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Review Article

# AYURVEDIC HERBAL DRUGS IN THE MANAGEMENT OF RECURRENT UTI IN PEDIATRICS

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**ABSTRACT**

Urinary tract infection (UTI) is a common bacterial infection encountered in pediatric age group. The incidence varies with age, being more prevalent among boys during infancy and later on in girls. It generally resolves with proper antibiotic treatment. However certain part of pediatric population is at high risk of developing recurrent UTI due to its high association with urinary tract malformation. Recurrent UTI is known to be associated with long term consequences – renal parenchymal damage and scarring due to presence of infection in anatomical malformations. Long term antimicrobial prophylaxis is usually considered with an aim to sterilize urine to prevent from recurrence. But its utility is declining due to emergence of increasing number of multi drug resistant bacteria and poor compliance to treatment**.** These issues have led to a continuous exploration of different modes of alternative therapy. Thus an attempt has been made in this review paper to formulate more efficacious and safe Ayurvedic herbal management in context with Recurrent UTI.

**Keywords:** UTI, Recurrent urinary tract infection, Ayurveda, Herbal drugs, Pediatrics.

## INTRODUCTION

Urinary tract infection (UTI) is a common bacterial infection in pediatric age group, the prevalence being 1- 3% in boys and 3 – 10% in girls before the age of 14 years.[1] The incidence varies with age. During the first year of life, the male to female ratio is 3-5:1. Beyond 1-2 years, there is female preponderance with male to female ratio of 1:10.[2] UTI have been traditionally classified by site of infection (kidney- pyelonephritis, bladder – cystitis, urethra - urethritis) and by severity (complicated and uncomplicated).[3] However in pediatrics, a simpler and more practical approach is used to categorize UTI as a first infection versus recurrent infection. The initial UTI documented by a proper urine culture is the first infection. It generally resolves by adequate and appropriate oral and parentral antibiotic therapy. However a significant proportion of pediatric population especially infant and younger children are prone to develop recurrent UTI due to its high association with urinary tract malformation and concurrent bacteremia, which predispose children to acute morbidity and long-term known co morbid conditions - renal parenchymal damage and renal scarring that can cause hypertension and progressive renal damage.[4] Hence, rapid evaluation and treatment is essential.

### Risk factors for Recurrent UTI

Risk factors for recurrence include an age less than 6 months at first UTI, grade 3 – 5 vesicoureteric reflux (VUR). Less rigorous studies have identified that features such as infrequent voiding, poor fluid intake, stool retention, inadequate genital hygiene, dysfunctional voiding and bladder instability are associated with recurrent UTI.[5]

### Anatomic and functional abnormalities predisposing for recurrent UTI

Anatomical and functional abnormalities of the urinary tract predispose children to UTI because of inadequate clearance of uropathogens. It is essential to identify these abnormalities early because if uncorrected, they may serve as a reservoir for bacterial persistence and result in recurrent UTI. Children with a functional abnormality of the urinary tract are unable to empty the bladder e.g neurogenic bladder, frequently resulting in urinary retention, stasis and suboptimal clearance of bacteria from the urinary tract. Clean intermittent catheterization is helpful for emptying the neurogenic bladder, but catheterization itself may introduce bacteria to this normally sterile space. Chronically elevated bladder pressure secondary to poor emptying also may cause secondary VUR, in which the elevated pressure increases the potential renal damage of pyelonephritis. Similarly congenital anatomic anomalies, such as posterior urethral valves (PUV) and VUR, do not predispose children to colonization but increase the likelihood of inadequate washout in the routine ways and also increase possibility of pyelonephritis and potential renal deterioration due to ascending lower UTI to upper tracts. [6,7]

