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Analysis of anticancer and antibacterial activity against bacteria resistant to aminoglycoside from the extract of *Azima tetracantha* L

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Abstract

Hospital-obtained infections account for 40% of all cases, infections of the urinary tract, known as UTIs are the most common infections contracted in healthcare facilities. The current research focused on assessing the anti-bacterial properties of medicinal plants against bacteria that have developed resistance to aminoglycosides. The collected urine samples from UTI patients at various hospitals were inoculated on HiCrome Differential Agar for the isolation of pathogens. The identification of aminoglycoside-resistant bacteria was based on their cultural and morphological features. One of the methods disc diffusion was employed to analyze the antibiotic sensitivity of aminoglycoside-resistant bacteria to various commercial antibiotics, including *Azima tetracantha* L. The powdered specimens were analysed to screening of phytochemical using aqueous, acetone, and methanol extracts according to established protocols. GC-MS analysis was also performed on the *Azima tetracantha* L. plant extract, revealing various phytochemical compounds. According to previous studies, these compounds are recognized for their diverse medicinal properties. In additionally in this study we have evaluated the IC_{50} value of the plant crude extract.

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Introduction

Infections of Urinary tract, known as UTIs are characterized by the growth of microorganisms within the urinary tract, leading to an adverse impact on the surrounding environment. The condition where presence of bacteria is in the urine is known as bacteriuria. UTIs are commonly categorized into two distinct types: symptomatic and asymptomatic bacteriuria. *Escherichia coli* originating from the gut is implicated in 80 to 85% of community-acquired urinary tract infections, whereas *Staphylococcus saprophyticus* is responsible for 5 to 10% of these cases.

Although less common, viral or fungal infections can also cause urinary tract infections. In healthcare settings, a wider variety of pathogens are involved, including *Escherichia coli* (27%), *Klebsiella pneumoniae* (11%), *Pseudomonas aeruginosa* (11%), *Enterococcus* species (7%), and the fungal agent *Candida albicans* (9%). Antibiotics represent landmark advancement in current medical practice, but their easy accessibility and increased application have led to a slow development of microbial resistance. The issue of resistance to antimicrobial agent is escalating globally, with significant concern in developing countries, including India (Gottlieb and Nimmo, 2011).

As reported by the World Health Organization in 2014, antimicrobial resistance is emerging as an escalating global health concern, with nations around the world recognizing its serious implications for contemporary medicine. Enterococci, initially recognized as a nosocomial pathogen in the 1990s, have become more critical not only due to their potential to induce serious infections but also because of their increasing resistance to various antimicrobial drugs.

Serious cases of infection of urinary tract are commonly resistant to treatment, and the associated mortality rate remains high (Patterson and Zervos, 1990). Traditionally, infections caused by enterococci were treated with drugs that target the cell wall (e.g., penicillin or ampicillin) combined with an aminoglycoside (such as streptomycin or gentamicin). Nevertheless, the emergence of high-level resistance to aminoglycosides, β-lactam antibiotics, and vancomycin in certain strains, combined with HLAR's link to multidrug resistance, has led to a failure in achieving the intended synergistic effects of this therapy (Jesudason *et al.*, 1998). Streptomycin was the preferred aminoglycoside for clinical use until 1970, when it was discovered that more than half of enterococci had developed high-level resistance to the drug. The initial report of high-level gentamicin resistance (HLGR) in *E. faecalis* came in 1979 (Murray, 1990).

The Indian medicinal plant *Azima tetracantha* L is widely recognized for its importance in the various treatment ailments. While some chemical compounds from this plant have been previously isolated and their structures identified, a comprehensive study to pinpoint the specific constituents responsible for the therapeutic effects of these crude drugs has not yet been documented. A variety of tropical medicinal plants are traditionally employed for their therapeutic effects against these diseases (Shankar, 1998). Medicinal and aromatic plants, along with their essential oils, are abundant in antibacterial and antifungal compounds and could serve as an alternative approach to fighting bacterial and fungal infections (Preethi *et al.*, 2010). As a result, the current investigation focused on examining the antibacterial properties of *Azima tetracantha* L. against bacteria that have developed resistance to aminoglycosides. Anticancer studies of *Azima tetracantha* L is not well studied so far. In this study the IC_{50} value of the plant extract have been analysed.

