



Insights on Effective Complementary Strategies in the Management of Urinary Tract Infections

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Abstract

Urinary tract infections (UTIs) are common health issues that occur frequently in both women and men. These infections occur in the urinary tract, leading to discomfort and potential complications. Prompt medical attention is essential to diagnose and treat UTIs effectively. Aim of this research was to provide an overview of effective complementary strategies in the management of UTIs. This review paper focuses on the current and future treatment strategies for UTI infections. Various natural remedies have been investigated as potential complementary therapies to enhance health outcomes for UTI patients. The efficacy of frequently employed natural products, including cranberry juice/extracts, ascorbic acid, hyaluronic acid, probiotics and multi-component formulations designed for the treatment and prevention of UTIs, has been explored. The probiotics serve to break down food and increase our immunity. Usually, multiple doses of antibiotics are used to treat these infections, but there are many side effects and bacterial resistance rates are increasing. Complementary UTI management strategies, including effective dietary regimens and new formulations, are attaining approvals. Drinking liquids daily significantly suppresses UTI infections. Incorporating daily consumption of cranberry juice may still be regarded as a viable complementary strategy to aid in the management of UTI infections.

Key words: Urinary tract infections; Microorganisms; Vitamins; Probiotics; Dietary supplements; Drug resistance, bacterial.

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Introduction

A urinary tract infection (UTI) is an infectious condition that impacts different segments of the urinary tract, including the kidneys, ureters, bladder and urethra. This infection manifests in two forms upper and lower UTIs. An infection in the upper urinary tract is specifically referred to as a kidney infection or pyelonephritis, while an infection in the lower urinary tract is termed a bladder infection or cystitis. In certain instances, there may be discoloration of the urine, with a potential presence of blood.¹

UTIs rank as the second most prevalent infection following respiratory tract infections. Various approaches are employed to manage and prevent different infections of UTIs, encompassing antibiotic therapy, consumption of bioactive natural foods, probiotic use and adherence to sound personal hygiene practices. Despite these efforts, addressing UTIs successfully remains a challenge. The choice of medication and duration of therapy hinge on factors such as the specific bacterial strain, its susceptibility, the patient's medical history, symptoms and immune status.²

Causative agents

Common organisms *Escherichia coli* and *Staphylococcus saprophyticus* cause UTIs. Less common organisms include *Proteus mirabilis* and *Enterococcus* species.

Symptoms and risks

Common indicators of lower UTIs include a burning sensation during urination, frequent urges to micturate, pain while urinating, stress or force above the pubic bone (even between urination), difficulty in passing urine and general lethargy. In men, in addition to painful urination and the presence of leucocytes in the urine (*pyuria*), there may be a perception of fullness in the rectum.

In the case of children with UTIs, symptoms can range from being asymptomatic to presenting with less specific indicators like irritability, inability to control, loose bowel movements, loss of appetite and fever. Observable manifestations might encompass cloudy or milky urine, potentially exhibiting a pink or reddish hue in the presence of significant blood. Should the infection advance to the kidneys, resulting in acute pyelonephritis, symptoms may involve fever, flank pain, nausea and vomiting. The severity of symptoms can vary, typically lasting around 6 days.

Complications

Frequent infections, particularly in women facing three or more UTIs, pose risks such as permanent kidney damage from pyelonephritis, an elevated likelihood of delivering low birth weight or premature infants for pregnant women and the potential for sepsis—a life-threatening complication, particularly if the infection spreads to the kidney.³ Simple UTIs are the most common type and usually occur when there are no functional or anatomical abnormalities within the urinary tract. In contrast, complex UTIs occur when there is an abnormal urinary tract, increasing the susceptibility to infection.⁴

Pathophysiology

The normal state of the urinary tract is sterility. Urine, although typically sterile, becomes a conducive culture medium for bacterial growth when its pH is 5.5 or lower, accompanied by a high concentration of urea and the presence of organic

acids resulting from a diet rich in fruits and proteins. The organic acids contribute to urine acidification. Typically, a residual thin film of urine persists in the bladder after micturition. Bacteria present in this residual urine are usually expelled by the mucosal cells, which produce organic acids. If the mechanisms of the lower urinary tract fail and the infection involves the upper tract or kidneys, it can lead to pyelonephritis.

Host defence mechanisms at this level involve local leukocyte phagocytosis and renal production of antibodies that, in the presence of complement, can kill bacteria. Postmenopausal women with bladder or uterine prolapse may experience an increased frequency of UTIs due to incomplete bladder emptying, allowing residual bacteria to impact local bladder mucosal defences. Additionally, individuals with diabetes mellitus, characterised by high urine glucose content and compromised host immune factors are more prone to urinary infections.⁵

Primary tubular diseases encompass conditions where the tubules are damaged by ischaemic or toxic agents, such as in the case of acute tubular necrosis (ATN). Tubulointerstitial diseases involve inflammatory processes affecting both the tubules and the *interstitium*. An example of this is pyelonephritis, which can manifest in acute or chronic forms.

Tubulointerstitial diseases

Tubulointerstitial nephritis refers to an inflammatory process primarily affecting the renal interstitial tissue, often accompanied by varying degrees of tubular damage. The interstitial reaction is secondarily associated with several primary conditions, including glomerular, tubular, vascular and obstructive diseases.

Acute pyelonephritis

Acute pyelonephritis is a sudden, purulent inflammation of the kidney resulting from the presence of pyogenic bacteria. The majority of acute pyelonephritis cases stem from infections originating in the lower urinary tract. The predominant pathogenic organism responsible for UTIs is *E coli*, accounting for approximately 90 % of cases. Following *E coli*, other organisms such as *Enterobacter*, *Klebsiella*, *Pseudomonas* and *Proteus* are identified, albeit with decreasing frequency. These bacteria enter the urinary tract and subsequently invade the kidney through one of two routes ascending infection or haematogenous infection (Figure 1).

