Throughout history, there has been a continual battle between humans and the multitude of the microorganisms that cause infection and disease. The Pseudomonads are a diverse bacterial group of established and emergent pathogens. The members of the genus are major agents of nosocomial and community acquired infections, being widely distributed in the hospital environment where they are particularly difficult to eradicate (John Smith et al., 2000, Farhat et al., 2009). It is the most common pathogen isolated from patients who have been hospitalized longer than one week and it is a frequent cause of nosocomial infections. Pseudomonad infection are complicated and can be life threatening. *Pseudomonas aeruginosa* is not an obligate parasite, but the species of Pseudomonad commonly associated with human diseases (Govan et al., 1992, Fang et al., 1993, Bert et al., 1998, Warren et al., 2000) and commonly causes nosocomial infections (Banerjee et al., 2000). *P. aeruginosa* infections account for 20% of pneumonia and 16% of urinary tract infections (Ishihara et al., 1995). It is implicated in a wide spectrum of nosocomial infection, including bacteremia, secondary meningitis, wound infection, but their most important role appears to be as agents of nosocomial pneumonia and particularly ventilator-associated pneumonia (VAP) in patients confirmed to hospital intensive care units (ICU’s).

Beginning around the middle of the 20th century, major advances in antibacterial drug development and other means of infection control helped turn the tide in favor of humans. Almost as soon as antibacterial drugs were developed, bacteria responded by manifesting various forms of resistance. As the antimicrobial usage increased, so the level and complexity of resistance mechanisms exhibited by bacterial pathogens. The struggle to secure the upper hand against infections continues to this day, although the number of scientists who are developing new antibacterial agents is the beginning to dwindle, even as bacteria evolve ever more clever mechanisms of resistance (Krause, 1992). Organisms such as *P. aeruginosa* are having increasing clinical importance because of their innate resistance to multiple agents and their ability to develop high-level multidrug resistance (MDR). Perhaps not surprisingly, this resistance owes much to the presence of broadly-specific efflux systems which export and, thus provide resistance to multiple antimicrobials. The organism’s intrinsic resistance has long been attributed to the outer membrane, a barrier of limited permeability (Nikaido,
1989). While the reduced uptake likely does limit the access of antimicrobials to their targets within the cells, this is dependent upon additional resistance mechanisms such as drug efflux (Poole et al., 1993, Ma et al., 1994). Indeed, it is now clear that the intrinsic multidrug resistance of this organism results from the synergy between outer membrane impermeability, and the chromosomally-encoded multidrug efflux pumps of the RND-MFP-OMP type (Germ et al., 1999, Li et al., 2000). Active efflux is now recognized as an important component of bacterial resistance to most of classes of antibiotics. This mechanism is mediated by efflux pumps, which are membrane-associated active transporters promoting the extrusion of toxic compounds, including antibiotics, from the cells (Webber et al., 2003, Li et al., 2004, Piddock et al., 2006). Antibiotic efflux was first described in 1980, when it was discovered as a mechanism for tetracycline resistance in enterobacteria. Through the years, the role of the efflux mechanisms in bacterial resistance has been shown for almost all antibiotics (Levy et al., 2002, Levy, 2002, Li et al., 2004, Poole et al., 2005, Piddock et al., 2006, Stavri et al., 2007). Phylogenetically, bacterial antibiotic efflux pumps belong to five super families that are classified in two mechanistically distinct types: primary transporters that couple drug extrusion from the cell with ATP hydrolysis and secondary transporters energized by trans-membrane electro-chemical gradients of either protons or sodium ions (Saier et al., 2001, Marquez, 2005, Lynch et al., 2006, Pages et al., 2005). The primary transporters are also called ATP binding cassette (ABC) transporters. The ABC transporters are ubiquitous membrane systems, and are distributed in both prokaryotes and eukaryotes (Chang, 2003). Antibiotic efflux systems classified as secondary transporters include; the major facilitator (MFS) superfamily, the resistance nodulation division (RND) superfamily, the small multidrug resistance (SMR) subfamily of drug/ metabolite transporters (DMT) superfamily, the multidrug and toxic compound extrusion (MATE) subfamily belongs to multidrug/oligosaccharide-lipid/polysaccharide flippase (MOP) superfamily (Pages et al., 2005). These multiple efflux pumps are responsible for providing a large amount of multidrug resistance in P. aeruginosa (Schweizer, 2003). The present work focuses on the regulation of MexAB-OprM is the one specific efflux pump in P. aeruginosa, is expressed constitutively in cells grown in standard laboratory media, where it contributes to intrinsic resistance to a number of antimicrobials including fluoroquinolones, β-lactams, tetracycline,
macrolides, chloramphenicol etc (Kohler et al., 1996, Poole et al., 1996, Shrikumar et al., 1997., Shrikumar et al., 1998, Li et al., 1998). Addressing antibiotic resistance requires a multifaceted approach to reduce inappropriate use, prevent disease transmission, and to develop novel/alternative therapy for it.