Materials and methods

Over the course of 12 months (from September 2018 to August 2019), urine samples were obtained from patients hospitalized in different hospitals in Thanjavur for the purpose of isolating aminoglycoside-resistant bacteria responsible for UTIs. Pure bacterial strains obtained from the growth on HiCrome™ UTI Agar (HiMedia M1418), Blood agar (HiMedia M073), and MacConkey Agar (HiMedia MH081) plates incubated at 37°C were subjected to conventional identification procedures to determine their genus and species. To find out the genus, gram staining, catalase test, motility growth in the presence of 6.5% NaCl, bile esculin test and PYR (L pyrolidonyl naphthylamidase) were conducted. Additionally, the species of each isolate was further determined through biochemical tests, along with an assessment of sugar fermentation patterns for arabinose, sorbitol, mannitol, sorbose, and sucrose (Manero and Blanch, 1999).

The resistance of antimicrobial outline of the isolates were determined for seven antibiotics—ampicillin, gentamicin, vancomycin, chloramphenicol, ciprofloxacin, erythromycin, and tetracycline—using the Kirby-Bauer disc diffusion technique, following CLSI standards (Bootle, Mast Mersey Side, UK). Additionally, the method of micro-dilution was employed to identify HLGR strains (MIC≥500 µg/ml). The results were interpreted, and the MIC was determined following CLSI guidelines (8-1024 µg/ml) (NCCLS, 2002).

The current study involved the *Azima tetracantha* L. leaf with the plant authenticated and verified by the Department of Botany at St. Joseph's College (Autonomous), Tiruchirappalli, India, with additional verification provided by Dr. S. Soosairaj, a botanist from the Department of Botany at St. Joseph's College (Autonomous), Tiruchirappalli. The number of the specimen is 2021/3000. The plant leaf powder (20g) was immersed in 75 ml of methanol and left to dissolve for 24 hours. Afterward, the filtrates were collected and subjected to evaporation under liquid nitrogen (Divya *et al.*, 2017). Phytochemical analysis of the prepared plant materials was conducted using established qualitative methods (Das *et al.*, 1964; Harborne, 1973), and the active compounds in *Aristolochia indica* L. were identified through GC-MS. The method of disc diffusion was employed to evaluate the antibacterial activity against UTI bacteria resistant to aminoglycosides (Azoro, 2002).

Cytotoxicity assays (MTT Assay) the cells were grown in DMEM media in 96 well plate. Once it reaches 80% confluence the cells were treated with different concentration (0.1, 0.25, 0. 50, 1.00, and 2.00 IU/ml, respectively) of plant extract for 24h. Then the drug treated cells were washed twice with phosphate buffer saline (PBS). The 0.5 mg/ml MTT solution was introduced into each well and the plate was further incubated at a temperature of 37 °C for 4h and the MTT solution is replaced with 200 µl of DMSO. The plate was agitated at 150 rpm for 5 minutes, and the optical density was subsequently measured at 490 nm using a plate reader (ELx 800; Biotek, Winooski, VT, USA). The procedure was repeated no fewer than three times before the data was analyzed and used to create a graph.

Results and discussion

Aminoglycosides, known for their high potency, are broad-spectrum antibiotics that have been used extensively for treating severe Gram-negative infections. Over the past few years growing attention towards enterococci, driven by their capacity to cause severe infections and their rising resistance to various antimicrobial agents (Murray, 1990). As a chromogenic medium, HiCrome UTI agar aids in the swift isolation and initial identification of numerous UTI bacteria, including different species, from urine sample. The investigation involved 536 urine samples collected from UTI patients from July 2018 to June 2019, with 443 samples (83%) showing positive urine culture results and 93 samples (17%) showing negative results (Fig. 1). Our results regarding UTI and polymicrobial growths from urine cultures are in agreement with a number of studies performed in India (Delost, 1997). *Escherichia coli* was identified as the most prevalent bacterium in positive urine infections, comprising 35% of the cases in this investigation. As noted by Ciragil *et al.*, 2006, 20 to 30% of UTI urine samples exhibit significant growth of major infective bacteria, including *Escherichia coli*, in cases of both community and hospital-acquired infections (Salvatore *et al.*, 2011). The occurrence of urinary tract infections caused by *Klebsiella pneumoniae* seems to be increasing, posing a significant health issue, particularly in hospital environments (Cristea *et al.*, 2017).

