Urinary tract infections: Virulence factors, resistance to antibiotics, and management of uropathogenic bacteria with medicinal plants—A review

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ABSTRACT

Urinary tract infections (UTIs) are among the most common infections in most countries and they are usually caused by the so-called uropathogenic (UP) microorganisms, including Escherichia coli (80%–90%), Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Proteus mirabilis, and Klebsiella pneumoniae. Over the years, the growth of resistance to antibiotics has complicated the treatment of UTIs and has direct consequences on the cost of treatment, the severity of infections, and the length of hospitalization. Medicinal plants, used for thousands of years to treat various diseases, constitute a serious alternative to antibiotics in the public health issue of antimicrobial resistance. In this review, the in vitro and in vivo use of medicinal plants and their nanoparticles (silver, gold, zinc, copper oxide, magnesium oxide, iron, etc.) in the management of uropathogens and their virulence factors (VF) as well as in the management of UTIs themselves have been discussed. Given the advantages offered by the biologically active compounds of medicinal plants as well as their green-synthesized nanoparticles whether used as such or in combination with conventional antibiotics, it can be concluded that herbal medicine can significantly help in the management of UTIs.

INTRODUCTION

Urinary tract infections (UTIs) are very common infections in human population and can be defined as any infection, commonly of bacterial origin, which occurs in any part of the urinary system (Motse et al., 2019a). UTIs can be grouped as urethritis (localized in the urethra), cystitis (infection of the bladder), pyelonephritis (infection of the kidneys), and vaginitis (infection of the vagina) (Bissong et al., 2017; Fosso et al., 2017). Nowadays, UTIs are serious public health issues and are responsible for nearly 150 million disease cases every year worldwide (Motse et al., 2019a). 80%–90% of UTIs are caused by the so-called uropathogenic Escherichia coli (UPEC) (Abraham et al., 2015; Ejrnaes et al., 2011), while 5%–10% are due to Staphylococcus saprophyticus (Nickel, 2008). These infections are rarely viral or fungal but can involve a much wider range of pathogens, especially Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae, Proteus mirabilis, Acinetobacter baumannii, Streptococcus, and Enterococcus faecalis (Amdekar et al., 2011; Flores-Mireles et al., 2015; Mann et al., 2017; Saka and Okunuga, 2017; Salvatore et al., 2011). UTIs are more likely to occur in women than men over all age groups (Abou Heidar et al., 2019) and up to 50% of women report having had at least one urinary tract infection in their lifetime (Agarwal et al., 2020). These infections are usually treated with antibiotics (Abou Heidar et al., 2019). For acute uncomplicated UTIs, it is recommended to use trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, or fosfomycin for 3–5 days (Gupta et al., 2011). However, high levels of resistance to TMP-SMX and ciprofloxacin preclude their use as empiric treatment for UTIs in patients who were previously exposed to them or who are at risk to be infected with extended-spectrum β-lactamases-(ESBLs-) producing bacteria (Bader et al., 2019; Bissong et al., 2019a; Ngah et al., 2019).
Second-line treatment is sometimes considered and usually includes oral cephalosporins (fluoroquinolones; cefixime) and β-lactams (amoxicillin-clavulanate) (Bader et al., 2020). In addition, depending on the case, other antibiotics may be used. However, notwithstanding the panoply of antimicrobials that can potentially be prescribed against UTIs, the problem of antibiotic resistance is also topical in UP strains. Indeed, in recent years, several studies have been carried out in different countries to assess the resistance to antibiotics of UP bacteria and the published results are clear. The resistance of UP strains is increasing, within some cases multidrug-resistant bacteria (MDR), and is not different from the global increase of the resistance to antibiotics observed around the world including all research areas (Dehbanipour et al., 2016; Karam et al., 2019; Kot, 2019; Lee et al., 2018; Mbarga et al., 2020, 2021; Motse et al., 2019b; Nzalie et al., 2016; Signing et al., 2020). Antibiotic resistance is a global issue that has led to a major mobilization in the search for new antimicrobial compounds and alternative ways of fighting bacterial infections. In this context, medicinal plants appear as a credible alternative (Wojnicz et al., 2012). Indeed, it is well known that plants have been used for millennia in the treatment and prevention of various diseases, including bacterial infections. Some of these herbal remedies have been shown to be effective in preventing and treating UTIs. Cranberries are one of the best-known products in this field. However, there are several other plants with well-known antimicrobial properties which can contribute to the fight against antibiotic resistance in general and to the fight against uropathogens in particular (Wojnicz et al., 2012). The aim of this review is to discuss the plants commonly used to manage UTIs and particular importance is devoted to the mechanism of infections, host and risk factors in UTIs, uropathogens (UPs) themselves, their virulence factors (VFs), multidrug resistance issue, and a general view of the research carried out on the bacteriostatic and bactericidal properties of plant extracts on UPs.

