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Review

Plants and urinary tract infections: a critical review

Lovepreet Kaur

Department of Biotechnology, Khalsa College, Amritsar, Punjab, India

*E-mail: lovepreetkaur1712@gmail.com

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Abstract: Usually, the bacteria are present in colonies near the urinary tract opening in both men and women. However, infections arise when these colonies infiltrate the bladder before urination and remain unremoved by urine. This condition leads to a urinary tract infection (UTI). More than 100 million people are affected by uropathogens per year. The most common uropathogens that lead to UTIs include gram-positive bacteria, gram-negative bacteria, and fungi. Women are more likely to be affected by these pathogens than men. UTIs are categorized into upper, lower, and uncomplicated or complicated UTIs. In addition, UTIs could be symptomatic or asymptomatic. Some of the most common symptoms of UTI are a frequent and strong need to pass urine, pain in the lower abdomen while passing the urine, a stronger smell than usual, a burning sensation while urinating, fever, chills, nausea, and pain in the suprapubic region. The most well-known treatment for this condition is the prescription of antibiotics such as ampicillin, gentamicin, ciprofloxacin, nalidixic, and levofloxacin. However, the reports suggest that major uropathogens have become antibiotic-resistant. This causes patients to experience prolonged symptom resolution times and higher re-consultation rates. To prevent this condition, medicinal plants should be used for sound urinary tract health. Medicinal plants comprise phytochemicals, namely flavonoids, tannins, phenolic acids, essential oils, and alcohols, that help alleviate the symptoms of UTI. This paper aims to mention some commonly found plants that can be used to prevent or cure urinary tract infections.

Keywords: Urinary Tract Infection, uropathogens, uncomplicated, complicated, antibiotics, medicinal plants, phytochemicals

Introduction

Urinary tract infections (UTIs) are a prevalent bacterial illness that affects 150 million people worldwide annually and causes morbidity in individuals of all ages (Stamm & Norrby, 2001). An estimated 10.5 million doctor's visits (or 0.9% of total ambulatory visits) and 2-3 million ER visits were made for UTI symptoms in the United States alone in 2007 (Schappert & Rechtsteiner, 2011). The social costs of

these infections, including medical expenses and lost productivity, are currently estimated to be around US$3.5 billion annually in the United States alone. In elderly men, women, and infant boys, urinary tract infections (UTIs) are a major source of morbidity (Flores-Mireles et al., 2015). UTIs are basically categorized as complicated or uncomplicated. Complicated UTIs are UTIs related to factors that compromise the urinary tract or host defence, including urinary obstruction, urinary retention caused by pregnancy, neurological disease, renal failure, immunosuppression, renal transplantation, and the presence of foreign bodies, for example, indwelling catheters, calculi, or other drainage objects (Lichtenberger & Hooton, 2008; Levison & Kaye, 2013). Uncomplicated UTIs, on the other hand, influence those who have no neurological or structural urinary tract issues and are healthy (Hooton, 2012; Nielubowicz & Mobley, 2010). UTIs can be caused by bacteria (both Gram-negative and Gram-positive) and fungi. Uropathogenic *Escherichia coli* (UPEC) is the most prevalent pathogen for UTIs, followed by *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida spp.* (Figure 1). Additionally, there is crystal clear evidence of a relationship between urological diseases and lifestyle risk factors such as sexual habits, tobacco smoking, nutrition, physical activity, alcohol consumption, etc. (Bientinesi et al., 2021). To treat UTIs, antibiotics are prescribed, but their long-term intake increases the likelihood of antibiotic resistance among the microbiota present in the vagina and bladder (Kostakioti et al., 2012). Besides that, prolonged recurrences, pyelonephritis with sepsis, kidney injury in young infants, preterm birth, and consequences from repeated use of antibiotics, such as high-level antibiotic resistance and Clostridium difficile colitis, are among the most severe aftereffects. The presence of niches no longer occupied by the transformed microbiota increases the probability of colonization by multidrug-resistant uropathogens. Significantly, the 'golden era' of antibiotics is ending, creating a greater emergence to opt for natural alternatives to treat such issues rather than relying on synthetic medications (Flores-Mireles et al., 2015).