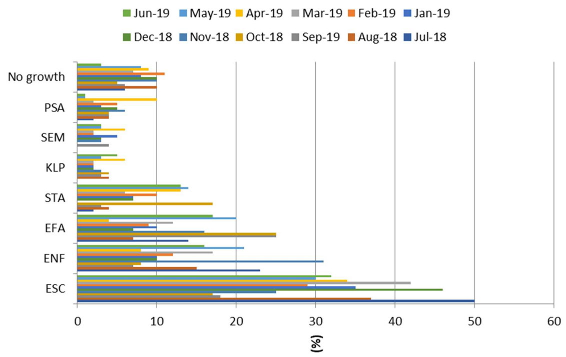

Fig. 1. Isolation of UTI bacteria
ESC - *Escherichia coli;* ENF - *Enterococcus faecium;* EFA - *Enterococcus faecalis;* STA- *Staphylococcus aureus;* KLP - *Klebsiella pneumoniae;* SEM- *Serratia marcescens;* PSA- *Pseudomonas aeruginosa*

Table 1. Prevalence of the isolated bacteria in collected urine samples

Bacteria	Observation	
	No. of positive UTI	Percentage (%)
Escherichia coli	187	35
Enterococcus faecium	83	16
Enterococcus faecalis	74	13
Staphylococcus aureus	48	9
Klebsiella pneumoniae	16	3
Serratia marcescens	15	3
Pseudomonas aeruginosa	20	4
No growth	93	17
Total number of samples	536	

Enterococcus faecium was identified as a positive urine-infecting bacterium in 16% of cases, whereas a similar study conducted in France reported that *Enterococcus faecium* made up 13% of isolates from UTI specimens (Goldstein, 2000). The study found that *Serratia marcescens* was present in 3% of UTIs. Other studies have reported similar findings, which could be explained by the frequent occurrence of *Serratia marcescens* in the human body flora (Silverman *et al.*, 1998). Among the isolated organisms in these patients, *Escherichia coli* was the most frequently observed at 35%, followed by *Enterococcus faecium* at 20% and 12%, *Staphylococcus aureus* at 9%, *Serratia marcescens* and *Klebsiella pneumoniae* each at 3%, and *Pseudomonas aeruginosa* at 4% (Table 1). The pattern of findings in this study was comparable to those reported by Savitha and Thanga mariappan, which included *Escherichia coli* (48.04%), *Klebsiella* (8.82%), *Pseudomonas aeruginosa* (0.98%), *Proteus* spp. (4.9%), and Gram-positive organisms (37.26%) (Savitha and Thangamariappan, 2011).

Antibiotic resistance has quickly become a major worldwide problem, now regarded as one of the most pressing scientific issues of the contemporary era. Table 2 presents the results of phenotypic resistance to aminoglycoside antibiotics, as determined using the standard disc diffusion by Kirby-Bauer method. The progressive rise in aminoglycoside resistance rates, along with associated phenotypes and mechanisms in Gram-negative bacteria from infected patients globally, has resulted in the broad distribution of resistance patterns among different bacterial species (Ramirez and Tolmasky, 2010). The phenotypic screening for aminoglycoside antibiotics resistance showed a marked rise in resistance levels in the bacterial isolates against different aminoglycoside drugs. Research employing the Kirby-Bauer method to investigate high-level aminoglycoside resistance in Enterococci isolates revealed comparable resistance to gentamicin, streptomycin, and their combination, as reported in Chennai, India (Padmasini *et al.*, 2014). Resistance to aminoglycosides in enterococci is commonly accompanied by multidrug resistance. In this study, *E. faecium* and *E. faecalis* and demonstrated resistance to as many as five distinct drugs (Table 2).

