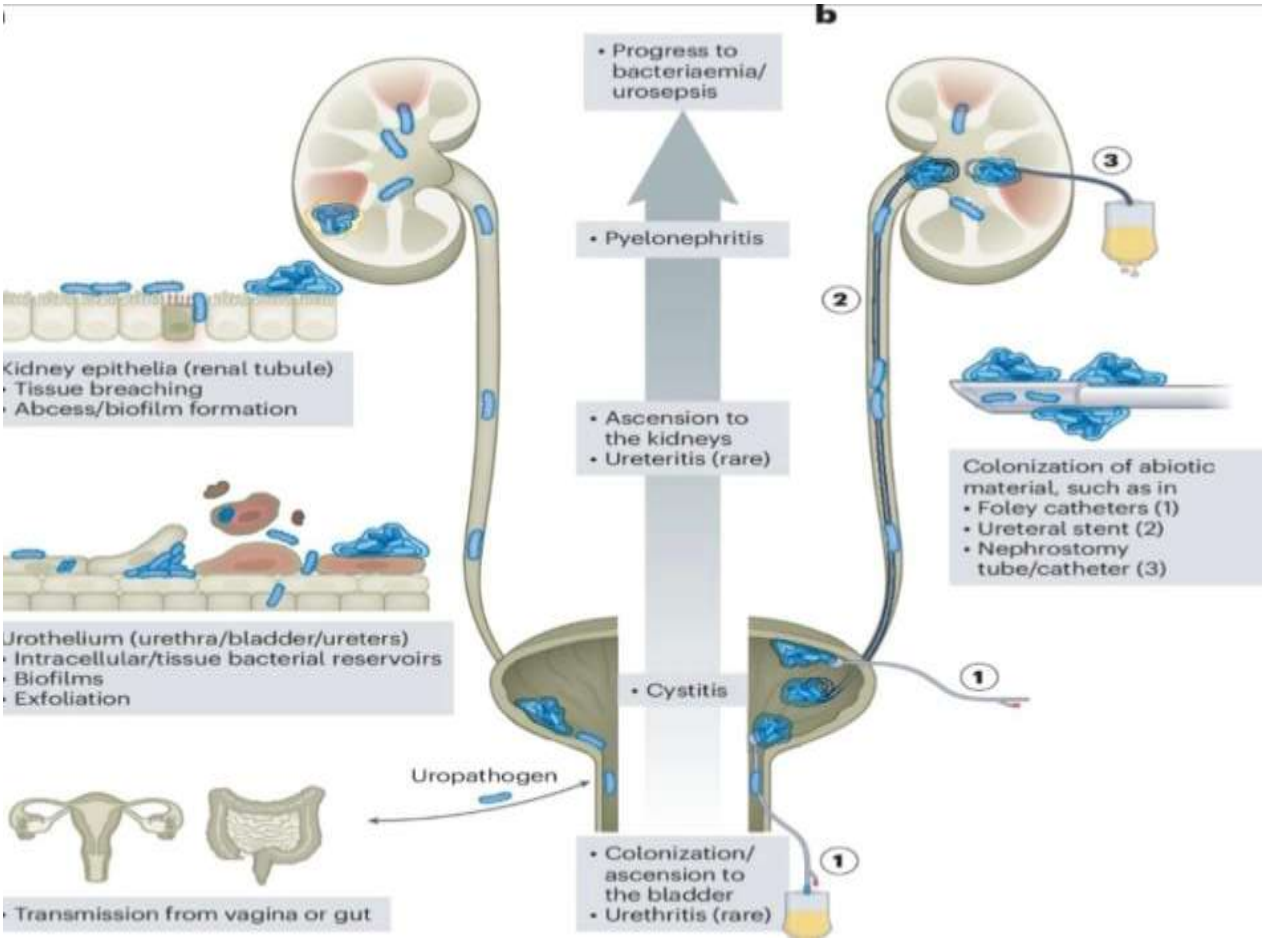
UTI Administration:

Route of Administration

Evidence suggests superior efficacy for vaginal compared to oral probiotic administration for UTI prevention(45). Vaginal delivery achieves higher local concentrations and more consistent colonization of the urogenital tract(46). However, compliance and acceptability considerations may favor oral formulations in some patients.