**Review methodology**

This review article was done by exploiting numerous review articles, original articles, and related books from reputable databases, such as Web of Science, PubMed, and Scopus. The papers published with toll-access have been made available using the facilities provided by People's Friendship University of Russia, Moscow, Russia. The literature investigation process was conducted between October and December 2020 and the literature investigations were conducted in English and French. The keywords explored during literature searching consisted of combinations of the following words: “Urinary tract infections,” “Uropathogenic bacteria,” “Uropathogens,” “Medicinal plants,” “Herbal medicine,” “Antimicrobial activity,” “Infection du tractus urinaires,” “Plantes médicinales,” “Activité antibactérienne.”

**Mechanism of infection**

**Ascending infection**

The bacteria most involved in UTIs are the same bacteria that colonize the intestine and enter the urinary tract after colonizing the periurethral region (Klein and Hultgren, 2020). The ascension of bacteria from the urethra to the bladder is the most common route of infection in UTIs (Walsh and Collyns, 2020).

It has been shown that if the bacteria were instilled directly into the bladder and a ureter was ligated, the unlit kidney was more likely to develop pyelonephritis (Walsh & Collyns, 2020). Studies suggest that up to 95% of UTIs develop in an ascending fashion (Lane et al., 2007). In fact, the infection begins with periurethral colonization by UPs, then there is a migration to the bladder to establish the infection, and if the infection is not treated, there is an ascent to the upper urinary tract or ureters and kidneys. Once in the kidneys, UPEC can enter the bloodstream, causing bacteremia and sometimes death (Lane et al., 2007).

**Hematogenous infection**

This mode of contamination is infrequent. It assumes that UTIs can be a result of hematogenous spread of bacteria, for example, in prolonged bacteremia, often associated with a deep source of infection such as endocarditis (Walsh and Collyns, 2020). This mode of contamination has been demonstrated in animal models. One of the first studies on the subject, carried out by De Navasquez (1950), showed that the intravenous injection of *S. aureus* can cause pyelonephritis. However, a similar result was more difficult to achieve with Gram-negative bacteria, suggesting that this is not the common route of infection for most UTIs, since most of these infections are caused by Gram-negative bacteria, in particular UPECs (Motse et al., 2019a; Walsh and Collyns, 2020).

**Host and risk factors in UTIs**

**Age and sex**

The incidence of UTI is higher in women compared with men across all age groups. This is explained by the anatomy of women because, compared to men, their urethra is shorter and there is relative proximity between the urethra and the anus (Walsh and Collyns, 2020). The prevalence of UTIs among sexually active young women has been reported to vary from 0.5 to 0.7 per person-year, while this incidence rate among young men was only 0.01 (Rowe and Juthani-Mehta, 2013). However, the incidence of UTI decreases during middle age but rises in older adults. In addition, several other factors such as sexual intercourse and the use of spermicides have also been shown to increase the risk of UTI in women (Walsh and Collyns, 2020). In fact, spermicides affect the vaginal microbial flora, which leads to a reduction in lactobacilli and allows proliferation of potentially pathogenic bacteria in the genital tract (Walsh and Collyns, 2020). Furthermore, menopause can also significantly increase the risks of recurrent UTIs (Bleiberg and Nguyen, 2020). Indeed, the reduction in estrogen levels can promote vaginal atrophy and lead to vaginal dryness and an increase in pH, which alters the vaginal flora and also reduces the level of lactobacilli, then causing a proliferation of potentially pathogenic bacteria such as mentioned above.

**Structural abnormalities**

Recurrent UTIs can be favored by certain pathologies of the renal tract (Walsh and Collyns, 2020). These are particularly pathologies inducing a residual volume of urine postvoiding. Neurogenic bladder and vesicoureteric reflux are a good illustration of this phenomenon, as the protection of the unidirectional flow of urine is reduced and thus increases the risk of urinary tract infection. Kidney stones are also associated with UTIs and may
even provide to bacteria a surface for biofilm formation (Walsh and Collyns, 2020). This pathology makes it difficult to eliminate bacteria through the flow of urine and more difficult to eradicate by the host’s immune response due to the biofilms formed (Walsh and Collyns, 2020).

Genetic factors

The genetic hypothesis is often mentioned as a risk factor predisposing some people to UTIs. Indeed, Walsh and Collyns (2020) reported that women from families in which UTIs have been recorded are more prone to develop this infection. In addition, other parameters involving the genotypic aspect such as proteins that prevent bacterial adhesion (uroplakins; uromodulin), cells of the innate immune system (including neutrophils), and polymorphisms of various genes have been shown to be associated to recurrent UTIs. In addition, the decrease in certain IL-8 receptors such as CXCR1 and CXCR2 (which play a role in the recruitment of neutrophils) has been associated with recurrent UTIs in children. Finally, it has been established that CXCR2 levels are lower in women with recurrent UTIs than in controls (Walsh and Collyns, 2020).

