Non-antibiotic potential of medicinal plants to combat urinary tract infections

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Urinary tract infections (UTIs) are highly prevalent with frequent recurrent episodes. With advances in research and development of modern tools, the pathogenesis of uropathogens is well understood and various associated virulent features have been identified. These include, adherence and invasion of epithelial cells, biofilm formation, quorum sensing, production of certain metabolic enzymes/pigments and release of cytotoxins. Due to increasing reports on antibiotic resistance in UTIs, emphasis is being made on 'non-antibiotic' approaches for treatment of UTI. In recent years, research on traditional plants has gained popularity and medicinal plants are being considered as promising alternatives. Based on the available literature, this review compiles reports on plants and/or their compounds that affect virulent parameters of uropathogens to combat UTI. Along with the virulent features, the immunomodulatory effect of plants to eradicate pathogens is also briefly covered. The use of plants to target virulent mechanism(s), in order to prevent or treat UTI would minimize the increasing drug resistance as well as prevent disruption of healthy gut microbiota.

Keywords: Immunomodulation, medicinal plants, urinary tract infections, virulence.

URINARY tract infections (UTIs) arise due to the presence of microbial pathogens in the urinary tract. Amongst the several infections that are prevalent globally, UTIs are most common and affect people, especially women, across all age groups. About 50% women suffer from UTI at least once in their life span and recurrent infections are common[1,2]. UTI is a complex infection and clinically classified under two broad categories – complicated and uncomplicated[3].

Gram-negative, Gram-positive bacteria as well as some fungi cause UTIs[4]. Though organisms such as *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, group B *Streptococcus* (GBS), *Staphylococcus aureus*, *Candida albicans* are the common causative agents associated with UTI, the bacterium uropathogenic *Escherichia coli* (UPEC) is frequently reported[5]. Antibiotics are generally prescribed for treating UTI, often leading to not only emergence of drug resistant strains, but also alteration of the vaginal and gastrointestinal tract microbiota[6]. Researchers globally are now pointing towards the diminishing 'golden era' of antibiotics and emphasis is being made towards targeting alternative approaches. With increased information, especially through applications of newer molecular tools (for e.g. transcriptome sequencing)[7], combined with information from basic sciences and animal models (for e.g. catheter-associated bladder infection murine model 'CAUTI' for characterization of virulence parameters of *Enterococcus fecalis*)[8], there is now a better understanding of virulence features of uropathogenic organisms.

It is well acknowledged that bacteria causing UTI express different virulence determinants which include those essential for the initial adhesion and then subsequent colonization of mucosal surfaces[9]. The bacteria also invade the host tissues for overcoming the defence mechanisms resulting in persistent and at times chronic infections. The virulent parameters include surface factors (type 1 and P pili, fimbriae and adhesins) as well as secreted factors (polysaccharide coatings, toxins, metabolic enzymes). Biofilm formation and quorum sensing are also the key features associated with UTI pathogenesis[4,9].

Targeting the key virulence factors associated with uropathogens to combat UTIs seems a promising approach[6,10]. As a probable promising alternative to antibiotics, traditional medicine usage is also being explored[11]. Available reports illustrate that extracts (aqueous/organic) from different parts of medicinal plants and/or their secondary metabolites have been studied for treatment and/or prevention of UTIs[12–14]. Several of these describe the antimicrobial activity of plant extracts as their mode of action. However, plants have varied mechanism of action such as reducing bacterial colonization/toxin production and not necessarily limited to their antimicrobial effect[15]. Controlling the virulence of pathogenic bacteria is considered as a key feature in microbiology and medicine[16].

The present review is a compilation of available literature on the effect of plants on the virulence of uropathogenic bacteria to appreciate the alternative targets available to combat UTIs. Since the host's immunity also has a crucial role in UTI, the immunomodulatory effect of plants is also briefly covered in this review. The review highlights that plants can be promising in case of non-antibiotic approach for combating UTIs which can also minimize drug resistance and maintain healthy gut/vaginal flora.

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Methodology

Literature survey

A comprehensive literature search using databases like Google Scholar, Science Direct and PubMed was undertaken. Articles published in English language in peer review journals between January 2011 and March 2018 were screened for laboratory studies reporting the non-antibiotic potential of medicinal plants, namely, effect of plants on virulence of uropathogens and/or affecting host immunity for preventing/treating UTI. Information on possible phytoconstituents, if any, contributing towards the activity was also extracted from the same reports. For plants shortlisted for inclusion in the review, further literature was screened for traditional uses and antimicrobial action (not necessarily restricted to uropathogens) to add credence as well as for better appreciation of their efficacy. However, though recent references were preferred to compile this additional information (as shown in Table 1), the citations were not restricted to any timeline. As the numbers of articles found were large, only representative studies have been included to comprehend the breadth of work undertaken with plants for UTI with respect to their varied mechanisms of action.