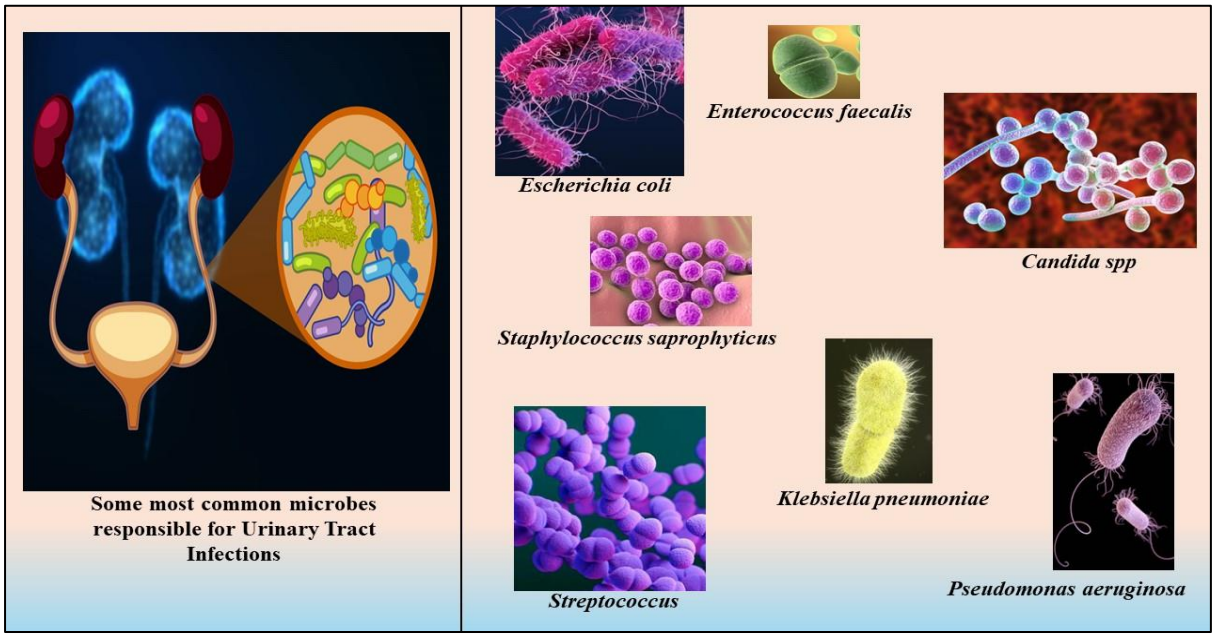

Figure 1: UTI causing micro-organisms

Because medicinal plants have a wealth of bioactive chemicals with antibacterial qualities, they have become attractive options for the treatment and prevention of urinary tract infections. For ages, traditional herbal medicines have been utilized in many cultures to treat urinary illnesses. A recent scientific study has confirmed the effectiveness of these remedies. This review attempts to mention the plants that can cure UTIs efficiently.

What is Urinary Tract Infection (UTI)?

Urinary tract infections (UTIs) are a common bacterial infection that affects approximately 40% of women. Although UTIs can cause life-threatening sepsis, the majority of infections are less severe. However, urinary tract infections (UTIs) cause significant suffering and impose high healthcare and social expenses (Sheerin, 2011). To elaborate, bacteriuria, or the presence of bacteria in the urine, is known as a UTI. Although symptomatic illness can develop with as little as 10^3 bacteria/mL, for epidemiological purposes, "significant" bacteriuria is defined as at least 10^8 bacteria/mL in urine. Inflammation and a urine WBC count greater than 8 cells/mL are indicators of a symptomatic infection (Lee & Neild, 2007). In both men and women, the bacteria usually form colonies near the urinary tract opening. These colonies often wash out while urinating. However, infections arise when these colonies infiltrate the bladder before urination and remain unremoved by urine (Salvatore et al., 2011). Women have a smaller distance between the urethral and bladder openings, which increases the likelihood of bacteria entering the bladder and staying there before being eliminated by urination. Women are more likely than men to acquire bacterial colonies due to the vaginal cavity and the rectum's close location to the urethral entrance. An additional noteworthy aspect of these bacterial colonies is that, even in cases where they make it to the bladder, where they can proliferate, UTI symptoms are rarely evident (Foxman, 2010).