Catheterization

The involvement of catheters or other urine drainage devices in the increased occurrence of recurrent urinary tract infection is well known, especially since they promote the formation of bacterial biofilms and provide a reservoir of potential pathogens in contact with the bladder (Rowe and Juthani-Mehta, 2013). Stickler (2014) demonstrated that almost all catheters in situ for more than 4 weeks become colonized with bacteria and Walsh and Collyns (2020) reported that if the biofilms formed are crystalline, they can block urine flow, exacerbating the problem.

Microorganisms involved in UTIs, virulence factor, and MDR issue

The microorganisms involved in UTIs are generally called uropathogens (UPs). Most UTIs are caused by E. coli (UPECs) and sometimes by other bacteria such as S. saprophyticus, P. aeruginosa, S. aureus, K. pneumoniae, P. mirabilis, Acinetobacter baumannii, Streptococcus, and E. faecalis or fungi such as Candida albicans (Amdekar et al., 2011; Mann et al., 2017; Saka and Okumuga, 2017; Salvatore et al., 2011). Nowadays, the growth of the resistance to antibiotics of UPs increasingly generates important complications in the management of UTIs (Sweileh et al., 2018). Indeed, numerous studies are carried out each year to evaluate the antibiotic resistance of UPs isolated from patients with UTIs and the results almost all indicate an increase of the antibiotic resistance over the years (Magyar et al., 2017; Sultan et al., 2015; Sweileh et al., 2018). In a study conducted in Hungary to assess the antibiotic resistance of uropathogens between 2004 and 2015, Magyar et al. (2017) found that the five most commonly occurring bacteria were E. coli, E. faecalis, K. pneumoniae, P. aeruginosa, and P. mirabilis; and in this period, the resistance of E. coli to ciprofloxacin increased significantly from 19% to 25%, resistance rates of K. pneumoniae to cephalosporins were very high (reaching 60%), and they observed a significant increase in the rate of carbapenem-resistant P. aeruginosa (Magyar et al., 2017). In the same vein, Sweileh et al. (2018) conducted a global research on antimicrobial resistance in uropathogens using bibliometric analysis from 2002 to 2016. This study consisted of reviewing data provided by 1,087 articles (on antibiotic resistance of UPs) published in reference journals and they reported that increasing resistance of UPs is observed in different parts of the world. Otherwise, a parallel has been established between the pathogenicity, the VFs, and the resistance of UPs to antibiotics (Karam et al., 2018; Montaz et al., 2013; Paniagua-Contreras et al., 2017; Rodriguez-Siek et al., 2005). Indeed, the pathogenicity of UPs is associated with the expression of several VFs, such as adhesion elements, toxins, capsules, flagella, serum resistance factors, and iron uptake systems (Rodriguez-Siek et al., 2005). In addition to their involvement in pathogenicity, several studies have revealed that there is a correlation between VFs and antibiotic resistance (Karam et al., 2018; Montaz et al., 2013; Paniagua-Contreras et al., 2017; Shah et al., 2019; Tabasi et al., 2015). Shah et al. (2019) reported that the comparison of MDR between UPEC-positive VF and UPEC negative VF showed significant differences (69% vs. 16%, p = 0.0001) and a comparative study of ESBLs also showed the same correlation. In a similar study conducted in Tehran (Iran), Karam et al. (2018) indicated that biofilm production is associated with antibiotic resistance and that iron receptors and hemolysin production also contribute to reduced antibiotic sensitivity of UPEC.

In general, in bacteria, whether they are UPs or not, several mechanisms such as changes in cell permeability and multiple efflux pumps, mutations of the antibiotic target, and horizontal transfer of resistance genes are responsible for the development of the antibiotic resistance (Fig. 1) (Mukherjee, 2019; Palma et al., 2020). However, despite the current knowledge on resistance to antibiotics and all the phenotypic observations, the mechanisms of the involvement of VFs in antibiotic resistance in UPs are not yet clearly identified (Alabsi et al., 2014). In a study carried out by Alabsi et al. (2014) to assess the association of some virulence genes with antibiotic resistance among UPEC isolated from UTI patients in Alexandria (Egypt), it has been established that there is a significant association between the presence of the pap gene and resistance to gentamicin but it was not significantly associated with resistance to TMP/SMX, aminoglycosides, nitrofurantoin, quinolones, and β-lactam antibiotics. Otherwise, there was no correlation between the genes sfa, aer; and cnf1 and UPEC resistance to any antibiotics; and Alabsi et al. (2014) finally concluded that resistance of UPEC could be attributed to other VFs. In the same vein, without establishing the mechanism of the implication of VFs in antibiotics resistance, Raeispour and Ranjbar (2018) also concluded that UPEC strains causing infections are more likely to harbor certain virulence genes.

