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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 (VFs) 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-synthetized 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

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et al., 2020). 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 médécinales," "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 (Bleibel 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 Okunuga, 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 antibioresistance over the years (Magyar *et al*., 2017; Sultan *et al*., 2015; Sweileh *et al*., 2018). In a study conducted in Hungary to assess the spectrum and 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; Momtaz *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; Momtaz *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

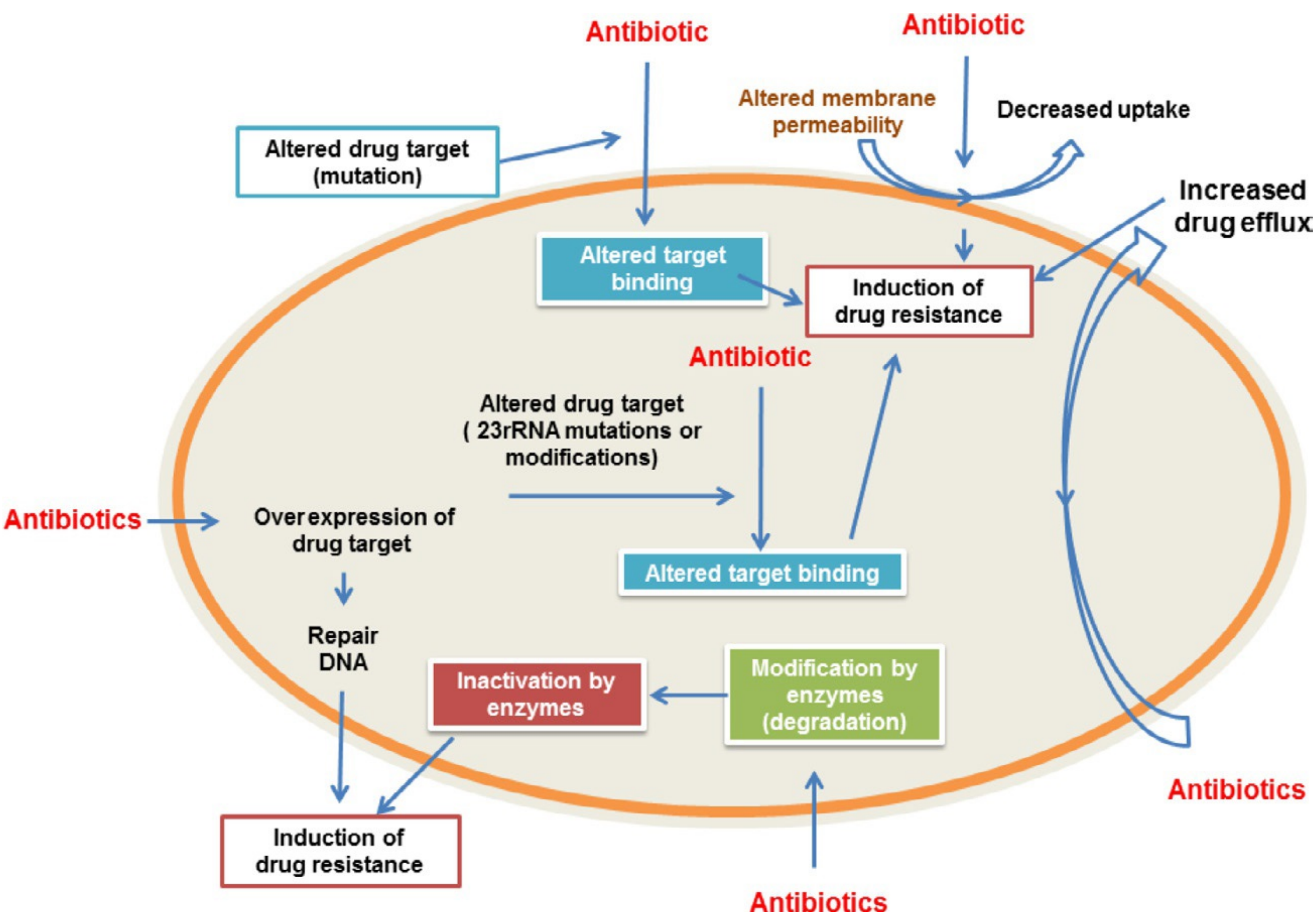

Figure 1. Mechanisms of antimicrobial resistance (Mukherjee, 2019).