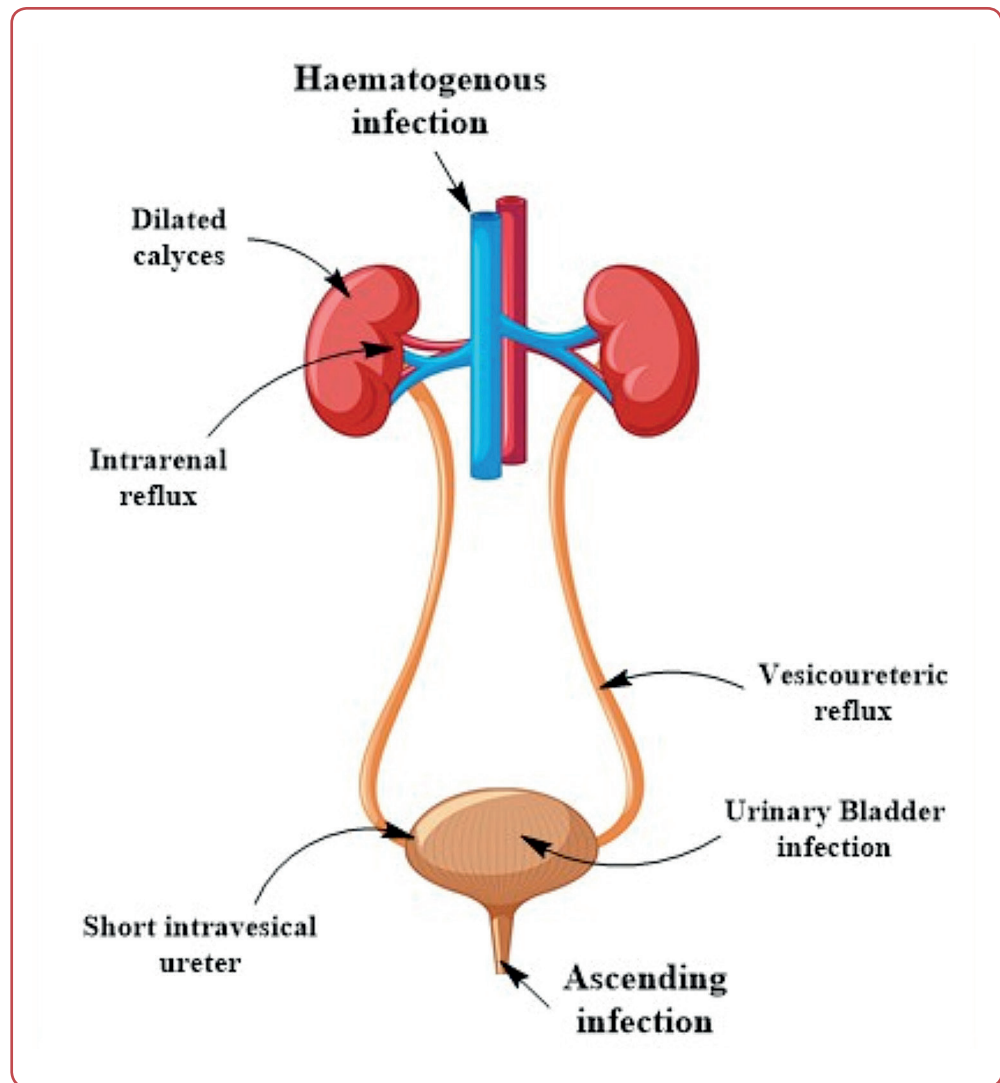


Figure 1: Pathogenesis of reflux nephropathy

The primary mode of infection is ascending, where pathogenic organisms, often inhabitants of the colon, can lead to faecal contamination of the urethral orifice. This is particularly notable in females within the reproductive age group. Various factors contribute to this, including the shorter urethra in females, making them more susceptible to faecal contamination, hormonal influences that facilitate bacterial adherence to the mucosa, the absence of prostatic secretions with antibacterial properties and potential urethral trauma during sexual intercourse. While ascending infection can occur in individuals with normal health, the susceptibility to such infections increases in patients with conditions like diabetes mellitus, pregnancy, urinary tract obstruction or instrumentation. Haematogenous infection is a less common occurrence, where acute pyelonephritis can arise from the dissemination of infection through the bloodstream. This tends to be more prevalent in individuals with blockage

in the urinary tract or those who are debilitated or immunosuppressed.

Typically, acute pyelonephritis manifests with a sudden onset marked by chills, fever, loin pain, lumbar tenderness, dysuria and increased frequency of urination. Urinalysis reveals a notable presence of bacteria, pus cells and pus cell casts in the urinary sediment. The infection is commonly treated by initiating specific antibiotics, guided by the identification of bacteria through culture and subsequent sensitivity testing. This approach effectively resolves the infection in the majority of patients.

Complications arising from acute pyelonephritis are more frequently observed in individuals with diabetes mellitus or those experiencing urinary tract obstruction. The three significant complications associated with acute pyelonephritis are:

Papillary necrosis. Papillary necrosis, or necrotising papillitis, is more commonly seen in conditions like analgesic abuse nephropathy and sickle cell disease. However, it can also manifest as a complication of acute pyelonephritis, affecting either one or both kidneys.

Pyonephrosis. Pyonephrosis occurs when abscesses fail to drain, leading to the transformation of the kidney into a multilocular sac filled with pus. This condition is termed pyonephrosis or renal carbuncle.

Perinephric abscess. Abscesses within the kidney may extend beyond the kidney capsule into the perinephric tissue, resulting in the formation of a perinephric abscess.⁶

UTIs may not always present noticeable symptoms. However, when symptoms do occur, they may include: persistent strong urge to urinate; a sensation of burning during urination; frequent urination, accompanied by passing small amounts of urine; cloudy appearance of urine; urine that is red, bright pink, or cola-coloured, indicating the presence of blood; strong-smelling urine; pelvic pain, particularly in women, is concentrated in the central pelvic region and around the area of the pubic bone. In older adults, UTIs can sometimes go unnoticed or be mistaken for other health conditions.

Distinct types of UTIs may give rise to more specific symptoms, with the manifestations varying depending on the specific segment of the urinary tract that is affected. The signs and symptoms of a UTI are contingent on the specific part of the urinary tract affected:

Kidneys: back or side pain; elevated fever; shivering and chills; nausea and vomiting;

Bladder: pelvic pressure; discomfort in the lower abdomen; discomfort during urination; presence of blood in urine;

Urethra: burning sensation during urination; discharge.

Diagnostic and treatment approaches

Diagnosing a UTI involves a straightforward urine test where samples are examined for the

presence of nitrates and leukocytes. The confirmation of a UTI diagnosis typically requires a urine culture. Physicians commonly address UTIs with antibiotic treatment, and in cases of recurring infections, they may prescribe prolonged antibiotic courses. However, the challenge with frequent and extended antibiotic usage lies in the potential disruption of beneficial bacteria in the body, crucial for vital functions and defence against harmful bacteria. This cycle of infection, treatment and re-infection can become a concern. Considering the adverse effects of antibiotics on the body and the rising issue of bacterial antibiotic resistance, individuals experiencing recurrent UTIs may find it beneficial to explore natural methods to mitigate the risk of infection. Additionally, it is essential to bolster your body's well-being by replenishing beneficial bacteria during and after antibiotic treatment, which can be achieved through the use of a multispecies probiotic supplement. This practice is highly advantageous for enhancing overall long-term health and fitness.

Complementary strategies for the prevention of UTI

Antibiotics usually are the first treatment for UTIs. Overall health and the type of bacteria found in urine determine which medicine is used and how long. Simple cystitis in women may be treated with a 3-day regimen of any of several antibiotics, including trimethoprim-sulphamethoxazole one double-strength tablet twice daily for 3 days, nitrofurantoin extended release: 100 mg twice daily for 7 days, fosfomycin, pivmecillinam and ciprofloxacin. Phenazopyridine 250 mg twice daily for 3 days, 200 mg twice daily for 2 days can provide pain relief from dysuria and bladder spasms. It is available over the counter and by prescription.

The group of antibiotics known as fluoroquinolones isn't commonly recommended for simple UTIs. These drugs include ciprofloxacin, levofloxacin and others. The risks of these drugs generally outweigh the benefits of treating uncomplicated UTIs. In cases of a complicated UTI or kidney infection, healthcare provider might prescribe a fluoroquinolone medicine if there are no other treatment options. Healthcare provider also may give a pain reliever to take that can ease burning

while urinating. Usually, pain goes away soon after starting an antibiotic.⁷

Herbal medicines used in the prophylaxis of UTI

Frequent UTIs after antibiotic therapy indicate microbial resistance to allopathic drugs. Alternative treatments should be explored.