Recently, significant change has been observed focus on plant extracts and compounds with biological activity obtained from medicinal plant species. According to Hamburger and Hostettmann (Hamburger and Hostettmann, 1991), the number of plant chemicals may surpass four hundred thousand, including more than ten thousand secondary metabolites, whose key functions in plants are still not fully understood. Several studies have indicated that plants, including parts such as leaves, stems, bark, and flowers, possess antimicrobial properties. It has been found that extracting these plants with solvents like ethanol, acetone, and methanol typically yields antibacterial effects (Bushra Beegum and Ganga Devi, 2003).

The presence of flavonoids and saponins was confirmed in all the extracts from *Azima tetracantha* L. plant leaves. The antimicrobial characters of flavonoids have been documented (Chattopadhyay *et al.*, 2001). Furthermore, phytoflavonoids and phenolic compounds are associated with strong antioxidant activity and are effective in preventing a range of diseases (Zhang, 2009). The phytochemical tannins exhibit both antimicrobial activity (Satdive *et al.*, 2004) and antioxidant benefits. Both tannins and terpenoids were present in the acetone and methanol extracts of the leaves. Only the methanol extracts exhibited the presence of phlobatannis, steroids, and glycosides (Table 3). The findings of this study also validate the occurrence of saponins, identified through qualitative tests, which are commonly understood to be soapy substances with general cleansing and antiseptic functions (Hirat and Suga, 1983).

Table 2. Distribution of the high-level aminoglycoside resistance bacterial species with respect to aminoglycoside antibiotic resistance

Bacteria	Zone of inhibition (mm in diameter)				
	Amikacin	Gentamicin	Kanamycin	Streptomycin	Tobramycin
Escherichia coli	10±1.43	-	-	-	-
Enterococcus faecium	11±1.40	-	-	12±1.76	-
Enterococcus faecalis	08±1.41	-	11±1.07	08±1.40	14±1.21
Staphylococcus aureus	10±1.21	-	10±1.47	-	-
Klebsiella pneumoniae	-	-	-	-	-
Serratia marcescens	-	-	-	-	-
Pseudomonas aeruginosa	-		-	-	-

Values are expressed Mean ± Standard Deviation (M±SD); n = 6

Table 3. Anticancer activity of of *Azima tetracantha* L against Hela cell line

Sl	Concentration IU/ml	Absorbance 540nm	% cell viability
1	0.10	0.72	66.0
2	0.25	0.57	49.5
3	0.50	0.35	30.4
4	1.00	0.18	15.6
5	1.50	0.08	7.82
6	2.00	0.03	2.60
7	Control cells	1.15	100

The methanol extract of *Azima tetracantha* L. leaves revealed the presence of forty identified compounds. The chromatogram illustrating the peaks of the test compounds relative to their retention times is presented in Fig. 2. According to the peak report, the predominant compounds identified were 2-Methyl-2-Nonene, Dodecane, Neophytadiene, 2-Pentadecanon, 6,10,14-Trimethyl-, 5,9,13-Pentadecatrien-2-One, 6,10,14-Trimethyl-, (E,E)-, Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester, Sulfurous acid, cyclohexylmethyl hexyl ester, Phytol, γ-Sitosterol, β-Sitosterol, Friedelan-3-one, and α-Tocospiro. Previous studies identified methoxylated flavones, including apigenin 7-methyl ether and apigenin 7,4'-dimethyl ether, in *Azima tetracantha* L. Additionally, chrysoeriol 7-O-glucuronide and acacetin were found solely in *Azima tetracantha* L, while kaempferol 40-dimethyl ether, a dimethyl ether flavonol, was also reported in the plant (Umadevi and Daniel, 1991; Rao and Gunasekar, 1987).