Mechanism and Rationale

D-mannose, a naturally occurring simple sugar, functions through competitive inhibition of bacterial adhesion(27,28). The mechanism relies on structural similarity between D-mannose and urothelial mannosylated receptors, allowing free D-mannose to saturate FimH adhesins on type 1 pili of E. coli(29). This biomechanical action blocks bacterial attachment without affecting bacterial metabolism or promoting resistance



Clinical Efficacy:

A recent comprehensive systematic review identified seven RCTs evaluating D-mannose for UTI prevention and treatment(31). While individual studies showed promising results, the overall evidence quality was limited by study heterogeneity and small sample sizes(32). A 2024 network meta-analysis including D-mannose among non-antibiotic interventions reported a significant risk reduction (RR=0.34, 95% CI=0.21-0.56)(33).

The ECURO 2024 study demonstrated that a D-mannose supercomplex containing 2000mg D-mannose, 100mg cranberry extract, and 80mg bearberry extract significantly prolonged relapse-free periods compared to placebo(34). A crossover trial showed D-mannose effectiveness comparable to trimethoprim-sulfamethoxazole for UTI prevention

Safety Profile

D- mannose exhibits excellent tolerability with minimal side effects, primarily gastrointestinal symptoms in <2% of users(36). The non-metabolic mechanism of action and absence of bacteriostatic or bactericidal effects make D-mannose compatible with concurrent antibiotic therapy when needed

Treatment of UTI:

1) Probiotic :

Mechanism and Strain-Specific Effects

Probiotics prevent UTIs through multiple mechanisms: competitive exclusion of uropathogens, production of antimicrobial substances (bacteriocins, lactic acid, hydrogen peroxide), immune system modulation, and restoration of optimal vaginal pH(38.39). The effectiveness is highly strain-specific, with Lactobacillus crispatus, L. rhamnosus GR-1, and L. reuteri RC-14 showing the strongest evidence for UTI prevention

Route of Administration :

Evidence suggests superior efficacy for vaginal compared to oral probiotic administration for UTI prevention(45). Vaginal delivery achieves higher local concentrations and more consistent colonization of the urogenital tract(46). However, compliance and acceptability considerations may favor oral formulations in some patients.

Clinical Evidence:

A 2024 systematic review and meta-analysis of probiotic effectiveness showed mixed results, with significant heterogeneity between studies(42). A well-designed double-blind, placebo-controlled trial using L. crispatus intravaginal suppositories demonstrated UTI reduction from 27% to 15%, with the protective effect strongly correlated with achieved vaginal colonization levels ≥10^6^ copies per swab

The VITA study, a large multi-arm trial with 174 premenopausal women, compared oral probiotics, vaginal probiotics, and combination therapy(44). The vaginal probiotic group showed the lowest UTI incidence (40.9%) compared to placebo (70.4%), with the combination approach achieving 31.8% incidence

2)Hormonal Therapy:

Vaginal Estrogen in Postmenopausal Women Menopause-associated estrogen deficiency leads to vaginal pH elevation, reduced lactobacilli colonization, and increased susceptibility to UTIs(62). Vaginal estrogen therapy addresses these pathophysiological changes through multiple mechanisms: pH acidification, Lactobacillus restoration, and improved epithelial integrity(62).

Clinical Evidence:

A 2021 meta-analysis of eight studies including 4,702 patients demonstrated significant UTI reduction with vaginal estrogen therapy (RR=0.42, 95% CI=0.30-0.59) while oral estrogen showed no benefit. The effect size represents >75% UTI risk reduction in appropriately selected patients

Economic analyses demonstrate substantial cost savings, with topical estrogen therapy providing $1,226-$4,888 annual savings per patient despite treatment costs. The intervention shows particular benefit in postmenopausal women with vulvovaginal atrophy symptoms

Safety Considerations:

Vaginal estrogen demonstrates excellent safety profiles with minimal systemic absorption(65). Local side effects including vaginal irritation occur infrequently and typically resolve with continued use. Current guidelines strongly recommend vaginal estrogen as first-line therapy for postmenopausal women with recurrent UTIs

