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A REVIEW ON ANTIBIOTIC RESISTANCE AND THE USE OF MEDICINAL PLANTS IN THE MANAGEMENT OF UROPATHOGENIC BACTERIA

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ABSTRACT

UTIs are the most prevalent infections and are caused by uropathogenicmicrobes such as *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, and Enterococcus spp.* Antibiotic resistance has hampered the management of UTIs over the years, with direct repercussions on the treatment cost, the infection severity, and the duration of hospitalization. This review discussed the route of infections, risk factors connected to UTIs, antibiotic resistance issues as well as an alternative therapy to overcome the problem of antibiotic resistance. The medicinal plants which have been utilized for thousands of years to cure a variety of ailmentsrepresent a significant antibiotic substitute. This study has included both the therapy of UTIs themselves as well as the use of medicinal herbs to treat uropathogens.This review could help in the development of an effective UTI therapy formulation.

Keywords: Urinary tract infection (UTI), multi-drug resistance (MDR), uropathogens, antimicrobial resistance (AMR), medicinal plants.

INTRODUCION

In the human population, urinary tract infections (UTIs) are particularlyfamiliar infections and usually composed of bacterial origin as well as defined as an infection that can occur anywhere throughout the urinary tract (Valmadrid et al., 2021). UTIs are classified as cystitis (bladder infection), urethritis (localized in urethra), vaginitis (vaginal infection), and pyelonephritis (infection of the kidneys) (Ross & Hickling, 2022, Giannoumis, 2021). UTIs are currently regarded as a major public health issue, responsible for almost 150 million infectious diseases worldwide annually (Mohamed et al., 2022). The ostensible uropathogenic *E. coli* (UPEC) causes approximately 80 % to 90 % of UTIs (Klebba et al., 2021), whereas 5 % to et al., of UTIs cases are because of *Staphylococcus saprophyticus* (Hashemzadeh et al., 2021). A higher range of pathogens is involved in these infections, particularly*Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus, Klebsiella pneumoniae, Acinetobacter baumannii, Proteus mirabilis, and Enterococcus faecalis* instead of viral or fungal infection (Saka and Okunuga, 2017). In all age categories, women are more susceptible to UTIs than males (Nahab et al., 2022).

Antibiotics are used to treat these infections (Patel et al., 2021) and suggested giving gentamycin, ciprofloxacin, trimethoprim/sulfamethoxazole (SXT), and nitrofurantoin for up to 3-5 days to cure the acute uncomplicated UTIs (Devis et al., 2022).The emergence of high resistance to SXT as well as ciprofloxacin makes them difficult to treat such infections in individuals who have already been exposed to these medications or who are at risk of contracting bacteria that produce extended-spectrum-β lactamases (ESBLs).Sometimes, to overcome these types of infections, second-line antibiotic treatment is used which includes β-lactams (amoxicillin-clavulanate) and oral cephalosporins (ceftriaxone,cefixime). Other antibiotics may also be administered depending on the circumstances (Arsene et al., 2021). Antimicrobial resistance is a topical concern among uropathogenic superbugs. Several studies in recent years have been conducted in various states to evaluate the resistance of UP bacteria to antimicrobials. The reported findings show that antibiotic resistance is increasing every day and that this is partly related to the rise of multidrug-resistant (MDR) microorganisms. As a result, this conclusion is consistent across the globe in terms of UP bacterium resistance to antibiotics. The reported consequences are very comprehensible that resistance towards antibiotics is rising day by day and in some cases due to the production of multidrug-resistant bacteria (MDR) (Mbarga et al., 2021). The bacteria are resistant to multiple antibiotics and are major worldwide contributors to morbidity as well as mortality (Jin et al., 2023).Thus, this result is found similar around the globe regarding the resistance of UP bacteria towards antibiotics (Signing et al., 2020). So, to overcome these problems, medicinal plants appear to be a viable option due to the emergence of antibiotic resistance worldwide. For centuries, people have utilized plants to treat and prevent a wide range of illnesses, including bacterial infections.These medicinal plants include *Vaccinium macrocarpon*, *Tribulus terrestris*, *Allium sativum*, *Moringa oleifera*, *Ocimum Sanctum*, *Zingiber officinale*, etc. These plants have the potential to cure UTIs through their anti-microbial as well as anti-inflammatory properties (Shaheen et al., 2019).Thus, herbal remedies are very efficient in preventing and treating UTIs (Poulios et al., 2021). This review aims to discuss the mechanism of infection involved in UTIs, Risk associated factors, involvement of UPs along with multidrug resistance problems, and the applicationof medicinal plants in the management of UTIs.