Cranberry

North American *Vaccinium macrocarpon* Ait (cranberry) contains active ingredients like benzoic acid, proanthocyanidins (type A), ursolic acid, citric acid, D-mannose, hippuric acid, quinic acid, terpenes, flavonols⁸ and anthocyanins like hydrocinnamic acid and hydroxybenzoic acid. Nowadays utility of cranberry has augmented as the traditional and prophylactic approach in the treatment of repeated UTIs. Quinic acid has been suggested to excrete hippuric acid in substantial proportions, acting as an antimicrobial and urine acidifier.^{9, 10} Howell et al reported that the isolated A-type proanthocyanidins linkages at a concentration of 60 µg/mL of cranberry cocktail or juice¹¹ prevent the linkage of type 1 and P-fimbriated uropathogenic bacteria mainly *E coli* to uroepithelial cells.¹²⁻¹⁴

In vivo studies have explained that when the adhesion of bacteria is impeded, they cannot invade the mucosal layer of the tract and thus aid in maintaining urinary tract health.¹⁵⁻¹⁷ Cranberry

has also reported substantial results on the motility of *Pseudomonas mirabilis* and *P aeruginosa*¹⁸ and on the biofilm formation of *P aeruginosa*, *E faecalis* and *E coli*.¹⁹⁻²¹ The extract of cranberry was also shown to have higher activity in decreasing the pH of urine and reducing the recurrence of UTI infections.²² Cranberry remnants found in stool substantially promote a shift towards a milder UTI infection caused by bacterial flora consequently reducing the recurrence.²³

Foxman et al²⁴ found significant reduction in the occurrence of UTI infections in both normal and catheterised patients after gynaecological surgery when treated with cranberry capsules in a randomised, double-blinded, placebo-controlled clinical trial. The active compounds in cranberry were found to be effective remedies for UTI as well as acute cystitis²⁵ in middle-aged women. However, the effect of the drug was not distinct for older adults and patients with neurogenic bladder experiencing multifaceted UTI. However, excessive consumption of these compounds may lead to adverse effects such as an increase in body weight, digestive problems and drug interactions with anticoagulants.²⁶ Because of the different dosages, concentrations and types of formulations such as juice, beverages and tablets of cranberry used, the diversity makes it challenging to decide on any single dosage formulation or combination.²⁷ Some of the clinical studies of different forms of cranberry are shown in the Table 1.

Table 1: Summary of clinical data of cranberry in treatment of urinary tract infections (UTIs)

Type of the study	Dose	Type of the formulation	Number of patients	Duration of treatment	Therapeutic effect	References
A randomised, placebo-controlled, double-blind study	240 mL	Cranberry juice	185 women	24 weeks	UTI episodes in women were lowered	[28]
Randomised, double-blinded study	125 mL	Cranberry beverage	Two groups of patients aged 20 to 79 years	24 weeks	Women above the age of 50 were found to be effectively treated for UTI.	[29]
Randomised clinical study	4 oz – 8 oz (daily)	Cranberry juice	176 premenopausal women	168 days	Showed protective effects against UTI and a decrease in the count of <i>E coli</i> strains (P-fimbriated)	[30]
Randomised clinical study	500 mg	Cranberry powder (proanthocyanidin content 0.56 %)	182 patients	12 months	Significant reduction in UTI	[31]

Uva ursi (bearberry leaf)

Arctostaphylos uvaursi (*Uva-ursi* or bearberry) leaf is recommended as a traditional medicine for the treatment of bladder inflammation and UTI. This wild flowering is mainly cultivated in various parts of countries such as Asia, Europe and North America. Researchers have discovered that bearberry mainly contain arbutin as a phytochemical that can fight against infection.³² This arbutin is metabolised into the body and converted into hydroquinone, which passes through the kidney into the urinary tract.³³ Hydroquinone may relieve inflammation and pain in the bladder or urinary tract (Figure 2). It may also stop the growth of harmful bacteria and support a healthy bacteria balance.³⁴ The herb also has protein precipitation effects, aiding in contracting and stiffening mucous membranes of the body because of its tannin content. Crude leaf preparations and extracts of bearberry leaf have shown low antibacterial action against recognised UTI-causing pathogens *in vitro* experiments. These include, but are not limited to, *S aureus*, *Candida albicans*, *E coli* and *Proteus vulgaris*.³⁵

Researchers also suggested that the herb was found to be most effective at alkaline pH (above 7) so, healthcare practitioners recommended sodi-

um or potassium citrate was taken before bearberry. The antibacterial effect of the herb was found to be destroyed in acidic pH.³⁶ The herb is also available in different solid dosage forms with a dose of 150-505 mg, to be taken 1-3 times daily. It can also be prepared as tea from dried leaves or a powdered extract. However, this herb was also found to have various side effects like nausea and vomiting, irritability and insomnia. It also interacted with other herbs, supplements, or medications. One of the metabolised products of phytochemicals hydroquinone in bearberry was also reported to have hepatotoxicity effects so it should not be recommended for more than 5 days for treatment and people who have digestive problems, metabolic disease, high blood pressure, Crohn's disease, ulcers or kidney disease should not take bearberry.³⁵

Cinnamon

Cinnamon (family: *Lauraceae*) illustrates anti-inflammatory, free radical scavenging activity, as well as antibacterial and antimicrobial effects. The various essential oils and aldehydes like eugenol, trans-cinnamyl acetate, trans-cinnamaldehyde (TC) and proanthocyanidins are the major active phytoconstituents present in bark responsible for the prevention of UTI. Cinnamal-