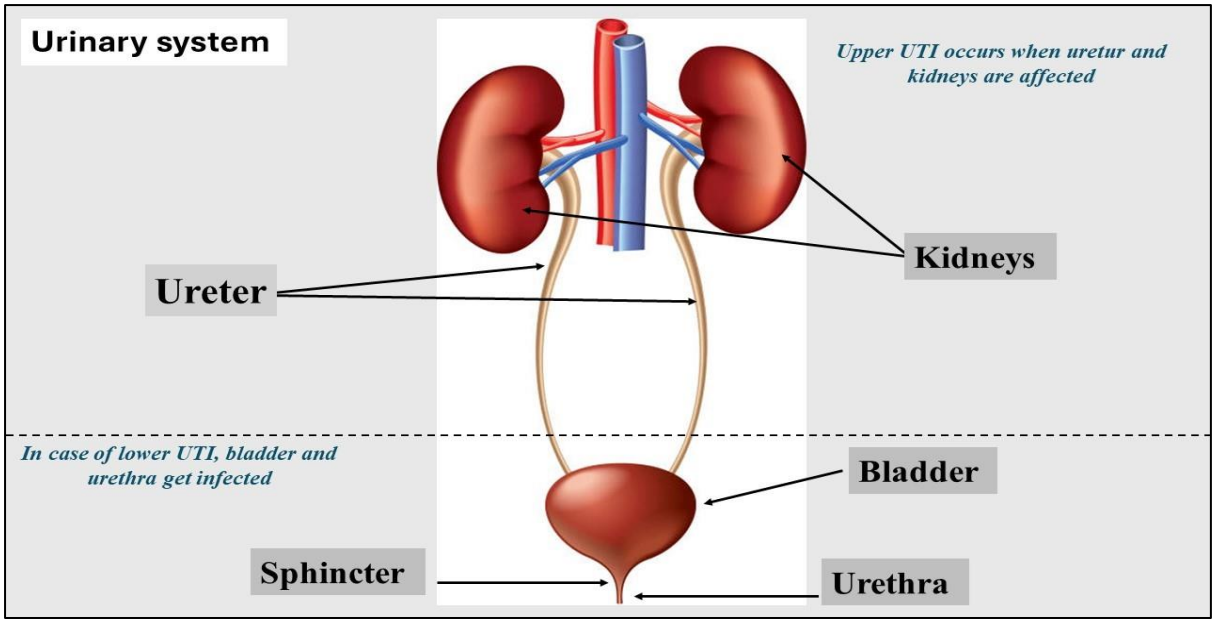

Figure 2: Labelled diagram of human urinary system along with the information about upper and lower UTI

Table 1: Various factors associated with uncomplicated UTI

Factors linked with uncomplicated UTI						
Bacterial virulence	**Acquired**			**Host defence**		
	Ageing	Antimicrobials	Sexual intercourse	Non-secretor status	Colonization of vagina and mucosa	Polymorphisms of genes regulating complement, neutrophil biology

Table 2: Various factors associated with complicated UTI

Factors linked with complicated UTI					
Metabolic		**Functional and anatomical abnormalities**			
Immunosuppression	Diabetes	Pregnancy	Foreign body	Renal scarring	Outflow obstruction

There are two types of urinary tract infections: upper or lower, and uncomplicated or complicated based on the area of the infection and the condition of the body of the host (Kaur & Kaur, 2021). Upper UTI occurs when the ureter and kidneys are affected, whereas in lower UTI, the bladder and urethra are affected, as shown in Figure 2. Contrarily, an uncomplicated UTI arises when there are no anatomical or functional abnormalities inside the urinary tract; however, when there is an atypical urinary tract or any element that makes an individual more vulnerable to infection, a complicated UTI develops (Sheerin, 2011). There are various factors associated with both types of UTIs, as shown in Tables 1 and 2 (Lee & Neild, 2007).

Symptoms of UTI

In case of UTI, there are chances of occurrence of following sings:

(i) Lower UTI:

- Pain during urination
- Pain in suprapubic region
- Visible haematuria

(ii) Upper UTI:

- Fever
- Chills
- Vomiting
- Nausea
- Flank pain
- With or without symptoms of cystitis (Salvatore et al.,2011; Hooton, 2012).

