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Review Article

Urinary Tract Infections: Characterization and Herbal Antimicrobial Activity: A Review

Imad Hadi Hameed[1*], Abeer Fauzi Al-Rubaye[2], Mohanad Jawad Kadhim[3]

[1]*College of Nursing, University of Babylon, Iraq*
[2]*Department of Biology, College of Science for women, University of Babylon, Iraq*
[3]*College of Biotechnology, Department of Genetic Engineering, Al-Qasim Green University, Iraq*

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ABSTRACT
Medicinal plants are part and parcel of human society to combat diseases from the dawn of civilization. According to World Health Organization (WHO), about 80% of the world population rely chiefly on plant based traditional medicine specially for their primary health care needs and there has been a worldwide move towards the use of traditional medicines due to concerns over the more invasive, expensive and potentially toxic main stream practices. This review gives a bird's eye view on the updated information on urinary tract infections (UTIs), different categories of urologic herbs, historical use and modern scientific investigations on some important urologic herbs, clinical studies, some isolated chemical compounds and their possible side effects.

Keywords: Medicinal plants; Urinary Tract Infections ; Historical use; Scientific analysis ; Clinical studies ; Bioactive constituents; Possible side effects.

INTRODUCTION

UTI may be asymptomatic. However, some patients report incontinence, a general lack of well-being, or both[1]. Cystitis clinically manifests as irrigative voiding symptoms that include frequent and painful urination of small amounts of turbid urine, urgency, suprapubic or lower abdominal pain, and incontinence. Fever tends to be absent in infections limited to the lower urinary tract. In men, urinary retention should be ruled out, because it is frequently associated with cystitis and possible prostatitis. The manifestations of UTI in older adults may include confusion, lethargy, anorexia, and incontinence. The absence of dysuria, and the presence of vaginal discharge significantly decrease the probability of UTI[2]. Lower urinary tract infection is also referred to as a bladder infection. The most common symptoms are burning with urination and having to urinate frequently (or an urge to urinate) in the absence of vaginal discharge and significant pain[3]. These symptoms may vary from mild to severe[4] and in healthy women last an average of six days[5]. Some pain above the pubic bone or in the lower back may be present. People experiencing an upper urinary tract infection, or pyelonephritis, may experience flank pain, fever, or nausea and vomiting in addition to the classic symptoms of a lower urinary tract infection[4]. Rarely the urine may appear bloody or contain visible pus in the urine[5]. In young children, the only symptom of a urinary tract infection (UTI) may be a fever. Because of the lack of more obvious symptoms, when females under the age of two or uncircumcised males less than a year exhibit a fever, a culture of the urine is recommended by many medical associations. Infants may feed poorly, vomit, sleep more, or show signs of jaundice. In older children, new onset urinary incontinence (loss of bladder control) may occur[6]. Urinary tract symptoms are frequently lacking in the elderly[7]. The presentations may be vague with incontinence, a change in mental status, or fatigue as the only symptoms[4], while some present to a health care provider with sepsis, an infection of the blood, as the first symptoms[8]. Diagnosis can be complicated by the fact that many elderly people have preexisting incontinence or dementia[7]. It is reasonable to obtain a urine culture in those with signs of systemic infection that may be unable to report urinary symptoms, such as when advanced dementia is present. Systemic signs of infection include a fever or increase in temperature of more than 1.1 °C (2.0 °F) from usual, chills, and an increase white blood cell count.

Anatomical and physiological factors

Among several factors contributing to the risk of acquiring UTIs, anatomical and physiological factors are predisposing to UTI. Urinary tract abnormalities affecting the flow of urine and emptying of the bladder increase the risk of UTI. Urine voiding disorders such as those associated with prolapse, multiple sclerosis, bladder cancer, or bladder stones increase the risk[9]. Women with any urinary tract abnormality are more prone to pyelonephritis refractory to oral therapy or complicated by bacteraemia. This is due, in part, to the female anatomy in that a much shorter urethra allows pathogens easier access to the bladder[10]. Constipation increases the

*Author for Correspondence: imad_dna@yahoo.com

residue after micturiation, causes functional obstruction and affects the flow of urine[11,12].