A mention of cranberry (alone or its formulations/compounds derived from it) was often found in context of its prophylactic applications and immunomodulation and hence a separate section for its known uses is included at the end of this review.

Before discussing the effect of plants on virulence features of uropathogens, the antibiotic treatment in UTIs is briefly mentioned. This also addresses some of the issues associated with antibiotic usage thereby necessitating research on alternative targets including medicinal plants which is the focus of this review.

Antibiotics in UTI

Antibiotics are the primary treatment for UTIs. Broad spectrum drugs such as fluoroquinolones and cephalosporins are commonly used. Antibiotic therapy in UTI is often empirical at times leading to treatment failures[17,18]. Rampant and irrational use of antibiotics causes antibiotic resistance and increasing reports of drug resistant uropathogens are being documented[19–21]. The high infection rate coupled with antibiotic resistance also results in recurrent UTI episodes. Due to increased resistance to standard drugs, treatment of UTI poses a challenge and there is a possibility that UTIs may become untreatable occasionally[22,23]. The scarcity of newer drugs is also a cause of concern[23].

Alternative therapies for combating UTI

Because of the above mentioned issues associated with antibiotics in UTI, researchers across the globe have been exploring different 'non-antibiotic' alternatives[24,25]. Efforts in this direction have identified various approaches which include nutraceuticals, phytotherapy (including use of Chinese traditional medicine), use of simple interventions like vitamin C, lactobacilli (and other probiotics), cranberry products, acupuncture as well as advanced interventions such as D-mannose, vaginal estrogens, gastrointestinal decolonization of multi-resistant bacteria and vaccinations (urovac, ro-vaxom)[25–27].

Targeting virulent mechanisms as an approach for combating UTI

Another approach towards minimizing resistance is the use of 'anti-virulence' compounds (for e.g., Bicyclic 2-pyridones, a potential inhibitor of pili formation)[28]. These target the important stages in disease process and interfere with crucial factors of pathogenesis[29]. With regards to UTI, uropathogens are equipped with several virulence factors that permit them to successfully establish infection in the urinary tract (Table 1). Key bacterial virulence parameters include adhesive fimbriae, which facilitate them to adhere to specific receptor(s) on the uroepithelium, and flagella that permit bacteria to swim across the urinary tract. Uropathogens are also capable of secreting toxins (e.g. haemolysin) which disrupt the epithelial barrier to gain access to the underlying tissues. Besides these, biofilm formation, quorum sensing, production of metabolic/cytolytic enzymes (e.g. urease, protease, lipase), pigment production (such as prodigiosin) also aid in successful infection[4,9]. As discussed in the subsequent sections, medicinal plant extracts as well as their phytoconstituents have these 'non-antibiotic' potential and thus they can be promising alternatives.

Plant names, virulent mechanism(s) of uropathogens affected, the phytoconstituent(s) attributed, traditional uses and antimicrobial reports are listed in Table 1 as a summary of the review.

Effect of plants on virulence mechanisms of uropathogens

Plants affecting bacterial adhesins

Adherence is an important initial stage in infectious diseases. Likewise, this parameter is a significant determinant of virulence of uropathogens. The cell surface appendages like type IV pili, flagella and fimbriae are crucial for the adhesion of several pathogens over different surfaces[4]. Models using bladder cell lines 5637 and T24 are frequently used to study the *in vitro* anti-adhesive properties.