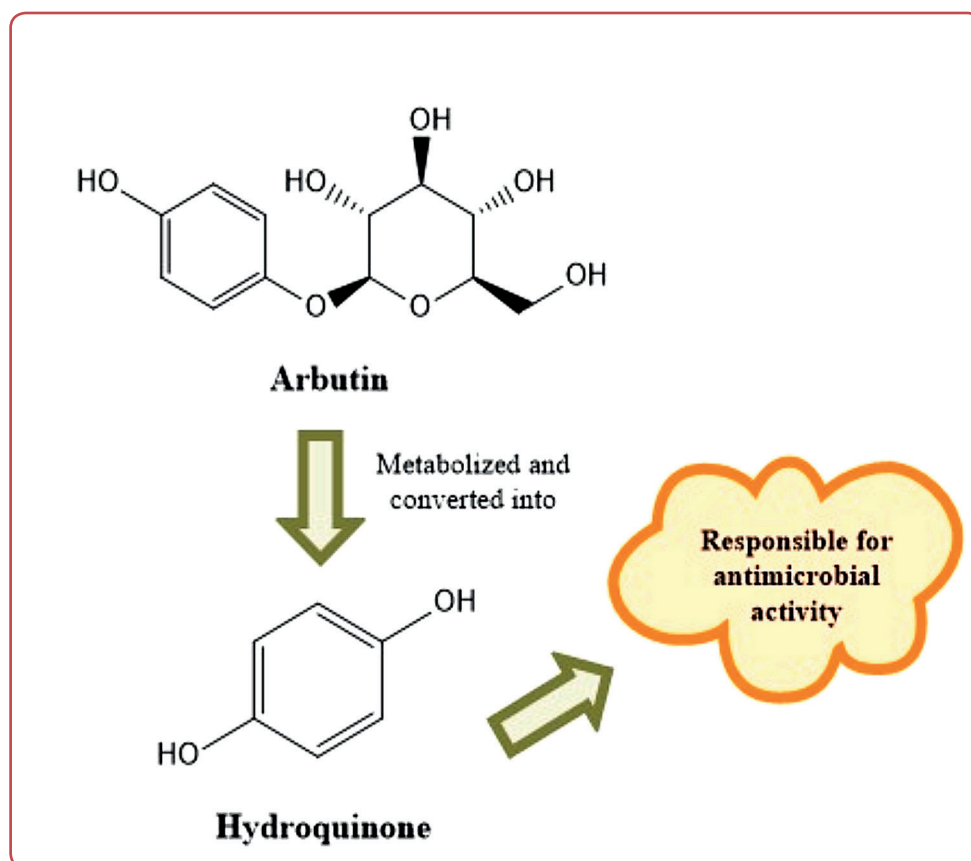


Figure 2: Mechanism of action of bearberry

dehyde, the active aldehyde content of cinnamon, destroys both types of bacteria with cytoplasmic membranes. It also inhibits cell-based amino acid decarboxylation. This inhibiting action causes microbial cell death by depleting energy.³⁷ In a study conducted by Amalaradjou et al it was demonstrated that TC down-regulated major virulence genes in *E coli*, leading to the inhibition of the formation of biofilm on urinary catheters. An active aldehyde content of 1-1.5 % was found to be effective in preventing and inactivating the formation of UPEC biofilm on cultures and catheters, without showing cytotoxic effects on the epithelial cells of the human bladder. Based on scientific studies, it has been proven that TC is highly recommended as a surface coating agent for catheters or the solutions used to lock catheters, effectively preventing UTIs. Trans-cinnamaldehyde significantly reduced the attachment, accumulation and invasion of pathogens by uroepithelial cells by inhibiting the expression of major genes associated with host tissue.³⁸ Narayanan et al³⁹ found a reduction in UPEC colonisation in the various parts of the urinary tract such as the urethra, bladder as well as a significant incidence of antibiotic-resistant UTIs in female mice (C57BL/6) by the treatment of different concentrations of Trans cinnamaldehyde (0.1, 0.2 and 0.4 %) for 10 days. Figure 3 explains the mechanism of action of oil as an antibacterial.

Garlic

Garlic (*A sativum*) is a rich source of phenolic compounds and contains allicin (allyl-2-propene

thiosulphate) as an active ingredient found in homogenates of freshly crushed garlic. Allicin exhibits antibacterial activity against Gram-positive bacteria, *E coli* and Gram-negative bacterial strains.⁴⁰ Along with its antibacterial activity, allicin and other actives such as ajoene, S-allyl-cysteine, diallyl sulphide, proteins, minerals and flavonoids⁴¹ also exhibit antimicrobial activity due to their chemical interaction with thiol groups in several enzymes (such as alcohol dehydrogenase and thioredoxin reductase) that are responsible for the metabolism and functioning of cysteine proteinase in bacteria. In an experimental UTI model, the authors demonstrated that garlic significantly reduced the virulence of *Pseudomonas aeruginosa*.⁴²

The potential regulatory mechanisms against UTIs of allicin were based on immunological and inflammatory response modules, particularly through AKT/NF-B signalling. During the experiment, the authors demonstrated that allicin had a strong inhibitory effect on the AKT/NF-B pathway, cytokines (IL-6 and IL-1) and MALT1 overexpression. The PI3K inhibitor or MALT-siRNA transfection of HUCs (human uroepithelial cell model) also partially inhibited the activation of the AKT/NF-B pathway and the production of cytokines. Additionally, it was demonstrated that allicin outperformed the PI3K inhibitor and siRNA-MALT1 in terms of therapeutic effects by creating the PCA algorithm to assess the therapeutic score. Additionally, allicin dramatically reduced the infection, up-regulation of MALT1 expression

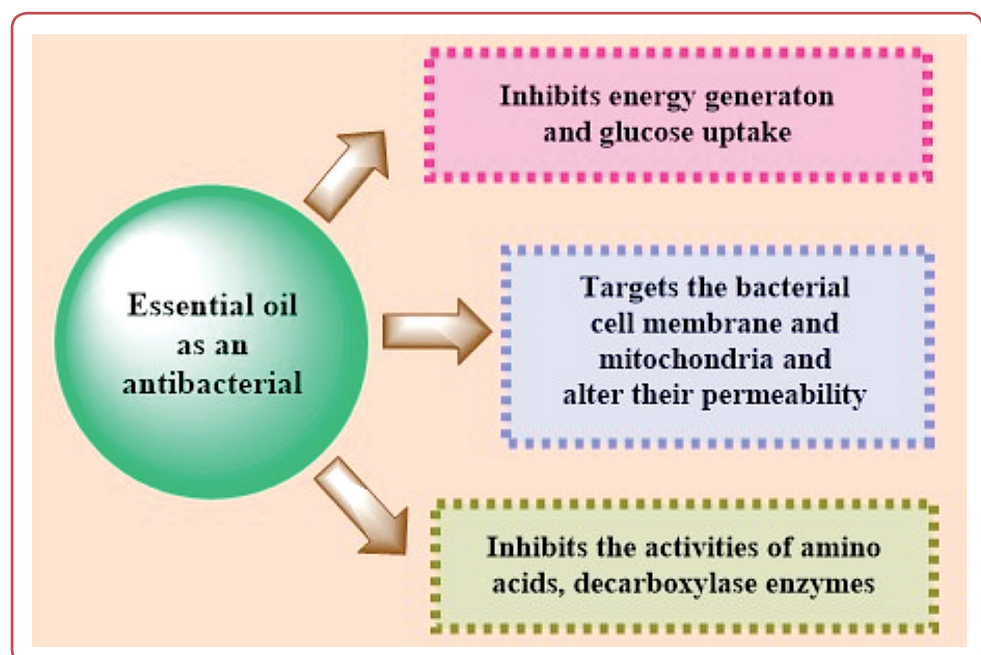


Figure 3: Mechanism of action of oil as an antibacterial



in the bladders, a notable rise in the bacterial load of urine and aberrations in serum biochemical markers in rats with an *E coli*-induced UTI model. As a result, allicin has anti-infective effects in UTIs primarily through the MALT1/NF- κ B axis or AKT/NF- κ B pathway, which offers a theoretical foundation for understanding how allicin works to treat UTIs.⁴³

Hyaluronic acid

Hyaluronic acid (HA), commonly known as hyaluronan or hyaluronate, is a non-sulphated glycosaminoglycan (GAG) composed of repeated -1,4-D-glucuronic acid and -1,3-N-acetylglucosamine units.⁴⁴⁻⁴⁶ HA is viscoelastic, biocompatible, hygroscopic and may be able to generate highly hydrated matrices.⁴⁷ It's predominantly available as an extracellular matrix mucopolysaccharide and is present in most tissues and bodily fluids. Articular cartilage and synovial fluid contain the greatest HA. Since HA promotes cell proliferation and migration, it can serve as a protective barrier for the urothelium, which is important for urinary health.⁴⁸

Although HA itself does not cause any effect on *E coli*, it still inhibits the infection and the layer of urothelial cells (Figure 4).⁴⁹⁻⁵² Based on the studies, HA is recommended as a therapeutic agent for preventive purposes against UTIs in children and pregnant women.

Role of other herbal medicines in the prevention of UTI

Although modern antibiotics are being used in UTIs, UTIs can be quickly and easily treated with an herbal treatment with no side effects. All these herbs are discerned to know different types of phytoconstituents show potential in the treatment of urinary disorders and could be alternatives to uropathogenic resistance to the antibiotic during a UTI. Herbs known for the management of UTIs and other urinary disorders are divided into important categories (Table 2).

