Chapter 2  
Review of Literature

2.1 Urinary Tract Infections (UTIs)
Urinary tract infections (UTIs) are among the most prevalent infectious diseases, with a substantial financial burden on society which affects millions of people across the globe each year. These infections accounts for about 8.3 million doctors visits each year (Burt et al., 2004). Urinary tract infection is one of the commonest bacterial infections encountered in daily clinical practice (Moges et al., 2014) and one of the important causes of morbidity and mortality in Indian population, affecting all age groups across the life span. UTI is the third most common cause of admission to hospitals in India with over 250 million annual diagnoses of Urinary Tract Infections (UTIs) worldwide; it remains one of the most common community-acquired as well as nosocomial infections (Ronald et al., 1991; Barisic et al., 2003; Gonzalez and Schaeffer, 1999). More over, the incidence of nosocomial UTI has been increasing and its treatment has become more complicated because of the pathogens with increasing resistance to antimicrobial agents (Shingemura et al., 2005).

2.2 Terminology regarding UTIs

2.2.1 Bacteriuria
It is defined as the multiplication of bacteria in urine within the renal tract and the presence of $1,00,000 \times 10^5$ per ml in the mid-stream sample of urine (Kass, 1957).

2.2.2 Significant bacteriuria
It has been used to describe the numbers of bacteria in voided urine that usually exceed the numbers caused by contamination from anterior urethra (i.e. $\geq 10^5$ bacteria / ml). A person is diagnosed with UTI, when significant bacteriuria is found, i.e., a concentration greater or equal to 100,000 ($10^5$) organisms per ml of urine. The implication is that in the presence of at least $10^5$ bacteria / ml of urine, infection must be considered seriously (Das et al., 2006, Stamn 1983).

Tambekar et al., 2006 tested 174 urine samples for isolation and identification. They found 68 samples to be significant bacteriuria with Escherichia coli (E.coli)(59%), followed by Pseudomonas aeruginosa (15%), Klebsiella pneumoniae (10%), Proteus mirabilis (9%), Staphylococcus aureus (6%) and Citrobacter freundii
The urinary tract infections were found to most frequently occur in females (63%) than males (37%).

### 2.2.3 Symptomatic bacteriuria
Symptomatic bacteriuria refers to significant bacteriuria in a patient with symptoms. Generally, infection of renal shows clinical symptoms like burning sensation during micturation, increased frequency of micturation etc (Leigh, 1990).

### 2.2.4 Asymptomatic bacteriuria
In some UTI cases the clinical symptoms may remain unnoticeable / suppressed even, even, to the patients, despite the presence of significant bacteriuria. Such symptomless infection of urinary tract is called covert or asymptomic bacteriuria.

Symptomatic and asymptomatic bacteriuria are almost equally distributed, ranging from 40% - 50% (Leigh, 1990).

### 2.2.5 Significant bacteriuria in catheterized patients
A count of \( \geq 10^3 \) CFU / ml is considered significant in patients receiving no antibiotics, while a lower count \( \geq 10^2 \) bacteriuria/ml is considered significant in patients receiving systemic antibiotics (Cheesbrowgh, 1984).

### 2.2.6 Pyuria
The presence of white blood corpuscles (WBCs) in the urine is known as pyuria. It indicates inflammatory response of the urothelium to invading bacteria. Presence of > 10 WBCs / HPF is considered significant. Cheesbrowgh, 1984 observed that it is suspected in a patient with chronic fever when there is pyuria but the routine culture is sterile.

### 2.3 Manifestation

#### 2.3.1 Uretheritis
Uretheritis is an infection of the urethra. Symptoms are dysuria (painful or difficult urination) and frequencies are similar to those associated with lower UTIs. Uretheritis is a common infection because of *Chlamydia trachomatis; Neisseria gonorrhoeae and Trichomonas vaginalis* which are considered to be sexually transmitted. Cheesbrowgh (1984) observed that Infection of the anterior urinary tract (urithritis) is mainy caused
by *N. gonorrhoeae* (espically in man). *M. Tuberculosis* is usually carried in the blood to kidney from another site of infection.

### 2.3.2 Cystitis

Cystitis is infection of the bladder. Patients with cystitis complain of dysuria, frequency, and urgency (compelling need to urinate). In some individuals, the urine is exceptionally bloody. Cystitis is caused by uropathogenic bacteria in the faecal flora that colonise the vaginal and periurethral openings, and ascend the urethra into the bladder (Sen, 2008).

David *et al.*, 2013 observed that the clinical entity is termed cystitis and represents bladder mucosal invasion most often by enteric *coliform* bacteria (e.g. *E.coli*) that inhibit the periurethral vaginal introitus and ascend into the bladder via the urethra.

In another study carried out by Gunther *et al.*, 2001; Sahm *et al.*, 2001; Haryniewicz *et al.*, 2001, *E. coli* was the primary cause of uncomplicated infections of the urinary tract including cystitis.

### 2.3.3 Pyelonephritis

Pyelonephritis refers to the inflammation of the kidneys parenchyma, calices (cup shaped division of the renal pelvis) and pelvis (upper end of the ureter that is located inside the kidney). It is most commonly caused when bacteria enter in the bladder ascend the ureters and invade the kidneys. The classical presentation of an upper urine tract infection includes fever and flank (lower back) pain and frequently, lower tract symptoms (frequency, urgency and dysuria). Cheesbrowgh, 1984 observed that the causative agent of *pyelonephritis* may be any of these that cause cystitis, but *staphylococcus aureus* is responsible for some of the cases. *Proteus* infections are also associated with renal stone. *S. saprophyticus* infections are usually found in sexually active young women.

#### 2.3.3.1 Acute pyelonephritis

It is a clinical syndrome characterized by flank pain, tenderness and fever. It is often associated with dysuria, urgency and frequency. However, these symptoms can also occur in the absence of infection (in case of in renal infarction or renal calculus).
2.3.3.2 Chronic pyelonephritis

This may rise from either infection or metabolic disorders. It refers to pathologic changes in the kidney caused by infection only. However identical pathologic alterations are found in several other entities, such as chronic urinary tract obstruction, analgesic nephropathy, hypokalemic nephropathy, vascular disease and uric acid nephropathy.

In chronic pyelonephritis, one or both kidneys contain gross scars, but even when involvement is bilateral, the kidneys are not equally damaged. This uneven scarring is useful in differentiating chronic pyelonephritis from diseases that cause symmetrical contracted kidneys e.g., chronic glomerulonephritis. In severe pyelonephritis, kidneys are somewhat enlarged and discrete, yellowish and, raised abscesses are apparent on the surface. The pathognomic histologic feature is suppurative necrosis or abscess formation within the renal substance.

2.3.4. Acute urethral syndrome

Acute urethral syndrome occurs primarily in young, sexually active women, who experience dysuria, frequency and urgency but yield fewer organisms than $10^5$ cfu/ml urine on culture. (The classic criteria of greater than $10^5$ colony-forming units of bacteria per milli liter [cfu / ml] of urine is highly indicative of infection in most patients with UTI). Almost 50% of all women who seek medical attention for complaints of symptoms of acute cystitis fall into this group.

2.3.5 Uncomplicated UTI

It refers to infection in a structurally and neurologically normal urinary tract. Uncomplicated infection occurs primarily in otherwise healty females and occasionally infant and adolescent and adult male. Blondeau et al., 2004 noted that the vast majority of uncomplicated UTIs are caused by the Gram negative bacillus E.coli with other pathogens including enterococci, Staphylococcus saprophytics, Klebsiella spp and Proteus mirabilis. Another study done by Acharya and Jadav, 1980 found that E.coli was the predominant urinary pathogen followed by Klebsiella, Pseudomonas aeruginosa and Proteus. Similiarly Susan and Kay, 2005 found E.coli as the leading cause of UTIs followed by Staphylococcus saprophyticus.
Lee and Neild, 2007 found *E.coli* as a key organism. Uncomplicated infection was caused by *E.coli*, Coagulase–positive *Staphylococcus, Enterococcus faecalis* and *Klebsiella spp*. The presence of other gram negative organism (*Pseudomonas spp.*, *Proteus sp.*) suggests pre–existing disease or a stone.

Steadman and Topley, 1998; Raksha *et al.*, 2003 found that *Escherichia coli* was the most frequent urinary tract pathogen isolated from 50 to 90% of all uncomplicated urinary tract infections as it was present in the gastrointestinal tract and provide a pool for initiation of UTI.

Another literature by Foxman, 1990 and Eva *et al.*, 1990 indicated that uncomplicated UTI in ambulatory patients was due to *E.coli, Staphylococcus aureus, Proteus spp., Klebsiella spp.* and *Pseudomonas areginosa*.

### 2.3.6 Complicated UTI

It refers to infection in a urinary tract with functional or structural abnormalities, including indwelling catheters and calculi. Complicated infections occur in both sexes. In general, infection in men, pregnant women, children, and patients who are hospitalized or in health care associated settings may be considered complicated. In a patient with complicated infection, infecting microorganisms are more likely to be resistant to antimicrobial agents.

Foxmen *et al.*, 2003 reported that the spectrum of bacteria causing complicated UTI is much broader than of those causing uncomplicated UTI. However, the most commonly encountered microorganisms are Gram negative bacteria including *E.coli, Citrobacter spp., Enterobacter aerogenes, Pseudomonas aeruginosa,* and *Proteus vulgaris* whereas *Klebsiella spp., Staphylococcus aureus,* and *Salmonella spp.* are found rarely.

Sefton, 2000 reported that in complicated urinary tract infections and hospitalized patients, organisms such as *Enterococcus faecalis* and highly resistant Gram-negative rods including *Pseudomonas* spp. are comparatively more common. The relative frequency of the pathogens varies depending upon age, sex, catheterization, and hospitalization.
2.3.7 Recurrences of urinary tract infection

UTIs could reoccur due to relapses or re-infections. Relapses involve the same infecting microorganism that was present before the start of therapy and could be attributed to the persistence of the organism in the urinary tract. Re-infections involve a different microorganism than the original infecting bacterium i.e., it is a new infection. Re-infection may occur with the same microorganism, which may have persisted in the vagina or feces and could be mistaken for a relapse (Hooton and Stamm, 1997). Dwyer et al., 2002 found that the patients may experience recurrent infection from rectal reservoir.

