Urinary tract infection (UTI) is a broad term that describes microbial colonization in the urine and infection of the structures of the urinary tract like kidney, ureters, bladder, urethra (Kunin, 1997). UTI usually starts as a bladder infection termed as cystitis, but can develop to acute kidney infection termed as pyelonephritis and ultimately resulting in scarring and renal failure.

UTI is the most widespread infection in women worldwide following intestinal infection (Dielubanža, 2011). UTIs affect an estimated 1 out of 3 women before the age of 24 (Foxman et al., 2000; Nicolle et al., 2008). Upto 40 to 50% of the female population develop a symptomatic UTI at some time at some stage in their lives (Foxman et al., 2000; Nicolle et al., 2008) or develop complicated UTIs (Neal et al., 2008). The lifetime threat of symptomatic UTI among women has been found to be 60% (Foxman et al., 2000).

Recurrent urinary tract infections (rUTI) are widespread among young healthy women even though anatomically and physiologically they have normal urinary tracts (Hooton et al., 2001). The rUTIs were reported in 16-25% of women within 6 months of an UTI episode and in 40-50% of women within one year of an UTI episode despite antimicrobial treatment. The rUTIs are thus common and pose a major problem (Karkkainen et al., 2000). Risk factors linked with an increased probability of UTI in women includes urinary catheterization, urinary tract obstruction, use of spermicides, neurologic malfunction, pregnancy, and, a diaphragm, or anticholinergic agents (Hooton  et al., 2001).

*Escherichia coli* are the most important human pathogens, responsible for up to 90% of all community acquired and almost 50% of nosocomial UTI (Jones et al., 1997; Zhanel., 2000). Uropathogenic *Escherichia coli* (UPEC) strain possesses a number of virulence factors that facilitate them to colonize the urinary tract and persist in the face of highly effective host defenses. As shown in Figure 1, a number of virulence determinants facilitate the ability of UPEC to colonize the urinary tract and exert cytopathic effects, including P fimbriae (Roberts et al., 1994), Dr adhesions (Goluszeko et al., 1997), flagella (Lane et al., 2005), lipopolysaccharide O antigen (Schilling et al., 2001), type 1 fimbriae (Connell et al., 1996), hemolysin (Van den Bosch et al., 1982; Welch et al., 1981) cytotoxic necrotizing factor 1 (Rippere-Lampe et al., 2001), capsule polysaccharide (Bahrani-Mougeot et al., 2002) and TonB-dependent iron transport
systems (Torres et al., 2001). During UTI outer membrane proteins of UPEC like porins (OmpA, OmpC, OmpX, NmpC, and LamB) outer membrane assembly factors, including YaeT and YeaF, as well as nucleoside and vitamin B12 receptors Tsx and BtuB are overexpressed (Hagan and Mobley, 2007).

Figure 1: Virulence factors of Uropathogenic *Escherichia coli*, adapted from Reid et al., 2003.

UPEC infection begins with the colonization of the bowel with a uropathogenic strain in addition to the commensal flora. This strain, by virtue of virulence factors that are encoded in pathogenicity islands, is capable of infecting host, as it colonizes the periurethral area and ascends the urethra to the bladder and up to the kidney (Figure 2; Kaper et al., 2004).
**Figure 2:** Ascending reinfection. Uropathogens originate from the rectal flora and colonize the periurethral area leading to ascension through the urethra into the bladder, adapted from Kaper et al., 2004 (PMNs: Polymorphonuclear leukocytes).

UPEC possesses different adhesive organelles or pili such as P pili and type 1 pili on its surface which assist adhesion to particular organ niche (Mulvey, 2002; Hultgren et al., 1993; Dodson et al., 2001). Type 1 pilus which facilitates adhesion to and following invasion of bladder epithelial cells (Hultgren et al., 1993; Mulvey et al., 2001; Hung et al., 2002) possesses the FimH adhesin which binds mannose. In the bladder, there are mannosylated residues on proteins that line the luminal surface of superficial epithelial cells (Hung et al., 2002).