### Need of Alternative therapy

Chronic anti microbial prophylaxis is usually prescribed to prevent recurrent UTI associated with known urinary tract malformation with an aim to sterilize urine because renal damage and scarring have been shown to occur in the presence of infection[8]. Various antibiotics like cotrimoxazole, cephalosporins and fluoroquinolones have been used but no one is found to be superior. Recurrences can occur due to unresolved bacteriuria, bacterial persistence or reinfection in known urinary tract malformations. Unresolved bacteriuria is commonly caused by inappropriate antimicrobial therapy due to poor compliance, inadequate or infrequent dosing. Bacterial persistence or reinfection occurs due to persistent nidus of infection in urinary tract usually shielded from antimicrobial therapy. These protected sites are often the anatomic abnormalities. This patient population is associated with a higher incidence of multidrug-resistant uropathogens[7] and non–E coli uropathogens, particularly Pseudomonas and Enterococcus[9,10]. These bacterial pathogens have evolved numerous defense mechanisms against antimicrobial agents; hence resistance to old and newly produced drugs is on the rise. This phenomenon of antibiotic resistance exhibited by the pathogenic

microorganisms has led to screening of several Ayurvedic herbs for their potential antimicrobial activity with more efficacious and safety profile.

There is no such clinical entity similar to recurrent UTI mentioned in Ayurvedic texts. However the urinary disorders are dealt under two broader heading in Ayurveda - Mootrakriccha and Mutraghata. The difference in two clinical scenarios is based on the intensity of obstruction. The former is characterized by painful micturition whereas the latter with obstruction/retention of urine. Dysuria being predominant symptom in UTI, it can be compared with Mutrakriccha, more precisely with Pittaja Mutrakricha that occurs due to vitiation of doshas which reach urinary bladder area compressing the urinary passage leading to difficulty in micturition and gives rise to following features - yellow colored urine, voidance with burning sensation and pain or hematuria.[11,12,13] Various drugs have been mentioned in Ayurvedic texts to cure UTI (Pittaja Mootrakrichha) like *Gokshura, Shatavari, Laghu Panchamula gana, Trin Panchamula gana* etc. to be given in various combinations with proper *Anupana* (vehicle or adjuvant) and in appropriate forms i.e. Kwath (Decoction) etc. After considering pathogensis and consequences of Recurrent UTI according to modern medicine, herbal management can be divivded under two broader categories : (a) urinary anti septic herbs like *Punica granatum, Tribulus terrestris, Terminalia chebula, Ocimum sanctum, Cinnamomum cassia, Azadirachta indica*, *Ocimum sanctum etc.* effective against major uropathogens namely E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa.
(b) Nephroprotective herbs like *Tinospora cordifolia, Boerrhavia diffusa, Crateva nurvula* etc.

## EXPERIMENTAL STUDIES

### A. Urinary Anti septic Herbs

***Guduchi* (*Tinospora cordifolia*) -** In a study antibacterial activity of aqueous, ethanol and chloroform extracts of leaves and stem of *Tinospora cordifolia Hook.F.Thoms* were tested on clinical isolates of urinary pathogens viz., Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris and Pseudomonas aeruginosa by agar well diffusion method. Ethanol extract of leaf showed greater inhibitory action than other tested extracts.[14]

***Shigru* (*Moringa oleifera*) -** The antimicrobial efficacy of ethanolic (EthMO) and hydroalcholic extract (HyMO) of *M. oleifera* stem bark against some human clinical bacterial isolates (Klebsiella spp. Pseudomonas spp. Proteus spp. and E. coli) was evaluated in vitro. In case of E. coli and K. pneumonia isolates, the highest zone of inhibition was 20.33±0.88 mm and 15.00±0.58 mm which were exhibited by EthMO. HyMO exhibited highest activity against P. mirabilis (17.67±0.67 mm). HyMO also exhibited significant inhibitory effect against E. coli and P. aeruginosa (15.00±0.58 mm) isolates.[15]