Mode Of Infection Associated To UTIs

a) Ascending Infection

The bacteria that colonize the intestine are responsible to infect periurethral area through the passage of the urinary tract and become the reason for causing UTIs (Klein and Hultgren, 2020). The most common path of infection in UTIs is a bacterial escalation from the urethra to the bladder. It was revealed that if the microorganisms were inculcated directly into the urinary bladder and due to interconnection of ureters, a caliginous kidney was more likely to build up pyelonephritis. According to reports, up to 95 % of UTIs progress in an ascending manner (Arsene et al., 2021). In reality, infectivityinitiates with the periurethral colonization by uropathogens, then this becomes migrated to the bladder to ascertain the infection, and it becomes gradually moved to the upward urinary tract, ureters leading to kidneys as well, in the case of ignorance to treatment.Once the infection is spread to kidneys, uropathogenic*Escherichia coli* (UPEC) have the potential to enter the bloodstream and gradually cause bacteremia and in extreme cases death (Hassan et al., 2021).

b) Hematogenous Infection

This hematogenous manner of infectivity is rare. UTIs can occur as a result of bacterial hematogenous dissemination, for instance, in chronic bacteremia, frequentlylinked with a profound source of illness like endocarditis (Arsene et al., 2021). In animal models, this mechanism of infection has been shown. A previous study found that intravenous injection of *S. aureus* can result in pyelonephritis (Schuler et al., 2021). Although, it was very difficult to achieve these similar results with Gram-negative bacteria. Thus, it is advised that such type of mechanism is not the primary means of infection for the majority of UTIs, because Gram-negative microbes are the main root of these infections, particularly UPECs (Arsene et al., 2021). The urinary system and its sites of infection are represented in Figure 1.

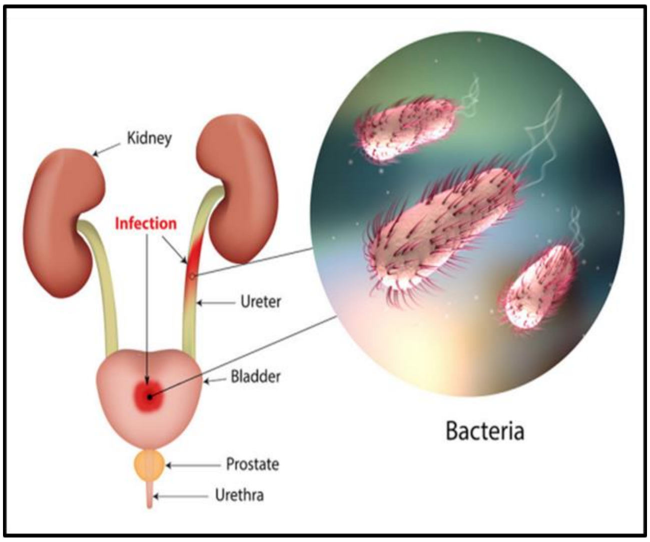

Figure 1: The urinary tract system and its infection sites (Terlizzi et al., 2017)

Risk-Associated Factors in UTIs

a) Age and sex

Among all age categories, UTIs occur more frequently in women than in men. This happens because the anatomy of women is different from men's. Women have short urethral tubes compared to men and have comparative proximity between urethra and anus (Lal et al., 2021). The incidence rate of UTIs in sexually active young men was found only 0.01 per person/year, while UTIs prevalence among young women varies from 0.5 to 0.7 per person/year (Rowe and Juthani-Mehta, 2013). During the middle age group, the occurrence of UTI declinesbut gradually increases in older age groups. A higher incidence of UTIs in women has also been associated with several other factors, including sexual activity and the use of spermicides.The use of spermicides affects the vaginal flora, resulting a decrease in lactobacilli and allowing harmful bacteria to proliferate in the genital tract (Arsene et al., 2021). In addition, menopause significantly increases the risk of recurrent UTIs (Łaniewski and Herbst-Kralovetz, 2022).