Zea mays L.'s stigmata and *Agropyron repens* L.'s rhizome – two traditional plants used in UTI, were observed to decrease the adhesion of UPEC strain 2980 (ref. 30). The bladder cell line T24 was used for the study, and interaction of the plant extracts with proteins associated

Table 1. Plants cited in the present review listing the virulent mechanism(s) affected, the phytoconstituent(s) attributed, the traditional uses and antimicrobial activity

Botanical name (part/compound)	Common name/ Family	Virulent mechansim(s) affected	Phytoconstituent(s) attributed*	Traditional uses	Antimicrobial activity
Zea mays L. (stigmata)	Corn silk/Poaceae	Bacterial adherence[30]	alternanthin, apiferol, derhamnosylmaysin, 3-deoxy-rhamnosylmaysin, 3-O-methyl derhamnosylmaysin	Treatment of UTIs, kidney stones, cystitis; as diuretic, antidepressant; for hyperglycemia[72]	No antibacterial against common pathogens such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. pyogenes, S. aureus*, *S. pneumoniae*[72]
Agropyron repens L. Beauv (rhizome)	Couch grass; Quack grass/ Poaceae	Bacterial adherence and invasion[30,36]	Not provided	As diuretic, demulcent, tonic; calming pain and spasm in urinary tract; in children's for UTI related diseases like calculi, cystitis, incontinence[73]	Antibacterial against *Bacillus subtilis*, not against other common pathogens such as *E. coli*, *K. pneumoniae*[74]
Urtica spp, *Urtica dioica* L. (leaves)	Nettle/Urticaceae	Bacterial adhesions/ colonization/biofilm formation[30,32]	Dicaffeoylquinic acids, ferulic, *p*-coumaric, protocatechuic	As anti-inflammatory, diuretic; treatment of UTI; in diabetes, nervousness[75]	Antibacterial against clinical isolate of UPEC[32], *S. aureus* and *E. coli*[75]
Betula spp. *Betula pendula* Roth. (leaves)	Silver birch/ Betulaceae	Bacterial adherence/biofilm formation[30,32]	Caffeic acid derivatives, *p*-coumaric acid 3,40-dihydroxypropiophenone-3-b-d-glucoside, quercetin-3-galactoside, quercetin-3-glucuronide	Treatment of renal ailments, UTI; in rheumatism, gout, bone related problems[76]	Antibacterial against clinical isolate of UPEC[30]
Orthosiphon stamineus Benth. (leaves)	Java tea; Cat whiskers/ Lamiaceae	Bacterial adherence[30]	Not provided	As diuretic; for kidney/bladder inflammation; in rheumatism, gout, edema, hypertension, abdominal pain[77]	Antibacterial against Gram-positive bacteria (e.g. *agalactiae*, *S. aureus*), Gram-negative bacteria (e.g. *P. mirabilis*, *K. pneumoniae*)[77]
Galium odoratum L. Scop. (leaves)	Sweet woodruff/ Rubiaceae	Bacterial colonization/biofilm formation[32]	Caffeoylquinic isomer, kaempherol derivatives, iridoids, protocatechuic acid, quercetin	Treatment of haemorrhoids, jaundice; for nervous agitation, circulation/venous disorders; as topical application for swellings and wounds[78]	Antibacterial against clinical isolate of UPEC[32]
Vaccinium vitis-idaea L. (leaves)	Lingonberry/ Ericaceae	Bacterial adherence/biofilm formation[32]	Derivatives of caffeoylquinic, caffeoyl-hexose-hydroxyphenol and coumaroyl-hexosehydroxyphenol acids, iridoids, procyanidins (A and B dimers), quercetin derivatives	As diuretic and antiseptic in UTIs[32,79]	Antibacterial against clinical isolate of UPEC[32]
Citrus reticulata Blanco (seeds)	Mandarin/Rutaceae	Bacterial invasion[33]	Not provided	Control urination in UTI; anti-inflammatory[33]	No antibacterial activity against UPEC strain[33]; antibacterial for ATCC *E. coli* and *S. aureus*[80]
Clinopodium boliviannum Benth. Kuntez (leaves and stems)	Khoa/Lamiaceae	Bacterial invasion[34]	Not provided	Used as an anti-infective and anti-inflammatory; gastrointestinal remedy[34]	No antibacterial activity against UPEC[34]
Labisia pumila var. *alata* (Standardized aqueous extract)	Kacip Fatimah/ Myrsinaceae	Bacterial invasion[35]	Anthocyanin, gallic acid	Treatment of genitourinary tract ailments[35]	No antimicrobial activity against *E. coli*, *P. mirabilis*, *P.aeruginosa*, *S. saprophyticus* and *C. albicansi*[35]

(*Contd*)