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-synthetized 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 phytocompounds, 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.

Table 1. MIC and MBC of some plants with antibacterial properties against specific uropathogens.

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
	*Anthocephalus 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

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 Abdulridha *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 Abdulridha *et al*., 2020).

Some plants well known in various countries of the world such as cranberries (*Vaccinium oxycoccos* 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 Abdulridha *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

Table 2. Some plants commonly used to treat UTIs and green-synthetized nanoparticles with antibacterial activity.

Family	Botanical name	Common/local names	Parts used	How it is used?	Active phytochemicals	Sources	Green-synthetized nanoparticles
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, phytocidin, diallyl-disulfide, and diallyl-trisulfide	Shaheen *et al.*, 2019	CuO (Velsankar *et al.*, 2020); NiO (Haider *et al.*, 2020)
Apiaceae	*Apium graveolens* L.	Celery, *Apium*	Seed, aerial parts, and fruits	Seed essential oil, seed, fruit, and aerial part extract	Succinic acid, 5,8-dimethoxy psoralen, trans-cinnamic acid, isofraxidin, transferulic acid, beta-sitosterol, falcarindiol, oplopandiol, lunularic acid, lunularin, and eugenic acid	Shaheen *et al.*, 2019	Fe (Roy *et al.*, 2015); Co3O4 (Urabe and Aziz, 2019); ZnO (Azeeza and Barzinjya, 2020)
	Coriandrum sativum	Coriander, Chinese parsley, dhania, cilantro	Leaves and seeds	Food condiments, essential oil of seeds	Carvone, geraniol, limonene, borneol, camphor, elemol and linalool, phenolic compounds, 2E-alkenals, and alkanals	Bezalwar and Charde, 2019; Saeed, 2010	TiO2 (Hu *et al.*, 2020); Ag (Ashraf *et al.*, 2019)
	Petroselinum crispum var. crispum	Parsley, French persillade	Seeds, leaves, and roots	Essential oil, raw leaves can be chewed, leave as food additive, infusion of leaves, seed, and roots	Ascorbic acid, carotenoids, flavonoids, apiole, terpenoic compounds, coumarin, phenylpropanoids, phthalides, tocopherol, and furanocoumarins	Poulios *et al.*, 2020	Au (El-Borady *et al.*, 2020); CeO2(Nadeem *et al.*, 2020)
	Trachyspermum copticum	Ajowan, Ajwain, bishop's weed	Leaves and fruits	Essential oil of fruits, infusion of leaves powder	Terpinene, p-cymene, xylene, palmitic acid and oleic acid, beta-pinene, and thymol	Shaheen *et al.*, 2019	–
Asteraceae	*Bidens pilosa* L.	Black-jack, hairy beggarticks, farmer's friends, cobblers' pegs	Whole herb	Infusion or decoction of the whole herb is taken	Glycosides, saponins, alkaloids, flavonoids, steroids, anthraquinones, and tannins	Lima Silva *et al.*, 2011	Fe and ZnO (Kyomuhimbo *et al.*, 2019)
	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 (Behboodi *et al.*, 2019); Au (Torabi *et al.*, 2019)
	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 catortenoids	Saeed, 2010	–
	Arctium lappa	Greater burdock, *lappa*, 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, cynarin, chlorogenic acid, quercitrin, luteolin, and rhamnoside	Shaheen *et al.*, 2019	–
Combretaceae	*Terminalia chebula*	black or chebulic myrobalan, haritaki, halilaj	Fruits and roots	Powder of dried fruit, decoction of roots	Chebulin, tannic acid, gallic acid, beta-sitosterol, fatty acids, and betulinic acid	Shaheen *et al.*, 2019	Ag (Ankegowda *et al.*, 2020)
Cucurbitaceae	*Cucumis sativus* L.	Cucumber (Sasa)	Fruits and seeds	Fruit water, seed oil, seed extracts	Terpenoids, saponins cardiac glycosides, tannins, and phytosterol	Sood *et al.*, 2012	CuO (Vats *et al.*, 2020); Fe (Sharma *et al.*, 2016)
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 terpineol	Saeed, 2010	–
	Juniperus communis	Juniper	Fruits, bark, and leaves	Essential oil, maceration, infusion or decoction of leaves and bark, gin of fruits	Sesquiterpene, β-pinene, limonene, sabinene, monoterpene hydrocarbons, and myrcene	Shaheen *et al.*, 2019	–
Ericaceae	*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 delphininol, cyanidol, malvidol, and petunidol	Saeed, 2010	–
	V. oxycoccos	Cranberry	Fruits and leaves	Raw fruit, encapsulated extracts, juice, tincture (alcohol extract)	Anthocyanidin flavonoids, cyanidin, peonidin and quercetin, catechin, and proanthocyanins	Saeed, 2010	–
	A. uva-ursi	Uva Ursi, bearberry, kinnikinnick, bear grapes	Leaves	Leaves are used as tea	Ursolic acid, tannic acid, gallic acid, resin, hydroquinones, phenolic, glycosides, and flavonoids	Saeed, 2010	–