An intricate developmental cascade is consequently activated upon entry of UPEC into superficial bladder cells. The bacteria divide quickly following invasion and form small clusters, establishing intracellular bacterial communities (IBCs); being intracellular allows them to evade being killed by antibiotics. Dramatic phenotypic events are then observed which progress
throughout several stages, culminating in the development of communities which obtain biofilm-like properties. These give the bacteria shelter from environmental changes and insults (Donlan and Costerton, 2002). Finally, UPEC will extricate from the intracellular biofilm and rupture into the bladder lumen. Though, they then rebind to the epithelium to structure another generation of IBCs and a reservoir. Throughout this reservoir stage, both host and bacteria are quiescent, and UPEC can continue in this state for months after an initial infection, despite antibiotic treatment (Anderson, 2003; Justice, 2004).

There are a number of practiced and proposed therapeutics for UTI management which include antibiotic therapy (Dethlefsen et al., 2008), estrogen treatment (Brandberg et al., 1987; Cardozo et al., 1998; Johnson et al., 1996; Kjaergaard et al., 1990; Parson et al., 1982; Privette et al., 1988; Raz et al., 1993), cranberry juice (Avon et al., 1994; Franco, 2005; Patel and Daniels, 2000), forskolin (a drug that increases intracellular cyclic AMP (cAMP) levels which expels UPEC from intracellular vesicles into the extracellular milieu and exposé the bacteria susceptible to immune responses and antibiotics) (Bishop et al., 2007), vaccination and probiotics.

While antibiotic therapy remains the standard treatment for UTI, overuse leads to deleterious alterations of the normal host microbiota (Dethlefsen et al., 2008) and selection for resistant strains (Czaja et al., 2007; Foxman et al., 2007; Gupta et al., 1999; Johnson and Stamm, 1989; Murray et al., 1985). Alternative therapies have its own drawbacks and there are no licensed vaccines available for treatment of UTI in humans (Sivick et al., 2010). The management of UTI can be a difficult task given the prevalence of disease and high rate of recurrence, broad range of associated morbidity, rapidly developing drug resistance and limited complement of antimicrobial agents and prerequisite for timely symptom relief and infection control (Dielubanza et al., 2011).

Lactobacilli are the predominant microorganisms in the lower genital tract of healthy premenopausal women with $10^7$–$10^8$cfu/g of vaginal fluid (Andreu et al., 1995). They favor an acidic environment and sustain the same by producing lactic and other acids such as deoxycarboxylic acid, phenols ethanol, etc. Lactobacilli provide a barrier and are able to interfere
with the ability of the pathogens to colonize the vagina and consequently reduce the risk of pathogen ascension from periurethral area into the bladder. *Lactobacillus* protects the vagina from colonization by uropathogens competing for the adhesion receptors, interference and co-aggregation, competing for nutrients and production of antimicrobial substances like $\text{H}_2\text{O}_2$, lactic acid, bacteriocins and bacteriocin-like substances (Boris et al., 1998). Not all lactobacilli own these properties with the same intensity (Pelletier et al., 1997). Valore et al., (2002) examined vaginal fluid for antimicrobial components and reported that the vaginal fluid with the highest levels of antimicrobial activity also contained the highest levels of lactic acid. *In vitro* studies showed that the acidity produced by lactobacilli can inhibit the proliferation of *C. albicans, E. coli, G. vaginalis*, and other pathogens (Reid et al., 1987). Moreover, most lactobacilli are able to produce hydrogen peroxide, which has a toxic potential towards other bacteria. Its antimicrobial effect is based on its oxidative properties which effect in irreversible changes in the microbial cell membrane (Vandenbergh, 1993).

Fluctuation in number of *Lactobacillus* with changes in glycogen levels and hormonal status, use of spermicide, sexual activity and antibiotic leads to UTIs (Reid et al., 2003). Hence, vaginal lactobacilli play a critical role in the maintenance of reproductive health in women.