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Botanical name (part/compound)	Common name/ Family	Virulent mechansim(s) affected	Phytoconstituent(s) attributed*	Traditional uses	Antimicrobial activity
Lactuca indica L. (Whole plant)	Indian lettuce/ Compositae	Bacterial invasion[37]	Not provided	As diuretic, antibacterial and anti-inflammatory[37]	Antibacterial against *S. aureus*; not against *P. mirabilis* and *E. coli*[37]
Hibiscus sabdariffa L. (calyces)	Hibiscus; red sorrel/ Malvaceae	Biofilm formation[40]	Anthocyanins (D3S)	For relieving pain during urination, for diarrhoea/dysentery, in hypertension, gynaecological disorders[64]	Antifungal against *C. albicans*, antibacterial against drug resistant *Acinetobacter baumanni*[40,64]
Equisetum arvense L., (leaves)	Horsetail/ Equisetaceae	Biofilm formation[32]	Caffeic acids, caftaric, ferulic kaempherol dihexoside, kaempherol-dirhamnosyl-hexoside; protocatechuic, quercetin dihexoside	As anti-inflammatory, diuretic; treatment of UTI; in diabetes, for anaemia[81]	Antibacterial against clinical isolate of UPEC[32]
Herniaria glabra L. (leaves)	Smooth rupturewort/ Caryophyllaceae	Biofilm formation[32]	Caffeoylquinic and feruloylquinic isomers; kaempherol and isorhamnetin derivatives, iridoids, quercetin	Treatment of UTI, kidney stones; as diuretic, in hypertension[82]	Antibacterial against clinical isolate of UPEC[32]
Tinospora cordifolia, Willd. (dried stem)	Amrita; Guduchi/ Menispermaceae	Quorum sensing[40]	Methyl 16-methylheptadecanoate, 2-(5-ethenyl-5-methyloxolan-2-yl) propan-2-ol, methyl hexadecanoate, 2-methoxy-4-vinylphenol	As immunomodulator; in leprosy, diabetes, jaundice, UTI[58]	Antimicrobial against gram positive bacteria (e.g., *B. subtilis*, *S. aureus*), gram negative bacteria (e.g., *E. coli*, *K. pneumonie*); fungi (e.g., *A. fumigates*, *Mucor* sp)[40,58]
Psidium guajava L. (leaves)	Guava; peru/ Myrtaceae	Quorum sensing/urease production[41,49]	Quercetin and quercetin-3-O-arabinoside	Used in gastrointestinal, respiratory infections; uterine and vaginal problems; diabetes[83]	Antibacterial (e.g., *S. flexneri*, *V. cholerae*); antiprotozoal (*G. lamblia*), antiviral (rotavirus)[83]
Zingiber officinale Rosc. (phenolic compounds from rhizome)	Ginger; adrak/ Zingiberaceae	Quorum sensing[41]	Phenolics (unspecified)	Used for cardiovascular health, respiratory disorders; in nausea; rheumatic disorders; gastrointestinal problems[84,85]	Antimicrobial against bacteria (e.g., *E. coli*, *S. aureus*); fungi (e.g., *B. cereus*, *S. cerevisiae*)[84]
Syzygium aromaticum L. (Dried clove buds)	Cloves/Myrtaceae	Quorum sensing[42]	Not provided	Common spice, used in asthma, allergies[42]	Antibacterial against oral pathogens, *E. coli*[42]
Vitex trifolia, L. (leaves)	Arabian Lilac/ Labiatae	Biofilm formation[43]	3-O-methyl ellagic acid	For pain, fever, jaundice[65,86]	Moderate antibacterial activity, does not inhibit EHEC[65]
Anethum graveolens L., (Seeds)	Dill/Apiaceae	Biofilm, quorum sensing as well as allied virulence features such as biosynthesis of prodigiosin, production of cytolytic enzymes[44]	Not provided	Treatment of certain gastrointestinal disorders, UTI complaints and mental disorders; in cholesterolaemi[44]	No antibacterial action against *Serratia marcescens*[44]
Punica granatum L. (Rind)	Pomegranate; Dadim/ Punicaceae	Bacterial motility[46]	Not identified	Treatment of diarrhoea, other gastrointestinal problems, as an astringent[87]	Antibacterial against *S. aureus*, *P. aeruginosa*, *S. typhi*[87]