2.3.8 Urosepsis

The term is commonly used to describe the sepsis syndrome caused by urinary tract infection. It includes clinical evidence of urinary tract infection and two or more of the following symptoms:

1. Body Temperature- >38 °C or < 36º C
2. Heart rate -> 90beats/min
3. Respiratory rate- > 20/min or PaCO2 < 32 mm of Hg
4. White blood count- > 12,000/mm3 or < 4000 / mm3; or 10 % band forms.

2.3.9 Chronic Urinary Tract Infection

True chronic infection occurs due to persistence of the same organism for months or years with relapses after treatment. Re-infection does not mean chronicity any more than repeated episodes of pneumonia indicate chronic pneumonia.

2.4 Etiologic agents of UTIs

The UTI is can usually caused by bacteria and, rarely from virus, fungus. E.Coli is the most common urinary pathogen causing 60 - 90% infections. Cystitis is mainly caused by E.coli, some time by S.saprophyticus, and in hospital acquired infection by, Klebsiella species, proteus mirabilis, and Pseudomonas aeruginosa or Enterococcus faecalis. Candida infection may occure in diabetic and immunocompromised patients.

Cheesbrowgh in 1984 observed that the causative agent of phelonephritis may be any of these that cause cystitis and that Staphylococcus aureus is responsible for some of the cases. Proteus infections are also associated with renal stone. S. saprophyticus infections are usually found in sexually active young women. Infection of the anterior urinary tract (urithritis) is mainy caused by N. gonorrhoeae (especially
in men). *M. Tuberculosis* is usually carried in the blood to kidney from another site of infection. It is suspected in a patient with chronic fever when there is pyuria but the routine culture is sterile.

The etiological agents of UTIs acquired through community and hospitals are different. Only a limited amount of data has been published regarding changes in the frequency of causative agents among outpatients (Wilson & Gaido, 2004). According to an International survey of the antimicrobial susceptibility of pathogens from uncomplicated UTIs, *E. coli* accounts for 77.0% of isolates (Kahlmeter, 2003).

Quantitative bacteriological examination was carried out by Lystad and Gardborg, 1963, on 287 urine specimens from 74 girls and 44 boys with UTI. They found that quantitative method can be used to distinguish between infection and contamination. In another study Kuroda et al., 2005 reported that *Staphylococcus saprophytics, Staphylococcus aureus, S.epidermidis* adapt specifically to the urinary environment by exhibiting a notable ability for adherence and rapid growth in the urinary tract.

*E.coli* and *Klebsiella* groups were reported by Rayan et al., 1978. Another study done by Das, 2006 reported that *Enterobacteriaceae* group, namely, *E. coli* (59.4%), *Klebsiella* spp.(15.7%), *Enterococcus faecalis*(8.1%), and *Proteus mirabilis* (7.4%), were the most common pathogens isolated, followed by gram-positive cocci, namely- *Staphylococcus aureus*(3.4%) and *Staphylococcus saprophyticus*(1.4%).

Vinita et al., 2010 reported that *E.coli* was the most common uropathogen (57.76%) isolated and 94.29% of *E.coli* showed resistance to ampicillin, 92% to amoxycillin- salbactam, 70.86% to gentamicin, 65.71% to amikacin, 89.71% to cefuroxime, 72.57% to cefotaxime,76% to cefixime, 90.28% to ciprofloxacin, 61.14% to chlormphenicol, 42.86% to nitrofurantoin, 28% to piperacillin-tazobactam and 8.57% to imipenem.

Devanand Prkash et al., 2013 concluded that the UTI prevalence was 53.82% in patients; however, the prevalence was significantly higher in females than in males (females: 73.57%; males: 35.14%; \(P = 0.000\)). Females within the age group of 26–36 years and elderly males of ≥48 years showed higher prevalence of UTI. Gram negative bacteria (90.32%) were found in high prevalence than Gram positive (9.68%). *Escherichia coli* (42.58%) was the most prevalent gram negative isolate. Nitrofurantoin (78.71%) was the most resistant drug among all uropathogens. Tested
carbapenems were found the most susceptible drug against isolated uropathogens which showed 92.26% and 84.52% susceptibility, respectively.

Susan and Kay, 2005 found *E.coli* as the leading cause of UTI followed by *Staphylococcus saprophyticus*. The prior literature specifically Acharya and Jadav, 1980 reported that *E.coli* was leading causative agent amongst *Klebsiella, Pseudomonas aeruginosa* and *Proteus* sp. while Ronald et al. 1978 observed that the *E.coli* and *Klebsiella* were the leading organisms.

Naber, 2001 reported that the bacterial spectrum consisted of about one-third of *E.coli*, one quarter each of enterobacteria and entrococci, one seventh *Staphylococcus* and *P.aeruginosa*. Al-Ali *et al.*, 2005 concluded that the *E.coli* was the most common organism infecting the urinary tract, others include *Klebsiella spp, Enterobacter spp, Pseudomonas aeruginosa* and other *Enterococci, Staphylococcus saprophytics, Staphylococcus aureus, Staphylococcus epidermidis, Acienetobacter spp., B-hemolytic streptococci* group B and D, *Candida albicans, Salmonella spp.*, and *Mycobacteria*.

### 2.4.1 Community-Acquired

*E.coli* was by far the most frequent cause of un-complicated community-acquired UTIs. Other bacteria frequently isolated from patients with UTIs are *Kebsiella spp.*, other *Enterocobacteriaceae*, and *Staphylococcus saprophyticus*. In more complicated UTIs, particularly in recurrent infections, the relative frequency of infection caused by *Proteus, Pseudomonas, Klebsiella*, and *Enterobacter spp* increases.

Ronald, 2002 observed that *Escherichia coli* was the predominant uropathogen isolated in acute community-acquired uncomplicated infections, followed by *Staphylococcus saprophyticus Klebsiella spp.*, *Enterobacter spp.*, and *Proteus* spp., and *enterococci* infrequently cause uncomplicated cystitis and pyelonephritis.

Sefton, 2000 reported that many different microorganisms can cause UTIs though the most common pathogens causing the simple ones in the community are *Escherichia coli* and other *Enterobacteriaceae*, which accounts for approximately 75% of the isolates.
2.4.2 Hospital – Acquired

A hospital environment plays an important role in determining the organisms involved in UTIs. Hospitalized patients are most likely to be infected by *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, *Staphylococci*, other *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Enterocci*. The introduction of a foreign body into the urinary tract, especially one that remains in place for a time (e.g., Foley catheter), carries a substantial risk of infection, particularly if obstruction is present. As many as 20% of all hospitalized patients who receive short-term catheterization develop a UTI. In the community and hospital settings the aetiology of UTIs and the antimicrobial susceptibility of urinary pathogens have been changing over the years (Gales *et al.*, 2000).

Many different organisms can infect the urinary tract, but by far the most common are the gram-negative bacilli (Braunwald *et al.*, 2001; Wilson and Gaido, 2004).

According to an International survey of the antimicrobial susceptibility of pathogens from uncomplicated UTIs, *E. coli* accounts for 77.0% of isolates (Kahlmeter, 2003). However, there is some evidence that the percentage of UTIs caused by *E. coli* is decreasing, being replaced by other members of the *Enterobacteriaceae* (Haryniewicz *et al.*, 2001; Weber *et al.*, 1997).

On the other hand, another literature by Braunwald *et al.* in 2001 indicated that other gram-negative rods, especially *Proteus* and *Klebsiella* and occasionally *Enterobacter*, account for a smaller proportion of uncomplicated infections. These organisms, plus *Serratia* and *Pseudomonas*, assume increasing importance in recurrent infections, associated with urologic manipulation, calculi, or obstruction. Gram-positive cocci were isolated more frequently from a hospital setting and the most common were *Enterococcus species* (Wilson and Gaido, 2004; Haryniewicz *et al.*, 2001). *Staphylococcus saprophyticus*-novobiocin-resistant, coagulase-negative species accounts for 10 to 15% of acute symptomatic UTIs in young females. More commonly, *Enterococci* and *Staphylococcus aureus* cause infections in patients with renal stones or previous instrumentation or surgery. Isolation of *S. aureus* from the urine should arouse suspicion of bacteremic infection of the kidney (Braunwald *et al.*, 2001). Table 2.1 shows the percentage distribution of etiologic agents of UTIs among
outpatients and inpatients by bacterial pathogens (Adapted from Wilson and Gaido, 2004).

E. coli, K. pneumoniae, C. freundii, Proteus, Pseudomonas, Serratia, Coagulasenegative staphylococcus, and Enterococcus faecium are species implicated in catheter-associated urinary tract infection (Johnson, et al., 1999; Braunwald et al., 2001). However, the types of organisms associated with catheter associated urinary tract infection (CAUTI) have changed over the last 5 years in a UK institution (Wazait et al., 2003). A study done by Teshager Ayalew (2005) in South Ethiopia reported that E. coli was the most frequently isolated pathogen in all years, but its frequency declined over time (35.6 %, 32.5 % and 26.6 %, respectively) and Enterococcus was the second most frequent overall, with a significant increase in frequency with time (11.8 %, 15.3 % and 22.0 %, respectively).