Through genetic engineering, a member of the vaginal microflora may be enhanced to form a proficient defensive shield against the UPEC. The principal *Lactobacillus* species isolated from the vaginal mucosa of healthy women include *Lactobacillus iners, L. crispatus, L. gasseri, L. jenesenii*, followed by *L. acidophilus, L. fermentum, L. plantarum, L. brevis, L. casei, L. vaginalis, L. delbrueckii, L. salivarius, L. reuteri*, and *L. rhamnosus* (Anukam et al., 2005; Burton et al., 2003; Fredricks et al., 2005; Heinemann et al., 2005).

A microbicide is any compound or substance whose purpose is to reduce the infectivity of microbes, such as viruses or bacteria. The microbicide is an anti-infective medication formulated for topical self-administration before intercourse to protect against HIV and other pathogens (Stone, 2002). The live microbicide concept is based on the engineering of commensal bacteria belonging to the human microbiota in order to get the *in vivo* and *in situ* production of anti-infective agents. Recently, the potential of genetically improved lactobacilli strains as delivery
agents for anti-HIV, anti-\textit{S. aureus} drugs has generated hope for the development of a live and self-renewable microbicide (Vangelista et al., 2010; Liu et al., 2011). Similar strategy can be used for the treatment of UTI. The probiotic \textit{Lactobacillus} of vaginal origin having antimicrobial proteins specifically targeting UPEC may be a better alternative therapy for antibiotic resistance uropathogens. Antimicrobial proteins are the natural antibiotics, the basic element of a novel generation of drugs for the treatment of bacterial and fungal infections (De Lucca, 2000). They are active against a large spectrum of microorganisms, including bacteria and filamentous fungi - in addition to protozoan and metazoan parasites (Liu et al., 2000). Cathelicidin and colicin E2 are the antimicrobial proteins effective against uropathogenic \textit{E. coli}.

Cathelicidins are expressed in circulating neutrophils myeloid bone marrow cells, in epithelial cells of the skin and gastrointestinal tract, as well as in the epididymis and lungs (Zaiou et al., 2002). The gene product is synthesized as a propeptide, designated human cationic antimicrobial peptide-18 (hCAP-18) or pro-\textit{LL37}. The neutrophil propeptide is cleaved extracellularly into cathelicidin and the C-terminal peptide \textit{LL37}. Both cleavage products have a broad antimicrobial effect with complementary action. In addition to antimicrobial activity, antimicrobial peptides were suggested to be multifunctional modulators of different immune reactions (Scott et al., 2002; Bowdish et al., 2005). Notably, \textit{in vitro} studies have shown that Cathelicidins inhibit the growth of pathogens that have a major role in the urinary tract infection, but have no effect on urogenital commensal bacteria (Turner et al., 1998).

Colicin is a type of bacteriocin produced by \textit{E. coli} which is toxic to some strains of \textit{E. coli} (Feldgarden et al., 1999). Colicins are composed of three globular protein domains (Cascales et al., 2007). The first domain regulates the target and binds to the BtuB receptor on the sensitive cell. The second domain is involved with translocation, co-opting the machinery of the target cell. The third domain is the ‘killing’ domain and makes a pore in the target cell membrane, or act as a nuclease to degrade the DNA or RNA of the target cell. Colicins exhibit a ‘1-hit killing kinetic’ which doesn't necessarily mean a single molecule is sufficient to kill, but certainly that it only takes a small number. The colicins are highly effective toxins. Colicin E2 prevents colonization of UPEC on urinary catheters (Barbara et al., 2005). Evaluation of a \textit{ColE2}-producing transformant of \textit{L. lactis} ssp. lactis having the inhibitory activity of \textit{ColE2} against
*E. coli* O157:H7 (Liu et al., 2011) Expression of colicin E2 in probiotic *Lactobacillus* makes it more potent Microbicide against UTIs.