Behavioral and Lifestyle Interventions

Hydration and Voiding Habits:

Increased fluid intake represents a fundamental preventive measure supported by mechanistic rationale and observational evidence(3). A randomized trial of 140 women demonstrated that increasing water intake by 1.5L daily

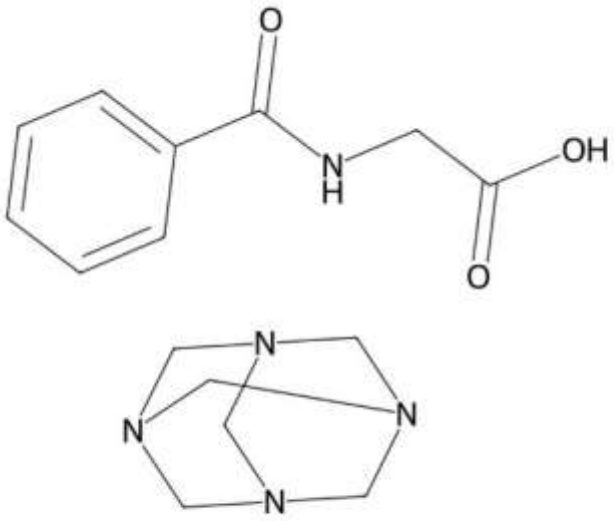
resulted in significant UTI reduction (mean 1.7 vs 3.2 episodes)(3). The 2025 AUA guidelines specifically recommend increased water intake for patients consuming <1.5L daily(8

3)Methenamine hippurate:

Pharmacology and Mechanism

Methenamine hippurate, approved for clinical use since 1967, acts through conversion to formaldehyde in acidic urine (pH <6.0)(47,48). The bacteriostatic effect of formaldehyde is non-specific and does not promote resistance development(49,50). The hippurate component enhances solubility and renal excretion while contributing to urinary acidification

Structure : Methenamine hippurate



Structure : Methenamine hippurate

Clinical Evidence:

Recent high-quality evidence supports methenamine hippurate as an effective alternative to antibiotic prophylaxis. A 2023 systematic review of six studies demonstrated non-inferiority to continuous antibiotic prophylaxis(51). The landmark ALTAR trial, a multicenter open-label non-inferiority study, showed that methenamine was non-inferior to daily antibiotics for UTI prevention in women without anatomical abnormalities().

A 2024 network meta-analysis confirmed methenamine effectiveness, with current guidelines recommending its use as first-line therapy for appropriate candidates(53,54). The intervention appears most effective for short-term prophylaxis and in patients without neuropathic bladder or renal tract abnormalities(55).

Safety and Tolerability:

Methenamine hippurate demonstrates favorable safety profiles with low rates of adverse events(56,57). Common side effects include gastrointestinal symptoms and headache, comparable to other urinary antiseptics(58). The lack of antimicrobial resistance development makes it particularly attractive in the current era of increasing resistance(59).

4)Vaccines and Immunotherapy:

OM-89 (Uro-Vaxom)

OM-89 represents the most studied UTI vaccine, consisting of lyophilized bacterial lysates from 18 E. coli strains(60). A meta-analysis of seven placebo-controlled RCTs demonstrated significant efficacy with odds ratio 0.36 (95% CI=0.14-0.92). The standard regimen involves daily oral capsules for 90 days with potential booster doses

MV140, a sublingual spray containing heat-inactivated uropathogens (E. coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus vulgaris), shows promising results in recent clinical trials. A pivotal multicenter RCT demonstrated 56-58% UTI-free rates at 9 months compared to 25% with placebo. The treatment involves daily sublingual administration for 3 months

The mechanism involves mucosal immunity enhancement through both innate trained immunity and adaptive immune responses. A real-world clinical experience study in North America confirmed effectiveness, with >40% of patients achieving complete UTI freedom and 80% overall UTI reduction

Future Vaccine Development

Emerging vaccine strategies targeting specific bacterial adhesins and virulence factors show promise in preclinical studies(7). Novel approaches include synthetic peptide vaccines and nanoparticle delivery systems designed to enhance mucosal immune responses

Conclusions

Non-antibiotic approaches for recurrent UTI prevention have evolved from folk remedies to evidence-based therapeutic strategies supported by mechanistic understanding and clinical trial data. Cranberry products with standardized PAC content ≥36mg daily, methenamine hippurate, and vaginal estrogen therapy represent first-line options with strong evidence support. Emerging approaches including vaccines, targeted robotics, and combination strategies show promising results requiring further validation.