Finally, no research published in reference journals provides precise information on the specific mechanisms of the implication of VFs in antibiotic resistance but it is clear that this correlation is well existing. Studies should be carried out in this direction because in-depth knowledge of these mechanisms could guide towards new therapies for the prevention of UTIs and the fight against resistance of UPs to antibiotics. Otherwise, more globally, to overcome this problem of resistance which has real consequences in the management of UTIs (complications of the treatment, the continuity of the transmission chain of resistance genes between UPs and between Ups, and other commensal or
pathogenic bacteria), it became necessary to search for new antimicrobial molecules against UPs, including phytochemicals, green-synthesized nanoparticles, and even a potential combination of phytochemicals and conventional antibiotics.

Use of plants extract, phytochemicals, and green-synthesized nanoparticles against UTIs and UPs

The use of medicinal plants in the treatment and prevention of various diseases including UTIs is a very ancient practice (Shaheen et al., 2019). Due to easy availability, fewer reported side effects, cost-effectiveness, tolerance towards the patients with UTIs, and lack of bacterial resistance, herbal remedies are regaining more and more popularity and reliability worldwide (Shaheen et al., 2019). Given the growth of resistance to antibiotics, more and more researchers are assessing the antibacterial properties of various plants and their constituents. Indeed, according to search engines like Google Scholar, before the year 2000, only 4,290 concerning UTIs and medicinal plants were published while between 2000 and 2020 more than 17,300 articles were published on the same topic. A similar increase has been observed with modern databases such as PubMed, Scirus, ScienceDirect, and Scopus. Most of these researches are carried out in vitro to determine the effectiveness of the antibacterial activity of specific plant extracts against UPs, to isolate the active phytochemicals, to green-synthesize nanoparticles and test their antibacterial properties on UPs, to study the synergy between the plant extracts and conventional antibiotics, and to determine the minimum inhibitory concentration (MIC) and bactericidal inhibitory concentration (MBC).

Table 1 shows MIC and MBC of some plants against specific UP strains. These studies show that MICs and MBCs vary depending on the medicinal plants and the UP strains on which the extracts were tested. Indeed, a lower MIC value indicates that less drug is required for inhibiting the growth of the microorganism; therefore, plants with lower MICs such as methanolic leaves extracts of *Amaranthus tricolor* (against UPEC, MIC = 0.36 mg/ml; and *K. pneumoniae*, MIC = 0.62 mg/ml) (Sowjanya et al., 2015), *Anogeissus acuminata* (against *S. aureus*, MIC = 0.67 mg/ml) (Sowjanya et al., 2015), and *Cassia tora* (against *E. faecalis*, MIC = 0.67 mg/ml) (Mishra and Padhy, 2013) could be more advantageous in terms of efficacy and harmlessness since, for a possible standardization of their use, optimum efficacy could be obtained by administering small amounts of extract. However, further studies should be conducted to confirm the validity of such a hypothesis under in vivo conditions and in the treatment of UTIs.

![Diagram: Mechanisms of antimicrobial resistance](image-url)
The exact mechanism of the herbal drugs used to treat UTIs is not yet fully understood, but studies have shown that plant constituents and secondary metabolites act as diuretics, antioxidants, immunomodulators, and antimicrobials, preventing the fixation of pathogens in the urinary tract and stopped the proliferation of microorganisms (Shaheen et al., 2019). These diverse properties of medicinal plants are due to the presence of various phytochemical constituents including secondary metabolites as presented in Table 2. However, with regard specifically to the bacteriostatic and bactericidal effect of plant extracts, it has been established that phytochemicals act either by using the usual mechanisms of conventional antibiotics (by inhibiting the synthesis of the bacterial wall, by action on membrane cells, by inhibition of nucleic acid synthesis, by inhibition of protein synthesis, or by inhibition of folate metabolism) or by inhibition of efflux pumps (Khosravani et al., 2020). The inhibition of efflux pumps has various advantages in this age of antibiotic resistance (Sadeq Abdurridha et al., 2020). Indeed, efflux pumps allow bacteria to flush antibiotics out of bacterial cells and therefore reduce their sensitivity to conventional antibiotics. Thus, the inhibition of these pumps would make bacteria, including MDR bacteria, more sensitive to conventional antibiotics, and would make it possible to suppress resistance to antibiotics while reducing MICs (Sadeq Abdurridha et al., 2020).