(Continued)

Family	Botanical name	Common/local names	Parts used	How it is used?	Active phytochemicals	Sources	Green-synthetized nanoparticles
Euphorbiaceae	*Emblica officinalis*	Amla, Indian gooseberry, emblic myrobalan	Fruit	Raw and dried fruits, powder, juice	Tannins, alkaloids, phenolic, vitamin C, flavonoids, ellagic acid, chebulinic acid, quercetin, chebulagic acid, emblicanin-A gallic acid, emblicanin-B, punigluconin, pedunculagin, citric acid, and trigallayl	Khan, 2009	Se (Gunti*et al*., 2019); ZnO (Mari *et al*., 2019); Ag (Ramesh *et al*., 2015); MgO (Ramanujam and Sundrarajan, 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 (Saratale *et al*., 2019; Sheikh and Ishnava, 2020); CuO (Ramesh *et al*., 2020)
	Caesalpinia nuga (L.) Aiton	Lata	Leaves and roots	Powder of root and leaves	Phenols, saponins, tannins, flavonoids, carbohydrates, and glycosides	Harjit *et al*., 2016	-
	Clitoria ternatea	Darwin pea, aparajita, bluebellvine, blue pea, butterfly pea, cordofan pea	Root, bark, and seed	Root can be used in food like rice; decoction or infusion of bark and seed can be used	Phenols, flavonoids, and saponins	Manjula *et al*., 2013	Fe (Fatimah *et al*., 2020); Au (Chan *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, lupeol, D-camphor and fenchone, cyanidin, delphinidin, and beta-sitosterol	Komal *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 decoction of the dried whole plant or of any dried part	Flavonoids, polyphenol, flavonols, flavones, rosmarinic acid, eugenol, vicenin, orintin carnosic acid, beta-sitosterol, luteolin, myrtenal, and apigenin	Shaheen *et al*., 2019	–
	M. piperita	Peppermint	Leaves	Oil, infusion of leaves (peppermint tea), flavoring ingredient	Menthone, menthol, limone, menthofuran, and pulegone	Shaheen *et al*., 2019	–
Lauraceae	*Cinnamomum verum*	Cinnamon, true cinnamon tree	Bark and leaves	Bark is used as spice, infusion, or decoction 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 (Jaba)	Flower	Infusion or decoction of flowers, essential oil	Glycosides, flavonoids, steroids, tannins, phenols, saponins, phlobatannins, and terpenoids	Shaheen *et al*., 2019;Yang *et al*., 2020	Ag (Surya *et al*., 2016); CuO (Dinesh *et al*., 2020); ZnO (Manokari *et al*., 2017)
	Malva sylvestris	Mallow	Leaves, fruits, and seeds	Leaves are used in salad, seed and leaves can be used in decoction	Alkaloids, tannins, phenols, flavonoids, andsaponins	Shaheen *et al*., 2019	Fe_3O_4 (Mousavi *et al*., 2020); Ag (Feizi *et al*., 2018; Esfanddarani *et al*., 2017); CuO (Taran *et al*., 2017)
Meliaceae	*Azadirachta indica* A. Juss	Neem	Fruit, leaves, and bark	Infusion, decoction, or maceration of bark and leaves, oil of the fruits	Alkaloids, polyphenols, saponins, flavonoid, anthraquinones, cardiac glycosides, terpenoids, terpenes, steroids, and tannins	Biu *et al*., 2009; Shaheem *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	Kaempferol, thiocarbamate glycoside, acetylated carbamate, amino acids, tocopherol, moringine, and spirochin	Shaheen *et al*., 2019	Ag (Bindhu *et al*., 2020); CuO (Pagar *et al*., 2020)
Myrtaceae	*Syzygium cumini*	Jamun, black plum, jambolan, malabar plum, Java plum	Bark and fruits	Infusion, decoction, or maceration is taken; juice and salads of fruits	Flavonoids, steroids, alkaloids, amino acid, cardiac glycosides, phytosterols, saponins, phenols, tannins, and terpenoids	Shaheen *et al*., 2019	Fe, Ag, and Cu (Asghar *et al*., 2020)
Nyctaginaceae	*Boerhavia diffusa*	Punarnava, red spiderling, biskhapra	Leaves and roots	Leaves as vegetarian dish, infusion of raw or dried root	Lignin, phenolics, steroids, glycosides, arachidic acid, behenic acid, saturated fatty acids, vitamins C, and boeravinone B	Shaheen *et al*., 2019	Ag (Mathiyazhagan *et al*., 2020)
Phyllanthaceae	*Phyllanthus amarus*	Sleeping plant	The whole plant	Decoction of the whole plant, juice	Tannins, flavonoids, triterpenoids, lignins, gallic acid, geraniin, corilagin, niranthin, and phyllanthin	Shaheen *et al*., 2019	Ag (Ajitha *et al*., 2018); CuO (Buvaneswari and Revathy, 2018)
Ranunculaceae	*Hydrastis canadensis*	Goldenseal, orangeroot, yellow puccoon	Leaves	Infusion of leaves, food supplement	Berberine, hydrastine, canadine, alkaloids, polyphenols, saponins, and flavonoid	Mandal *et al*., 2020	ZnO (Wade *et al*., 2020)