Structural Abnormalities

Certain pathologies of renal tract can be favored the recurrent UTIs. These pathologies have become the reason for inducing a remaining volume of urine post-voiding. Kidney stones are associated to UTIs that make available a surface for biofilm formation by bacteria. The presence of biofilms makes it hard to eradicate bacteria during the urine flowalong with the elimination by immune response of the host (Arsene et al., 2021).

Catheterization

The use of urine catheters and other urinary drainage types of equipment is widely known to enhance the frequency of recurrent UTIs, particularly since they can form bacterial biofilms and serve as a reservoir for the creation of pathogenic microorganisms that can infect the bladder (Chakrabarty et al., 2022). A previous study reported that almost all catheters become colonized with pathogenic bacteria in situ for more than 4 weeks (Stickler, 2014). The situation might be made worse if the crystalline biofilms are created and obstruct the normal flow of urine (Walsh and Collyns, 2020).

Uropathogens Responsible for UTIs, Virulence Factors and the MDR Problem

Microorganisms involved in UTIs are usually referred to as uropathogens (UPs). The majority of UTIs are due touropathogenic*E. coli* (UPECs) and besides UPECs, UTI can be caused by other bacteria such as *K. pneumoniae, P. mirabilis, P. aeruginosa, S. saprophyticus, S. aureus*, *Acinetobacter baumannii*as well as *Enterococcus spp.* or fungi, for instance, *Candida albicans* (Sing et al., 2019; Gaston et al., 2021).

Currently, the increase in the resistance to antibiotics by uropathogens(UPs) produces a critical barrier in the administration of UTIs (Tache et al., 2022). Thus, several studies reported an increase in antibiotic resistance over the yearsin UTI patients (Sweileh et al., 2018; Esposito et al., 2021). The five most common bacteria were *E. coli, K. pneumonia, P. mirabilis, P. aeruginosa*, and *E. faecalis*, according to a study conducted in Hungary between 2004 and 2015 to evaluate the spectrum as well as antibiotic resistance of uropathogens. During this time, K. pneumoniae resistance rates to cephalosporins reached a high60%, *E. coli* resistance to ciprofloxacin increased dramatically from 19 % to 25 %, and a considerablerise in the prevalence of carbapenem-resistant *P. aeruginosa*was observed (Magyar et al., 2017). Another study conducted in 2018 revealed uropathogenic resistance to antimicrobials by the use of bibliometric analysis from the year 2002 to 2016. This global study reported that the resistance of UPs to antibiotics increased with time in different divisions of the world. On the other hand, parallel findings have been recognized between the pathogenicity specifically virulence factors (VFs), and UPs resistance toward antibiotics (Paniagua-Contreras et al., 2017). The expression of certain VFs is associated with the pathogenicity of UPs, for instance, capsules, toxins, adhesion elements, serum resistance markers, flagella, and iron assimilation mechanism (Jahapriya, 2018; Sora et al., 2021).

Several studies reported that there is a correlation between VFs and antibiotics in the association to cause pathogenicity (Karam et al., 2019). According to a previous study, the evaluation of multidrug resistance between UPEC-positive virulence factorsas well as UPEC-negative virulence factorsprovedconsiderablevariations (approx. 69 % vs. 16 %, $p = 0.0001$), and the same correlation was observed in a comparative study of ESBLs (Shah et al., 2019). A similar study revealed that the formation of biofilm is linked with antimicrobial resistance and the production of hemolysin also contributed to the reduction of antibiotic sensitivity of UPEC (Karam et al., 2019). In general, several pathwaysaid in the development of antibiotic resistance, such as antibiotic target mutations, horizontal transfer of resistance genes, cell permeability alterations, as well as several efflux pumps indicated in Figure 2 (Arsene et al., 2021).