Age

UTI affects people in varying incidences depending on age group. The Incidence of UTI is highest during the first year of life and peaking again during adolescence. Approximately 3 % of prepubertal girls and 1 % of prepubertal boys are diagnosed with a UTI. Bacteriuria is more common at the extremes of life[13]. In women after the menopause vaginal prolapsed changes in vaginal flora and urinary incontinence contribute to the increased susceptibility to UTIs[14].

Sex

Gender is an important factor in UTI. Women are much more susceptible than men to community-acquired UTIs except in association with anatomic or functional abnormalities in the first year of life[15]. In young sexually active women, sexual activity is the cause of 75–90% of bladder infections, with the risk of infection related to the frequency of sex[3]. The term "honeymoon cystitis" has been applied to this phenomenon of frequent UTIs during early marriage. In post-menopausal women, sexual activity does not affect the risk of developing a UTI. Spermicide use, independent of sexual frequency, increases the risk of UTIs[16]. Diaphragm use is also associated[17]. Condom use without spermicide or use of birth control pills does not increase the risk of uncomplicated urinary tract infection[3]. Women are more prone to UTIs than men because, in females, the urethra is much shorter and closer to the anus[18]. As a woman's estrogen levels decrease with menopause, her risk of urinary tract infections increases due to the loss of protective vaginal flora. Additionally, vaginal atrophy that can sometimes occur after menopause is associated with recurrent urinary tract infections[19].

Chronic prostatitis may cause recurrent urinary tract infections in males. Risk of infections increases as males age. While bacteria is commonly present in the urine of older males this does not appear to affect the risk of urinary tract infections[20].

Pregnancy

Pregnancy is one of the factors which increase the risk of UTI partly due to the pressure of gravid uterus on the ureters causing stasis of urine flow and is also attributed to the humoral and immunological changes during normal pregnancy[21,22]. UTI is common with varying prevalence by age, sexual activity and the presence of genitourinary abnormalities[23]. In pregnancy UTI carries risk of foetal loss, pre-term labour, intrauterine growth retardation, maternal anemia and also the chance of recurrent infections[24].

Chronic Medical Condition

Urinary tract infection (UTI) is a major problem in diabetics. The risk of developing infection in diabetic patients is higher and urinary tract is the most common site for infection[16]. Changes in host defense mechanisms, the presence of diabetic cystopathy and micro-vascular disease in the kidneys may play a role in the higher incidence of UTI in diabetic patients. Different medical condition like kidney problem, neurogenic bladder, sickele cell anemia, immune system problem like HIV patient and urinary tract abnormality are also increase the risk for UTIS[25].

Urinary catheters

Urinary catheterization increases the risk for urinary tract infections. The risk of bacteriuria (bacteria in the urine) is between three and six percent per day and prophylactic antibiotics are not effective in decreasing symptomatic infections[18]. The risk of an associated infection can be decreased by catheterizing only when necessary, using aseptic technique for insertion, and maintaining unobstructed closed drainage of the catheter[26,27]. Male scuba divers utilizing condom catheters or the female divers utilizing external catching device for their dry suits are also susceptible to urinary tract infections[28].

Others Factors

A predisposition for bladder infections may run in families. Other risk factors include diabetes[3], being uncircumcised, and having a large prostate[4]. Complicating factors are rather vague and include predisposing anatomic, functional, or metabolic abnormalities. In children UTIs are associated with vesicoureteral reflux (an abnormal movement of urine from the bladder into ureters or kidneys) and constipation. Persons with spinal cord injury are at increased risk for urinary tract infection in part because of chronic use of catheter, and in part because of voiding dysfunction[29]. It is the most common cause of infection in this population, as well as the most common cause of hospitalization. Additionally, use of cranberry juice or cranberry supplement appears to be ineffective in prevention and treatment in this population[29].