Some plants well known in various countries of the world such as cranberries (Vaccinium oxyccocos and Vaccinium macrocarpon) and blueberries (Vaccinium corymbosum), both from the Ericaceae family, are widely used medicinal plants in the treatment of UTIs (Saeed, 2010; Shaheen et al., 2019). Numerous studies have reported the effectiveness of cranberry and blueberry in prevention and treatment of UTIs (Sadeq Abdurridha et al., 2020; Shaheen et al., 2019; Tempera et al., 2010; Wojnicz et al., 2012). The anti-UTI effects of cranberries and blueberries are attributed to fructose and proanthocyanidins (PACs) which inhibit VFs such as P fimbria by preventing pathogens from colonizing the urinary tract. Indeed, as shown in Figure 2, the type 1 fimbriae which is sensitive to mannose is blocked by fructose and PACs block the others type 1 fimbria mannose-resistant: this reduces the adhesion capacity of the bacteria and enables the bladder to "flush out" the UPs when urine is expelled (Sihra et al., 2018). In addition, randomized controlled trials have shown that cranberry juice can reduce the

| Uropathogens   | Antibacterial plants/part used/solvent | MIC (mg/ml) | MBC (mg/ml) | Reference                  |
|----------------|----------------------------------------|-------------|-------------|----------------------------|
| E. coli        | Mentha piperita/leaf/EthOH             | 125         | –           | Pulipati et al., 2016      |
|                | A. tricolor/leaf/MethOH                | 0.36        | –           | Sowjanya et al., 2015      |
|                | Anthocepalus cadamba/bark/MethOH       | 9.63        | 21.67       | Mishra and Padhy, 2013     |
|                | C. tora/leaf/MethOH                    | 4.27        | 9.63        | Mishra and Padhy, 2013     |
| E. faecalis    | A. tricolor/leaf/MethOH                | 2.5         | –           | Sowjanya et al., 2015      |
|                | C. tora/leaf/MethOH                    | 0.67        | 1.51        | Mishra and Padhy, 2013     |
|                | Albizia lebbeck/leaf/MethOH            | 9.63        | 21.67       | Mishra and Padhy, 2013     |
|                | A. acuminata/leaf/MethOH               | 0.67        | 1.51        | Mishra and Padhy, 2013     |
|                | A. cadamba/bark/MethOH                 | 3.41        | 4.27        | Mishra and Padhy, 2013     |
| P. mirabilis   | A. acuminata/leaf/MethOH               | 4.27        | 9.63        | Mishra and Padhy, 2013     |
|                | C. tora/leaf/MethOH                    | 3.41        | 4.27        | Mishra and Padhy, 2013     |
|                | A. cadamba/bark/MethOH                 | 4.27        | 9.63        | Mishra and Padhy, 2013     |
| P. aeruginosa  | M. piperita/leaf/EthOH                 | 125         | –           | Pulipati et al., 2016      |
|                | A. tricolor/leaf/MethOH                | 1.25        | –           | Sowjanya et al., 2015      |
|                | A. acuminata/leaf/MethOH               | 1.51        | 3.41        | Mishra and Padhy, 2013     |
|                | Artocarpus heterophyllus/bark/MethOH   | 9.63        | 9.63        | Mishra and Padhy, 2013     |
| K. pneumoniae  | M. piperita/leaf/EthOH                 | 125         | –           | Pulipati et al., 2016      |
|                | A. acuminata/leaf/MethOH               | 4.27        | 9.63        | Mishra and Padhy, 2013     |
|                | A. cadamba/bark/MethOH                 | 9.63        | 21.67       | Mishra and Padhy, 2013     |
|                | A. tricolor/leaf/MethOH                | 0.62        | –           | Sowjanya et al., 2015      |
| S. aureus      | M. piperita/leaf/EthOH                 | 62.5        | –           | Pulipati et al., 2016      |
|                | A. acuminata/leaf/MethOH               | 0.67        | 1.51        | Mishra and Padhy, 2013     |
|                | A. cadamba/bark/MethOH                 | 1.51        | 3.41        | Mishra and Padhy, 2013     |
|                | A. heterophyllus/bark/MethOH           | 9.63        | 9.63        | Mishra and Padhy, 2013     |
|                | C. tora/leaf/MethOH                    | 1.51        | 3.41        | Mishra and Padhy, 2013     |
| S. saprophyticus| A. tricolor/leaf/MethOH                | 5.0         | –           | Sowjanya et al., 2015      |
Table 2. Some plants commonly used to treat UTIs and green-synthesized nanoparticles with antibacterial activity.