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Botanical name (part/compound)	Common name/ Family	Virulent mechansim(s) affected	Phytoconstituent(s) attributed*	Traditional uses	Antimicrobial activity
Cuminum cyminum L. (Seeds)	Cumin; jeera/ Apiaceae	Quorum sensing/allied virulence features such as bacterial motility, pigment production[47]	Methyl eugenol	Common spice, used for gastrointestinal disorders; as diuretic, anti-oxidant[88]	Antimicrobial against bacteria (e.g., *S. marcescens*, *P. aeruginosa*, *P. mirabilis*); fungi (e.g., *Aspergillus* spp, *Trichophyton mentagophytes*, *Candida tropicalis*); antiviral (e.g., HSV-1)[88]
Urena lobata L. (root)	Caesarweed/ Malvaceae	Bacterial motility[48]	Not provided	As diuretic, febrifuge; in rheumatism, malaria[89]	Antibacterial against gram positive (e.g. *S. aureus*, *B. subtilis*) as well as gram negative bacteria (e.g. *E. coli*, *P. aeuroginosa*)[51]
Emblica officinalis, Gaertn. (fruits and leaves)	Amla/Phyllanthaceae	Urease production[49]	Not provided	In leprosy, anaemia; anti-inflammatory; as diuretic[90]	Antibacterial against *S. aureus*, *P. mirabilis*, *K. pneumoniae*, *P. aeruginosa*[52]
Acacia nilotica, L. (leaves)	Babool/Fabaceae	Urease production[49]	Not provided	Used as astringent, chemoprotective, as anti-anti-inflammatory and in leucoderma[52]	Antibacterial against *S. aureus*, *P. mirabilis*, *P. aeruginosa*[52]
Rosa indica, L. (flower)	Rose/Rosaceae	Urease production[49]	Not provided	Used in digestive problems; fluid retension; elimination of wastes through kidneys[52]	Antibacterial against *K. pneumoniae*, *S. aureus*, *E. coli*, *Vibrio* spp, *Salmonella* spp.[91]
Terminalia chebula Retz., (fruit)	Chebulic myrobalam, Gallnut/ Combretaceae	Urease production[49]	Not provided	For diabetes; heart, digestive, urinary and skin diseases[92]	Antimicrobial against bacteria (e.g., *E. coli*, *Clostridium perfingens*); antifungal (e.g., *Candida* spp. and *Trichophyton* spp.); antiviral (HIV-1)[92]
Allium sativum L. (allicin)	Garlic/Alliaceae	Urease production[50]	Allicin	As spice, antiseptic, anti-arthritic, hypolipidaemic[93]	Antibacterial against *P. mirabilis*, *E. coli*, *S. aureus*[50,93]
Tamarindus indica L. (bark)	Tamarind/ Leguminosae	Anti-hemolytic[53]	Polyphenols (unspecified)	As antiallergic, antimicrobial, antibiotic, antityrosinase, antioxidant, analgesic and spasmogenic[94].	Antibacterial against gram positive and gram negative bacteria[94]
Hyptis suaveolens L. (leaves)	Pignut; American mint/Lamiaceae	Biofilm formation as well as haemolysis inhibition, production of protease/prodigiosin as well as bacterial motility[55]	Undecanoic acid	In cancer, as antifertility[95]	No antibacterial activity against common uropathogens *P. mirabilis*, *P. vulgaris*, *E. coli*, *S. marcescens*, *K. pneumoniae*[55]
Scutellaria baicalensis L. (Baicalein)	Baikal; Chinese skull-skull-cap/Lamiaceae	Biofilm formation, bacterial motility and some other allied virulence features[56]	Baicalein	Anti-cancer, anti-inflammatory, respiratory disorders[96]	Antimicrobial against bacteria (eg., *E. coli*, *S. aureus*), fungi (e.g., *C. albicans*)[56,96]
Vaccinium macrocarpon L. (flavanoids, fruit extracts)	Cranberry/Ericacea	Bacterial adherence (UPEC), bacterial hydrophobicity, inhibition of enzymes (such as gelatinase, lipase), quorum sensing[61–64]	Derivatives of caffeoylquinic, caffeoyl-hexose-hydroxyphenol and coumaroyl-hexosehydroxyphenol acids, iridoids, procyanidins (A and B dimers), quercetin derivatives	Treatment of UTI, as an anti-inflammatory, anti-oxidant[6]	Antibacterial against UPEC[67,68]

*The phytoconstituents are listed from the same publication referred for virulent mechanism(s) affected. It may be noted that majority of these phytoconstituents are phenolics.

with the bacterial outer membrane was documented to be the mechanism. *Urtica* spp. leaves, *Betula* spp. *Orthosiphon stamineus* Benth., also included in the same study exhibited anti-adhesive effects by directly interacting with T24 cells.