Antimicrobial peptides

Antimicrobial peptides (AMPs) are small cationic proteins produced by white cells and epithelial cells as antibiotics, when the innate immune system is challenged by pathogens. AMPs have a wide antimicrobial spectrum that includes bacteria, virus, and fungus. The antimicrobial function of AMPs is associated with electric charge, secondary structure, and amphiphilic characteristics[30]. Increased electric charge of AMPs strongly attracts the negative charge of microbial membranes. Amphipathicity is a characteristic that derives from hydrophilic and hydrophobic amino acid of AMPs that facilitates interaction with hydrophilic conditions and hydrophobic microbial membranes[31]. Secondary structure can modify antimicrobial function by 3-dimensional structure. These characteristics make AMPs stick to microorganism, block microbial binding, trigger other components of immune system, and weaken membrane of microorganism. AMPs bind to the negatively charged microbial membrane by the cationic portion, thus inhibiting membrane function and causing death of microorganisms. Some AMPs influence cellular protein or DNA synthesis by passing the cell membrane[31]. Because of these effects, AMPs are regarded as potential therapeutics for drug resistance. AMPs have some desirable properties. AMPs show antimicrobial function at low density. Because microorganisms cannot change their cell membrane easily, they maintain susceptibility to

AMPs. AMPs surmount weakness of antibiotics that lose their ability to permeabilize cell membranes[32]. AMPs display synergistic effects with antibiotics [33]. Despite the broad dispersion in nature, not many AMPs are known to exist in the kidney and urinary tract. AMPs of urinary tract are defensins, cathelicidin, hepcidin, and ribonuclease 7 (RNase 7). AMPs of kidney and urinary tract are THP, lactoferrin, lipocalin and secretory leukocyte proteinase inhibitor[31]. AMPs can kill bacteria by disrupting the microbial membrane (A–C) or translocating across the membrane and binding to intracellular targets (D). Models of membrane disruption include the following: (A) Barrel-stave model: (A1) Cationic AMPs (+) bind to the negatively charged bacteria lipid bilayer (−) and disrupt the microbial membrane by forming an aqueous channel or "barrel-stave" (A2). (B) Carpet Model: AMPs blanket the microbial membrane and disrupt it by forming micelles. (C) Torodial Pore Model: AMPs bind to phospholipid head group on the microbial membrane allowing its hydrophobic portion to intercalate into the microbial membrane and cause the lipid bilayer to fold back on itself[33-47].

Defensins

Defensins are one of the AMPs that attack bacteria, virus, fungus and protozoans[34]. Defensins not only attack foreign cells directly but also attract immature dendritic cells[31]. In humans, defensins are classed as α-defensins or β-defensins by their disulfide bridge pattern. Some genes of α-defensins and β-defensins are encoded in chromosome 8p22 and 8p23, but regions of other genes display variations from 2 to 14 per diploid genome.

Hepcidin

Hepcidin (liver expressed antimicrobial peptide1, LEAP1) is made in liver and secreted in the urinary tract. LEAP-1 is related to iron homeostasis and overexpressed LEAP-1 results in severe iron deficiency[48]. LEAP-1 has broad spectrum as a bactericide and its function derives from direct antimicrobial effect and reduction of usable iron that is needed for bacterial survival[49].

Ribonuclease 7

RNase 7 was initially found in epidermis and subsequently found in bladder, ureter and kidney[50]. Concentration of RNase 7 is higher than other AMPs and shows sufficient bactericidal effect. Rapid and strong action of RNase 7 from Gram positive and negative bacteria results from distraction of cell membrane, that is independent with ribonuclease activity[39]. Antimicrobial processes of RNase 7 are not fully identified.

Lactoferrin and Lipocalin

Lactoferrin is found in distal collecting tubules. It causes chelation of iron and modification of membrane integrity[50,51]. Lipocalin reduces siderophore-iron of bacteria and shows bacteriostatic function. Mice without lipocalin are more susceptible to bacteria that utilized siderophores[52].

Tamm-Horsfall Protein

THP, the most plentiful protein in human urine, is secreted in the loop of Henle[53]. THP does not have bactericidal activity itself, but blocks bacterial binding to epithelium and promotes bacterial wash-out by urine. THP activates dendrite cells by a TLR4 dependent mechanism.