Symptomatic and Asymptomatic UTI

Both symptomatic and asymptomatic UTIs take place after the growth and proliferation of microorganisms in the urinary tract. There are chances of growing these microbes with symptoms (symptomatic) or without symptoms (asymptomatic). Symptoms of UTI include a frequent and strong need to pass urine, pain in the lower abdomen while passing the urine, a stronger smell than usual of urine, and a burning sensation while urinating. There are higher chances of the occurrence of symptomatic UTIs than asymptomatic ones (Mandokhail, 2015). Asymptomatic bacteriuria (ABU) is carrying $>10^5$ bacteria/mL (asymptomatically), with or without pyuria, in two successive cultures. People with asymptomatic UTIs can carry bacteria for many months or years without experiencing any symptoms (Wult & Svanborg, 2016).

How are UTIs treated?

(i) **Antibiotic treatment:** Originally, amoxicillin was the first-line treatment for urinary tract infections (UTIs). However, due to the rising occurrence of *E. coli* resistance, studies have shown that trimethoprim/sulfamethoxazole is an antibiotic that has greater cure rates. Amoxicillin/clavulanate, cefixime, nitrofurantoin, cefprozil, levofloxacin, fosfomycin, and nalidixic acid are further frequent antibiotics used to treat bacterial UTIs. Antibiotics have reduced the rate of bacterial infection-related morbidity and death. However, we've seen a rise in antibiotic resistance among these uropathogens in recent years. Understanding an antibiotic's mechanism of action is essential for creating drugs that work. Table 3 demonstrates the five mechanisms by which antimicrobial drugs work (Kaur & Kaur, 2021).

Table 3: includes different mode of actions of antibiotics.

Mode of action	Mechanism	Example of antibiotics
Inhibitor of cell wall synthesis	Targets cell walls; selectively kill or inhibit bacterial growth	Ampicillin, carbencillin, piperacillin, amoxiclav, meropenem, aztreonam
Inhibitor of nucleic acids	As nucleic acids (DNA, RNA) store the genetic information of the cell which is mandatory for the cell division. So, few	Nitrofurantoin, levofloxacin, ciprofloxacin, nalidixic acid

	antibiotics attack the nucleic acids of bacteria in order to stop the DNA formation.	
Inhibitor of protein synthesis	By targeting the protein synthesis, it disturbs the normal cell metabolism of bacteria; causing inhabitation of growth and multiplication of bacteria.	Gentamicin, amikacin, tobramycin
Inhibitor of metabolic processes	Since folate is required for the synthesis of DNA, specific antibiotics inhibit folate synthesis resulting into terminating the replication of cell	Cotrimoxazole
Inhibitory of membrane function	When attacked on the cell wall, leakage of crucial solutes which are important for the survival of cell takes place	Polymyxin B

Limitations of using antibiotics for treating UTIs

Antimicrobial resistance in UTIs

Microorganisms that cause UTIs are known as uropathogens. UTIs are typically caused by *E. coli* (UPECs), but can also be caused by other bacteria such as *S. saprophyticus*, *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, *P. mirabilis*, *Acinetobacter baumannii*, *Streptococcus*, and *E. faecalis*, or fungi like *Candida albicans* (Amdekar et al., 2011; Mann et al., 2017; Arsene et al., 2021). However, the regular use of antibiotics to treat diseases over the past 20 years has resulted in a constant and progressive rise in virulent and antibiotic-resistant bacteria that conventional antibiotic treatment is unable to eradicate (Mancuso et al., 2023). Antimicrobial resistance may stem from unreasonable antibiotic use and the spread of resistance genes via transport mechanisms such as plasmids, bacteriophages, transposons, and integrons (Ghosh et al., 2023). Many studies have provided evidence of the antibiotic resistance of uropathogens. In 2017, Magyar *et al.* found that during 2004 and 2015, resistance of the most commonly UTI-causing bacteria (*E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae,* and *E. faecalis*) had increased from 19% to 25%. It has also been stated in a report of global research that in distinct parts of the world, there is a surging resistance to uropathogens (Sweileh et al., 2018). Enterococcus spp. has recently evolved high levels of resistance to glycopeptides, including vancomycin, which is thought to be one of the last lines of defence against multidrug-resistant organisms. Enterococci developed resistance to glycopeptides by expressing vancomycin and teicoplanin A-type resistance (van) genes that encode the penicillin-binding proteins (PBPs) Van A, Van B, Van D, Van E, Van G, and Van L (Pendleton et al., 2013; Gupta et al., 2014). As a result, patients with resistant isolates experience prolonged symptom resolution times, greater re-consultation rates, and require several courses of antibiotics (Sheerin, 2011). Cock et al. (2021) mentioned that more than a fifth of people contracting a UTI develop the infection within half a year of the original infection. Almost

5% of people developing UTIs undergo such infections more than three times each year (Brumbaugh & Mobley, 2012).