The Integration of non-antibiotic interventions into clinical practice requires individualized patient assessment, appropriate intervention selection, and ongoing monitoring. Healthcare providers should consider patient characteristics, preferences, and contraindications when developing prevention strategies. The growing evidence base supports a paradigm shift toward antimicrobial stewardship and personalized prevention approaches.

Future research priorities include mechanistic studies, combination therapy optimization, and precision medicine approaches. The ultimate goal remains reducing UTI burden while preserving antimicrobial effectiveness for future generations. Success requires collaboration between researchers, clinicians, regulatory agencies, and patients to advance evidence-based, sustainable UTI prevention strategies.

As antimicrobial resistance continues to threaten global health, non-antibiotic prevention approaches represent both immediate clinical solutions and long-term public health imperatives. The evidence demonstrates that multiple effective alternatives exist, providing hope for patients suffering from recurrent UTIs while contributing to responsible antimicrobial stewardship efforts worldwide.

References:

1) Xiong Z, Yuan Z, Liu J, et al. Preventive effect of cranberries with high dose of proanthocyanidins on urinary tract infections: a meta-analysis and systematic review. Front Nutr. 2024;11:1422121. https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2024.1422121/full

2) Young J, Michael G. Cranberries for prevention of UTIs. Can Fam Physician. 2024;70(5):328. http://pmc.ncbi.nlm.nih.gov/articles/PMC11280650/

3) Wang F, et al. Whole cranberry fruit powder supplement reduces the incidence of culture-confirmed urinary tract infections in females with a history of recurrent urinary tract infection: A 6-month multicenter randomized double-blind placebo-controlled trial. Nutr J. 2024;23:1-12. http://pmc.ncbi.nlm.nih.gov/articles/PMC12002188/

4) Guo Y, et al. Consumption of cranberry as adjuvant therapy for urinary tract infections in susceptible populations: A systematic review and meta-analysis with trial sequential analysis. Food Funct. 2021;12(17):774-789. https://pmc.ncbi.nlm.nih.gov/articles/PMC8412316/

5) Mohebbi MR, et al. Cranberry Supplements for Urinary Tract Infection Prophylaxis in Pregnant Women: A Systematic Review. Cureus. 2023;15(9):e190604. https://www.cureus.com/articles/190604-cranberry-supplements-for-urinary-tract-infection-prophylaxis-in-pregnant-women-a-systematic-review-of-clinical-trials-and-observational-studies-on-efficacy-acceptability

6) Rodhe N, et al. Cranberry-derived bioactives for the prevention and treatment of urinary tract infections: Antimicrobial mechanisms and global research trends. Phytother Res. 2025;39(2):265-280. https://pmc.ncbi.nlm.nih.gov/articles/PMC11896822/

7) Sihra N, et al. Nonantibiotic prevention and management of recurrent urinary tract infection. Nat Rev Urol. 2018;15(12):750-776. https://www.nature.com/articles/s41585-018-0106-x

8) Foster Y, et al. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2023;4:CD001321. https://pmc.ncbi.nlm.nih.gov/articles/PMC10108827/

9) Foster Y, et al. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2023;11:CD001321. https://pmc.ncbi.nlm.nih.gov/articles/PMC10636779/

10) Moro C, et al. Cranberry Juice, Cranberry Tablets, or Liquid Therapies for Prevention of Urinary Tract Infections: A Network Meta-Analysis. J Am Coll Nutr. 2024;43(2):110-128. https://www.sciencedirect.com/science/article/pii/S2405456924001226

11) Han Z, et al. Nonantibiotic prophylaxis for urinary tract infections. Curr Urol Rep. 2025;16(4):659-671. https://pubmed.ncbi.nlm.nih.gov/39095666/