**Table 2.1. Percentage distribution of etiologic agents of UTIs among outpatients and inpatients by bacterial pathogens (Source: Wilson and Gaido, 2004).**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Out patients percentage with pathogens</th>
<th>In patients percentage with pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>53-72</td>
<td>17.5-56.7</td>
</tr>
<tr>
<td>Coagulase negative staphylococci</td>
<td>2-7.5</td>
<td>2.1-12.5</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>6-12</td>
<td>6.2-15.0</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>4-6</td>
<td>3.8-8.2</td>
</tr>
<tr>
<td>Enterocococcus spp.</td>
<td>0.6-5.8</td>
<td>0.9-6.5</td>
</tr>
<tr>
<td>Morganalla morgani</td>
<td>3.1-4.4</td>
<td>4.7-6</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>0.1</td>
<td>0.2-3</td>
</tr>
<tr>
<td>Enterocococcus spp.</td>
<td>1.7-12</td>
<td>6.5-15.8</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
<td>1.6-3.5</td>
</tr>
<tr>
<td>Staphylococcus saporophyticus</td>
<td>0.2-2</td>
<td>0.4</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>0.1-4</td>
<td>1.3-11</td>
</tr>
</tbody>
</table>

**2.5 Pathogenicity of UTI**

UTI occurs as a result of the interaction between bacterial virulence and host biological and behavioral factors, as opposed to highly efficient host defense mechanisms. There are three possible routes whereby bacteria can invade and spread within the urinary tract ascending, haematogenous and lymphatic pathways (Bailey and Scott, 2002).
2.5.1 Ascending route
Most bacteria originating from the bowel reservoir infects the perineal area and ascends through the urethra to the upper urinary tract. Such infections are called infections by ascending route. For UTI to occur by the ascending route, enteric gram-negative bacteria and other microorganisms that originate in the gastrointestinal tract must be able to colonize the periuretheal area. Once these organisms gain an access to the bladder, they may multiply and then pass up to the ureters and kidneys. Although the ascending route is the most common route of infection in females, ascent in association with instrument (e.g. urinary catheterization, cystoscopy) is the most common cause of hospital acquired UTI in both sexes (Bailey and Scott, 2002). The fact that UTI is much more common in women than in men gives support to the importance of the ascending route of infection.

2.5.2 Haematogenous route
This kind of infection is uncommon. Infection of the renal parenchyma by bloodborne organisms rarely occurs in humans. The kidney is frequently the site of abscesses in patients with Staphylococcus aureus bacteremia or endocarditis or both (Bailey and Scott, 2002).

2.5.3 Lymphatic route
This is another rare mode of infections of the urinary tract. In necrotizing enterocolitis or retroperitoneal abscesses bacteria directly extend to the urinary tract via the lymphatics (Bailey and Scott, 2002).

2.6 Clinical feature
According to Schilling et al., 2001 Urinary tract infections have traditionally been viewed as acute and often self limiting infections. However, this concept has been challenged by recent findings demonstrating that an acute bladder infection results from a complex series of host pathogen interactions. Such interactions that can cause to bacterial invasion, persistence and that ultimately can determine the course of the infectious disease.

Gunther et al., 2001 said that, UTIs can be classified as asymptomatic bacteriuria, cystitis, or acute pyelonephritides. Cystitis predominantly involves colonization of the bladder. The urine often becomes grossly cloudy and malodorous, and it is bloody in about 30% of cases. White blood cells and bacteria can be detected
by examination of unspun urine in most cases. However, some women with cystitis have only $10^2$ to $10^4$ bacteria per milliliter of urine, and in these instances bacteria cannot be seen in a Gram stained preparation.

Braunwald et al., 2001 reported that physical examination generally reveals only tenderness of the suprapubic area. According to Gunther et al., 2001 the more severe upper urinary tract disease acute pyelonephrities involves colonization of the kidneys and represents an infection capable of progressing to bacteremia. Symptoms of acute pyelonephrities generally develop rapidly over a few hours or a day and include fever, chills, nausea, vomiting, and diarrhea. Symptoms of cystitis may or may not be present. Besides fever, tachycardia, and generalized muscle tenderness, physical examination reveals marked tenderness on deep pressure in one or both costovertebral angels or no deep abdominal palpation (Warren, 1997).

In some patient, signs and symptoms of gram-negative sepsis predominate. Most patients have significant leukocytosis and bacteria detectable in Gram-stained unspun urine. Leukocyte casts are present in the urine of some patients, and the detection of these casts is pathogenomonic. Hematuria may be demonstrated during the acute phase of the disease; if it persists after acute manifestations of infection have subsided, a stone, a tumor, or tuberculosis should be considered (Braunwald et al., 2001).

Most catheter-associated bacteriurias are asymptomatic (Warren, 1997). Two studies of hospitalized patients with catheter related UTI found that the majority were asymptomatic; and that patients with and without UTI did not differ in signs and symptoms of fever, dysuria, urgency, and flank pain. Importantly, patients’ reports of UTI symptoms, fever, and elevated plasma white blood cell count did not predict catheter-associated UTI (Madigan and Neff, 2003). The complications in short-term catheterized patients include fever, acute pyelonephritis, bacteremia and death; patients with long term catheters in place are at risk for these complications and catheter obstruction, urinary tract stones, local periuinary infections, chronic renal inflammation, chronic pyelonephritis, and over years, bladder cancer (Warren, 1997).

Although the symptoms are similar for children and adults, they are harder to observe in children. A child may have a fever and chills, experience nausea and vomiting, complain of pain in the abdomen, back, or pelvis, or while urinating. The child may also become irritable and lose appetite (Brain et al., 2000).
2.7. Host Factors

The occurrence of UTI depends on various demographic, genetic, social as well as some anatomic and metabolic factors. It also depends on age, sex, race and predisposing factors (Anderson et al., 2004).

2.7.1. Demographic Factors:

Age: UTI affect all age groups and sex worldwide (Miranda et al., 2010). Wald, 2004 stated that UTI was a common problem in children, Shrestha et al. 2005; Eelder, 2007 additionally reported that the prevalence varies with the age and sex of children and that UTI occurs in about one percent of boys and three to five percent of girls.

UTIs are first experienced in the neonatal stage and are frequently observed in the adult stage. Approximately 5% of girls and 1% of boys have a UTI by 11 years of age, while, 0.01 - 1% of neonate have a UTI, the percentage can be as high as 10% in low birth weight and preterm babies (Van Howes, 2005, Gupta et al., 1999; Guidoni et al., 2008). Another peak of UTIs is seen in old age probably beacue of prostate enlargement and other related problems of old age (Susan, 2005).

Goldman et al., 1996 reported that in the majority of males UTI occurred during the first month of life. The peak occurrence was in the initial 13 days. Urine culture revealed \textit{E.coli}, \textit{Klebsiella} and other bacteria (\textit{proteus, staphylococcus aureus} and \textit{pseudomonas aeruginosa}). \textit{E.coli} predominates in female than male. Bonacorsi et al., 2006 found \textit{E.coli} as the leading cause of bacterial UTI in male infants with and without bacteremia. Hellerstein et al., 2007 stated that \textit{E.coli} was the dominant gram negative species in young girls, whereas \textit{E.coli} and \textit{Proteus species} predominante in boys.

A study done by Neelam et al., 2010 concluded that \textit{Escherichia coli} was the most frequent bacteria to cause UTIs in infants and children, Other organisms causing UTI were \textit{Klebsiella, Enterobacter, Enterococci, Staphylococcus, Proteus, Pseudomonas aeruginosa} and \textit{Group B streptococcus}.

Sex: Females are more prone to UTIs due to anatomical and physiological reasons; by virtue of its position urinogenital tract in females is more vulnerable to bacterial infections caused by both internal and external flora (Maripandi et al., 2010). Pastore, 1999 observed that women are more prone to develop UTIs.
Gebre, 1998 also found that about 20% of women experience a single episode of UTI during their lifetime, while approximately 3% of women have more than one episode of UTI per year. Pregnancy also makes them more susceptible to infection. Application of contraceptive (spermicidal gels and drugs) is other factors that alter the vaginal pH and affect the number of commensal lactobacilli which predispose to colonization of bacteria in vagina and further migration towards urethra. UTIs in man are relatively uncommon but can be very serious when it occurs (Hooton, 2001). UTIs predominate in neonate males due to higher incidences of obstructive anomalies of urinary tract in than in girls (Foxman, 2003, Gales et al., 2002). While UTIs are rarely seen in boys and young men, in women the rate of UTIs gradually increases with age (Wadhwa, 2002). Schaeffer et al., 2001 observed that Urinary tract infection was frequently caused in female (63%) than male (37%).

2.7.2. Genetic Factors: P-blood group antigens which are present on uroepithelial cells act as receptors for E. coli adherions. In persons having secretor status, ABO blood group antigens are secreted in body fluids and they cover the receptors for E. coli (adhesions). Naturally UTIs are uncommon in such patients. However in persons having no secretor status, the receptors for E. coli adhesins are uncovered and exposed for attachment of bacteria which leads to frequent UTI.

2.7.3. Social Factor: Mastrubation habits predispose the patients for repeated UTIs. Herzog L., 1989 showed that circumcision reduces the risk of UTIs. Malnutrition, poor hygiene, low socioeconomic statuses are associated with UTIs and these factors are rife in rural settings (Bankole et al., 2011).

2.7.4. Anatomic Factors: Some people are more prone to getting a UTI than others. Any abnormality of the urinary tract that obstructs the flow of urine (e.g., a kidney stone) sets the stage for an infection (Wadhwa, 2000). Pregnancy is the most important anatomic as well as physiological predisposing factor of UTI. About 4 - 7% of pregnant female suffer from UTIs during their antenatal period and about 25 - 30% of them progress towards acute pyelonephritis. The important cause for their predisposition is dilatation of pelvis and ureters, obstruction to flow of urine from the bladder and hormonal changes. Stagnations of urine in the upper urinary tract (due to ureteric strictures and calculi) or in the lower urinary tract (due to vesical calculi),
leads to enlargement of prostrate or urethral structure, favours microbial growth along with inflammation.

Anatomic abnormalities like vesicorectal and vesicovaginal fistulae, trauma to urinary tract (accidental or surgical) predispose the patient to UTIs. Such patients are hospitalized and remain catheterised for a prolonged period which leads to colonization of hospital strains resulting into UTIs. UTIs may also occur in infant who are born with abnormalities of the urinary tract, which sometimes need to be corrected through surgery (Wadhwa, 2000).

2.7.5. Metabolic Factor: People with diabetes are also at risk because of changes in the immune system. Any disorder that suppresses the immune system raises the risk of urinary infection (Wadhwa, 2000). In diabetic patients, there is increased prevalence of perineal colonization by potential pathogens. Presence of glucose in urine increases frequency and severity of infection in diabetes. Additionally, a higher glucose concentration in the urine may create a culture medium for pathogenic microorganisms (Edward et al., 2005).