Nutrition therapy

Nutrient utilisation is essential for UTI control, prophylaxis and therapy. Micronutrients such as probiotics, vitamins and minerals have been employed against UTIs.

Probiotics

Latin "pro" and Greek "bios" mean life. Elie Metchnikoff, 1907, introduced probiotics. Metchnikoff says probiotics mean digestive microbes that can help with digestive diseases.⁶⁶ "Useful living microorganisms that have a positive effect on health and physiology" is how the WHO describes probiotics. Foods and supplements contain probiotics (in capsule, pill and powder forms). Probiotic foods and treatment agents may contain bacteria such as *Lactobacillus* and *Bifidobacterium* from

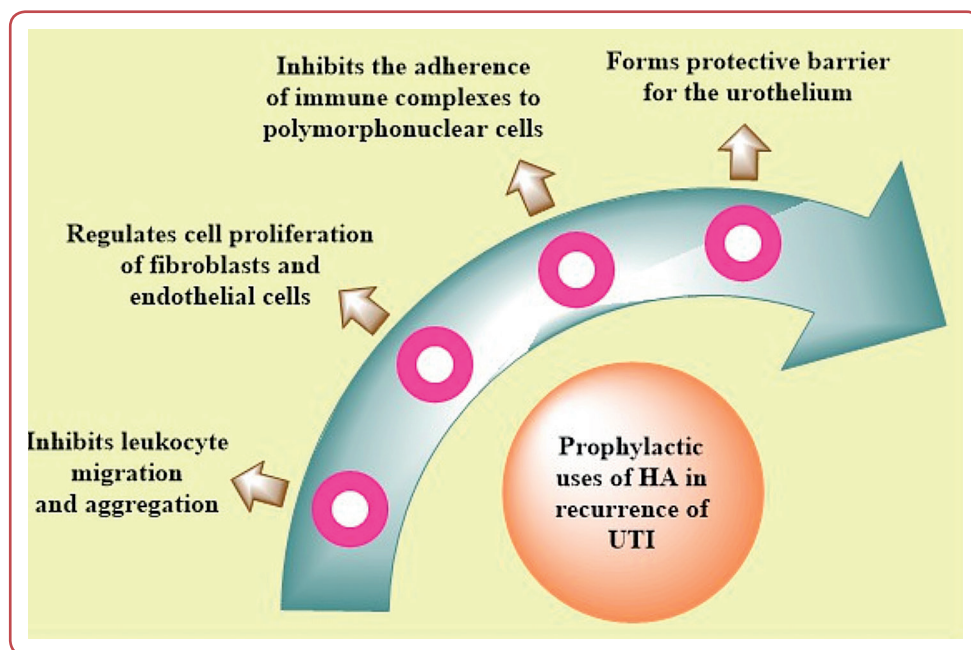


Figure 4: Mechanism of action of hyaluronic acid in recurrence of urinary tract infections (UTIs)

Table 2: Mechanism of actions of medicinal plants against urinary tract infections (UTIs)

N	Medicinal plant	Common name	Active constituents responsible for activity	Mode of action against UTI	References
1	<i>Vaccinium macrocarpon</i> Family: <i>Ericaceae</i>	Cranberry	Proanthocyanidins, anthocyanidin, catechin, flavonols, myricetin, quercetin and phenolics	Inhibits the attachment of <i>E coli</i> bacteria to uroepithelial cells.	[28]
2	<i>Tribulus terrestris</i> Family: <i>Zygophyllaceae</i>	Kharkhask, Gokharu, puncture vine	Saponin fractions contain aglycones such as gitogenin, tribuloside, tribulosin, neohecogenin, neo-tigogenin, hecogenin, chlorogenic, flavonoids such as kaempferol, steroids such as stigmasterol, β -sitosterol and cinnamic amide	It is used as an antimicrobial, diuretic, and antibacterial agent and also works against <i>E coli</i> ; <i>K pneumoniae</i> ; <i>S aureus</i> bacteria	[53]
3	<i>Cinnamomum verum</i> Family: <i>Lauraceae</i>	Dar chini, Cinnamon	Trans cinnamaldehyde	Inhibits the biofilm formation of pathogens such as <i>E coli</i> .	[54]
4	<i>Petroselinum crispum</i> L Family: <i>Umbelliferae</i>	Parsley	Apigenin	Showed diuretic and inhibition of inflammation activity which are vital in the treatment of UTIs. The constituents of the drug interfere with the analgesic paths like opioidergic, GABAergic, cholinergic and glutamatergic systems which are most important to relieve the classical symptoms of UTIs.	[55]
5	<i>Juniperus communis</i> Family: <i>Cupressaceae</i>	Juniper	Terpenoids, terpinene-4-ol, oxygenated sesquiterpene, monoterpene hydrocarbons such as β -pinene, myrcene, sabinene and limonene	Antimicrobial and diuretic activity and effective in UTI because of terpinene- 4-ol.	[56]
6	<i>Hybanthus enneaspermus</i> Family: <i>Violaceae</i>	Spade flower	Aurantiamide acetate, isoarborinol, β -sitosterol and triterpene	Alcoholic and water extracts were found to be effective against all pathogens responsible for the occurrence of UTI.	[57]
7	<i>Phyllanthus amarus</i> Family: <i>Phyllanthaceae</i>	Bhoy amlı, Gale-of-wind	Tannins, phenylpropanoids, terpenoids, phenolic compounds, flavonoids, alkaloids, saponins	The aqueous and methanolic extract exhibited appreciable antibacterial properties inhibiting the growth of all bacteria that cause UTI.	[58]
8	<i>Acacia farnesiana</i> (L.) Family: <i>Fabaceae</i>	Vilayatikikat, Sweet acacia, Huisache	-	UTI oliguria, burning sensation and polyuria.	[59]
9	<i>U dioica</i> Family: <i>Urticaceae</i>	Nettle	A high content of hydroxycinnamic acids (caffeic acid, chlorogenic acid and rosmarinic acid) and flavonoid (quercetin)	Showed antimicrobial activities and effective against UTI due to its diuretic activity.	[60]
10	<i>Berberis aquifolium</i> , <i>H Canadensis</i> , <i>B vulgaris</i> , and <i>B aristata</i>	Daruahaldi, Golden-seal, Creeping Mahonia. Holly-leaved Barberry	Isoquinoline alkaloids-Berberine	By preventing <i>E coli</i> from adhering to bladder epithelium, berberine inhibits the growth of germs and fights UTIs.	

11	<i>Armoracia rusticana</i> Family: <i>Brassicaceae</i>	Horseradish	Isothiocyanates	It prevents recurrent UTIs in paediatric patients because of its antibacterial activities.	[61]
12	<i>Agathosma betulina</i>	Buchu	Phenolic compounds	Through its interaction with T24 cells, it demonstrated antibacterial activity and anti-adhesive capabilities.	[62]
13	<i>Moringa oleifera</i> (Stem bark) Family: <i>Moringaceae</i>	Sargavo; Known as a natural antibiotic for UTI	Alkaloids (moringine and moringinine), β -sitosterol, 4-hydroxymellin, procyanidin, octacosanoic acid, flavanoids and phenolic	By inhibiting the adherence of germs that cause infections to the bladder wall, stem bark aids in the pathogen's removal and works well for UTIs.	[63]
14	<i>Terminalia chebula</i> Family: <i>Combretaceae</i>	Harde, Haritaki, Black myrobalan	4,2,4 – chebulyl – D – glucopyranose, anthraquinones and flavonoids (Tannic acid, ellagic acid, gallic acid and ellagitanins acid)	The acetone and ethanol extract were found to have potential antibacterial activity against UTI associated with <i>Proteus vulgaris</i> strains.	[64]
15	<i>Ocimum sanctum</i> Family: <i>Lamiaceae</i>	Tulsi	Essential oil – Eugenol	It was found to be effective against UTI causing microorganisms.	[65]

the start or add them during preparation. For probiotics to enter the digestive system and aid the body, they must withstand bile and stomach acids. The concept of competitive exclusion may be used by microorganisms to protect the urogenital tracts against infections.⁶⁷ Probiotics have a lot of promise to reduce the risk of antibiotic overuse and the occurrence of bacteria resistant to antibiotics (Figure 5).