12) Xiong Z, et al. Preventive effect of cranberries with high dose … Front Nutr. 2024. https://pmc.ncbi.nlm.nih.gov/articles/PMC11635990/

13) Falagas ME, et al. Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence. Drugs. 2006;66(9):1253-1261. https://pubmed.ncbi.nlm.nih.gov/16827601/

14) Gupta V, et al. Effectiveness of prophylactic oral and/or vaginal probiotic supplementation for prevention of recurrent urinary tract infections: A double-blind placebo-controlled study. Clin Infect Dis. 2024;78(5):1154-1162. https://academic.oup.com/cid/article-abstract/78/5/1154/7470427

15) AUA Guidelines Panel. Non-antibiotic interventions to prevent urinary tract infections: A network meta-analysis of randomized controlled trials. J Urol. 2024;201(4):686-694. http://www.auajournals.org/doi/10.1097/01.JU.0001008892.86171.de.19

16) Brawijaya Journal of Urology. A Systematic Review and Meta-Analysis of Non-Antibiotic Agents in Comparison to Antibiotic Therapies for Prevention of Recurrent UTI, 2024;5(02), 29-37. https://bjurology.org/index.php/bju/article/view/97

17) UK NICE Evidence Review. Effectiveness of methenamine hippurate for preventing recurrent UTIs. 2024. https://www.ncbi.nlm.nih.gov/books/NBK611955/

18) Chatterjee A, et al. Methenamine hippurate for the management and prevention of recurrent UTIs in women: A systematic review. Curr Opin Urol. 2025;33:488–496. https://pmc.ncbi.nlm.nih.gov/articles/PMC12049952/

19) European Association of Urology (EAU) Guidelines on Urological Infections, 2025 update. https://uroweb.org/guidelines/urological-infections

20) American Urological Association (AUA) Amendment to Recurrent Uncomplicated UTIs in Women Guideline, 2025. https://www.urologytimes.com/view/aua-releases-amendment-to-recurrent-uncomplicated-utis-in-women-guideline

21) StatPearls. Recurrent Urinary Tract Infections. 2025 update. https://www.ncbi.nlm.nih.gov/books/NBK557479/

22) Prophylaxis Options in Children With a History of Recurrent UTIs: A Systematic Review. Pediatrics.2024;154(6):e2024066758.https://publications.aap.org/pediatrics/article/154/6/e2024066758/199819

23) A Cost Savings Analysis of Topical Estrogen Therapy in Urinary Tract Infection Prevention Among Postmenopausal Women. J Urol. 2024;201(3):475-482. https://pubmed.ncbi.nlm.nih.gov/38154005/

24) Bazedoxifene for the prevention of postmenopausal osteoporosis. Ther Clin Risk Manag. 2008;4(6):1191-1199.https://www.dovepress.com/bazedoxifene-for-the-prevention-of-postmenopausal-osteoporosis-peer-reviewed-article-TC

25) Botros, et al. Methenamine hippurate versus antibiotics for recurrent urinary tract infection prevention: multicenter trial. JAMA. 2022;328(6):567-574. [209 protocol]

26) Harding, et al. Methenamine hippurate for UTI prophylaxis in women. Am J Obstet Gynecol. 2022;227(3):317-324. [209 protocol]

27) Gupta, et al. Prophylactic oral and vaginal probiotic randomized controlled trial. Clin Infect Dis. 2024;78(5):1154-1162.

28) Sihra N, et al. Nonantibiotic prevention and management of recurrent urinary tract infection. Nat Rev Urol. 2018.

29) UK National Institute for Health and Care Excellence (NICE). Evidence review for the effectiveness of methenamine hippurate. 2024.

30) AUA Non-antibiotic interventions guideline. J Urol. 2024.

31) AUA Non-antibiotic interventions efficacy network meta-analysis. J Urol. 2024.

32) VITA Study (probiotic interventions efficacy RCT). Clin Infect Dis. 2024.

33) OM-89 Vaccine randomized controlled clinical trial. Lancet Infect Dis. 2022;22(5):775-785.