However, regardless of recent advances in antibiotic resistance research and phenotypic elucidation, the methods by which VFs contribute to antibiotic resistance in UPs remain unknown. According to the previous study conducted by Albasi et al., to investigatethe connection between certain virulence genes and antibiotic resistance amongst UPECs strains from patients with UTI in Egypt, it was recognized that there remains a considerable connection between the pap gene and gentamicin resistance, but resistance to SXT, quinolones, nitrofurantoin, aminoglycosides along with β-lactam antibiotics was not found significantly. On the other hand, no correlation was found between the genes are, SFA and the resistance of UPEC toward antibiotics. Thus this study concluded that there could be other VFs associated with the resistance of UPEC toward antibiotics (Alabsi et al., 2014).

Another study determined that UPEC strains can cause infections by association with certain virulence genes without determining the mechanism through which VFs contribute to antimicrobial resistance (Raeispour and Ranjbar, 2018). Finally, it is clear that a correlation is present between them and there is no study published in peer-reviewed publications that providesparticular information on precise mechanisms of inference of VFs in antibiotic resistance. Studies should be needed to perform in this path because comprehensive awareness of these processes could lead to new therapeutics for UTI prevention and antibiotic resistance in UPs. Now it becomes necessary to search for new therapies for the fight against UPs, including medicinal plants with their phytochemicals.

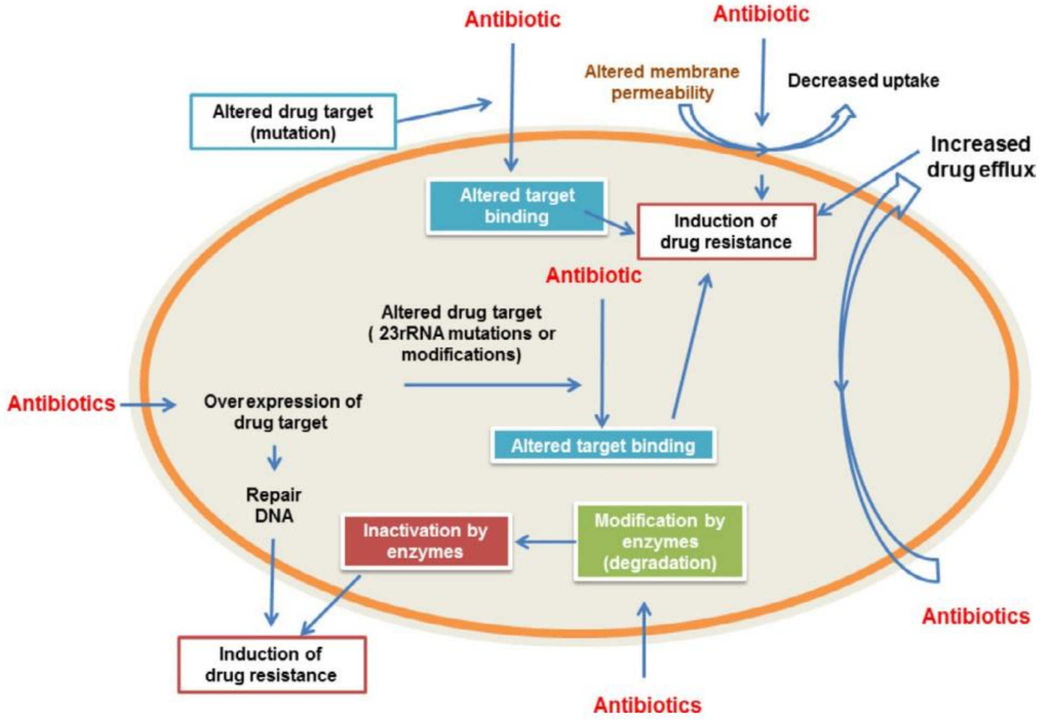

Figure 2.Antimicrobial resistance mechanism (Arsene et al., 2021)