***Abdhiphala* (*Barringtonia acutangula* (L.) Gaertn) -** In vitro antibacterial activity of aqueous, ethanolic, petroleum ether and chloroform extracts of *Barringtonia acutangula* was investigated against urinary pathogens - Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis and Escherichia by disc diffusion assay method and the minimum inhibitory concentration was evaluated. Ethanol (95%) extract exhibited broader spectrum of inhibition followed by chloroform, petroleum ether and aqueous extracts against the urinary tract pathogens under test.[16]

***Buchu* (*Agthosma betulina*) -** The anti bacterial activity of ethanolic extract derived from leaves of *Agthosma betulina* was studied on selected Urinary tract pathogens. The ethanolic extract was more effective against Staphylococcus saprophyticus, Proteus mirabilis and E.coli, with a zone of inhibition of 25mm, 24mm and 23 mm diameter (at conc 300µg) respectively and was less effective against Pseudomonas aeruginosa and Staphylococcus aureus with zone of inhibition of 14mm each (at conc. 300µg). Among the other bacterial species studied Klebsiella pneumoniae and Enterococcus faecalis showed a zone of inhibition of 19mm and 18mm (at conc.1000 µg.) respectively.[17]

**Polyherbal formulation**

(i) In a study, methanolic leaf extracts of 21 timber-yielding plants were studied for in vitro antibacterial activity against nine species of Multi drug resistance (MDR) uropathogens- Enterococcus faecalis, Staphylococcus aureus, Acinetobacter baumannii, Citrobacter freundii, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. The study reported that methanolic leaf extracts of *Anogeissus acuminata* had the maximum zone of inhibition size-29 mm against S. aureus and 28 mm against E. faecalis and P. aeruginosa. *Cassia tora* had 29 mm as the zone of inhibition size for E. faecalis, E. aerogenes, and P. aeruginosa. Based on the minimum inhibitory concentration and minimum bactericidal concentration values, the most effective 10 plants against uropathogens were arranged in decreasing order as follows: *Cassia tora* , *Anogeissus acuminata* , *Schleichera oleosa*, *Pterocarpus santalinus*, *Eugenia jambolana*, *Bridelia retusa*, *Mimusops elengi*, *Stereospermum kunthianum*, *Tectona grandis* and *Anthocephalus cadamba*. The following eight plants had moderate control capacity: *Artocarpus heterophyllus*, *Azadirachta indica*, *Dalbergia latifolia*, *Eucalyptus citriodora*, *Gmelina arborea*, *Pongamia pinnata*, *Pterocarpus marsupium*, and *Shorea robusta*. [18]
(ii) The antibacterial activity of aqueous, ethanol, ethyl acetate, methanol, Petroleum ether and chloroform extracts of *Biophythm sensitivum*, *Myristica fragrans*, *Aerva Lanata* and *Boerrhavia Difffusa* was determined against 5 UTI isolates. i.e. Escherechia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Staphylococcus aureus, streptococci viridians, by disc diffusion method. The study concluded that crude extracts of the selected plants especially the Ethanol, Methanol, Ethyl acetate extracts exhibited significant activity against UTI pathogens.[19]
(iii) The antibacterial activity of aqueous, ethanol and acetone extracts of 15 medicinal plants - *Corriander sativum, Abutilon indicum, Boerhavia diffusa, andrographis paniculata, Plantago ovata, Bacopa monnieri, Bauhinia variegata, Flacouratia ramontchi, Embelia tfgerium, Euphorbia ligularia, Zinziber officinale, Terminalia chebula, Azadirachta indica, Ocimum sanctum*and *Cinnamomum cassia* was determined against 33 UTI isolates i.e. Proteus mirabilis (10), Escherichia coli (6), Proteus vulgaris (6), Klebsiella pneumoniae (5), Enterobacter cloacae (2), Providencia pseudomallei (2), Pseudomonas aeruginosa (1) and Klebsiella oxytoca (1) by disc diffusion method. The study concluded that crude extracts of the selected plants especially the acetone and ethanol extracts exhibited significant activity against UTI pathogens.[20]
(iv) 17 Indian medicinal herbs were investigated to evaluate in vitro antibacterial activity of aqueous, ethanol and acetone extracts against 66 multidrug resistant isolates of major urinary tract pathogens - Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa *and* Enterococcus faecalis by Agar disc diffusion method. Ethanolic extract showed considerably more activity than the acetone and aqueous extract. The study concluded that ethanolic extract of *Zingiber officinale* and *Punica granatum* had maximum antibacterial activity against E. coli , *Terminalia chebula* and *Ocimum sanctum* against K. pneumonia and *Cinnamomum cassia* against Pseudomonas aeruginosa while *Azadirachta indica* and *Ocimum sanctum* against Enterococcus faecalis.[21]
(v) The antibacterial activity of essential oils extracted from medicinal plants (*Ocimum gratissimum L., Cybopogum citratus (DC) Stapf.,* and *Salvia officinalis L.*) was assessed on bacterial strains derived from 100 urine samples. Microorganisms were plated on Müller Hinton agar. Plant extracts were applied using a Steers replicator and petri dishes were incubated at 37°C for 24 hours. *Salvia officinalis L.* showed enhanced

