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SHORT COMMUNICATION

Antibacterial Potential of *Azadirachta indica* against ESBL and Carbapenemase-producing Multidrug-resistant UPEC

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Abstract

Background: The increasing prevalence of antibiotic-resistant *Escherichia coli* strains presents significant challenges in the treatment of Urinary Tract Infections (UTIs), especially in resource-limited settings. Nearly 50% of *E. coli* isolates are ESBL producers and exhibit resistance to commonly used antibiotics. Genetic analysis has identified a high occurrence of resistance genes such as CTX-M-15 and NDM, which confer resistance even to last-line antibiotics. **Aim:** To evaluate the antibacterial efficacy of *A.* against genetically confirmed ESBL- and carbapenemase-producing uropathogenic *E. coli,* i.e. UPEC strains isolated from UTI patients. **Methods:** A total of 273 UPEC strains were isolated from symptomatic UTI patients (146 females and 127 males). Phenotypic and molecular identification of ESBL and carbapenemase production was conducted using CLSI 2022 guidelines, with PCR used to detect CTX-M and NDM resistance genes. The antibacterial potential of *A. indica* extract was assessed using the Kirby-Bauer disc diffusion method and compared with the standard antibiotic Gentamicin. **Results:** Among the 273 UPEC isolates, 70% were Multidrug-Resistant (MDR), with 82 isolates producing ESBL and 62 producing carbapenemase. The *A. indica* extract demonstrated significant antibacterial activity, with zones of inhibition averaging 20.18 ± 0.89 mm against ESBL-producing strains and 20.91 ± 1.3 mm against carbapenemase-producing strains—comparable to Gentamicin at 100% concentration. Resistance was more prevalent among hospitalised patients than outpatients. **Conclusion:** The study highlights the high prevalence of MDR UPEC strains and underscores the urgent need for effective alternatives to conventional antibiotics. The significant antibacterial activity of *A. indica* against ESBL- and carbapenemase-producing UPEC suggests its potential use as an adjunct or alternative therapy in UTI management. Incorporating plant-based treatments such as *A. indica* could provide a sustainable, cost-effective strategy to combat antibiotic-resistant infections, particularly in resource-constrained environments. **Major Findings:** *Azadirachta indica* extract under study showed promising antibacterial activity against both ESBL- and carbapenemase-producing strains, with efficacy comparable to Gentamicin, highlighting its potential as a natural therapeutic option.

Keywords: *A. indica,* Carbapenemase, *E. coli*, ESBL, MDR, Phytochemicals, UTI

1. Introduction

Urinary Tract Infections (UTIs) are among the most prevalent bacterial infections, with Uropathogenic *E. coli* (UPEC) responsible for 80–90 % of cases[1]. The increasing prevalence of Multidrug-Resistant (MDR) strains, particularly Extended-Spectrum Beta-Lactamase (ESBL) and Carbapenemase-producing

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E. coli, has rendered many conventional antibiotics ineffective, posing a significant public health challenge[2]. The rise in antimicrobial resistance has imposed the exploration of complementary/alternative treatments, including plant-based therapies. *Azadirachta indica* (*A. indica*), commonly known as neem, has gained attention for its potent antibacterial properties, making it a promising candidate for combating multidrug-resistant bacterial infections[3].

Studies have demonstrated the efficacy of *A. indica* against MDR *E. coli,* with research reporting substantial zones of inhibition and low Minimum Inhibitory Concentrations (MICs), particularly against ESBL-producing strains. The antibacterial effect of *A. indica* is attributed to its rich bioactive composition, including phenolics, flavonoids, tannins, and saponins, which enhance its ability to target Gram-negative bacteria[4,5]. Furthermore, clinical studies have indicated that *A. indica* extracts exhibit comparable or even superior antibacterial activity to conventional antibiotics, particularly against resistant strains[1].

The alarming prevalence of antibiotic-resistant *E. coli* further underscores the need for natural and safe/adjuvant alternative treatments. A study reported that 48% of *E. coli* isolates were found as ESBL producers, with significant resistance to common antibiotics.

Additionally, genetic analyses have revealed a high prevalence of CTX-M (Cefotaximase-M) genes, particularly CTX-M-15, in resistant Gram-negative isolates, while the NDM (New Delhi metallo-β-lactamase) gene has been frequently associated with carbapenemase production, contributing to resistance against last-resort antibiotics[6-8]. The widespread presence of these resistance genes highlights the growing difficulty in treating UTIs using conventional antimicrobials.

Azadirachta indica has been proposed as an effective and cost-efficient alternative therapy, particularly in pediatric and resource-limited settings, where antibiotic resistance poses a critical threat[1]. The potential for *A. indica* to work synergistically with conventional antibiotics further enhances its appeal, as it could reduce the antibiotic dosages while maintaining the antibacterial efficacy[9].

In this way, integrating traditional plant-based therapies with modern medical approaches could provide a sustainable solution to the global antimicrobial resistance crisis. Therefore, this article aims to explore the antibacterial Potential of *A. indica* against ESBL and Carbapenemase-Producing Multidrug-Resistant UPEC.