2.8 Host Defence Mechanism

With the exception of urethral mucosa, the normal urinary tract is resistant to colonization by bacteria and for the most part, efficiently and rapidly eliminates pathogenic and non pathogenic microorganisms that gain access to the bladder. This is achieved by the presence of several lower urinary tract antibacterial defense mechanisms. Table 2.3 shows the antibacterial host defences in the Urinary Tract. Following factors help in host defence mechanism.

**Urinary Factors**

1. Urinary pH and osmolarity levels.

2. Secretary IgA

3. Secretion of blood group antigens

4. Substances like Tamm Harsfall protein

**Physiological Factors**

1. Normal bladder emptying
2. Ureteric peristalsis

**Anatomical Factors**

1. Normal urinary tract allows free and complete urinary drainage

**Sexual Factors:**

1. Longer length of urethra in males prevents easy infection.

**Immunological and Cellular Factors**

1. Local antibody response
2. Systemic antibody response
3. Local inflammatory reaction
4. Shedding of urothelial cells which are attached with bacteria.
5. Complement mediated bacterial lysis

**Cidal Effect of Serum**

**Social Factors:** Circumcision / Mastrubation

**Table 2.2 Antibacterial host defences in the Urinary Tract**

| 1. Urine (Osmolarity, pH, Organic acids) |
| 2. Urine flow and micturition |
| 3. Urinary tract mucosa (antibacterial activity, peptides cytokines) |
| 4. Urinary Inhibitors of bacterial adherence |
| a) Tamm-Horsfall protein |
| b) Bladder mucopolysaccharide |
| c) Low molecular weight oligosaccharides |
| d) Secretary immunoglobulin (SIgA) |
| e) Lactoferrin |
| 5. Inflammatory Response |
| a) Polymorphnuclear neutrophils (PMNs) |
| b) Cytokines |
| 6. Immune System |
| a) Humoral immunity |
| b) Cell mediated immunity |
| 7. Miscellaneous |
2.9 Pathogenesis of UTIs

UTIs are the results of the interaction between the uropathogens and the host. Infection is determined in part by the virulence factors of the bacteria, the inoculum size and the inadequacy of host defense mechanisms. Pathogenesis of a UTI starts when uropathogenic bacteria colonize site outside urinary tract (large intestine, perineal area, and vagina). These bacteria spread up the urinary tract to the bladder. They attach to the mucosa and colonize the bladder overcoming the host defense mechanisms like urine flow. They establish a population of \( >10^5 \) bacteria / ml. The established bacteria produce hemolysins which lyse the cells of urinary tract and invade the superficial cells forming intracellular bacterial communities (IBCs). Further they produce capsular polysaccharide that contributes to biofilm formation. These events give edge to bacteria against immune defense mechanisms and antibiotics and they can ascend up the urinary tract. The virulence factors present in them not only localise the site of infection but also stimulates inflammatory response.

2.10 Methods for localization of infection of the UTI

Clinical features: Suggestive of pyelonephritis, cystitis, urethritis, perinephric abscess (Pommerville, 2004).

Urine analysis: Presence of cast suggests pyelonephritis and presence of bits of tissue indicates renal papillary necrosis (Edmondson et al., 1947).

Culture: Urethral catheterization and bladder washout methods to distinguish lower from upper urinary tract infection (Pappas, 1991).

Serology: Four fold rise or high antibody titers (against ‘O’ or common bacterial antigen) indicates renal involvement (Thomas et al., 1974).

Antibody coated bacteria: Its presence indicates invasion of kidney (Thomas et al., 1974).

Functional: In renal involvement, ability to concentrate urine is affected (Risdon et al., 1968)

2.11 Laboratory diagnosis of UTIs

2.11.1 Collection of urine

Midstream clean caught urine method was described by Norden and Kass in 1968. It is a reliable method, where midstream urine is collected with all aspetic precautions in a sterile container.
Suprapubis aspiration method is the most reliable method of urine collection in infants. Urine is aspirated with a needle and syringes from the site 2 cms above symphysis in midline all aseptic precautions.

2.11.2 Transport of urine

Collected urine sample should be transported to laboratories as soon as possible. In case of delays, samples can be refrigerated at 4°C or 1.8% boric acid can be added to them. This prevents the multiplication of bacteria.

2.11.3 Urine examination

2.11.3.1 Macroscopic examination

Appearance of cloudy or turbid urine: This is seen in the presence of bacteria, proteins, crystals or leucocytes. Cloudiness may also develop if urine is left to stand, due to precipitation of urates (acids) or phosphates and carbonates (alkaline). Roy et al., 1974 showed that proteinuria was associated more often with bacteriuric urine.

2.11.3.2 Microscopic examination

Urine is examined microscopically as a wet preparation to detect presence of the following.

Significant pyuria: (WBCs > 10 cells/hpf). Pyuria may be masked in alkaline pH of urine due to lysis of WBCs. Pyuria may also be absent, when UTI occurs in diabetic patients and in patients with bacterial endocarditis. Pyuria with sterile culture may be found in renal tuberculosis, leptospirosis, urethritis due to gonococcal and Chlamydia trachomatis or when the patient has taken treatment (Rello, 2012).

RBCs: Normally not more than 2 or 3 RBCs/hpf should be present. Haematuria is found in Schistosomiasis, bacterial infections, Leptospirosis, glomerulonephritis, stones and malignancy (Reynard et al., 2013).

Casts: Casts include hyaline cast, waxy cast, cellular cast (WBCs, RBCs), Granular casts. They are cylindrical made up of proteins. Presence of one cast in the enteric field at low power is considered as abnormal (Chew, 2010).

Crystals: These are retractile formed from different chemicals. They are screened in fresh urine when renal stones are suspected (Whipple, 1895).

Bacteria: They are seen as tiny rods or cocci. Gram staining of the urine sample is done when bacteria and or white cells are seen in wet preparation. Presence of >5 bacteria/oil immersion field is considered as a positive test (Kass, 1957).
Microscopy of urine from symptomatic patients can be of great diagnostic value (Cheesbrough, 2000; Wilson and Gaido, 2004; Braunwald et al., 2001). Bacteruria can be detected microscopically using Gram staining of uncentrifuged or centrifuged urine specimens, or direct observation of bacteria in urine specimen. Gram stain of uncentrifuged urine specimens is a simple method (Wilson and Gaido, 2004). Detecting bacteria in uncentrifuged (fresh) urine indicates urinary infection i.e., bacteruria in excess of $10^4$ / ml (Cheesbrough, 2000). However, bacteria can not usually be detected microscopically in infections with lower colony count ($10^2$ to $10^3$). The detection of bacteria by urinary microscopy thus constitutes firm evidence of infection, but the absence does not exclude the diagnosis (Braunwald et al., 2001).

### 2.11.3.3 Screening for bacteriuria

According to a physician Bell et al., 1998, the diagnosis of UTIs begins with the screening of patients with symptoms suggestive of UTIs. Braunwald et al., 2001 suggested that determination of the number and types of bacteria in the urine is an extremely important diagnostic procedure. Thus, only patients who had pyuria and significant bacteruria obtained from appropriate urine samples (a clean-catch midstream and catheter samples of urine) are included in the microbiological analysis (Wazait et al., 2003; Haryniewicz et al., 2001).

Bacteriuria refers to urine that contains $10^5$ organisms or more per ml ($10^8$/l) in pure culture (Cheebsrough, 2001). This is true usually in symptomatic patients. In asymptomatic patients, two consecutive urine specimens should be examined bacteriologically before therapy is instituted, and $\geq 10^5$ bacteria of a single specimen per milliliter should be demonstrable in both specimens (Braunwald et al., 2001).

Since the large number of bacteria in the bladder urine is due in part to bacterial multiplication during residence in the bladder cavity, samples of urine from the ureters, or renal pelvis may contain $< 10^5$ bacteria per milliliter and yet indicate infection. Similarly, the presence of bacteruria of any degree in suprapubic aspirates or of $> 10^2$ bacteria per milliliter of urine obtained by catheterization usually indicates infection (Cheesbrough, 2001; Braunwald et al., 2001).

Routine urine culture should be plated using calibrated loops for the semi quantitative method. This method has the advantage of providing information regarding the number of CFU / ml, as well as providing isolated colonies for identification and susceptibility testing (Wilson and Gaido, 2004).
The types of media used for routine cultures should be limited to blood agar and MacConkey agar (Wilson and Gaido, 2004; Manges et al., 2001). For urine specimens obtained from outpatients, it is not necessary to routinely inoculate a medium that is selective for gram-positive bacteria (Wilson and Gaido, 2004; Haryniewicz et al., 2001).

In contrast, urine specimen obtained from hospitalized patients are likely to contain Enterococcus, which have emerged as the second most common cause of nosocomial infections (Haryniewicz et al., 2001; Kawalec et al., 2000). Laboratories may want to consider inoculating urine specimens obtained from hospitalized patients, or from patients in whom gram-positive bacterial infection is suspected but not documented, to a medium that is selective for gram-positive cocci. A medium such as phenyl-ethyl alcohol agar suppresses the growth of swarming proteus spp and other gram negative bacilli that can overgrow gram positive cocci in the specimen. Furthermore, Cystine lactose electrolyte-deficient (C.L.E.D) agar is now used by most laboratories to isolate urinary pathogens because it gives consistent results and allows the growth of both Gram-negative and Gram-positive pathogens. The indicator in C.L.E.D. agar is bromothymol blue and therefore lactose-fermenting colonies appear yellow. The medium is electrolyte-deficient to prevent the swarming phenomenon of Proteus species (Cheesbrough, 2001). Urine culture should be incubated overnight at 35°C - 37°C in ambient air before being read (Wilson and Gaido, 2004).

Rapid methods of detection of bacteruria have been developed as alternatives to standard culture methods. These methods detect bacterial growth by photometry, bioluminescence, or other means and provide results rapidly, usually in 1 to 2 hour. Compared with urine cultures, these techniques generally exhibit a sensitivity of 95 to 98% and a negative predictive value of > 99% when bacteruria is defined as 10^5 colony-forming units per milliliter is the standard of comparison (Braunwald et al., 2001).