inhibitory activity compared to the other two herbs, with 100% efficiency against Klebsiella and Enterobacter species, 96% against Escherichia coli, 83% against Proteus mirabilis, and 75% against Morganella morganii.[22]

**B. Nephroprotective Herbs**

***Guduchi* (*Tinospora cordifolia*) -** The effect of *Tinospora cordifolia* was studied on urotoxicity induced by acute dose of Cyclophosphamide (CP) using Swiss albino mice model. Administration of an alcoholic extract of the plant *T. cordifolia* (200 mg/kg i.p.) for 5 days reduced CP (1.5 mmol/kg body wt. i.p.) induced urotoxicity.[23]

***Ashwagandha* (*Withania somnifera*) -** The root extract of three different doses of *W. somnifera* (viz., 250, 500, and 750 mg/kg) was administered orally to rats for 14 days before Gentamicin induced nephrotoxicity (GEN) treatment and thereafter concurrently with GEN (100 mg/kg) for 8 days. *W. somnifera* at dose of 500 mg/kg significantly reversed nephrotoxicity changes as evidenced microscopically when compared to other two doses of *W. somnifera* (250 and 750 mg/kg), and there were no significant changes in the experimental animals compared to control. The study suggested the nephroprotective effect of *Withania somnifera* by its antioxidant activity and scavenging the free radicals.[24]

***Haridra* (*Curcuma longa*) -** The nephroprotective and diuretic effects of three medicinal herbs *Petroselinum sativu*m, *Eruca sativa* and *Curcuma lon*ga, alone and in combination were investigated against gentamicin (GM)-induced nephrotoxicity in rats. The results showed that GM induced nephrotoxicity was ameloriated by oral administration of aqueous infusion of *Petroselinum sativu*m, *Eruca sativa* and *Curcuma longa* herbs.[25]

***Varuna* (*Crataeva nurvala*) -** The alcoholic extract of *Craaeva nurvala* administered in dose of 250 and 500 mg/kg for 10 days showed protective activity against cisplatin 5 mg/kg induced nephrotoxicicty. The results suggested, that the alcoholic extract has significantly altered the dysfunction of renal proximal tubule cells by decreasing the concentration of blood urea nitrogen, creatinine, lipid peroxidation, glutathione and catalase.[26]

***Manjjistha* (*Rubia cordifolia*) -** In a study the hydro-alcoholic extract of *Rubia cordifolia* was investigated against Cisplatin induced nephrotoxicity in Swiss albino mice. Cisplatin at a dose of 12 mg/kg body wt was administered intraperitoneally while another set of animals were given hydro-alcoholic extract of *Rubia cordifolia* at different doses along with cisplatin treatment. The extract significantly decreased the cisplatin induced nephrotoxicity. The study concluded the nephroprotective reole of Hydro-alcoholic extracts of *Rubia cordifolia.*[27]