Uropathogenic bacteria are inhibited from adhering, growing and colonising by lactobacilli.⁶⁸ Evidence suggests that *E coli* can be significantly

slowed down by exposure to healthy microbial communities of *Lactobacillus* species. Antibiotic use for *E coli* infections decreases drug misuse, which increases drug resistance and weakens the urinary system's natural defences, making the body more susceptible to infection.⁶⁹⁻⁷²

Regular antibiotic usage or recurrent UTIs in women may benefit from lactobacilli. Vaginal recolonisation with lactobacilli may have health benefits and probiotics do not induce antibiotic resistance. Future studies on probiotics as potential antibiotic substitutes are warranted. Due

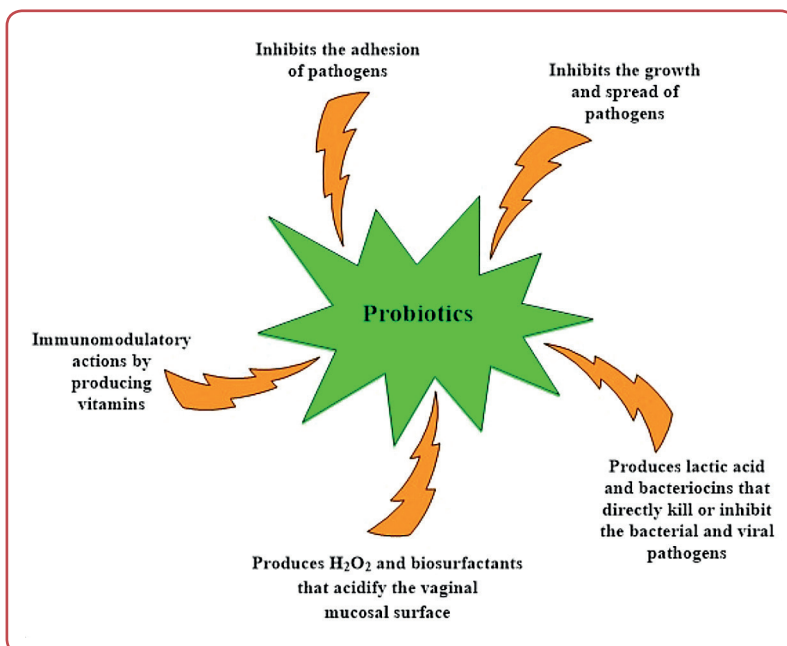


Figure 5: Role of probiotics against urinary tract infections (UTIs)

to the existence of some variables that promote UTIs, such as intimate perfumed washing gel, synthetic lingerie and tampons, it is crucial to restore a balanced microbial flora. In addition, the anti-inflammatory component of the previously outlined treatment makes it effective against both UTIs and cystitis (Table 3).

Vitamin C

Vitamin C (ascorbic acid) in a buffered form is commonly recommended as a supplement to reduce the threat of recurrent urinary tract infections (rUTIs) by increasing the urine's acidity (Figure 6). Vitamin C has been linked to improved immune system function. A healthy intake of vitamin C is crucial for preventing infection and reducing bladder inflammation. Vitamin C is vital for maintaining good health through the consumption of a diet that is rich in fruits (oranges, grapefruit or kiwifruit) and vegetables (red peppers). Recent *in vitro* evidence indicates that vitamin C in the urine may have a bacteriostatic effect. During a UTI, it was shown that bacteria might create nitrite, which has a bacteriostatic effect. Acidifying nitrite produces toxic reactive nitrogen oxides including nitric oxide (NO) and others.

Nitrite and vitamin C were investigated for their reducing agent effects on NO production and bac-

terial growth in slightly acidified urine. Incorporating nitrite into acidified urine greatly reduced bacterial growth. The inhibitory process was further aided by vitamin C. Vitamin C's function in UTI treatment and prevention and acidified nitrite's bacteriostatic actions due to the generation of reactive nitrogen species and other harmful intermediates are both illuminated by these results.^{79,80} Additive or synergistic effects have been used to assess the clinical benefits of combining cranberries with the probiotic *Lactobacillus rhamnosus* and vitamin C in a separate study. The findings suggested that the method may be a viable choice for the management of UTIs.⁸¹ It is recommended to administer a daily dosage of 100 mg to prevent UTIs. Another treatment protocol employed during the initial manifestation of symptoms involves the administration of 1,000 mg at two-hour intervals for a duration of two days, followed by a subsequent regimen of 1,000 mg thrice daily for a period of 5 to 10 days (Table 4).

Children with UTIs have been treated with vitamin A. The research investigation revealed a decrease in the incidence of UTIs within the treatment group as compared to the control group among paediatric subjects who received a supplementary dose of 200,000 International Units (IU) of the vitamin in conjunction with antibiotic treatment. Vitamin A supplementation, in con-

Table 3: Clinical study data of probiotics in prevention and treatment of urinary tract infections (UTIs)

Type of the study	Type of the formulation	Number of patients	Duration of treatment	Therapeutic effect	References
Pilot study	Lactobacilli in the form of vaginal suppository	185 women	12 months	Reduction in <i>E coli</i> positive cultures.	[73]
-	Oral probiotics (<i>Lactobacillus reuteri</i> and <i>Lactobacillus rhamnosus</i>)	280 post-menopausal women	12 months	Significant reduction in the prevalence of microbial resistance against antibiotics.	[74]
Meta-analysis	<i>Lactobacillus</i>	294 patients	12 months	Patients had a statistically significant reduction in the frequency of recurrent UTIs.	[75]
Randomised, placebo-controlled (Phase 2 trial)	<i>Lactobacillus crispatus</i> (Route: intravaginally)	100 pre-menopausal women with recurrent UTI in history	daily for 5 days, then once weekly for 10 weeks	Prevented recurrent infection of the urinary tract.	[76]
Randomised, placebo-controlled trial	<i>Lactobacillus rhamnosus GR-1</i> and <i>Lactobacillus fermentum RC-14</i> (Orally; capsules)	64 healthy women	60 days	-	[77]
Clinical study	Vaginal <i>Lactobacillus</i> strains	100 women with recurrent UTIs	-	Showed inhibition of <i>E coli</i> .	[78]

Table 4: Clinical study data on role of vitamin C in treatment of urinary tract infections (UTIs)

Type of the study	Drug regimen	Number of patients	Duration of treatment	Therapeutic effect	References
Randomised clinical trial	Three groups: First group was treated with ferrous sulphate, (200 mg/d), ascorbic acid (100 mg/d) and folic acid, (5 mg/d), daily; the second group was treated with only ferrous sulphate; the third group was treated with folic acid	110 pregnant women	3 months	In the first group, urinary infections were found significantly lower than in other groups.	[82]
Clinical trial	Vitamin C supplemetation	152 female child patients	14 days	Control the symptoms of UTI, including dysuria, fever, urinary urgency and dribbling urine.	[83]