Bacteriuria can be detected chemically when bacteria produce nitrite from nitrate. The biochemical reaction that is detected by the nitrite test is associated with members of the family Enterobacteriaceae (Wilson and Gaido, 2004). Urinary pathogens, e.g. E. coli, Proteus, and Klebsiella species, are able to reduce the nitrite normally present in urine in sufficient concentration. When first morning urine is tested, about 80 to 90% of UTIs caused by nitrate reducing pathogens can be detected. The test is negative when the infection is caused by pathogens that do not reduce
nitrate such as *Enterococcus faecalis*, *Pseudomonas*, and *Staphylococcus* species or when as previously mentioned the bacteria are too few in the urine (Cheesbrough, 2001).

Another limitation of the test is that it requires testing a specimen of the first urine produced in the morning, as > 4 hour is required for bacteria to convert nitrate to nitrite at levels that are reliably detectable (Wilson and Gaido, 2004). Occasionally the nitrite test is negative because nitrate is lacking in the urine due to person being on diet lacking vegetables (Cheesbrough, 2001). When carefully sought by means of chamber-count microscopy, pyuria is a highly sensitive indicator of UTI in symptomatic patients. Pyuria is demonstrated in nearly all acute bacterial UTIs, and its absence calls the diagnosis into question (Braunwald *et al.*, 2001).

The advantages to urine microscopy are that leukocytes, leukocyte casts, and other cellular elements are observed directly. One disadvantage to urine microscopy is that leukocytes deteriorate quickly in urine that is not fresh or that has not been adequately preserved. In addition, each of these methods has disadvantages that limit their utility as routine tests (Carroll *et al.*, 2011). Because of these disadvantages, urine microscopy should be limited to patients in whom pyelonephrities or other more serious infections are suspected.

Leukocyte esterase tests are based on the hydrolysis of ester substrates by proteins with esteriolytic activity. These proteins react with ester substrates to produce alcohols and acids that then react with other chemicals to produce a color change that is proportional to the amount of esterase in the specimen (Wilson and Gaido, 2004). The leukocyte esterase method is less sensitive than microscopy in identifying pyuria but is useful alternative where microscopy is not feasible (Braunwald *et al.*, 2001). Leukocyte esterase can be detected using a reagent strip test such as the BM-Test-LN, that detects with nitrite and leucocytes (LE) or a multi-test reagent strip with an area for leucocytes detection (Cheesbrough, 2001).

Leukocyte esterase tests can yield false-positive test results when the urine is contaminated with bacteria present in vaginal fluid; when the specimen contains eosinophils or *Trichomonas species*, both of which can act as sources of esterase; and when oxidizing agents or formalin react with the test strips to generate false-positive test results. Leukocyte esterase tests may show a decrease in positive test results when the specimen has an elevated specific gravity and/or elevated levels of protein and glucose; when boric acid preservatives are present; when large amounts of ascorbic or
oxalic acid are present; and when the patient has received antimicrobial agents, such as cephalothin, cephalexin, or tetracycline (Wilson and Gaido, 2004).

Although many authorities have recommended that urine culture and antimicrobial susceptibility testing be performed for any patient with a suspected UTI, it may be more practical and cost effective to manage women who have symptoms characteristic of acute uncomplicated cystitis without an initial culture. A positive result for pyuria and/or bacteruria provides enough evidence of infection to indicate that urine culture and susceptibility testing can be omitted and the patient treated empirically. However urine should be cultured, when a woman’s symptoms and urine examination findings leave the diagnosis of cystitis in question. Pre-therapy culture and susceptibility testing are also essential in the management of all patients with suspected upper tract infections and of those with complicating factors, as in these situations any of a variety of pathogens may be involved and antibiotic therapy is best tailored to the individual organisms (Braunwald et al., 2001). Susceptibility testing is also essential in the management of patients with a history of recurring UTI (Cheesbrough, 2001).

Thus, each laboratory should have guidelines by which pathogens are tested for antimicrobial susceptibility. These guidelines should be developed and antimicrobial susceptibility tests should be performed and reported according to the most recent version of the CCLS guidelines (CCLS, 2001).

2.12 Treatment

Antimicrobial therapy is seldom indicated for asymptomatic infection, but usually indicated for amelioration of symptoms (Nicolle, 2003). Except in acute uncomplicated cystitis in women, a quantitative urine culture, a gram stain, or an alternative rapid diagnostic test should be performed to confirm infection before commencing treatment. When culture results become available, antimicrobial sensitivity testing should be used to direct therapy (Braunwald et al., 2001).

Traditionally management of uncomplicated UTIs is based on two important principles: a) the spectrum of organisms causing acute UTI is highly predictable (E. coli accounts for 75% to 90% and Staphylococcus saprophyticus accounts for 5% to 15% isolates), and b) the susceptibility patterns of these organisms have also been relatively predictable. As a result, empiric therapy with short-course TMP-SMX has been a standard management approach for uncomplicated cystitis or TMP alone for
patients with sulfa allergies (Nicolle, 2003). However, antibiotic resistance is now becoming a major factor not only in nosocomial UTIs, but also in uncomplicated community-acquired UTIs (Gupta, 2002).

Another study reported that ciprofloxacin, ofloxacin, and TMP-SMX have similar efficacy when given for 3 days to treat acute symptomatic, uncomplicated lower urinary tract infection in women (MacCarty, 1999). In fact, guidelines recommended TMP-SMX for empirical treatment of uncomplicated UTI unless TMP-SMX resistance in a community exceeds 10% to 20%. The rationale for this 10% to 20% cutoff appears to be related to clinical and economical considerations and to concerns about the emergence of fluoroquinolone-resistant bacteria. In patients with uncomplicated UTIs caused by uropathogens resistant to TMP-SMX who were treated with this drug combination, clinical outcomes were studied recently and found to be suboptimal (< 60% clinical cure) (Miller and Tang, 2004; Perfetto et al., 2004).

On the other hand, the emergence and dissemination of antimicrobial resistance can be reduced with the use of agents that have favorable pharmacokinetic/pharmacodynamic profiles and convenient dose (Blondeau, 2004). Fluoroquinolone antimicrobial agents have taken on an expanding management role for UTIs. In fact, the recent Infectious Diseases Society of America clinical management guidelines for UTI recommend fluoroquinolones as first-line therapy for uncomplicated UTI in areas where resistance is likely to be of concern. Fluoroquinolones have demonstrated high bacteriologic and clinical cure rates, as well as low rates of resistance, among the most common uropathogens (Schaeffer, 2002). They are indicated for the management of acute uncomplicated UTIs, as well as complicated and severe UTI and pyelonephritis, in adults. Use of fluoroquinolones is recommended for uncomplicated UTIs in areas where the incidence of cotrimoxazole resistance exceeds 10%, and in patients who cannot tolerate sulfonamides or TMP, (Blondeau, 2004; Schaeffer, 2002).

There are currently seven fluoroquinolones with indications for UTI in the United States. However, only three are commonly used: levofloxacin, ciprofloxacin, and to a lesser extent, gatifloxacin (Schaeffer, 2002). Ciprofloxacin is a widely used fluoroquinolone with high bacterial activity against uropathogens and well-established clinical efficacy in the treatment of UTIs (Blondeau, 2004). Many of the fluoroquinolone agents have once-daily dosing regimens, enhancing patient’s adherence. In addition, levofloxacin and gatifloxacin have same-dose bioequvalency
between their intravenous and oral formulations, allowing for “switch” or step-down therapy from parenteral to oral formulations of the same agent at the same dose. Fluoroquinolone properties include a broad spectrum of coverage, low rates of resistance, and good safety profiles (Schaeffer, 2002).

A new, extended-release formulation of ciprofloxacin provides systemic drug exposure comparable with that achieved with twice-daily administration of conventional, immediate-release ciprofloxacin, while also attaining higher maximum plasma concentrations with less interpatient variability. Therapeutic drug concentrations with extended-release ciprofloxacin are established immediately after dose administration and maintained throughout the 24-hour dosage interval, permitting convenient, once-daily treatment. Clinical trial results confirm that extended-release ciprofloxacin is as safely used and effective as the conventional, immediate-release formulation of ciprofloxacin in patients with uncomplicated UTIs, complicated UTIs or acute uncomplicated pyelonephritis. These findings support the use of extended-release ciprofloxacin as a well tolerated, effective and convenient therapy for UTIs, which may improve patient’s adherence to therapy and, thereby, reduce the risk of infection recurrence and emergence of antimicrobial resistance (Blondeau, 2004).

Alternative first line agents include nitrofurantion, and fosfomycin (McCarty et al., 1999). Nitrofurantoin was the first truly effective and safe antimicrobial therapy for UTI but its spectrum of activity is limited (Nickel, 2005). On the other hand, Hooton (2003) indicated that use of nitrofurantoin does not share cross-resistance with more commonly prescribed antimicrobials and its more widespread use is justified from a public health perspective as a fluoroquinolone-sparing agent. Beta-lactams and fosfomycin should be considered second-line agents for empirical treatment of cystitis.

Complicating UTIs (those arising in a setting of catheterization, instrumentation, urologic anatomic or functional abnormalities, stones, obstruction, immunosuppression, renal disease, or diabetes) are typically due to hospital-acquired bacteria, including *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Pseudomonas*, *Enterococci*, and *Staphylococci*. Many of the infecting strains are antibiotic resistant. Empirical antibiotic therapy ideally provides broadspectrum coverage against these pathogens. In patients with minimal or mild symptoms, oral therapy with more sever illness, including acute pyelonephritis or suspected urosepsis, hospitalization and parental
therapy should be undertaken. Commonly used empirical regimens include imipenem alone, penicillin or cephalosporin plus an aminoglycoside, and (when the involvement of *Enterococci* is unlikely) ceftriaxone or ceftazidime (Braunwald *et al.*, 2001).