Two plant secondary metabolites namely, ursolic acid and asiatic acid were also studied for their anti-adhesion properties[31]. These metabolites not only decreased the adherence of UPEC but also altered the morphology of the epithelial cells leading to changes in hydrophobicity related to bacterial cell surface.

Galium odoratum L. and *Urtica dioica* L., two plants used traditionally in Poland were reported to alter the cell surface hydrophobicity of UPEC (a clinical isolate), thereby impeding the bacterial colonization[32]. *Betula pendula* Roth. and *Vaccinium vitis-idaea* L., part of the same study could inhibit the erythrocyte haemagglutination by the bacterial strain indicating dysfunctioning of P fimbriae thereby preventing its adherence to host cells[32].

Plants affecting bacterial invasion

Bacterial adherence is followed by intracellular growth and bacterial invasion plays a crucial role in infectious diseases. Similar to adherence assay, the human bladder cell lines 5637 and T24 are good models for studies related to the invasion of uropathogens also.

The decoction prepared from seeds of *Citrus reticulata* Blanco., a traditional plant from Vietnam, was observed to decrease invasion of UPEC to bladder cell lines[33]. A reduction in the expression of β1 integrin was proposed as its mechanism of action.

Clinopodium bolivianum Benth., a plant from South America was reported to reduce not only the invasion of bladder epithelial cells but also adherence and biofilm development by uropathogenic *E. coli* No. 12 (ref. 34). Reduction in bacterial (UPEC strain CFT073) invasion to epithelial cells T24 and 5637 by *Labisia pumila* var. *alata*, a traditional plant used by women in Malaysia was demonstrated[35]. The concerned authors concluded that reduction in the bacterial invasion, as well as induction of apoptosis, were the mechanisms by which this plant could eliminate UTI.

Extract from the rhizomes of *Agropyron repens* L., exhibited effect on bacterial adherence as well as invasion[36]. In another study, the Vietnamese dandelion (*Lactuca indica* L.) was observed to reduce the colonization of a clinical strain of *E. coli* No. 12 using three human bladder epithelial cell lines, viz. TERT-NHUC, 5637 and T24 (ref. 37). The decrease in colonization was attributed to modifications of cellular structures implicated with bacterial adherence/invasion and focal adhesion kinase (FAK) phosphorylation related inhibition.

Plants having anti-biofilm and anti-quorum sensing activity

Polymicrobial aggregates following successful colonization in the form of 'sludge', 'mats' result in 'biofilms'. The biofilms are thus communities of microbial populations of surface-attached cells surrounded by an extracellular matrix that is self produced. A complex regulatory system, 'quorum sensing', regulates a cell-to-cell synchronized communication along with inter- and intracellular signalling of the bacteria within the biofilm to bypass the host immune response. Quorum sensing triggers expression of genes contributing to pathogenicity, virulence and survival of pathogens[38]. The anti-biofilm and quorum sensing inhibitory activity of several plants to tackle UTIs are well reported.

Hibiscus sabdariffa L. tea, used as an herbal drink inhibited the biofilm formation of a clinical isolate of *Candida albicans* which was resistant to fluconazole[39]. *Urtica dioica* L., *Betula pendula* Roth., *Vaccinium vitis-idaea* L., *Equisetum arvense* L., *Galium odoratum* L., *Herniaria glabra* L., which are folk remedies of Poland were found to inhibit the biofilm formation by UPEC[32].

Tinospora cordifolia Willd, *Psidium guajava* L., *Zingiber officinale* Rosc., *Syzygium aromaticum* L. are reported to have inhibitory effect on quorum sensing in the common pathogen, *P. aeruginosa*[40–42]. Leaves of *Vitex trifolia* L. have also been studied to stall the biofilm formation by a clinical isolate of *Serratia marcescens*[43].

Anethum graveolens L., a popular spice and an aromatic herb, has been studied for its potential inhibition of biofilm formation and anti-quorum sensing properties of a clinical isolate of *S. marcescens*[44]. It was demonstrated that the methanol extract of the seeds of this plant could downregulate the expression of genes coding for initial adhesion and bacterial motility as well as interfere with the signalling of quorum sensing system.

Plants affecting bacterial motility/swarming, metabolic enzymes, cytotoxins and pigments

Parameters such as anti-swimming/anti-swarming motility (mediated by flagella), reduction of metabolic enzymes (urease, protease, lipase), inhibition of cytotoxic hemolysin, production of pigments are known to be controlled by quorum sensing[45–47]. These allied factors contribute to pathogenesis of UTI. For example, haemolysin has a cytotoxic effect on epithelial cells in the urinary tract and prodigiosin pigment is said to have anti-proliferative and immunosuppressive properties[46,47]. The existing detailed studies showing inhibition of these parameters in conjunction with effect on biofilms/quorum sensing as well as independent studies documenting the inhibition of these parameters by plant extracts are discussed below[48–55].