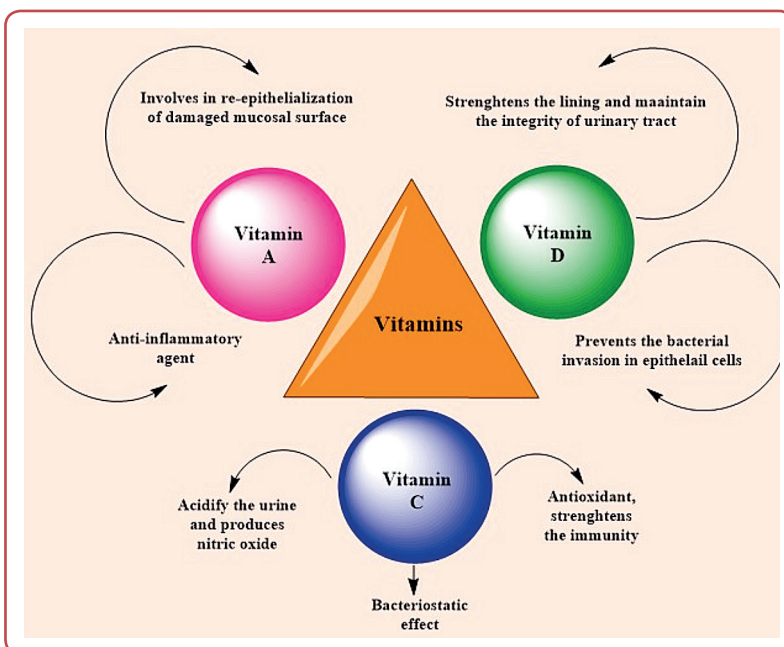


Figure 6: Role of vitamins in the prevention of in prevention and treatment of urinary tract infections (UTIs)

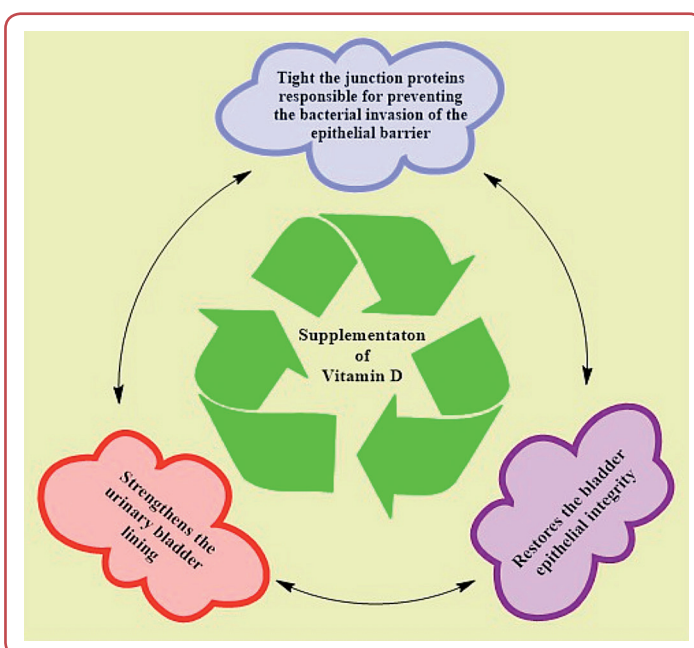


Figure 7: Role of vitamin D in the prevention of urinary tract infections (UTIs)

junction with antibiotic therapy, has been shown to reduce the severity of UTI symptoms in girls with acute pyelonephritis. Clinical symptoms of UTI improved and kidney damage and scarring from acute pyelonephritis were reduced, as shown by this study’s findings.⁸⁴

Increasing vitamin D levels regulates the innate immune system and protects against UTI.^{85, 86} Vitamin D insufficiency is a risk factor for UTIs, especially in females and supplementation can prevent first-time UTIs. Vitamin D3 (20,000 IU per week) for five years prevented UTIs in a randomised clinical trial (Figure 7). These studies showed that vitamin D supplementation prevents UTIs.^{87, 88}

Other agents

Citrate salts

Citrate salts can be used to treat UTIs because they alkalis the urine, which helps with dysuria and in the treatment of candidiasis.⁸⁹ It was demonstrated that after receiving sodium citrate treatment for 48 h, 80 % of the individuals’ symptoms dramatically improved.⁹⁰

D-mannose

D-mannose is a naturally occurring aldohexose sugar that functions as an inert monosaccharide. It is present in minor amounts in various food sources such as egg whites, coffee, baker’s yeast, fruits (apples, cranberries and mangos), as well as legumes (kidney beans, soybeans and

peanuts).⁹¹ The compound undergoes metabolism and is eliminated through urinary excretion. It has been extensively employed to prevent UTIs by competitively limiting the attachment of pathogens to cells lining the urinary tract. This inhibitory effect is attributed to the compound’s structural resemblance to the binding site of urothelial glycoprotein receptors involved in pathogen adherence.⁹²⁻⁹⁵

First, UPEC binds to uroepithelial cells by attaching to the epithelium of the bladder using FimH adhesin through the contact of mannose with the host cell surface.⁹⁶ An *in vivo* study in mice revealed that D-mannose blocked the adhesion and invasion of *E coli* bacteria and prevented the bio-film formation in the urinary tract epithelium.⁹⁷ In postmenopausal women, oral D-mannose supplementation reduces their perception of lower urinary tract symptoms.⁹⁸ Another study’s findings showed that the inter-relapse interval for simple UTIs is prolonged when antibiotic therapy is combined with long-term D-mannose dietary enrichment. The doses administered in the different research varied between 250 mg and 3 g per day.^{99, 100} However, due to its classification as a saccharide, D-mannose may not be suitable for individuals with impaired glycaemic control (Table 5).

Sugar derivatives were investigated for their potential use in preventing UTIs. Specifically, Klein et al developed and tested carbohydrates that inhibit bacterial-host contact and prevent UTIs. When this substance was taken orally, the number of bacteria in the urine and bladder dropped by a factor of two and four, respectively.¹⁰⁴

Table 5: Clinical study data of D-mannose in treatment of urinary tract infections (UTIs)

Type of the study	Dose	Type of the formulation	Number of patients	Duration of treatment	Therapeutic effect	References
Pilot study	Initially 5 g mannose two times daily for 3 days and then once a day for 10 days	D- mannose	43 women	One group receiving prophylaxis treatment for 6 months	Significant improvement against UTI symptoms and also showed promising results against recurrences.	[101]
Randomised cross-over trial	1 g 3 times a day, for 2 weeks and after 1 g two times in a day for 22 weeks	D- mannose	60 female patients (age: 22-54 years)	24 weeks	Effective treatment for recurrent UTIs.	[102]
Randomised clinical study	-	D- mannose	103 patients	6 months	Reduced the risk of recurrence of UTI.	[103]

Home remedies

Drinking plenty of water

Hydration state affects UTI risk. Regular urine flushes microorganisms from the urinary tract, preventing illness. It is recommended to keep yourself hydrated by sipping water at regular intervals and whenever the need is felt.

Consuming cranberry juice

Cranberry juice (unsweetened cranberry juice) is widely recommended because of its antibacterial properties preventing the adhesion of bacteria from sticking to the urinary tract, where they could cause an infection.