| Family       | Botanical name | Common/local names                 | Parts used                             | How it is used?                                  | Active phytochemicals                                      | Sources                                                                 |
|--------------|----------------|------------------------------------|----------------------------------------|-------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------|
| Amaryllidaceae | Allium sativum | Garlic                             | Garlic bulbs and cloves                  | Raw garlic can be taken as a pill or as it is, infusion of dried garlic, maceration, food additive, essential oil | Allicin, alliin, acrolein, phytoecdin, daily-lisdulfide, daily-trisulfide | Shaheen et al., 2019. CoO (Velsankar et al., 2020); NiO (Haidar et al., 2020) |
| Apiceae      | Apium graveolens L. | Celery, Apium                      | Seed, aerial parts, and fruits          | Seed essential oil, seed, fruit, and aerial part extract | Ursolic acid, tannic acid, gallic acid, resin, black or chebulic | Shaheen et al., 2019. Fe (Roy et al., 2015); Co3O4 (Urabe and Aziz, 2019); ZnO (Azeza and Barzinya, 2020) |
| Coriandraceae | Coriandrum sativum | Coriander, Chinese parsley, dhania, cilantro | Leaves and seeds                        | Food condiments, essential oil of seeds          | Carvone, geraniol, limonene, borneol, camphor, elemol linalool, phenolic compounds, 2E-alkenals and alkanals | Bezalvar and Charle, 2019; Poulos et al., 2020; Au (El-Borady et al., 2020); CeO2 (Nadeem et al., 2020) |
| Cucurbitaceae | Cucumis sativus | Black-jack, hairy beggarticks, farmer’s friends, cobbler’s pegs | Whole herb                              | Infusion or decoction of the whole herb is taken | Glycosides, saponins, alkaloids, flavonoids, steroids, anthraquinones, and tannins | Gupta et al., 2011; Fe and ZnO (Kymomihimo et al., 2019) |
| Cichoriaceae  | Cichorium intybus | Chicory, blue daisy, coffeeweed, cornflower, blue dandelion, blueweed | Leaves and roots                        | Infusion of the leaves and roots as tea, prebiotic | Flavonoids, terpenoids, tannins, inulin, saponins, and cardiac glycoside | Shad et al., 2013; Ag (Belbodi et al., 2019); Au (Torabi et al., 2019) |
| Dandelion     | Taraxacum officinale | Dandelion                           | Leaves and flowers                      | Raw or cooked leaves in soup or salads, wine of flowers, infusion, decoction, and maceration of leaves | Taraxacin, taraxacoside, inulin, phenolic acids, sesquiterpene lactones, triterpenes, coumarins, and catatoned | Saeed, 2010; – |
| Arcium kappao | Arcium kappao | Greater burdock, kappao, beggar’s buttons, thorny burr | Roots and seeds                        | Infusion of dried roots and seeds, dried root as tea ingredient | Caffeoylquinic acid, caffeic acid, quercetin, arctigenin, arctin, lignins, flavonoids, cyanin, chlorogenic acid, quercetin, kaempferol, and rutin | Shaheen et al., 2019. – |
| Cucurbitaceae | Cucumis sativus L. | Cucumber (Sasa)                     | Fruits and seeds                       | Powder of dried fruit, decoction of roots       | Chebulin, tannic acid, gallic acid, beta-sirotol, fatty acids, and betulinic acid | Shaheen et al., 2019; Ag (Ankegowda et al., 2020) |
| Cupressaceae  | Juniperus osteosperma | Utah juniper                        | Bark, fruits, and leaves                | Raw or cooked fruits and infusion and decoction of bark and leaves | Phenolic compounds, alpha-pinene, terpenoids, cadinene, camphene, and terpinol | Saeed, 2010; – |
| Juniperus communis | Juniperus communis | Juniper                            | Fruits, bark, and leaves                | Essential oil, maceration, infusion or decoction of leaves and bark, gin of fruits | Sesquiterpenes, beta-pinene, limonene, sabine, monoesters hydrocarbons, and myrcene | Shaheen et al., 2019; – |
| Eriaceae      | V. corymbosum | Blueberry, blue, swamp and tall huckleberry, high or swamp blueberry | Fruit and leaves                        | Raw fruit, juice, cake additives, jams, syrups, herbal teas, wines | Citric and malic acids, alkaloids, glucosides of delphinidin, cyanidol, malvidin, and petunidol | Saeed, 2010; – |
| V. oxyacoccos | Cranberry       | Fruits and leaves                   | Raw fruit, encapsulated extracts, juice, tincture (alcohol extract) | Anthocyanidin flavonoids, cyanidin, peonidin and quercetin, catechin, and proanthocyanins | – |
| A. uva-ursi   | Uva Ursi, bearberry, kinnikinnick, bear grapes | Uva Ursi                            | Leaves                                 | Leaves are used as tea | Ursolic acid, tannic acid, gallic acid, resin, hydroquinones, phenolic, glycosides, and flavonoids | Saeed, 2010; – |
| Family               | Botanical name                  | Common/local names                  | Parts used            | How it is used?                      | Active phytochemicals                                                                 | Sources                                                                                     |
|---------------------|---------------------------------|-------------------------------------|-----------------------|-------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Euphorbiaceae       | Emblica officinalis             | Amla, Indian gooseberry, emblic myrobalan | Fruit                 | Raw and dried fruits, powder, juice | Tannins, alkaloids, phenolic, vitamin C, flavonoids, ellagic acid, chokecherry acid, quercetin, cinnamic acid, emblicin-A, gallic acid, emblicin-B; punglicinom, pedunculagin, citric acid, and trigalcalyl       | Khan, 2009; Se (Gumreet al., 2019); ZnO (Mari et al., 2019); Ag (Ramesh et al., 2015); MgO (Ramnani and Sanduraj, 2014) |