Punica granatum L. (rind extract) inhibited motility of strain CFT073, a UPEC strain[48]. Anti-motility effect of *Cuminum cyminum* L. and *Urena lobata* L. root against *S. marcescens*, *P. mirabilis*, *P. aeruginosa* and cephalosporin resistant *Proteus* spp. respectively, have also been studied[49,50].

Extracts from *Emblica officinalis* Gaertn., *Acacia nilotica* L., *Rosa indica* L., *Terminalia chebula* Retz., *P. guajava*

were found to have anti-urease activity against different bacterial strains such as *P. vulgaris*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*[51]. Allicin, a natural product isolated from the plant *Allium sativum* L. (garlic) too was found to inhibit the urease activity of *P. mirabilis*[52].

Bark of *Tamarindus indica* L. (alcoholic extract) was reported to inhibit haemolysis of *P. vulgaris* and the researchers concluded that polyphenols present in the extract inactivated the oxidizing groups on bacterial toxin to exert inhibition[53].

Anethum graveolens L. showed inhibitory action against biosynthesis of prodigiosin pigment, production of protease and lipase enzymes by a clinical isolate of *S. marcescens*[44].

Hyptis suaveolens L. extract was reported to hinder the biofilm formation and allied virulence factors like haemolysis inhibition, production of protease/prodigiosin as well as bacterial motility in different uropathogens *E. coli*, *P. vulgaris*, *P. mirabilis*, *K. pneumoniae* and *S. marcescens*[54]. A major flavonoid monomer (baicalein) present in roots of the plant *Scutellaria baicalensis* L., a well known Chinese medicine, was documented to reduce bacterial motility and biofilm formation during *P. aeruginosa* infection[55]. In addition, this study showed the inhibitory effect of this flavanoid on allied virulence factors such as rhamnolipids, pyocyanin, elastase and protease.

Effect of plants on immune response in UTI

The urinary tract has a well organized and effective adaptive and innate immune system capable of overcoming the bacterial attack. Modulating the immune response could thus play an important role in UTIs[56]. Immune mechanisms revolving around the role of pattern recognition receptors – toll like receptors (TLR) such as TLR4, signalling pathways, recruitment of chemokines/cytokines in UTI towards expulsion of bacteria from urinary tract, are well defined[57].

Traditionally used plants such as *Tinospora cordifolia* can act as immunomodulators and help eliminate pathogens by enhancing the patient's immunity[58]. *Gynostemma pentaphyllum* L. (GP), a traditional Chinese medicine, has been documented to have a favourable impact on the innate immunity of the urinary tract, thereby combating bacterial infections[59]. Using *in vitro* and *in vivo* assay systems, the aqueous extract of GP was found to have a number of immunomodulatory effects including a reduction in the production of proinflammatory cytokines by the bladder epithelial cells upon bacterial infection; modulation of the expression of antimicrobial peptides, which could benefit diabetic patients suffering from UTIs. *Echinacea purpurea* L. known to be used in a number of ailments including UTI has been reported to possess anti-inflammatory and anti-oxidant activities[60]. The flavonoid baicalein from *S. baicalensis*, was reported to exhibit anti-inflammatory effects in *P. aeruginosa* infection through activation of MAPK and nuclear transcription factor (NFκB)-signalling pathways[56]. Curcumin, a major polyphenol from *Curcuma longa* L., was observed to improve symptoms of UTI via the reduction of inflammatory responses in a rat model for UTI. It was demonstrated that this compound affected the expressions of TLR2 and TLR4 mRNA to exert this beneficial effect[61]. Various immunomodulatory features of bearberry (*Arctostaphylos uva-ursi*) leaves, another plant used for the treatment of symptoms related to lower urinary tract, including anti-inflammatory action and effects on pro-cytokines have been reported[62]. In an UTI mouse model using *E. coli* as the test organism, the immunomodulatory effect of *Persicaria capitata* (Buch.-Ham. ex D. Don) was proposed to be the reason for effectiveness of this plant in UTIs. A possible metabolic reprogramming in tricarboxylic acid (TCA) cycle and enhanced macrophage activation were postulated to be the likely mechanisms[63]. The immunomodulatory effect of roselle (*Hibiscus sabdariffa*) was examined by Riaz and Chopra[64]. It was reported that the drink of this plant could down-regulate pro-inflammatory products such as interleukin-6 (IL-6), tumour necrosis factor (TNF-α) and NFκB pathways in lipopolysaccharide-(LPS)-induced mouse model of renal inflammation. Indications of immunomodulation by *V. trifolia* have also been obtained from anti-inflammatory studies including expression of inducible nitric oxide synthase and modulation of cytokines with aqueous extract of leaves of this plant[65]. A similar mechanism of action against UPEC infection was noted with plant *Andographis paniculata*[6]. As stated in the earlier section on plants affecting bacterial invasion, a decrease in β1 integrin expression in uroepithelial cell model for UPEC invasion by *Citrus reticulata* seed decoction and *Labisia pumila*, support the effect of these plants on innate immunity to prevent/treat UTIs[33,35].