Natural agents to treat UTIs: As alternative complementary agents, many medicinal plants are usually used to treat or prevent UTI. Several studies have proven the effective antimicrobial activities of plants. Such plants are called medicinal plants. For their antimicrobial activity, essential oils are usually given credit (Poulios et al., 2021). Table 5 mentions the most commonly used plants for UTI treatment:

(a) *Curcuma longa:* The common name of Curcuma longa is turmeric, or haldi. Native to South Asia, it is a perennial plant of the ginger family (Zingiberaceae) (Bisset, 1997). In Ayurveda and traditional Chinese medicine, turmeric has been used for centuries for its medicinal properties. It contains curcumin, a primary bioactive compound that contributes to its therapeutic activities, such as anti-microbial, antioxidant, and anti-inflammatory (Parsad, 2024). Other bioactives, such as alkaloids and flavonoids, result in its antibacterial activities (Cordell et al., 2001). Curcumin is an effective inhibitor of bacterial growth and proliferation, including antibiotic-resistant pathogens associated with UTIs. It also enhances the potency of traditional antibiotics and reduces the risk of resistance. Additionally, turmeric's immunomodulatory properties strengthen the body's natural defences against UTIs. Curcumin's ability to influence immune cell function, modulate inflammatory cytokine production, and increase phagocytosis supports a robust immune response to bacterial infections, potentially decreasing the severity and duration of UTI symptoms while preventing recurring infections. Turmeric's anti-inflammatory effects, in addition to its antibacterial and immunomodulatory capabilities, are very important in the treatment of UTIs. Inflammation is a significant factor in the development of UTIs, leading to tissue deterioration and worsening symptoms, including pain and discomfort. Curcumin's anti-inflammatory properties can reduce UTI-related inflammation and enhance tissue repair. Caution is advised with turmeric supplements, as high doses may cause gastrointestinal upset and interact with certain medications. Despite limitations, turmeric offers a natural alternative to conventional antibiotics for UTI management (Prasad, 2024).

(b) *Azadirachta indica:* It is often known as 'India Lilac' or 'Margosa' and belongs to the Meloideae subfamily of the Meliaceae family. Various elements of the neem plant (bark, leaves, blossoms, seeds, fruits, oil, neem cake, and gum) are used as traditional Ayurvedic treatments in our country. Neem oil, bark, and leaf extracts are used in conventional medicines to treat intestinal helminthiasis, leprosy, constipation, and respiratory diseases. It also enhances human health. Neem oil continues to be effective in treating a variety of skin problems. The root, bark, flower, leaf, and fruit all treat biliary illnesses, blood morbidity, eczema, burning feelings, skin ulcers, and phthisis (Girish & Shankara, 2008; Kirtikar & Basu, 1975). Its active components include azardirachtin, 1-maliantriol, salannin, nimbin, and nimbdin, which are somewhat soluble in water but easily soluble in organic solvents like alcohols (Kirtikar & Basu, 1975). Another study found that neem extract proved effective against S. *aureus* but not *E. coli.* Ethanol extracts were more effective in all cases, including

dry and fresh neem bark and leaves. Fresh leaves are more effective than dried leaves. The bark produces comparable results (Francine et al., 2015).

(c) *Occimum sanctum:* Its common name is Tulsi. *Occimum sanctum* is a medicinal herb with antibacterial properties that are effective against a wide range of antibiotic-resistant microorganisms (Sahu et al., 2019). It contains both essential oils and aromatic composites. It is both a culinary herb and a visually appealing, scented decorative shrub. *Occimum* reduces lipid peroxidation and boosts the activity of superoxide dismutases (Thaweboon & Thaweboon, 2009). The *Occimum* class contains components with antibacterial, antifungal, antioxidant, and radioprotective properties. Occimum's phytochemical research shows it contains phenolic chemicals, glycosides, flavonoids, tannins, and saponins, making it a useful medicinal herb. Herb tulsi exhibits strong antibacterial properties, with MICs of 20 mg/ml against E*. coli*, *Salmonella typhi*, and *Vibrio cholerae*. After 30 minutes of engagement, the plant demonstrated improved antibacterial activity against all three bacteria (Parveen, 2010).