The identification and development of efflux pump inhibitors appear to be an interesting approach to improve the clinical efficacy of antibiotics. These agents are expected to decrease the intrinsic bacterial resistance towards the antibiotics, reverse the acquired resistance associated with efflux pump over expression, and reduce the frequency of the emergence of resistant mutant strains (Marquez et al., 2005, Pages et al., 2005, Lynch et al., 2006, Lomovskaya et al., 2006, Mahamoud et al., 2007). Using the efflux pump inhibitors together with antibiotics can reduce the invasiveness of P. aeruginosa besides its role in lowering the antibiotic minimal inhibitory concentration (Hirakata et al., 2009).

At present major pathogenic bacteria that contribute the most to the global infectious disease burden such as Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumonia and Mycobacterium tuberculosis are resistant to standard antibiotic therapies (Fluit et al., 2001, Styers et al., 2006, Gandhi et al., 2006). This global emergence of multi-drug resistant bacterial strains has limited the effectiveness of current drugs, causing treatment failures (Hancock, 2005). The containment of this drug resistance requires that, new potent antimicrobial compounds be identified as alternatives to existing antibiotics (Overbye et al., 2005). However, the development of new antimicrobial drugs is not encouraging with only a few new drugs being licensed in recent years (Levy et al., 2004, Norrby et al., 2005). This mismatch between the slow development of new drugs and the fast emergence of resistant strains makes the future management of infectious diseases look miserable. As an alternative or perhaps a sustainable option and attempts to improve the efficacy of available antibiotics, particularly the older and cheaper drugs have been suggested (Lomovskaya et al., 2006).

Medicinal plants continue to play an important role in the healthcare systems of large extents of the world’s population, particularly in the developing countries, where the herbal medicine has a longer and uninterrupted history of use (Koduru et al., 2007). Up to 80% of
the African population depends on traditional herbal medicine for primary health care, accounting for around 20% of the overall drug market (WHO, 2004). The popularity of such plants in these communities owes largely to their local availability and price affordability (Voravuthikunchai et al., 2005) and also confirms their effectiveness. Plants produce a wide variety of secondary metabolites many of which have been reported to be of therapeutic value. More than 250 000 species of higher plants in the world, only about 5 -10% have been chemically investigated (Tshibangu et al., 2001). This raises the prospects of obtaining novel chemotherapeutic compounds if this vastly untapped resource could be adequately explored. The prospect of obtaining drugs from plants has been demonstrated by some notable examples of important pharmaceuticals derived from plant precursors. Indeed the plants might be a source of compounds that may potentiate the activity of antibiotics against resistant bacterial pathogens. These compounds have variably been termed resistance modifying, modulating or reversal agents. While the routine practice has been to screen plant extracts for direct antimicrobial compounds, the second option of searching for resistance modifying compounds that may improve the efficacy of antibiotics when used in combination. These compounds would be appears more attractive as it would allowed for the recycling of old and relatively cheaper antibiotics that have been rendered ineffective due to resistance. Several studies have proposed that plant derived compounds in combination with antibiotics are a new strategy for developing therapies for infections caused by bacterial species as they may enhance the activity of antibiotics in combination due to their synergistic effects (Obritsch et al., 2004, Garo et al., 2007, Coutinho et al.,2008, Coutinho et al.,2009).

Keeping these points in view, the present study was planned to explore medicinal plants as a source of Efflux Pump Inhibitor compounds as the plants contains a vast array of novel and useful bioactive compounds which have synergistic and antibacterial effects.
1.1 Aim and objectives:

Isolation and characterization of putative efflux pump inhibitor/inhibitors from plant sources against MDR strains of *Pseudomonas aeruginosa*.

**Objectives:**

1) Screening of desired drug resistant phenotype among clinical isolates.

2) Screening of crude plant extracts for efflux pump inhibitory activity.

3) Isolation and characterization of active compound/ compounds.