Chapter 1  

Introduction

Urinary tract infections are common infectious diseases worldwide (McLaughlin and Carson, 2004; Llenerrozos, 2004; Blair, 2007) it represents one of the most common diseases encountered in medical practice today and ails neonate to the geriatric age group (Kunin, 1994; Raju et al., 2001). Urinary tract infections (UTIs) is an important cause of morbidity in the general population, and is the second most frequent cause of visits to the doctor’s office (after respiratory tract infections) (Ronald and Pattulo, 1991). Symptoms of UTI include abdominal discomfort, burning pain during urination & frequent urges to urinate (Pommerville, 2004). UTI is the third most common cause of hospitalizations in India (Bano et al., 2012). Fig 1.1 shows the percentage of urinary tract infections among health care related infections.

![Fig.1.1. Health Care Related Infections Bactiguard (Source http://www.bactiguard.se/about/the-problem/health-care-related-infections).](image-url)

Among the most common infectious diseases, UTIs are some commonly encountered diseases by clinicians in developing countries with an estimated annual global incidence of at least 250 million (Ronald et al., 1991; Barisic et al., 2003). It has been estimated that globally symptomatic UTIs result in as many as 7 million visits to outpatient clinics, 1 million visits to emergency departments, and 100,000 hospitalizations annually (Wilson and Gaido, 2004). Kass (1957) gave a criterion of active bacterial infection of urinary tract according to which a count exceeding $10^5$ organisms/ml denotes significant bacteriuria and indicates active UTI.
The exact prevalence of UTIs is age and sex dependent. In the community, women are more prone to UTI. About 20% of women experience a single episode of UTI during their lifetime, and 3% of women have more than one episode of UTI per year (Gebre, 1998). Pregnancy also makes them more susceptible to infection (Pastore et al., 1999). During the first year of the life, UTIs are common in males, however the incidence of UTIs among males reduces after age 1 until approximately age 60 when enlargement of the prostate interfere with emptying of the bladder. Therefore, UTI is predominantly a disease of the female sex (Bailey and Scott, 2000). Other studies corroborate this as UTIs were noted to occur in about one percent of boys and three to five percent of girls (Elder, 2007).

A bacterial Urinary tract infection (UTI) is the most common kind of infection affecting the Urinary Tract. The urinary tract consists of the kidney, ureters, bladder, and urethra and is characterized as being either upper or lower based primarily on the anatomic location of the infection: the lower urinary tract encompasses the bladder and urethra whereas; the upper urinary tract encompasses the ureters and kidneys (Bailey & Scott’s, 2002). The overview of anatomy of the urinary tract is shown in Fig 1.2.

Fig.1.2. Overview of the anatomy of the urinary tract. (From Potter PH and AG: Fundamental of nursing, St Louis, 1985, Mosby.)
Urine, or pee, is the fluid that is filtered out of the bloodstream by the kidneys. Urine contains salts and waste products, but it doesn’t normally contain bacteria. When bacteria get into the bladder or kidney and multiply in the urine, a UTI can result. Sometimes UTI are classified as uncomplicated or complicated. Uncomplicated infection occurs primarily in otherwise healthy females and occasionally infant, adolescent and adult male. Most uncomplicated infections response readily to antibiotic agent to which the etiologic agent is susceptible. Complicated infections occur in both sexes.

There are four major types of UTIs: urethritis, cystitis, the urethral syndrome, and pyelonephritis. Uretheritis is an infection of the urethra, infection of bladder is known as cystitis. The term acute urethral syndrome is used to describe acute cystitis accompanied by pyuria. Patients with this syndrome are primarily young, sexually active women. Phethylonephritis is the infection of the kidney, risk of infection increases when there is urine retention due to the bladder not emptying completely or when urine flow is obstructed due to the renal stone. Enlarged prostate is the most common cause of recurring UTI in man. Persistent or recurrent urinary tract infections lead to renal failure (Forbes et al., 2007; Cheesbrough 1984). Urinary tract infection occurs more frequently in female than male, most likely because of anatomical difference. Sexual intercourse increases the possibility of UTI because bacteria can enter the urethra during organ contact (Pommerville, 2004).

UTIs are often caused by Enterobacteriaceae, and less likely because of viruses, fungus and TB. They do occasionally occur from parasite. E.coli is the most common urinary pathogen causing 60 - 90% infections. Cystitis is mainly caused by bacterium. The culprit is frequently E.coli but sometime S. saprophyticus or especially in hospital-acquired infection, Klebsiella species, Proteus mirabilis, Pseudomonas aeruginosa or Enterococcus faecalis. Candida infection may occur in diabetic and immunocompromised patients. The causative agent of pyelonephritis may be any of these that cause cystitis, but Staphylococcus aureus is also responsible for some of the cases. Proteus infections are also associated with renal stone. S. saprophyticus infection is usually found in sexually active young women. Infection of the anterior urinary tract (urethritis) is mainly caused by N. gonorrhoeae (especially in man). 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 (Cheesbrough, 1984; McCartney, 2006).