| Fabaceae            | Acacia nilotica                 | Babool, gum arabic tree              | Leaves, gum, bark, and seeds | Infusion or decoction of bark; Gum Paste and leaves are taken with cow's milk | Anthraquinones, tannins, saponins, flavonoids, and cardiac glycosides                   | Deshpande et al., 2013; Ag (Sarate et al., 2019); Sheikh and Ishnava, 2020; CuO (Ramesh et al., 2020) |
| Caesalpinia nuga (L.) Arnon | Lata                          | Leaves and roots                     | Powder of root and leaves | Powder of root and leaves            | Phenols, saponins, tannins, flavonoids, carbohydrates, and glycosides                  | Harjit et al., 2016; -                                                                          |
| Clitoria ternatea    |                                  | Root, bark, and seed                 | Root can be used in food like rice; decoction or infusion of bark and seeds can be used | Root can be used in food like rice; decoction or infusion of bark and seeds can be used | Phenols, flavonoids, and saponins                                                      | Manjula et al., 2015; Fe (Fatimah et al., 2020); Au (Chau et al., 2020); MgO and ZnO (Priya et al., 2020) |
| Lamiaceae            | P. vulgaris                     | Self-heal                            | Stems and leaves       | Salads, Infusion, in cooking, take as pill | Phytosteroids, tannins, lupinol, D-camphor and fenocine, cyanidin, delphinidin, and beta-sitosterol | Komral et al., 2018; Ag and Au (Fazal et al., 2016) |
| Ocimum sanctum or Ocimum tenuiflorum |                   | Holy basil, tulsi                     | leaves, stem, flower, root, and seeds | Infusion, maceration, or decocion of the dried whole plant or of any dried part | Flavonoids, polyphenol, flavonols, flavones, rosmarinic acid, eugenol, vicenin, orintin carnosic acid, beta-sitosterol, lupeol, beta-caryophyllene, lupeol, and agenin   | Shaheen et al., 2019; –                                                                           |
| M. piperita          | Cinnamon tree                   | Bark and leaves                      | Bark is used as spice, infusion, or decocion of bark and leaves | Bark is used as spice, infusion, or decocion of bark and leaves | Cinnamaldehyde, eugenol, transcinnamyl acetate camphor, and PACs                         | Shaheen et al., 2019; ZnO (Ansari et al., 2020) |
| Malvaceae            | Hibiscus rosa-sinensis          | China rose (Japa)                    | Flower                 | Infusion or decocion of flowers, essential oil | Glycosides, flavonoids, steroids, tannins, phenols, saponins, phytosterols, and terpenoids | Shaheen et al., 2019; Shaheen et al., 2020; Yang et al., 2020 |
| Malva sylvestris     |                                  | Mallow                              | Leaves, fruits, and seeds | Leaves are used in salad, seed and leaves can be used in decocion | Alkaloids, tannins, phenols, flavonoids, and aspsaninol                                 | Shaheen et al., 2019; Fe2O3 (Mouawad et al., 2020); Ag (Feizi et al., 2018); Esfandiarani et al., 2017; CuO (Taran et al., 2017) |
| Millifolium           | Azadirachta indica A. Juss     | Neem                                 | Fruit, leaves, and bark | Infusion, decocion, or maceration of bark and leaves, oil of the fruits | Alkaloids, polyphenol, saponins, flavonoid, anthraquinones, cardiac glycosides, terpenoids, terepenes, steroids, and tannins | Bia et al., 2009; Shaheen et al., 2019; Ag (Ahmed et al., 2016); ZnO (Bhuyan et al., 2015); CuO (Sharma et al., 2018); Au (Thirumurugan et al., 2010) |
| Moringaceae          | Moringa oleifera               | Moringa                             | Leaves, flower, and fruits | Eat raw dried fruit, Infusion of dried leaves as tea, oil | Flavonoids, steroids, alkaloids, amino acid, cardiac glycosides, phytoesterol, saponins, phenols, tannins, and terpenoids | Shaheen et al., 2019; Ag (Bindhu et al., 2020); CuO (Pagar et al., 2020) |
| Myrtaceae            | Syzygium cumini                | Jamban, black plum, jambolan, malabar plum, Java plum | Bark and fruits | Infusion, decocion, or maceration is taken; juice and salads of fruits | Flavonoids, steroids, alkaloids, amino acid, cardiac glycosides, phytoesterol, saponins, phenols, tannins, and terpenoids | Shaheen et al., 2019; Fe, Ag, and Cu (Asghar et al., 2020) |
| Nyctaginaceae        | Boerhavia diffusa              | Punarnava, red spiderling, bushape    | Leaves and roots       | Leaves as vegetable dish, infusion of raw or dried root | Lignin, phloencin, saponins, glycosides, arachidic acid, behenic acid, saturated fatty acids, vitamin C, and boeravonine B | Shaheen et al., 2019; Ag (Mathiyazhagan et al., 2020) |
| Phyllanthacae        | Phyllanthus amarus             | Sleeping plant                      | The whole plant, juice | Decocion of the whole plant, juice | Tannins, flavonoids, triterpenoids, lignins, gallic acid, geranium, corilgan, niranthin, and phyllanthin | Shaheen et al., 2019; Ag (Ajitha et al., 2018); CuO (Buvaneswari and Revathi, 2018) |
| Ranunculaceae        | Hydrastis canadensis           | Goldenseal, orangeroot, yellow puccoon | Leaves                 | Infusion of leaves, food supplement | Berberine, hydrastine, canada, alkaloids, polyphenol, saponins, and flavonoid          | Mandal et al., 2020; ZnO (Wade et al., 2020) |