Diagnosis

The diagnosis of UTIs begins with the screening of patients clinically suspected of having urinary tract infection due to their claiming with problems suggestive of UTIs by a physician. In straightforward cases, a diagnosis may be made and treatment given based on symptoms alone without further laboratory confirmation[16]. In complicated or questionable cases, urinalysis may be useful to confirm the diagnosis[54-57].

Urine Test

Urine testing is the second important element in diagnostic testing.

Urine collection

Several studies have dealt with the necessity of collecting midstream urine and of cleaning the perineum and vulva or glans penis[58-75]. However, these were mostly with fairly young and otherwise healthy women, so it is not clear whether they can be transferred to normal clinical practice. A pragmatic solution would be to make the method of urine collection dependent on the clinical problem. For an initial urine investigation with a dip stick, fresh spontaneous urine can be taken rather than midstream urine and it is unnecessary to clean the genitals. On the other hand, additional studies and urine culture require that the urine sample should be collected and processed with as little contamination as possible.

Practical test methods

The gold standard for a urine test is to perform a bacteriological urine culture, with identification of the pathogen, with quantification and sensitivity testing. To test whether the patient has a UTI at all, orientating indirect methods are often used in practice to detect the bacteria or inflammation (dipsticks). The bacterial count may be assessed by urine microscopy and immersion culture media.

A. Urine dipstick

Urinalysis involves a combination of a dipstick test and urine culture. The dipstick assay was first developed in the 1920s to assess for the presence nitrites, which are present as a result of bacterial growth. Dipstick tests have advanced into multiplexed sample analysis strips with 10 readouts capable of characterizing: (1) specific gravity, (2) pH, (3) nitrites, (4) leukocyte, (5) protein, (6) glucose, (7) urobilirubin, (8) bilirubin, (9) ketones and (10) erythrocytes. Tests are available to quickly check for purulent material or bacteria in the urine, but the tests are most effective if high levels of bacteria are present. False positives are rare, but false negative readings may occur, so a dipstick urine examination should be confirmed with urinalysis, which can detect lower levels of bacteria. Dipsticks test for leukocyte esterase and/or nitrates. The nitrate dipstick test is more accurate than the leukocyte esterase test, but dipsticks that check for both are most accurate. With the nitrate dipstick, false negatives may result if diuresis has decreased urinary nitrate level, if there is inadequate intake of dietary nitrates, or if infections are caused by enterococci or acinetobacter because these bacteria do not produce nitrates. Usually, a high nitrate level indicates infection, but with some bacteria, this is not the case, so a false negative may occur[76-83].

Molecular Diagnostics

Polymerase-chain reaction (PCR) is one of the most sensitive methods of detecting pathogenic bacteria in human samples. PCR-based assays amplify a specific region of DNA(e.g. 16S rDNA) using a heat-stable DNA polymerase and characterize the amplified region by restriction enzyme digestion (e.g. restriction fragment length polymorphism mapping) or sequencing. PCR performed with urine samples does not display the sensitivity of urine culture. PCR had a sensitivity of 95% for single pathogen UTIs while only a 57% sensitivity for multi-pathogen UTIs[84-89].

Treatment

The standard treatment for a UTI is a course of one or more antibiotics. No single antibiotic is recommended for treating every UTI, but nitrofurantoin (Furadantin®), trimethoprim-sulfamethoxazole (Bactrim™), pivemecillinam (Selexid®), fosfomycin trometamol (Monurol®), fluoroquinolone (eg, Cipro®), and beta-lactam (eg, Augmentin®) may all be used[67,68]. Although many antibiotics can be used to treat UTIs, one of the main factors that determines which antibiotics are chosen is the bacterial resistance pattern. There are strains of *E. coli* that are resistant to antibiotics and are found throughout the world[69]. Other strains of bacteria that cause UTIs, including species of *Proteus* and *Klebsiella*, have also developed resistance to specific antibiotics[90]. As a result, the choice of antibiotic is usually governed by susceptibility of the pathogenic organism responsible for an individual's case and/or community history of microbial antibiotic resistance[91-96]. This is typically determined by regional rates reported by local hospitals, although this information can overestimate the prevalence of resistance among bacteria in a region. Some guidelines recommend avoiding a particular antibiotic if local resistance rates to that antibiotic are greater than 20% [97-101].

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