It was noted that *E. coli* were responsible for 30% of all recurrent urinary infections followed by *Klebsiella* 18.8%, *Pseudomonas aeruginosa* 15.4% & *Proteus* 14.4% of all UTIs. Other gram-negative organisms caused 15.3% & gram-positive organisms 6.2% of urinary infections (Acharya and Jadav, 1980). The vast majority of UTIs are caused by the Gram negative bacillus *E. coli*, with other pathogen including *entrococci, Staphylococcus saprophyticus, Klebsiella sp.* and *Proteus mirabilis*. *E. coli* is the most common organism infecting the urinary tract; others include *Klebsiella spp, enterobacter spp, Pseudomonas aeruginosa, Enterococci, Staphylococcus saprophytics, Staphylococcus saprophytics, Staphylococcus aureus, S.epidermidis, Acinetobacter spp., B-heamolytic streptococci* group B & D, *Candida albicans, Salmonella sp* and *Mycobacteria* (Al-Ali et al., 2005). *E.coli* was the leading cause of UTIs followed by *Staphylococcus saprophyticus* (Susan and Kay, 2005).

Bacteria can invade and cause UTI via three major routes, ascending routes, hematogenous pathways and lymphatic route. Although the ascending route is the most common among females, instrumentations (e.g., urinary catheterization, cystoscopy) is the most common cause of hospital-acquired UTI in both sexes. UTI may also occur by the hematogenous. Hematogenous spread usually occurs as a result of bacteremia (Bailey, Scott, 2002). Lymphatic route is the rare mode of infections of the urinary tract.

The bladder and urinary tract are normally sterile. The urethra however may contain a few commensals, which can contaminate urine when it is being collected. Usually only a single type of organism is present in uncomplicated acute urinary infections. More than one type of organism is often seen in chronic and recurring infections. Vaginal contamination of the specimen is indicated by a mixed bacterial flora so it is difficult to collect uncontaminated specimen. Contamination can be prevented by using midstream urine collection method (Cheesbrough, 1984).

Microorganisms causing UTI vary in their susceptibility to antimicrobials from place to place and time to time (Orrett, 1998). So identification of the etiological agent and selection of an effective antibiotic agent to the organism in question is very
important for effective management of patients suffering from bacterial UTIs. Although the spectrum of agents causing UTIs is relatively constant, their antibiotic susceptibility patterns are different in different geographical locations.

At present, antibiotics are used for the treatment of several infections. Most urinary tract infections are successfully treated with number of antibiotics such as sulfonamide, ofloxacin etc. Ciprofloxacin is a widely used fluoroquinolone with high bactericidal activity against uropathogens (Blondeau & Joseph, 2004). These antibiotic therapies have been effective but increasing multiple antibiotics resistance is a major concern and increasing emergence of resistance to the currently available antibiotics has necessitated continued search for new antimicrobial compounds. To ensure appropriate therapy, current knowledge of the organisms that cause UTI and their antibiotic susceptibility is mandatory (Grubenberg, 1984).

“Survival of the fittest” holds good for all living organisms including bacteria. A majority of bacteria in nature are non-pathogenic i.e., a large number of them, live as commensals on our body leading a symbiotic existence. A limited population of bacteria which has become pathogenic was also sensitive to antibiotics to begin with (Kapil, 2005). In recent years, widespread use of antibiotics has resulted in an increasing incidence of antibiotic resistance among the urinary tract pathogens all over the world. Worldwide, antibiotic resistance is increasing among the urinary pathogens (Kahlmeter, 2003; Runehagen et al., 2002). However global antibiotic resistance by bacteria is becoming an increasing public health concern and the race to discover new antibacterial agents is on. Antibiotic resistance may develop in uropathogens due to frequent misuse of antibiotics (Grubenberg, 1984). Multidrug resistant pathogens travel not only locally but also globally and newly introduced pathogens spread rapidly in susceptible hosts (Gupta et al., 2002). Antibiotics are usually prescribed empirically before the laboratory results of urine culture are available (Tambekar and Khandelwal, 2005; Tambekar and Dhanorkar, 2006).

One approach involves the search for new therapeutic agents with novel modes of action from natural resources. Patients of UTI are experimenting with more and more alternative natural remedies such as cranberry juice which appear to contain antiadhesive compounds that are active against uropathogens and can help to prevent UTI (Sobota et al., 1984). Vitamin C may inhibit the bacteria by increasing the acidity
of the urinary tract (Pommerville, 2004). Among these medicinal plants, *Aloe vera* or *Aloe barbadensis* family is of particular interest due to its age-old reputation as a curative agent and its widespread use in complementary therapies. Plants belonging to the genus *Aloe* (*Liliaceae*) have been known for their medicinal properties for many centuries, and *Aloe barbadensis* Miller (*or* *Aloe-vera*) has gained therapeutic renown in the last decade. *Aloe Vera* (AV) has been used extensively in health drinks, topical creams, toiletries, and cosmetics, and there are many reported claims of its beneficial properties (Vogler 1999 & Ferro *et al.*, 2002).