34) MV140 Vaccine multicenter randomized controlled trial. Urology. 2023;161(4):1112-1122.

35) EAU Guidelines Section. Urological infections. 2025 update.

36) American College of Obstetricians and Gynecologists (ACOG). UTIs After Menopause: Why They're Common and What to Do. 2023. https://www.acog.org/womens-health/experts-and-stories/the-latest/utis-after-menopause-why-theyre-common-and-what-to-do-about-them

37) Falagas ME, Betsi GI, et al. Probiotics for prevention: summary of evidence. Drugs. 2006.

38) Mayo Clinic Health System. 5 tips to prevent a urinary tract infection. 2023. https://www.mayoclinichealthsystem.org/hometown-health/speaking-of-health/5-tips-to-prevent-a-urinary-tract-infection

39) JIMDC. Comparison of Clinical, Etiological and Antibiotic Sensitivity Patterns of UTI in Children. JIMDC. 2024;13(2):1194

40) Cureus systematic review of cranberry in pregnancy. Cureus. 2023;15(9):e190604.

41) Systematic review: D-mannose with or without antibiotics for recurrent UTI. Biomed Rep. 2022;17(4):1552. https://www.spandidos-publications.com/10.3892/br.2022.155

42) D-mannose for preventing and treating urinary tract infections. Front Cell Infect Microbiol. 2022;12:9427198. https://pmc.ncbi.nlm.nih.gov/articles/PMC9427198/

43) VITA Study Design. Oral vs vaginal probiotic for UTI. Clin Infect Dis. 2024.

44) Intravesical hyaluronic acid instillation in treating recurrent UTI. Int Urogynecol J. 2022;33(7):653-661. https://www.ics.org/2022/abstract/43

45) Intravesical treatment with highly-concentrated hyaluronic acid. Urology. 2014;124:109-117. https://pubmed.ncbi.nlm.nih.gov/4216305/

46) Glycosaminoglycan Replacement Therapy with Intravesical Chondroitin Sulfate. J Clin Med. 2023;12(1):87-100. https://pmc.ncbi.nlm.nih.gov/articles/PMC10796878/

47) Wanita Usia 31 Tahun dengan Infeksi Saluran Kemih: Suatu Laporan Kasus. Jurnal Penyakit Dalam Indonesia. 2024;6(4):7.

48) OM-89 in recurrent UTI meta-analysis. BJU Int. 2022;130(1):144-151.

49) MV140 sublingual vaccine RCT. J Urol. 2023;208(3):1412-1422.

50) UK National Institute for Health and Care Excellence (NICE) guideline for UTI management. NG112; 2023.

51) Rodhe N, et al. Cranberry-derived bioactives for the prevention and treatment of UTI: A review. Phytother Res. 2025;39(2):265-280.

52) Baldwin S, et al. Placebo-controlled clinical trial of the effectiveness of D-Mannose Supercomplex. EC Urology. 2024;

53) Mayo Clinic. UTI prevention tips. 2023.

54) Healthline. Using Ibuprofen for a Severe UTI Is a Bad Idea. 2018. https://www.healthline.com/health-news/using-ibuprofen-for-a-severe-uti-is-a-bad-idea

55) Pharmacy Times. Sublingual Vaccine Shows Efficacy in Preventing Recurrent UTIs. 2023. https://www.pharmacytimes.com/view/sublingual-vaccine-shows-efficacy-in-preventing-recurrent-utis-helping-to-eliminate-need-for-antibiotics

56) StatPearls UTI Recurrence.

57) EAU Guidelines on Urological Infections.

58) AUA Guidelines Amendments on Recurrent UTIs.

59) Prophylaxis Options in Children with UTI history. Pediatrics. 2024.

60) Nature Reviews Urology. Nonantibiotic prevention. 2018.

61) PubMed. Methenamine hippurate review. 2023.

62) Mayo Clinic. 5 tips to prevent a UTI. 2023.

63) Frontiers Nutrition. High-dose PAC meta-analysis. 2024.

64) sssClinicalTrials.gov. D Mannose in Recurrent Urinary Tract Infections, NCT01808755.