(Continued)

Family	Botanical name	Common/local names	Parts used	How it is used?	Active phytochemicals	Sources	Green-synthetized nanoparticles
Rubiaceae	*Galium aparine* L.	Cleavers, clivers, bedstraw, goosegrass, catchweed, stickyweed, sticky bob	Stems, leaves, and fruit	Stems and leaves as food additives, fruit as substitute of coffee, maceration, or infusion of leaves	Iridoid glycosides, alkaloids, phenolic acids, anthraquinone, flavonoids coumarins, and citric acid	Saeed, 2010	–
Rutaceae	*Agathosma betulina* (previously *Barosma betulina*)	Buchu, bucco	Leaves and stalks	Infusion as tea, maceration of leaves and stalks in vinegar, essential oil	Diosphenol and limonene are the most important in UTIs	Saeed, 2010	–
Theaceae	*Camellia sinensis*	Green tea, tea shrub	Leaves	Infusion of dried leaves	Glycosides, alkaloids, phenolic compounds, and caffeine	Kheirabadi *et al*., 2019	Au (Ahmeda *et al*., 2020); ZnO (Akbarian *et al*., 2019); Co3O4 (Urabe and Aziz, 2019); ZnO (El-Shenawy *et al*., 2019)
Violaceae	*Hybanthus enneaspermus*	spade flower	Leaves	Infusion of fresh or dried leaves	Flavonoids, phenols, saponins, anthraquinones, glycosides and tannins phenolic, terpenes, and alkaloids	Shaheen *et al*., 2019	–
Zingiberaceae	*Zingiber officinale*	Ginger	Root	Fresh ginger, juice, infusion of dried root, food ingredient	Zingiberene, zingiberol, α-zingiberene, dihydroparadols, shogaols, and gingerols	Shaheen *et al*., 2019	NiO (Haider *et al*., 2020); CuO (Varghese *et al*., 2020)
Zygophyllaceae	*Tribulus terrestris*	Goat's head, bullhead, Croix-de-Malte, abrojo, tackweed, and gokharu	Roots, leaves, and fruits	Infusion of dried roots and leaves powder, raw or fruits juice, the fruits are also available as pills	Saponins, stigmasterol, β-sitosterol, neo-tigogenin, gitogenin, chlorogenin, tribuloside, kaempferol, rhamnose, hecogenin, tribulosin, neohecogenin glucoside, and cinnamic amide	Shaheen *et al*., 2019	Ag (Hamidi *et al*., 2019)