Specifically, for the empirical management of CAUTIs, currently, the most appropriate agents seem to be co-amoxiclave, ciprofloxacin, and nitrofurantoin (Wazait *et al.*, 2003). When information on the antimicrobial sensitivity pattern of the infecting strain becomes available, a more specific antimicrobial regimen can be selected. Therapy should generally be administered for 10 to 12 days, with the exact duration depending on the severity of the infection and the susceptibility of the infecting strain. Follow-up cultures 2 to 4 weeks after cessation of therapy should be performed to demonstrate cure (Braunwald *et al.*, 2001).

In addition, there are special considerations in the management of UTIs among selected populations, including postmenopausal and pregnant women, and women with frequent recurrent UTIs (Nicolle, 2003). In pregnancy, acute cystitis can be managed within 7 days of treatment with amoxicillin, nitrofurantoin, or a cephalosporin. All pregnant women should be treated with oral amoxicillin, macrocrystalline nitrofurantoin, cefpodoxime proxetil, or TMP-SMX. After treatment, a culture should be performed to ensure cure, and culture should be repeated monthly thereafter until delivery. Acute pyelonephritis in pregnancy should be managed with hospitalization and parenteral antibiotic therapy, generally with cephalosporin or extended-spectrum penicillin. Continuous low-dose prophylaxis with nitrofurantoin should be given to women who have recurrent infections during pregnancy (Braunwald *et al.*, 2001).

In general, factors to be considered in the selection of appropriate antimicrobial therapy include pharmacokinetics, spectrum of activity of the antimicrobial agent, resistance prevalence of the community, potential for adverse effects, and duration of therapy. Ideal antimicrobial agents for UTI management have primary excretion routes through the urinary tract to achieve high urinary drug levels (Nicolle, 2003).

Gram-negative bacteria were the most common causative agents in hospital acquired infections. However, Gram-positive bacteria became more predominant, (Arnoni *et al.*, 2007). Nosocomial pathogens have shifted away from easily treatable bacteria towards more resistant bacteria. These shifts continue to present challenges for nosocomial infection control and prevention (Jain *et al.*, 2007).
2.13 Prevention

Women who experience frequent symptomatic UTIs (> 3 per year on average) are candidates for long-term administration of low-dose antibiotics directed at preventing recurrences. Such women should be advised to avoid spermicide use and to void soon after intercourse. Daily or thrice-weekly administration of a single-dose of TMP-SMX (80/400 mg), TMP alone (100 mg), or nitrofurantoin (50 mg) has been particularly effective. Norfloxacin and other fluoroquinolones have also been used for prophylaxis. Prophylaxis should be initiated only after bacteriuria has been eradicated with a full-dose treatment regimen. The same prophylactic regimen can be used after sexual intercourse to prevent episodes of symptomatic infection in women in whom UTIs are temporally related to intercourse. Other patients for whom prophylaxis appear to have some merit include men with chronic prostates; patients underlining prostatectomy, both during the operation and in the postoperative period; and pregnant women with symptomatic bacteriuria. All pregnant women should be screened for bacteriuria in the first trimester and should be treated if bacteriuria is demonstrated (Braunwald et al., 2001).

Non-antibiotic means of preventing UTIs, such as increasing colonization resistance with lactobacilli, or the use of vaccines, which prevent adherence of 20 uropathogens to uroepithelial cells, show very promising experimental results (Malinverni, 2002).

For preventing nosocomial UTI infections, the urinary indwelling catheter should be carefully managed (Arakawa, 2013). Because the most important risk factor for infection is duration of catheterization, indwelling urethral catheterization should be avoided or at least limited whenever possible (Saint and Chenoweth, 2003).

Additional methods to prevent this infection include aseptic insertion and maintenance of a closed drainage system, anti-infective catheters in patients with high risk for infection, and systemic antibiotics in selected patients (Madigan and Neff, 2003; Kumon et al., 2001; Saint and Chenoweth, 2003,).

In one study, the nitrofuranzone-containing urinary catheter was broadly active in-vitro against susceptible and multidrug resistant strains of diverse bacterial species characteristics of catheter associated urinary tract infection and it exhibited persistent inhibitory against some isolates for up to 5 days. On the other hand, systemic antimicrobial prophylaxis is not recommended by authorities in the field.
because of the associated risk of selecting resistant microorganisms (Johnson et al., 1999).

Alternative urinary collection strategies may be appropriate in certain patient groups. Specifically, condom catheters should be considered in patients requiring long-term indwelling drainage, and intermittent catheterization seems appropriate in patients with injured spinal cords (Warren, 1997).

UTIs are often treated with antibiotics with different broad-spectrum activity even when antibiotics with narrow spectrum of activity maybe appropriate because of concerns about infection with resistant organisms. Fluoroquinolones are preferred as initial agents for empiric therapy of UTI in area where resistance is likely to be of concern (Schaeffer, 2002; Biswas et al., 2006). This is because they have high bacteriological and clinical cure rates, as well as low rates of resistance, among the most common uropathogens (Goldstein, 2000; Gupta et al., 2002).

Sharma, 1997 stated that despite the widespread availability of antibiotics, UTIs remain the most common bacterial infection in the human population. Tambekar and Khandelwal, 2005; Tambekar and Dhanorkar, 2005 stated that antibiotic resistance may develop in uropathogens due to frequent misuse of antibiotics. Antibiotics are usually prescribed empirically before the laboratory results of urine cultures are available. On the other hand, Gupta et al., 2002 concluded that multidrug resistant pathogens travel not only locally but also globally and newly introduced pathogens spreading rapidly in susceptible hosts. Grubenberg, 1984 suggested that to ensure appropriate therapy current knowledge of the organisms that cause UTIs and their antibiotic susceptibility is mandatory.

Ehinmidu, 2003 reported that E. coli, S. aureus and P. aeruginosa strains were highly sensitive to ciprofloxacin and gentamicin and these isolates were resistant to ampicillin. Tankhiwale et al., 2004 observed maximum resistant to ampicillin (79.6%), co-trimoxazole (82%) and nalidixic acid (73.8%). They also reported that nitrofurantoin (62%), cephotaxime (58.7%) and norfloxacin (45%), constitute the reasonable option for treatment of UTI.

Aljumaili et al., 2013 found that E. coli was the principal isolate showing high susceptibility to Amikacin and Gentamicin (69.2%), followed by Norfloxacain, Nalidixic acid and Ofloxacain. Sahm, 2001 concluded that many bacterial species including E.coli were showing an increasing resistance to antibiotics. E.coli was an important pathogen of urinary tract.
Antibiotics today are the frontline therapeutic means of medical intervention in an infection, which plays a central role in the control and management of infectious diseases. Antimicrobial resistance occurs in intestinal bacteria due to antibiotic therapy for treating infections outside the urinary tract. The uses of antibiotics have an influence in the spread of antimicrobial resistance among bacteria (Rajesh et al., 2011).

The extensive uses of antimicrobial agents have invariably resulted in the development of antibiotic resistance, which, in recent years, has become a major problem worldwide (Kumar et al., 2006). The advent and continuous use of antibiotics in previous century led to success in limiting many of the prevalent bacterial diseases which affected man and animals in epidemic proportions. At the same time inadvertent and over use of antibiotics resulted into emergence of resistance in organisms against the commonly used antibiotics and urgency in developing new antibiotics to check the prevailing infection. The emergence of multi drug resistant organisms necessitates the search for alternative source of antimicrobial agents. Indian traditional system of medicine i.e., Ayurveda has successfully employed plants derived products in the treatment of almost all types of ailments in humans and animals (Benito et al., 2011).

Traditional medicine is in practice for many centuries by a substantial proportion of the population. It is recognized that in some developing countries, plants are the main medicinal source to treat various infectious diseases. Plant extracts represent a continuous effort to find new compound against pathogens. Approximately 20% of the plants are found in the world have been submitted to pharmacological or biological test, and a substantial number of new antibiotics introduced on the market are obtained from natural or semisynthetic resources (Mothana and Liniclequist, 2005).

The use of plant product for pharmaceutical purpose has gradually increased. According to World Health Organisation, medicinal plants would be the best source for obtaining a variety of drugs (Santos et al., 1995). The use of plant extracts, with known antimicrobial properties, can be of great significance in the treatment of various microbial infections. In the last decade, numerous studies have been conducted in different countries to prove such efficiency in number of medicinal plants. Most of the studies are restricted with crude extracts (Reddy et al., 2006; Erdo Urul, 2002; Atefl et al., 2003).
Medicinal plants play an important role for the health care. Medicinal plants have ability to cure both infectious and non-infectious diseases. According to an estimate about 25% of medicines are derived from plants. The use of herbs and medicinal plants is a universal phenomenon. As per World Health Organisation (WHO), about 80% of world population use medicinal plants to treat human disease (Serrentino, 1991). Its civilization is very ancients and the country as a whole has long been known for its rich resources of medical plants. Ayurvedic, Hoemooeo and Unani physicians utilize numerous species of medicinal plants that found their way a long time ago into the Hindu Material Media (Rao and Thammanna, 1987).

Many crude preparations of herbal drugs are in clinical use in medical and veterinary practice. Ethano pharmacologist, botanists, microbiologists and natural product chemists are earth for phytochemicals which could be developed for treatment of infectious diseases. Laboratory of the world have found literally thousands of phytochemicals which have inhibitory effects of all types of microorganisms invitro. More of these compounds are being subjected to animal and human studies to determine their potential to restrict the growth/multiplication of pathogenic organisms as well as examination of their effects on beneficial normal micro biota. Traditional healers have long used plants to prevent or cure the infectious condition. Plants are rich in a wide varity of secondary metabolite such as tannins, terpenoids, and flavanoids which have been invitro to have anti microbiral propertie (Johnson et al., 2011).

One approach involves the search for new therapeutic agent with novel modes of action from natural resource. Plants belonging to the genus Aloe (Liliaceae) have been known for their medicinal properties for many centuries, and Aloe baradensis Miller (or Aloe vera) is of particular renowned (Volger 1999; Ferro et al., 2002).