*Aloe vera* (*Aloe barbadensis* Miller) is a succulent from the *Aloe* family (500 different species) with its origin in African continent. The different species have somewhat different concentration of active ingredients (Yangi *et al.*, 1998; Van, 1995). The plant has many common names in India; it is often referred to as Ghrat Kumari. *Aloes* have long been used all over the world for their various medicinal properties (Agarry *et al.*, 2005). *Aloe vera* is a cactus–like plant that grows readily in hot and dry climates. Its leaves have a water retaining properties even in very warm and dry climates and therefore this plant can survive very harsh circumstances where most other plants disappear. The *Aloe* plant is the source of two herbal preparations: *Aloe gel* (AG) and *aloe* latex. When a leaf is cut, an orange-yellow sap drips from the open end that is latex. When the green skin of a leaf is removed a clear mucilaginous substance appears that contains fibers, water and the intergradient to retain the water in leaf. This is called gel. *Aloe vera* gel consists of 99.3% water. The remaining 0.7% is made up of solids with glucose and mannose (Agarry *et al.*, 2005).

*Aloe vera* is a wonder plant, whether we use it as a vital ingredient in beauty products or consume it as a dietary supplement. Humans have used *Aloe* for over 5000 years. Egyptian first wrote about the healing powers of the plant on their ancient papyrus text calling it the plant of immorality (Shelton, 1991). Cleopatra and Nefertiti bathed in *Aloe* juice to retain their youth and beautiful looks. *Aloe* is mentioned several times in the Bible. It was used in the burial of Jesus (Haller, 1990). History and legend tells that Aristotle convinced Alexander the great to conquer the island of Socorta in order to collect aloe plant to use as medicine for his army (Atherton, 1998). *Aloe* drawings have been found on the wall carriages of Egyptian temples erected in the fourth millennium BC. The Egyptian book of remedies (ca. 1500 BC) notes the use of *Aloe* in curing infections treating the skin and preparing drugs that were chiefly used as laxatives.
Aloe Vera have anti microbial, astringent, antibiotic, antioxidant, analgesic, antihistamine, anti-inflammatory, antiperspirant, antipruritic, catartic, demulcent, fungicidal, germicidal, diuretic, detoxicant, vermifuge, vulnery, emmenagogue, emollient, cosmetic, aphrodisiac, coagulant, antipyretic. A.Vera juice may help people with ulcerative colitis, an inflammatory bowel disease. A.Vera is known to have certain medical properties. As a drink it protects the mucous membrane of the stomach especially when irritated or damaged. A. vera juice is considered helpful for relieving many type of gastrointestinal irritation (Foster, 1999). It is used to relieve thermal or sunburns & to promote wound healing.

In addition, research suggests that Aloe gel can help stimulate the body immune system (Davis 1997). The gel is also said to promote wound healing due to the presence of some compounds like anthraquinone & hormones, which posses antibacterial, antifungal & antiviral properties (Agarry O.O. et al., 2005). Aloe vera is a natural substance with antibacterial activity particularly to Staphylococcus aureus, Streptococcus viridans, Streptococcus viridans, Streptococcus mestans, Corynebacteria xerosis, anti-viral, fungicidal activity (candida ablicans), virucidal activity (herpes simplex and herpes zoster), anti-inflammatory activity (Monti, 2005). Aloe vera Barbedensis is a natural substance with antibacterial, antiviral, fungicidal, anti-inflammatory activity and stabilizes and helps to recovery of hurtburns (Monti, 2006).

Although a lot of work has been carried out on the medicinal uses of Aloe vera, there is still little information on the uses of its leaf. This research aimed to conduct a systematic bacteriological examination of urine samples along with their antibiogram to know the trend of antibiogram of uropathogens in the Kumaun region and to provide evidence for the antibacterial effectiveness of aloe vera gel and whole leaf extract in in-vitro condition. Kumaon or Kumaun is one of the two regions and administrative divisions of Uttarakhand, a mountainous state of Northern India, other being Garhwal (refer to map of Kumanon in Figure 1.3, source: http://www.indianetzone.com/56/kumaon_division.htm). It includes the districts of Almora, Bageshwar, Champawat, Nainital, Pithoraghar and Udham Singh Nager. It is bounded on the north by Tibet, on the East by Nepal, on the south by the State of Uttar Pradesh, and on the west by the Garhwal region. The Kumaon region consists of
a large Himalayan tract, together with two submountainous strips called the Terai and the Bhabhar.

The microorganisms used in this study will be the bacteria (uropathogens) isolated from urine samples of patients suffering from urinary tract infection. The antimicrobial activity of *Aloe-vera* gel and leaf extract would be studied on UTI pathogens of Kumaun.

![Fig1.3 Kumaun region, Division of Uttarakhand, North India](http://www.indianetzone.com/56/kumaon_division.htm)

Keeping the above facts in mind, this research had the following objectives:

**1.1 Objectives**

1. Isolation & characterization of uropathogens from the mid-stream urine of patients.
2. Antibiotic sensitivity pattern of the isolated uropathogens.
3. Sensitivity pattern of these uropathogens against alcoholic as well as aqueous extract of gel and whole leaf of *Aloe vera barbadensis* Miller and determination of MIC.