The effectiveness of *Azima tetracantha* L in combating bacteria resistant to aminoglycosides, isolated from UTI infections, was assessed. The strongest antibacterial activity was found in the methanol extract, while the aqueous and ethanol extracts showed lesser effectiveness. The highest growth inhibition was recorded for *Escherichia coli* (24±1.35 mm diameter) and *Staphylococcus aureus* (24±1.57 mm diameter) among the three bacterial species, in contrast to the other isolated UTI aminoglycoside-resistant bacteria (Fig. 3). The clinical pathogen growth was inhibited by the *Azima tetracantha* L leaf extract that was shown by Hema *et al.,* 2012.

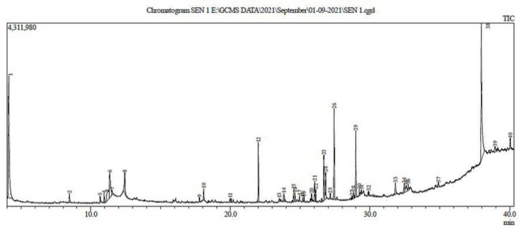

Fig. 2. *Azima tetracantha* L. plant leaves methanolic extract phytocompounds were confirmed by GC-MS

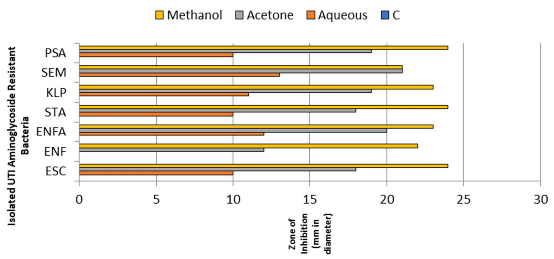

Fig. 3. Antibacterial bacterial activity of *Azima tetracantha* L against isolated UTI aminoglycoside resistant bacteria

ESC - *Escherichia coli;* ENF - *Enterococcus faecium;* EFA - *Enterococcus faecalis;* STA- *Staphylococcus aureus;* KLP - *Klebsiella pneumoniae;* SEM- *Serratia marcescens;* PSA- *Pseudomonas aeruginosa*

Anbukumaran *et al.*, 2016 previously found that *Azima tetracantha* exhibited the greatest antibacterial activity with various ethanol concentrations, surpassing the effectiveness of methanol and water extracts. Specific plant compounds, including anthraquinones (Simpson and Amos, 2017) and dihydroxyanthraquinones, as well as saponins (Man *et al.*, 2010), have been suggested to exhibit direct antimicrobial activity. Terpenoids are attributed with a variety of effects, including antimicrobial, antifungal, antiparasitic, antiviral, antiallergenic, antispasmodic, antihyperglycemic, anti-inflammatory, and immunomodulatory properties (Rabi and Bishayee, 2009; Wagner and Elmadfa, 2003). Moreover, glycosides, present in significant amounts in methanol extracts, are known for their broad therapeutic effectiveness.

MTT assay was used to determine the effect of *Azima tetracantha* L. on Hela cell viability. As can be seen in the table below the viable cells percentage decreased compared with wild type cells in a dose-dependent manner and observed in 24, 48, and 72 h. The IC50 value was determined as 267.5 µg/ml after 48 h. P value considered as < 0.05.

Conclusion

The current study demonstrated *Azima tetracantha* L. antibacterial effects against bacteria resistant to aminoglycosides that were isolated. Aminoglycoside antibiotics resistance was evaluated in UTI bacterial strains that were isolated. The predominant bacterial strains detected included *Escherichia coli, Staphylococcus aureus, Enterococcus faecium, Klebsiella pneumoniae, Serratia marcescens, and Pseudomonas aeruginosa.* This investigation supports the use of *Azima tetracantha* L. as a folk remedy, validating its medicinal applications. This investigation represents the first comprehensive antimicrobial analysis properties and the profile of GC-MS *Azima tetracantha* L. leaves. The methanolic crude extracts in their crude from demonstrated broad-spectrum antimicrobial activity and are rich in biologically active compounds. The GC-MS analysis particularly revealed ten bioactive compounds present in the methanolic extract, potentially offering new avenues for drug discovery aimed at treating different types of human UTI infections.

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