Studies with cranberries

Cranberries (*Vaccinium macrocarpon* L.), are a good source of dietary flavonoids (proanthocyanins and anthocyanins). Their use has been largely reported for UTIs especially in women. A number of laboratory investigations and clinical studies have been undertaken to demonstrate the varied mechanisms of actions including their ability to prevent adherence of UPECs to uroepithelial cells and suppression of inflammatory responses (reviewed by Vasileiou *et al*.[66]). It has been speculated that one of the possible modes of action of cranberry is the modification of bacterial P fimbriae or linkage with bacterial cells. This was based on the studies with purified proanthocyanidins derived from dried cranberry juice on *in vitro* adherence to the bladder and vaginal epithelial cells of P-fimbriated *E. coli* strains, both sensitive and multidrug resistant[67]. A detailed study by Wojnicz *et al*.[68] reported that cranberry extract restricts bacterial growth, affects bacterial hydrophobicity, inhibits synthesis of

lecithinase, gelatinase, haemolysin, lipase and DNase as well as arrests biofilm formation. Studies by Maisuria *et al*.[69] demonstrated the activity of proanthocyanidins derived from cranberry to affect quorum sensing in *P. aeruginosa*.

Discussion and conclusion

UTIs are a cause of global health concern as they significantly affect public health. The economic burden associated with the treatment of UTIs is also disturbing and the annual estimated cost in the United States is said to be as high as $1.5 billion (ref. 4). UTIs not only affect the quality of life; the mortality rates associated with this infection are also alarming – documented to be as high as 3% in women and 1% in men[24].

Though antibiotics are necessary and generally prescribed, development of resistance is common and hence 'non-antibiotic' approaches are being worked out. These include simple interventions such as vitamin C, probiotics to complex ones like use of vaginal estrogens. However, though these interventions look promising, more in depth studies are required.

A rich legacy of traditional knowledge exists world over and India alone is home to time honoured systems of medicine such as Ayurveda, Unani and Siddha. Plants exhibit a number of biological properties and have been investigated for their varied efficacy. Plants being rich in phytoconstituents are chemically complex and often two or more compounds may act synergistically. Moreover, different compounds may have different targets. The synergism and multi-targeting not only increases the efficacy but also minimizes the possibility of pathogens developing resistance[15,70].

As a promising non-antibiotic approach, this review collates information on medicinal plants and also their constituents for their effect on virulent features of uropathogens and immunity in UTI. As seen from Table 1, plants can affect all important stages of infection and phytoconstituents mainly phenolics are commonly attributed. Interestingly, in some studies the cited plants did not directly arrest the growth of pathogens (e.g. *Zea mays*, *Citrus reticulata*, *Anethum graveolens*) and thus strongly illustrate the alternative mechanisms – effect on bacterial virulence factors and immunomodulation to combat uropathogens. This non-antibiotic potential of plants in turn would generate a lesser amount of pressure towards the evolution of antimicrobial resistance[71]. It may however be noted that targeting virulence parameters with herbals would pose challenges when laboratory findings need to be translated for treatment of UTI in clinics.

In conclusion, this review highlights the multidimensional potential of medicinal plants used in traditional and complementary medicine and their possible application in developing treatment/preventive strategies for UTI. The non-antibiotic, rather 'beyond antibiotic' approach needs to be explored in order to minimize the threats of drug resistance related to the use of antibiotics. Such strategies will be beneficial not only as adjunct therapies to antibiotics but also in restoring homeostasis, particularly related to the gut microbiota.

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