(Continued)
A significant number of herbal extracts and botanicals have been identified for their potential in addressing urinary tract infections (UTIs) and preventing the adhesion of bacteria to the urinary epithelium. These plants are rich in various bioactives such as flavonoids, phenols, saponins, glycosides, alkaloids, phenolic compounds, and terpenes which provide them with antioxidant and antimicrobial properties.

For instance, extracts of *Arctostaphylos uva-ursi* (Vaccinium arctostaphylos) and *Hydrastis canadensis* (Goldenseal) have demonstrated efficacy in preventing adhesion of UTIs by binding to mannose-sensitive uroplakin receptors (bladder epithelial cells), and mannose-insensitive GAL glycolipid receptors (renal epithelial cells). The beneficial effects of these plants are due to their rich contents of bioactive compounds such as flavonoids, phenols, saponins, alkaloids, and terpenes. These compounds are responsible for the specific binding to bacterial adhesins, and inhibition of bacterial biofilm formation.

In vivo studies have confirmed the effectiveness of *Arctostaphylos uva-ursi* and *Hydrastis canadensis* in the prevention of UTIs. In a study by Saeed et al. (2010), the use of *Arctostaphylos uva-ursi* extracts in combination with cranberry juice resulted in a significant reduction in the number of symptomatic UTIs over a 12 months period in women with recurrent UTIs. Nowadays, the cranberries and blueberries products are marketed in the form of capsules, pills, juice, syrup, and lozenges.

![Figure 2. Mechanisms of action of antiadhesive activity of cranberry. PACs bind P fimbriae and prevent it from binding to mannose-insensitive GAL glycolipid receptors (renal epithelial cells). Fructose binds to type 1 fimbriae, preventing it from binding to mannose-sensitive uroplakin receptors (bladder epithelial cells).](image)

Arctostaphylos uva-ursi (Uva Ursi, Bearberry), another plant from the Ericaceae family, is also well known in the treatment of UTIs. Gohari and Saeidnia (2014) reported that the Uva Ursi was shown to be effective on bacterial inflammatory diseases in general when used at the rate of 3 g of infusion of the dried herb, 4 times daily. In addition, the use of leaf extracts of Uva Ursi has been authorized in some countries such as Germany (by German Federal Institute for Drugs and Medical Devices) for the management of UTIs. The antimicrobial effect of Uva Ursi is attributed to arbutin which is metabolized into hydroquinone whose antimicrobial and antioxidant properties are well known (Saeed Abdulridha et al., 2020).

Several in vivo and in vitro studies confirmed that the extracts of *Hydrastis canadensis* (Goldenseal) have antibacterial activity towards Gram-positive UPs, including methillin-resistant Staphylococcus aureus, due to alkaloid compounds such as berberine, hydrastine, and canadine, which has antibacterial activity against Gram-positive pathogens (Mandal et al., 2020; Saeed Abdulridha et al., 2020). Otherwise, other plant extracts like *Zingiber officinale* (Ginger), which is known for its anti-inflammatory and analgesic properties, have demonstrated antimicrobial skills.
CONCLUSION

UTIs are very common in most countries of the world and very current in women and the elderly. The treatment of these pathologies which uses conventional antibiotics is increasingly hard given the growing resistance to antibiotics. This review presented some plants known for their effectiveness in the management of UTIs. Medicinal plants have various advantages because they are safe, economical, and easy to use and their main advantage is that bacteria have not yet developed resistance against them. Notwithstanding the above, additional studies must be carried out to study and discuss the molecules responsible for the efficacy of these plants against UTIs, to understand the mechanisms of involvement of VFs in antibiotic resistance, and to standardize the use of different plant extracts that do not yet have legal authorization in the countries where they are used to be taken against UTIs. Finally, large randomized, double-blind clinical studies need to be conducted on each of these plants and their secondary metabolites to provide more evidence on the clinical efficacy and safety of these products.

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