Practice of healthy habits

Good restrooms and hygiene practices are the first lines of defence against UTIs. The first rule is to avoid urinary retention. A bacterial infection may develop from a subsequent accumulation of bacteria. Urinating during sexual activity may also help prevent UTIs by flushing out bacteria. The act of wiping from back to front has been associated with a higher likelihood of developing

UTIs. This practice can transfer bacteria to the urinary system, therefore increasing the risk.

Marketed review of herbal drugs

There is a strong correlation between diabetes and urological conditions. Bladder infections and UTIs are caused by diabetes. Blood flow, nerves and sensory functions are all negatively impacted, which can exacerbate the symptoms of urologic conditions. Diabetes affects a sizable percentage of the global population. The global UTI market is being propelled by factors such as the rising incidence of diabetes and kidney stones, which have been linked to an increase in UTI cases and the subsequent demand for drugs to treat them. The market is anticipated to expand thanks to rising R&D spending on antibiotics for UTIs, which represents a new class of drugs. As of August 2017, a new antibiotic combination drug was approved by the FDA for the treatment of UTI (Table 6).

Table 6: List of marketed formulations in India used for urinary tract infections (UTIs)

N	Brand name	Ingredients	Formulation	Company	Category
1	<i>Gokshuradi Guggul (500 mg)</i>	Harad, Baheda, Amla, Shudh Guggul and Gokhru	Tablet	<i>Patanjali</i>	Antibacterial
2	<i>K 4 Tablet</i>	Chandraprabha, Guduchi, Kanyalohadi, Haridra	Tablet	<i>Zandu</i>	Broad-spectrum Antiseptic
3	<i>Cystone</i>	Manjishtha, Nagarmusta, Apamarga	Tablet	<i>Himalaya</i>	Antibacterial
4	<i>Punamava</i>	Punarnava (Boerhaaviadiffusa) extract	Tablet	<i>Himalaya</i>	Antibacterial
5	<i>Renalka syrup</i>	Asparagus, Indian sarasaparilla, Nut grass	Syrup	<i>Himalaya</i>	Antibacterial
6	<i>Kamaryasava</i>	Makashika, Jaggery, Aloe vera juice	Liquid	<i>Dabur</i>	Antibacterial
7	<i>Divya Usirasav</i>	Ushira, Padma, Lodhra, Kiratatkta	Liquid	<i>Patanjali</i>	Antibacterial
8	<i>Uricare</i>	Shilajeet, Cyperus	Capsule	<i>Himalaya</i>	Antiseptic
9	<i>Chandanadi Vati</i>	Gokshura, Amla, Sandalwood, Daruharidra, Camphor, Cardamom, Pashaanbhed	Tablet	<i>Baidyanath</i>	Antiseptic
10	<i>Ushirasava</i>	Nelumbonucifera, Vetiverazianioides, Gmelinaarborea	Liquid	<i>Baidyanath</i>	Antiseptic
11	<i>Alka syrup</i>	Gokshura, Jeera, Coriander	Syrup	<i>Charak</i>	Antimicrobial
12	<i>Sandu Ushirasav</i>	Ushira, Kamal Pushpa, Gambhari, Lodhra, Parpatak	Liquid	<i>Sandu</i>	Antimicrobial
13	<i>ChandraprabhaVSati</i>	Acoruscalamus, Cyperusrotundus, Phyllanthusniruri, Tinosporacordiofolia	Tablet	<i>Baidyanath</i>	Antimicrobial

14	<i>Himplasia</i>	Gokshura	Tablet	<i>Himalaya</i>	Antimicrobial
15	<i>Stondab</i>	Varuna, Raktapunarnava, Gokshura, Guduchi, Shwetparpati, Shilajatu	Tablet	<i>Dabur</i>	Antibacterial
16	<i>Divya Chandraprabha-Vati tablet</i>	VaiVidang, ChitrakBark, Devdaru, Kapoor, Nagarmotha, Pippal, Kali Mirch	Tablet	<i>Patanjali</i>	Antibacterial
17	<i>Punarnava</i>	Punarnava (Boerhaaviadiffus) root extract	Capsule	<i>Zandu</i>	Antibacterial
18	<i>NuraStone</i>	Gokhru, PashanBhed, Giloy, Kutki, RalSafed	Capsule	<i>Nuralz</i>	Antibacterial
19	<i>Utis</i>	Gokhru, Giloy, Shilajatu	Syrup	<i>Ayursunpharma</i>	Antibacterial
20	<i>Urimass plus</i>	Gokhrubeej pit papla	Syrup	<i>Naturestask</i>	Antiseptic
21	<i>UTI uproot</i>	Gokhrupanchang, sounth, Marich, Baheda	Tablet	<i>Cureveda</i>	Antibacterial
22	<i>Cranberry plus</i>	Cranberry Extract	Capsule	<i>Herbs Nutri Products Pvt Ltd</i>	Antibacterial
23	<i>Guapha Ayurveda Lodhrasava</i>	Arjunachaal (Terminaliaarjuna)	Liquid	<i>Gupta Ayurvedic Pharmacy Pvt Ltd</i>	Antibacterial
24	<i>UTI Pure pulse</i>	Chirchita, Gokhru, Neem, Punarnava	Syrup	<i>Intas Ltd</i>	Antiseptic

Future prospects

Various databases were utilised to identify studies focusing on natural options, encompassing herbal medicines, vitamins, trace elements, sugars and probiotics, without imposing any time restrictions. Among these, cranberry stands out as the most extensively studied home remedy for UTIs. Continued exploration of the human microbiome, especially in the urinary tract, may reveal new insights into the role of beneficial bacteria. Probiotics, particularly strains like *Lactobacillus*, are being studied for their potential to maintain a healthy microbial balance in the urinary tract and prevent infections. Existing evidence suggests that proanthocyanins found in cranberry may play a crucial role in preventing bacteria from adhering to the walls of the urinary tract. This, in turn, impedes the subsequent steps of neuropathogenesis. The continuous exploration of preclinical and clinical studies in this domain holds the potential to contribute significantly to the development of novel formulations. These formulations could offer effective treatment for UTIs with minimal or negligible side effects, thereby advancing therapeutic options in this realm.

Conclusion

This review underscores the significant effectiveness of herbal medicines in addressing UTIs and explores the role of nutrition therapy, including probiotics, vitamins and other remedies. Herbal medicines demonstrate efficacy in promptly addressing initial signs of infection and offer short-term prophylaxis benefits. The incorporation of vitamins, trace elements and sugars proves to be a successful strategy for UTI prevention and when combined with antibacterial agents, yields positive outcomes. Probiotics emerged as a promising avenue for mitigating the risks associated with antibiotic overuse and combating antibiotic-resistant microorganisms. This study holds the potential to contribute to the development of a robust formulation for UTI treatment. Opting for non-antibiotic agents presents a valuable approach to reducing UTI incidence and alleviating symptoms. Natural substances, nutrients and probiotics stand out among these agents. Each operates through distinct mechanisms, suggesting that a co-formulation in a single dosage form could yield a natural and effective solution for both preventive and therapeutic aspects of UTI management. The review specifically highlights medicinal herbs used for UTI prevention or treatment, botanicals with established urobactericidal activity, clinical trials assessing the efficacy of cranberry products in UTI prevention and other natural therapeutics associated with UTI management.

Ethics

This study was a secondary analysis based on the currently existing data bases including Pub Med and did not directly involve with human participants or experimental animals. The ethics approval was not required for this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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