(d) *Terminalia Chebula:* This plant is native to Pakistan, India, Nepal, and the south-west of China (Tandon & Sharma, 2010). A study done by Hogade et al. (2011) proved that its aqueous fruit extract exhibits anti-microbial activity against *Bacillus aureus, Staphylococcus aureus, Pseudomonas aeruginosa, K. pneumonia,*and *Escherichia coli, and is* even more effective against *S. aureus.* Its aqueous extract at 100 µg/mL concentration showed more significant results as compared to standard drugs such as tetracycline and gentamycin. Its antibacterial activity is due to saponins, glycosides, tannins, alkaloids, tannic acid, vicenin, myrtenal, orintin, and some simple phenolic substances (Hogade et al., 2011; Karuppiah et al., 2012).

(e) *Vaccium macrocarpon*: Commonly known as cranberry, it is an evergreen shrub native to North America that is largely grown for its sour, red berries. Indigenous people have used cranberries for their therapeutic benefits, particularly in treating urinary tract infections (UTIs) and other urinary problems. Cranberry has received extensive attention in recent decades for its possible preventive and therapeutic properties against urinary tract infections, supported by both conventional understanding and modern studies. One of the important components thought to be linked to cranberries's efficacy in preventing UTIs is the presence of proanthocyanidins (PACs), a type of polyphenol found in abundance in cranberries and fructose. These PACs are considered to limit the adhesion of uropathogenic bacteria, notably *Escherichia coli,* to urinary tract epithelial cells, preventing colonization and subsequent infection by inhibiting VFs like P. fimbria. Type 1 fimbria is sensitive to mannose, and fructose blocks it, whereas PACs are responsible for blockage. The other type 1 fimbria is mannose-resistant. It leads to a reduction in the adhesion of bacteria and helps flush out the UPS from the bladder along with the urine. Other bioactive compounds, such as organic acids, flavonoids, and vitamins, can also help in combating UTIs. Various capsules, syrups, juices, and pills are available on the market that are derived

from cranberries (Saeed, 2010; Sihra et al., 2018; Shaheen et al., 2019; Arsene et al., 2021).

According to various studies, products such as extracts, juices, and supplements of cranberries can alleviate the likelihood of UTIs. Some factors need to be considered while expecting the results, such as dosage, formulations, and the response of each individual, which may vary from person to person. On the downside, it may not be suitable for all, especially those with a history of kidney stones or other certain medical conditions (Prasad, 2024).

(f) *Arctostaphylos uva-ursi:* Its common name is bearberry and belongs to the Ericaceae family, and traditionally, its leaves have been used for treating UTIs (Gaeta Kaabi et al., 2020; Saeed, 2010). It is an effective plant in the treatment of bacterial infections if its dried herb is used at the rate of 3 grams of infusion, 4 times a day (Gohari & Saeidnia, 2014). In Germany, its leaf extracts are used for the treatment of UTI (Gaeta Kaabi et al., 2020; Saeed, 2010). Its antimicrobial activity is due to the presence of arbutin, a glycolic compound. When arbutin is taken, it is metabolized into hydroquinone. Hydroquinone is known for its anti-microbial characteristics, and it helps extract bacteria via urinating (Gaeta Kaabi et al., 2020). Besides arbutin, this plant contains phenolic acids, flavonoids, and tannins that also help uva ursa express its therapeutic effects. Due to their diuretic nature, they help maintain the health of the urinary tract by reducing the symptoms of UTIs. However, overconsumption of this plant has some limitations, such as urinary irritation, upset gastro-intestine, and hepatotoxicity because of the accumulation of hydroquinone metabolites. So, it should be taken cautiously after consulting with a professional (Prasad, 2024).