_Aloe vera_ has been used to treat various skin conditions such as cuts, burns, eczema. It is alleged that sap from _Aloe vera_ ceses pain and reduces inflammation. Evidence on the effects of _Aloe vera_ sap on wound healing, however, is contradictory (Volger et al., 1999). Screening techniques of biological active medicinal compounds have been conducted on well-known species of plants used in traditional medicines and most plants have shown antimicrobial activity (Rabe et al., 1997).

_Aloe vera_ is as old as civilization and throughout history it has been used as a popular folk medicine. It is present in the arid regions of India and is believed to be effective in treating stomach ailments, gastrointestinal problems, skin diseases,
constipation for radiation injury for its anti-inflammatory effect, for wound healing and burns, as an anti-ulcer and diabetes. Currently the plant is widely used in skin care, cosmetics and as nutraceuticals (Klein et al., 1988).

2.14 Aloe vera (Aloe barbadensis Miller) a wonder plant

*Aloe vera* is a stemless or very short-stemmed succulent plant growing to 60-100 cm (24-29 inch) tall, spreading by offset. The species have number of synonyms: *Aloe vera barnadensis* Miller, *Aloe Indica Royal, Aloe perfoliata* L.var.vera and *A. vulgarisb Lam* (Yates, 2002).

Early records of Aloe vera use appear in Ebers Papyrus from 16th century BC in both Dicoride’ De Materia Medica and Pliny in the Elder’s Natural History written in the mid-first century CE (Barcroft and Myskja, 2003) along with the Juliana Anicia Codex produced in 512 AD (Reynold, 2004).

2.14.1 Origin and distribution

*Aloe vera* (*Aloe barbadensis* Miller) is a plant, which belongs to the family of Liliaceae and is most succulent with a whorl of elongated, pointed leaves (Strickland et al., 2004; Beckford and Badrie, 2000). The name is derived from the Arabic word “alloeh” which mean “bitter”, referring to the taste of the liquid contained in the leaves. *Aloes* are beleived to have originated in the Sudan. *Aloe vera* grows in arid climate and is widely distributed in Africa, India and other arid areas. The species is frequently cited as being used in herbal medicine. *Aloe vera* is a perennial, drought resisting, succulent plant (Foster, 1999).

The species is used widely in the traditional herbal medicine of China, Japan, Russia, South Africa, The United States, Jamaica, Latin America and India (Boudreau and Beland, 2006).

2.14.2 Taxonomic classification

**Kingdom:** Plantae

**Division:** Magnoliophyta

**Class:** Liliopsida

**Order:** Asparagales

**Family:** Asphodelaceae

**Genus:** Aloe

**Species:** barnadensis
Aloe is a genus containing about five hundred species of flowering succulent plants. The genus is native to Africa, especially South Africa’s Cape Province and the mountains of tropical Africa, and neighbouring areas such as Madagascar, the Arabian Peninsula and islands of Africa. Drinks made from or containing chunks of Aloe pulp are popular in ASIA as commercial beverage and as a tea additive (Rund, 1996). Aloe vera has a history of use in folk medicine for skin and other disorders, which goes back over thousands of years. More recently, Aloe vera (A. vera) has established a place in homeopathy, herbalism and even conventional medicine (Gjerstad and Riner, 1968).

Aloe vera is a wonder plant and has been used as vital ingredient in beauty product as well as consumed as a dietary supplement. It has been long recognized as an effective natural remedy for its wound-healing properties and its positive influence on other inflammatory skin disorders. Aloe vera (Aloe barbadensis Miller) belongs to the Liliaceal family, and is called the healing plant or the silent healer. Aloe contains 75 active constituents such as glycoprotein, anthraquinones, saccharides, etc., has a low molecular weight substance and contains pharmacological activity (Choi and Chung, 2003).

The Aloe plant is the source of two herbal preparations: Aloe gel (AG) and aloe latex. Aloe gel is a mucilaginous substance produced by parenchymal cells located in the central region of the leaf. The gel is composed mainly of water (99%) and mono and polysaccharides (25% of the dry weight of the gel). The gel is thought to have emollient and moisturizing effects and therapeutic properties (Rund, 1996). The most prominent monosaccharides in AG is mannose-6-phosphate, and the most common polysaccharides are called gluco-mannans (beta-(1, 4) acetylated mannan) (Shelton, 1991).

It is found to have 200 components and 74 known nutrients. This include some of B vitamins like B 12 and most of amino acids, iron, manganese, Calcium, zinc mineral, enzyme etc. Aloe vera has various medical cosmetic properties. The main components of Aloe vera are Anthraquinones (Aloin, Barboloin, isobarboloin, Anthranol, Aloetic acid, Ester of cinnamic acid, Aloe-emodin, Emodin, Chrysophanic acid, Resistannol.), Saccarides (Cellulose, glucose, Mannose, L-rhamnose Aldapentose), Muccopolysaccarides Vitamins (B1, B2, B6, Choline, Folic acid, C-a tocopherol, β –carotene), inorganic compounds (Calcium, Sodium, Manganese, Zinc, chorian, Potassium sorbate, Copper, Magnesium, Iron.), Enzymes (Cycloxygenase,
Oxidase, Amylase, Catalase, Lipase, Alkaline phosphatase, essential amino acids (Lusine, Threonine, Valine, Leucine, Isoleucine, Phenylalanine, Methionine), non-essential amino acids (Histidine, Arginine, Hydroxyproline, Aspartic acid, Glutamic acid, Proline, Glycine, Alanine, Tyrosine), and a variety of miscellaneous elements (Cholesterol, Triglycerides, Steroids, β-sitosterol, Lignins, Uric Acid, Gibberellins, Lectinlike substance, salicylic acid, Arachidonic acid) (Vogler et al., 1999).

The Aloe plant also contains different nutrient contents including vitamins, minerals, enzyme, sugars, phenolic compounds, lignin, saponins, sterol and aminoacid. Aloe vera contains many vitamins excluding vitamin D but including the important antioxidant vitamin A, C and F. Vitamin B (thiamine), B3 (Niacin), B2 (Riboflavin), choline and folic acid are also present. A trace of vitamin B12 also presents (Coats, 1979). Vitamine B complex and C are to play an important role in reducing stress and inflammation. Aloe contains the enzymes such as amylase, lipase and carboxypeptidase. Lipases can digestion by breaking down fats and sugars. Amylases hydrolyse starch to liberate dextrin. The pancreatic carboxypeptidase is metalloenzymes that are dependent on Zn$^+$ for their catalytic activity i.e., also called Zn proteases. It inactivates bradykinins and produces an anti-inflammatory effect (Obata, 1993; Shelton, 1991).

Aloe vera gel provides 20 of the 22 necessary amino acids required by human body. There are 7 of the 8 non-essential amino acids are Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Theronine and Valine. The 12 essential amino acids are Alanine, Arginine, Asparagine, Cystenine, Glycine, Glutamic acid, Histidine, Proline, Serine, Tyrosine, Glutamine and Aspartic Acid (Shelton, 1991). Aloe vera could be considered as a substitute for steroids in wound healing as it, unlike steroids, does not initiate connective tissue breakdown (Davis et al., 1987).

The thick, juicy leaves contain two distinct products. One is the thin clear gel or mucilagooges from the middle of a broken leaf. The other is bitter latex, referred to as juice, derived from the cells just under the surface of the leaf. The active ingredient in the gel is mucopolysaccharides, mostly in the form of aloins, with smaller amounts of hydroxyprolines, aloe emodin and aloe resins. A.Vera gel consists of 99.3% water and, the remaining 0.7% is made up of solids with glucose and mannose constituting a large part. Aloe-vera has six antiseptic agents (sulphur, lupeol, salicylic acid, cinnamic acid, nitrogen and phenol) which act as a team to prevent many internal and external infections (Agarry et al., 2005).
Aloe vera beneficial properties may be attributed to mucopolysaccharides present in the inner gel of the leaf, especially acemannan (acetylated mannans). Aloe vera juice may help people with ulcerative colitis, an inflammatory bowel disease. Aloe vera is known to have certain medical properties. As a drink it protects the mucous membrane of the stomach especially when irritated or damaged. Aloe vera juice is considered helpful for relieving many types of gastrointestinal irritations (Foster, 1999).

Aloe vera is a source of energy containing over 200 nutrients including 18 amino acids and a variety of vitamins and minerals. Aloe vera gel consists primarily of water and polysaccharides (pectins, hemicellulose, glucomannan, acemannan and mannose derivatives). Polysaccharides are a type of carbohydrate that stimulate skin growth and repair. Sugar acts as immune-modulators capable of enhancing and retarding the immune response (Green, 1996; Kahlon et al., 1991). It contains amino acids, lipids, sterols (lupeol, compesterol, and beta sitosterol) tannis, enzymes mannose-6-phosphate is a major sugar component (Davis et al., 1989).

Aloe latex contains compounds known as anthraquinones that stimulate the activity of gastrointestinal tract. The anthraquinones includes the hydroxyanthracene derivatives, aloins A and B, barbaloin, isobarbaloin, aloecic acid and emodin (Davis et al., 1989). Aloe vera has multiple pharmacologically active compounds. It stimulates phagocyte formation and nitric oxide production. It increases the cross linking of collagen, stimulates cell proliferation, inhibit arachidonic acid oxidation, has anti-inflammatory effects and reduces tumors necrosis factor-α levels (Inan et al., 2007).

Aloe has tremendous healing power when used both internally and externally. Aloe-vera can increase the proliferation of lymphocytes and stimulate natural immunity through killer cell activity. Aloe has a strong effect on the immune system as, it activates stimulates macrophages, monocytes, antibodies, T-cells, as and anti body forming B-cells in the spleen. The most important function of Aloe is to aid the digestive system, mucopolysaccharides (MSPs) found in Aloe vera. MSPs are long chained sugar molecules, which are found naturally in every cell of the body, however around the time of puberty, the body stops proucing them. When taken internally, they have shown to have immune stimulating effects. The MSPs of the Aloe vera interact with the body’s immune system. MSPs interject themselves into the cell membranes of the body resulting in much greater cell fluidity and permeability, allowing toxins to
flows out of the cell more freely and nutrients to flow in. MSPs will also lubricate the joints and relieve pain by dilating capillaries, which increase the supply of oxygen and blood to the area. It was suggested that its inhibitory action of *Aloe vera* extract on the arachidonic acid pathway via cyclooxygenase (Vazquez and Avila, 1996).