USE OF MEDICINAL PLANTS TO TREAT UTIs

The utilization of medicinal plants is a very ancient practice in the cure as well as management of numerous infections, particularly UTIs. Due to their accessibility, affordability, lack of bacterial resistance, absence of side effects, acceptance for those with UTIs, and lack of adverse consequences, herbal therapies are growing in acceptance and popularity across the globe (Arodes et al., 2022). Because of the rise in antibiotic resistance, researchers are paying full attention to investigating the antibacterial capabilities of several plants as well as their constituents. Based on research tools such as Google Scholar, only 4,290 published papers were found concerning UTIs before the year 2000 and from 2000 to 2020, about 17,300 articles were published regarding the use of medicinal plants. On modern databases such as Scirus, PubMeD, Scopus, and Science Direct, a parallel increase has been observed in usage of medicinal plants in the management of UTIs. Several studies reported based on in vitro investigations, the efficacy of various plant extracts towards UPs as antibacterial agents (Sabo and Knezevic, 2019).

The particular mechanism of action of herbal treatment utilized to manage UTIs is still rarely understood, but previous research has revealed that those plant components, as well as their secondary metabolites, serve as antioxidants, water tablets, immune modulators, and antibiotics, preventing the concentration of pathogenic bacteria in urinary tract system along with inhibiting the production of microbes (Shaheen et al., 2019). However, plant extracts have specifically bactericidal and bacteriostatic properties. Thus, it has been established that phytochemicals function through the traditional methods of conventional antibiotics, such as action on membrane cells, inhibition of bacterial cell wall construction, inhibition of protein synthesis mechanisms, inhibition of nucleic acid synthesis, inhibition of efflux pumps, and inhibition of folate metabolism (Khosravani et al., 2020). Table 1 represents the diverse characteristics of various therapeutic plants because they contain numerous phytochemical components, such as secondary metabolites.

Table 1: Medicinal plants with anti-microbial/anti-adhesive activity to fight against UTIs

Botanical Name	**Part used**	**Active phytochemicals**	**Effect**	**In vivo/In vitro/clinical**	**References**
Petroselinum crispum	Seeds, roots, and leaves	Carotenoids, flavonoids, ascorbic acid apiole, phenylpropanoids, tocopherol, terpenoid compounds, phthalides, coumarin as well as furanocoumarins	Anti-bacterial activity	In vitro	Poulios et al., 2020; Foudah et al., 2022
Allium sativum	Garlic cloves and bulbs	Alliin, acrolein, allicin, phytocidin, daillyl-disulfide, and dallyl-trisulfide	Anti-bacterial activity	In vitro	Fufa, 2019; Jafari-sales and Shadi-Dizaji, 2019
Alchomeacordifolia	Stem bark and leaves	Terpenoids, Friedelane-3-one-27-al, 3-O-acetyl-erythrodiol, 3-O-acetyl-aleuritolic acid, methylgallate	Anti-bacterial activity on UPEC	In vitro	Noundou et al., 2016
Arctostaphylosuva-ursi	Leaves	Hydroquinone conjugates, Arbutin	Anti-microbial	In vitro	Dietz et al., 2016; Simo, 2018
Betula pendula	Leaves	Quercetin-3-galactoside, quercetin-3-glucuronide, p-coumaric acid, derivatives of caffeic acid	Bactericidal activity	In vitro	Wojnicz et al., 2012
Curcuma longa	Rhizome	Curcumin	Involves in the inhibition of swarming and swimming behavior in anti-biofilm activity, improves	In vitro	Packiavathy et al., 2014