(g) *Hydrastis canadensis: Hydrastis canadensis,* the scientific name for goldenseal, is a perennial herb that is indigenous to the eastern regions of the United States and Canada (Pengelly et al., 2012). For ages, it has been an essential component of Native American traditional medicine, appreciated for its wide range of healing abilities. Biochemicals, including canadine, hydrastine, and berberine, are responsible for their anti-microbial nature against a range of gram-positive and gram-negative bacteria that are linked to urinary tract infections (UTIs) (Mandal et al., 2020). Apart from its anti-microbial nature, its other properties are anti-inflammatory, immunomodulatory, and antioxidant. All these properties help in the reduction of symptoms of UTI. There aren't many clinical trials assessing goldenseal's effectiveness in treating UTIs, although some preliminary evidence points to the herb's potential value as an adjuvant. It has been demonstrated that goldenseal supplements or extracts have antibacterial efficacy against uropathogenic bacteria in vitro; however, more studies are required to confirm these results in human situations. Goldenseal has certain safety concerns and limits, despite its potential for medicinal use. Use of goldenseal for an extended period or in excess can have negative effects, including hepatotoxicity, allergic responses, and an upset stomach. Goldenseal

may also interact with other pharmaceuticals, including blood thinners and diabetes medications, changing their efficacy or raising the possibility of negative side effects (Prasad, 2024).

(h) *Agathosma betulina:* commonly called Buchu, is native to South Africa and has become a crucial herb for natural remedies (Moolla, 2005). Buchu was primarily used to treat urinary tract infections, prostate-related incontinence, and kidney stones, among other urinary tract illnesses. Buchu leaf extract has therapeutic potential for urinary tract illnesses due to its essential oil's diosphenol and monoterpene content. The essential oil is absorbed in the intestine, excreted in the kidney, and passed through the urine tract, providing anti-bacterial effects on bacterial pathogens like *K. pnueumoniae*, *B. subtilis*, *E. coli*, *P. aeruginosa*, and *S. aureus* (Moolla, 2005; Geetha et al., 2012; Sandasi et al., 2010; Lis-Balchin et al., 2001).

Table 5: Medicinal plants along with the phytochemicals responsible for their anti-microbial properties.

Scientific name (Common name)	**Secondary metabolites**	**References**
Curcuma longa (Turmeric)	Curcumin, alkaloids, and flavonoids	Cordell et al., (2001); Prasad, (2024)
Azadirachta indica (Neem)	Azardirachtin, 1-maliantriol, salannin, nimbin, and nimbdin, alcohols	Kirtikar and Basu, (1975); Girish and Shankara, (2008); Francine et al., (2015)
Occimum sanctum (Tulsi)	Phenolic chemicals, glycosides, flavonoids, tannins, and saponins	Thaweboon and Thaweboon, (2009); Parveen, (2010); Sahu et al., (2019);
Terminalia Chebula (Hard)	Saponins, glycosides, tannins, alkaloids, tannic acid, vicenin, myrtenal, orintin, and some simple phenolic substances	Hogade et al., (2011); Karuppiah et al., (2012)
Vaccium macrocarpon (Cranberry)	Proanthocyanidins (PACs) and fructose	Saeed, (2010); Sihra et al., (2018); Shaheen et al., (2019); Arsene et al., (2021)

Arctostaphylos uva-ursi (Bearberry)	Phenolic acids, flavonoids, tannins, hydroquinone	Saeed, 2010; Gohari and Saeidnia, 2014; Gaeta Kaabi et al., (2020); Prasad, (2024)
Hydrastis canadensiss (Goldenseal)	Canadine, hydrastine and berberine	Mandal et al., (2020); (Prasad, 2024)
Agathosma betulina (Buchu)	Diosphenol and monoterpene (Essential oils)	Moolla, (2005); Geetha et al., (2012); Sandasi et al., (2010); Lis-Balchin et al., (2001).

Future prospectus

Although there are several medicinal plants that are effective in curing UTIs, still more research is required to confirm the advantages of these medicinal plants, optimize dosing structures, and address safety issues, even if clinical data for their effectiveness in managing UTIs is encouraging. To establish evidence-based guidelines for the prevention and treatment of UTIs, standardization of herbal medicines and thorough clinical trials are required. Additionally, it is important to screen medicinal plants to determine their unique anti-UTI therapeutic potential. Additionally, the stereochemistry and structural clarification of isolated chemicals from strong plants may be very beneficial for the development of innovative UTI treatments.

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