Additionaly studies suggest that *aloe* gel can help stimulate the body immune system (Davis, 1997). Although a lot of work has been carried out on the medical use of *A.vera* gel and leaf, it also has an antimicrobial activity. The gel is also said to promote wound healing due to the presence of some compounds like anthraquinone and hormones, which posses antibacterial, antifungal and antiviral activity (Agarry O.O *et al.*, 2005). Tan and Vanitha, 2002 also reports that *Aloe-vera barbadensis* Miller has immunomodulatory and antimicrobial activities it contains some compound that selectively modulates cells of the immune.

Immunomodulatory properties of the gel polysaccharides, especially the acetylated mannans from *Aloe vera* are now a proprietary substance covered by many patents. Reports also describe antidiabetic, anticancer and antibiotic activities (Reynolds and Dwech., 1999). *Aloe* emodin (AE), a hydroxyanthraquinone present in *Aloe vera* leaves, has a specific in vitro and in vivo antineuroectodermal tumor activity. The compound doesn’t inhibit the proliferation of normal fibroblasts or that of hemopoietic progenitor cells. AE might represent a conceptually new lead antitumor drug (Pecere *et al.*, 2006).

*Aloe* gel is bacteriostatic or bactericidal against a variety of common wound-infecting bacteria in vitro: *Staphylococcus aureus, Streptococcus pyogenes, Serratia typhosa and Mycobacterium tuberculosis* (Robson *et al.*, 1982; Lorenzetti *et al.*, 1998).

*Aloe vera* in vitro has antibacterial activity against some bacteria. The largest effect is against *Streptococcus pneumoniae*. *Aloe vera* may be used as antibacterial drug with low side effects (Wahyudianingsin. 2003). *Aloe vera* has antibacterial activity against a wide range of gram negative and gram positive bacteria and antifungal activity (Ferro *et Al.*, 2002, Agarry *et al.*, 2005). It effectively kills or greatly reduces or eliminates the growth rate of the following bacteria: *Staphylococcus aureus, Streptococcus pneumonia, Streptococcus pyogenes, Pseudomonas aeruginosa* and *E.coli* (Shupe *et al.*, 1999).

*Aloe vera* has a lot of activities / properties: antibacterial (particularly to *Staphylococcus aureus, Streptococcus viridans, Streptococcus viridans*, *Streptococcus*
mestans, Corynebacteria xerosis), antiviral, fungicidal activity (candida ablicans), virucide activity (Herpes simplex and Herpes zoster), anti-inflammatory activity (Monti, 2005).

It also exhibits antiviral activity against herpes simplex virus (Zandi et al., 2007). Emodin and barbaloin is the main representative of anthraquinone. Both disrupt the membrane by weakening hydrophopic interaction between hydrocarbon chains of phospholipids bilayer (Daiane et al., 2004).

Aloe vera showed antibacterial activity against Shigella flexneri and Streptococcus pyogene (Ferro et al., 2002). Aloe vera gel and alcoholic leaf extract has antibacterial activity. The leaf and gel inhibit the growth of Staphylococcus aureus. The gel also inhibits the Trichophyton mentagrophytes. Aloe leaf possesses inhibitory effect on Pseudomonas aeruginosa. The growth of Candida ablicans was also inhibited by Aloe vera leaf but was not affected by gel (Agarry et al., 2005).

Aloe liquid fraction activity against plant pathogenic fungi showed an inhibitory effect of the pulp of A. vera on Fusarium oxysporum at 10⁴ μ / l⁻¹ and over a long period (Rodriguez et al., 2005). Anti-microbial properties of Aloe vera inner gel are determined by screening method on a range of clinically releveant bacteria (Habeeb et al., 2007).

A lot of work has been carried out on medicinal uses of aloe vera. The reports describe antibacterial, anticancer and antibiotic activity of aloe vera (Reynold and Dwek, 1999). The pharmacological actions of aloe vera, as studied in vitro or in animals (in the most cases the total leaf extract was used), include anti-inflammatory, anti arthritic, antibacterial activity and hypoglycemic effects (Newall et al., 1996).

2.16 Studies in Aloe vera (Aloe vera barbadensis Miller)

Agarry et al., 2005 compared the antimicrobial activities of the gel and leaf of Aloe vera against Staphylococcus aureus, Pseudomonas aeruginosa, Trichophyton mentagrophytes, T.schoeleinii, Microporium canis and Candida albican. They observed that both the gel and the leaf inhibited the growth of S.aureus while the leaf inhibits the P. aeruginosa.

Similarly, Suleyman Alemdar et al., 2009 studied the antimicrobial activity of the aloe vera against Gram-positive bacteria (Mycobacterium smegmatis, Enterococcus faecalis, Micrococcus luteus and Bacillus sphericus), Gram-negative
bacteria (Pseudomonas aeruginosa, Klebsiella pneumoniae, E. coli and Salmonella typhimurium) and Candida albicans. The study showed that Aloe vera juice has antimicrobial activity against M. smegmatis, K. pneumoniae, E. faecalis, M. luteus, C. albicans and B. sphericus, but no inhibitory effect against the other bacterial strains.

Another experiment conducted by Gavimath et al., 2008 with petroleum ether extract of Aloe vera exhibited significant antibacterial activity against Pseudomonas aeruginosa, Salmonella typhi, Klebsiella pneumoniae, Proteus vulgaris, Escherichia coli and moderate activity against Staphylococcus aureus and Bacillus subtilis. They observed that chloroform, methanol and ethanol extracts exhibited moderate antibacterial activity while aqueous extract exhibited least antibacterial activity against all the seven types of bacteria.

Agars et al., 2005 analyzed the antibacterial activity of aloe extract on S.aureus and E. coli. They observed that alcoholic extract was effective on S.aureus. A similar study was done by Tian et al., 2003 where they found anti E.coli activity of aloe species extract.

Thirupati et al., 2010 conducted a study to determine the antimicrobial activity of Aloe vera extract with different solvents viz; hexane, ethyl acetate, petroleum ether and ethanol against Gram-positive bacteria (B. subtilis, S. aureus), and Gram-negative bacteria (E.coli, K. pneumonia, P.aeruginosa). They showed that more antimicrobial activity in ethyl acetate and ethanol extract.

Kedarnath et al., 2013 checked the antimicrobial activity of aloe vera extract against pathogenic bacteria like Staphylococcus aureus, Klebsiella pneumonia and E.coli and fungi like Aspergillus niger and reported significant activity against Klebsiella pneumonia and E.coli whereas in fungi, methanol extract was reported to show significant activity against Aspergillus niger and Candida.

Lalitha et al., 2012 studied the antimicrobial activity of Dimethyl sulfoxide (DMSO) crude extracts of Aloe barbadensis Miller (Aloe vera) gel against the bacterial and fungal pathogens of Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Psedomonas aeruginosa, Staphylococcus aureus, Aspergillus niger, Candida albicans and Penicillium spp. They observed the antibacterial and fungal activity in the DMSO gel extracts of A. vera barbadensis against all the tested bacteria and fungi with varied activity.
Ibrahim et al., 2011 investigated the phytoconstituents and antimicrobial activity of aqueous, ethanol and acetone extracts of the Aloe.vera gel against some human and plant pathogens by disc diffusion method. Among the three extracts, ethanol and acetone extracts recorded significant antimicrobial activity against all test pathogens.

Another study done by Cock et al., 2008 reported that the antibacterial and antifungal activity of the acetone extract was quite impressive as compared to ethanol and aqueous extracts.

In addition, Arunkumar and Muthuselvam et al., 2009 used three different solvents aqueous, ethanol and acetone to extract the bioactive compounds from the leaves of Aloe vera to screen the antimicrobial activity against selected human clinical pathogens by agar diffusion method. They observed the maximum antibacterial activities in acetone extracts other then aqueous and ethanol extracts.

Pugh et al., 2001; Lawless and Allan et al., 2000 screened the antimicrobial activity of Aloe vera gel against the pathogens viz., S. aureus, B. subtilis, K. pneumonia, Streptococcus pyogenes, Pseudomonas, E. coli, Helicobacter pylori and S. typhi. They observed the maximum zone of inhibition against Bacillus and the minimum inhibition activity against the pathogen E. coli.

Alemdar and Agaoglu et al., 2012 conducted a study to determine the antimicrobial activity of the A.vera juice against Gram-positive bacteria (Mycobacterium smegmatis, S. aureus, Enterococcus faecalis, M. luteus and B. sphericus), Gram-negative bacteria (P.aeruginosa, K. pneumoniae, E. coli and S. typhimurium) and C. albicans as in vitro. The study reported that Aloe vera juice has antimicrobial activity against M. smegmatis, K. pneumoniae, E. faecalis, M. luteus, C .albicans and B. sphericus, but has no inhibitory effect against the other bacterial strains.

Ferro et al., 2003 have reported that Aloe vera leaf gel can inhibit the growth of the two gram positive bacteria Shigella flexneri and Streptococcus progenies. Specific plant compound such as anthraquinones and dihydroxyanthraquinines as well as saponins have been proposed to have direct antimicrobial activity.

Rubina et al., 2008 studied ethanol, methanol and acetone extracts of Aloe vera gel for their antimicrobial activity against Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi and Klebsiella pneumoniae using agar well diffusion.
method. The extracts were reported to show varied levels of antimicrobial activity against the tested pathogens. The ethanol and methanol extracts showed higher activity while acetone extract, showed least or no activity against most of the tested pathogens.

Saba et al., 2011 evaluated the antibacterial activity of Aloe barbadensis Miller (Aloe Vera) by using agar diffusion assay and against Escherichia coli, Bacillus subtilius, Salmonella typhi, Pseudomonas, Klebsiella pneumonia and Staphylococcus epidermidis. The Aloe vera extract of methanol showed the maximum inhibitory activity as compared to other solvent extract.