			susceptibility of UPEC toward antibiotics		
Costusspicatus	Leaves	Caffeic acid, quercetin, ferulic acid, apigenin	Anti-microbial activity	In vitro	Uliana et al., 2015
Calluna vulgaris	Flowers and leaves	Flavonoids and total phenols	Anti-bacterial activity	In vitro	Vucic et al., 2014
Cyperusrotundus	Rhizome	Terpenoids, sasaponins	Anti-bacterial activity	In vitro	Vadivel et al., 2022
Cybopogumcitratus	Essential oils	Terpenoids, myrcene, geranial, neral	Anti-microbial activity	In vitro In vivo	Oliveira et al., 2019
Equisetum arvense	Leaves	Quercetin dihexoside, kaempherol-dirhamnosyl-hexoside, kaempheroldihexoside, protocatechuic acid, ferulic acid, caffeicacid and caftaric acid	Anti-adhesive, involved in anti-microbial activity, Inhibit the mass production of biofilm	In vitro In vivo	Carneiro et al., 2019
Gynostemmapentaphyllum	Leaves	Terpenoids, Gypenosides	Involves in the modulation of anti-microbial peptides	In vivo	Luthje et al., 015
Galiumodoratum	Leaves	Protocatechuic acid, derivatives of quercetin and kaempherol, caffeoylquinic isomer, iridoids	Weak anti-microbial activity	In vitro	Wojnicz et al., 2012
Moringaoleifera	Flowers, leaves, and fruits	Amino acids, thiocarbamate glycoside, kaempferol, acetylated carbamate, moringine, spirochin and tocopherol	Anti-bacterial activity	In vitro	Arodes et al., 2022
Piper arboreum	Leaves	Coumarins	Anti-bacterial activity	In vitro	Souto et al., 2021
Polygonumcapitatum	Whole plant	Gallic acid, catechin, quercitrin, triterpenoids, flavonoids, and steroids	Have moderate anti-bacterial activity	In vitro	Arsene et al., 2021

Rosmarinus officinalis	Leaves	Rosmarinic acid	Anti-bacterial activity	In vitro	Al Zuhairiet al., 2020
Salvia officinalis	Essential oils	1,8-cineole	Anti-microbial activity	In vitro	Peng et al., 2010
Tropaeolimajoris	Leaves	Benzyl-Isothiocyanate, Phenylethyl-Isothiocyanate	Intermidiate susceptibility	In vitro	Albrecht et al., 2007
Urticadioica	Leaves	Ferulic, protocatechuic, and dicaffeoylquinic acids	Anti-microbial activity Anti-adhesive effect	In vitro In Vivo	Fattahi et al., 2016; Arsene et al., 2021
Vacciniumvitis-idaea	Leaves	Derivatives of quercetin, caffeoylquinic derivatives, coumaroyl-hexose-hydroxyphenol and caffeoyl-hexose-hydroxyphenol acids, iridoids, and procyanidins (A and B dimmers)	Involves in the inhibition of biofilm mass production, Have high bactericidal activity	In vitro	Wojnicz et al., 2012
Zea mays	Stigma	Derhamnosylmaysin, apiferol, alternanthin	Involves in the reduction of bacterial adhesion	In vivo In vitro	Rafsanjany et al., 2013, 2015

CONCLUSION

UTIs are very common around the globe as well as frequently occurred in women plus the old age group. It has been found that up to 95 % of UTIs build up in an ascending manner. The utilization of traditional antimicrobials makes it difficult to treat pathologies associated with UTIs as a consequence of rising resistance toward antibiotics. This review discussed the methodology of the contribution of VFs in antibiotic resistance along with the exploit of a few plants recognized for their competency in the control of UTIs. The main advantage of using medicinal plants is that bacteria have not prospered resistance against antibiotics. Other advantages of medicinal plants included that they are secure, inexpensive, as well as accessible. Finally, there is a need to conduct large arbitrary, double-blind clinical studies on all of these plants along with their secondary metabolites to ensure its ctheical efficacy as well as safetthe y of these products.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR'S CONTRIBUTION

The initial draft was written by Hubza Ruatt Khan and Mehvish Javeed. Iqra Batool and Rabeea Anwar meticulously analyzed it, while Asma Ashraf corrected the grammatical errors. Sara Janiad revised the final draft and supervised it. All authors accept responsibility for the comments articulated in the published work.

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