***Punarnava* (*Boerrhavia diffusa*) -** The study investigated the nephroprotective effects of aqueous extract of *B. diffusa* root (200 – 400 mg/kg/day) against acetaminophen induced nephrotoxicity in rats. Histopathological changes showed that acetaminophen caused significant structural damages to kidneys like tubular necrosis, degeneration of epithelial cells, glomerular damage and congestion which was reversed with *B. diffusa*.[28] In another study, the methanolic extract of roots of *B. diffusa* for its nephroprotective and nephrocurative effects in cisplatin (10 mg/kg b.w.i.p.) induced nephrotoxicity in albino rats.[29]

***Brihat Gokshura* (*Pedalium murex*) -** Nephrotoxicity was induced in Wistar rats by intraperitoneal administration of Cisplatin 5mg/kg. Effect of concurrent administration of *Pedalium murex* ethanolic extract at a dose of 250 mg/kg given by oral route was determined using serum creatinine and blood urea and change in body weight as indicators of kidney damage. Cystone was used as standard drug. The study showed that the ethanolic extract of dried fruits of *Pedalium murex* has an excellent nephroprotective activity as compared to cystone.[30]

***Sahadevi* (*Vernonia cinerea*) -** The alcoholic extracts of aerial parts of vernonia cinerea has been examined for its effect on cisplatin-induced nephrotoxicity at a dose of 6mg/kg, i.p. in albino rats. The alcoholic extract showed pronounced curative activity and the ethyl acetate extract has exhibited good prophylactic activity and petroleum ether extract showed moderate protection for both curative and prophylactic models against cisplatin-induced toxicity.[31]

***Pashanbheda* (*Aerva lanta*) -** The ethanolic extract of the entire plant of *Aerva lanata* was studied for its nephroprotective activity in cisplatin and gentamicin induced acute renal injury in albino rats. The results suggest that the ethanolic extract of *Aerva lanata* possesses marked nephroprotective activity with minimal toxicity and could offer a promising role in the treatment of acute renal failure caused by nephrotoxins like cisplatin and gentamicin.[32]

***Shunti* ( *Zingiber officinale*) -** Nephrotoxicity was induced by i.p. administration of gentamicin 100 mg/kg/day for eight days in wistar rats. Effect of concurrent administration of ethyl acetate extract and fresh juice extract of *Zingiber officinale* at a dose of 200 mg/kg/day given by oral route. Gentamicin-induced glomerular congestion, peritubular and blood vessel congestion, epithelial desquamation, accumulation of inflammatory cells and necrosis of the kidney cells were found to be reduced in the groups receiving the ethyl acetate and dried fresh juice extract of *Zingiber ofiicinale* along with gentamicin. The study concluded that both extracts possess significant nephroprotective activity.[33]

## CONCLUSION

Urinary tract infection is a common bacterial infection encountered in pediatric age group. If not evaluated and treated promptly, there is a significant risk of Recurrent UTI in presence of associated factors leading to acute morbidity and long term sequeal – Renal parenchymal damage. The conventional use of antibiotic prophylaxis has led to multidrug resistant uropathogens, thereby creating a thirst for search of non conventional strategies like Ayurvedic herbal drugs for management of Recurrent UTI. The use of urinary anti septic herbal drugs listed in this review paper has shown full potential to combat with multidrug resistant uropathogens. In combination with nephroprotective herbs, it can have impact on reversing the renal parenchymal changes preventing it from known complications like hypertension and progressive renal damage. Although the studies listed in above review paper are of preliminary in nature and most of them are in vitro studies, the comprehensive clinical trials of Ayurvedic Polyherbal drug formulations, keeping in mind of above aforementioned properties can gain importance as one of the better alternative management after proper scientific validation. Further researches (particularly clinical studies) are indicated to support or refute the hypotheses presented in this review article.

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