Ag = silver; Cu = copper; CuO = copper oxide; Au = gold; Fe = iron; ZnO = zinc oxide; MnO = magnesium oxide; Se = selenium; TiO2 = titan oxides; Fe_3O_4 = ferrosoferric oxide; CeO2 = cesium oxide; and NiO = nickel oxide.

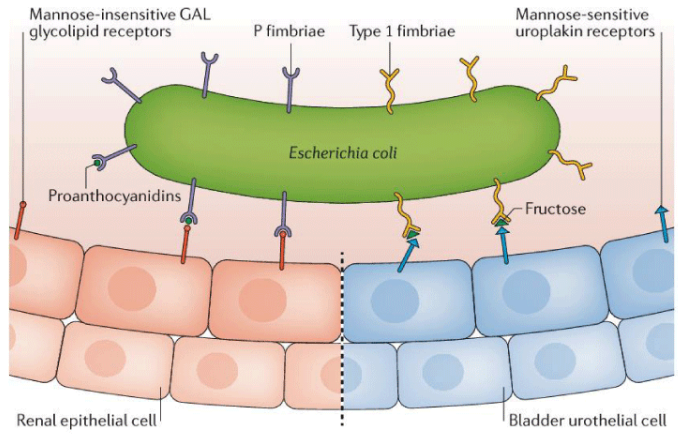

Figure 2. Mechanisms of action of antiadhesive activity of cranberry. PACs bind P fimbriae and prevent it from binding to mannose-insensitive GAL glycolipid receptors (renal epithelial cells). Fructose binds to type 1 fimbriae, preventing it from binding to mannose-sensitive uroplakin receptors (bladder epithelial cells) (Sadeq Abdulridha *et al*., 2020; Sihra *et al*., 2018).

number of symptomatic UTIs over a 12 months period in women with recurrent UTIs (Saeed, 2010). Nowadays, the cranberries and blueberries products are marketed in the form of capsules, pills, juice, syrup, and lozenges.

Arctostaphylos uva-ursi (Uva Ursi, Bearberry), another plant from the Ericaceae family, is also well known in the treatment of UTIs (Sadeq Abdulridha *et al*., 2020; Saeed, 2010). 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 (Sadeq Abdulridha *et al*., 2020; Saeed, 2010). The antimicrobial effect of Uva Ursi is attributed to arbutin which is metabolized into hydroquinone whose antimicrobial and antioxidant properties are well known (Sadeq 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 methicillin-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; Sadeq Abdulridha *et al*., 2020). Otherwise, other plant extracts like rosemary (*Rosmarinus officinalis*) have been found to be effective against UPs such as *E. coli, P. mirabilis, Prunella vulgaris, K. pneumoniae, P. aeruginosa,* and *S. aureus* (Sadeq Abdulridha *et al*., 2020). However, not being able to discuss the characteristics and individual effects of each of the plants commonly used in the prevention and treatment of UTIs, we have proposed to group together in Table 2 the plants commonly used to manage this pathology, of which the efficacy has been reported in the literature. This table includes the family of the plant, scientific name, usual name, the parts used, the way of using them, the phytochemicals that constitute it, and the nanoparticles which have been green-synthesized and which 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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CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

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