2. Materials and Methods

2.1 Collection of Sample

During May 2023 to November 2023, UPEC strains (273 Nos) were collected from symptomatic Urinary Tract Infection (UTI) patients (146 females, 127 males). The collected clean catch urine specimen (15 ml) was labelled and immediately transferred to the microbiology laboratory of JNMC, Wardha, for further study.

2.2 Isolation, Purification and Identification of *E coli*

To carry out isolation, urine samples were cultivated on MacConkey agar along with 5% blood agar. The plates were incubated overnight at 37°C. These isolates were purified and maintained on slants. Identification of *E coli* was carried out based on cultural and biochemical characteristics.

2.3 Antibiotic Susceptibility Test

It was carried out by Kirby-Bauer disc diffusion method using Muller-Hinton agar and antibiotic discs as per CLSI (Clinical and Laboratory Standards Institute)-2022 guidelines.

2.4 Screening of *E. coli* for ESBL and Carbapenemase Production

The combined disc method was used to screen isolates of *E. coli* for ESBL production as per CLSI 2022 guidelines. Whereas isolates of *E coli* resistant to antibiotics imipenem and meropenem were selected for Carbapenemase production

2.4.1 Phenotypic Confirmation of EESBL-producing E. coli

Modified Double Disc Synergy Test (MDDST) was used for phenotypic confirmation of ESBL producers. Isolates of *E. coli* were inoculated by keeping a disc of Amoxicillin + Clavulanate (20/ 10 µg) at the centre of the plate. Besides, three antibiotics of Third

generation cephalosporin, i.e., Ceftriaxone, Cefotaxim, Cefpodoxime, and antibiotics of Fourth generation cephalosporin, i.e. cefepime, were placed at 15mm and 20 mm, respectively. The rise in zone of amoxicillin-clavulanate towards the disc was interpreted as positive for ESBL production.

2.4.2 Phenotypic Confirmation of Carbapenemase-producing E. coli

Modified Hodge Test (MHT) was used for phenotypic confirmation of carbapenemase producers using CLSI guidelines. In Tryptic soya broth (1 ml), isolates of *E coli* were inoculated and incubated overnight. Further, it was stored at 20°C by the addition of glycerol (20%) for further molecular detection.

2.5 Molecular Detection of ESBL and Carbapenemase Genes

HiPurA® Genomic DNA (*Deoxyribonucleic Acid)* Purification Kit (HiMedia, Mumbai) was used for plasmid extraction of ESBL and Carbapenemase-producing *E. coli* isolates. Overnight incubated broth cultures (1.5 ml) of *E. coli* were harvested by centrifugation at 13,000 rpm for 2 minutes at 25 ± 2°C. Resulting cell pellets were thoroughly resuspended in lysis solution (180 µl). Subsequently, 20 µl of proteinase K solution (20 mg/ml) was added to the sample, incubated at 55°C for the next 30 min. Thereafter, 20 µl of RNase solution was added to the lysate, vortexed for a few seconds and incubated at 25 ± 2°C for the next 5 minutes. To complete the lysis process, additional Lysis Solution (200 µl) was added and vortexed (15 seconds), followed by incubation at 55°C (10 min).

Based on standard protocol, DNA isolation was performed by adding 200 µl Ethanol (95%) to the lysate, followed by vortexing. Then it was transferred to HiElute Miniprep Spin Column and centrifuged at 10,000 rpm for one minute at 25 ± 2°C. DNA washing was carried out. To perform elution, the spin column was placed in a fresh uncapped collection tube, and 200 **µl** of elution buffer was added to it. After incubation for 1 minute column was centrifuged (10,000 rpm, 1 min.). The purified DNA was then stored at -20°C for further molecular studies.

2.5.1 PCR Amplification of ESBL-encoding Genes in E. coli Isolates

All Uropathogenic-ESBL producing isolates were subjected to molecular characterisation by amplifying selective ESBL genes (CTX-M, SHV, and OXA-10/11). The HiMedia Hi-PCR® Extended Spectrum β-lactamases (ESBLs) Gene Probe PCR kit was used for the specific detection of ESBL-encoding genes in a single-tube multiplex reaction. Before PCR amplification, the reaction mixture was centrifuged at 6,000 rpm for 10 seconds and loaded into the BIO-RAD CFX96 Real-Time PCR System. The thermo cycling conditions were programmed as per the provided guidelines.

2.5.2 PCR Amplification of Carbapenemase-Encoding Genes in E. coli Isolates

All Uropathogenic *E. coli* isolates which were confirmed as Carbapenemase producers were subjected to molecular characterisation by partial amplification of selective carbapenemase genes, including NDM, KPC, IMP, VIM, OXA-23, OXA-48, OXA-51, and OXA-58. HiMedia, Hi-PCR® Carbapenemase Gene (Multiplex) Probe PCR kit was used for specific detection of carbapenemase-encoding genes in a single-tube multiplex reaction, allowing sensitive and accurate identification of both single and co-present genes. For PCR amplification, the reaction mixture was centrifuged (6,000 rpm, 10 seconds) before loading into the BIO-RAD CFX96 Real-Time PCR System. The thermo cycling conditions included an initial denaturation at 95°C for 10 minutes, followed by 45 cycles of denaturation at 95°C for 5 seconds and annealing/extension at 60°C for 1 minute, with plate read detection at FAM/HEX/Texas Red/Cy5/Cy5.5. A final hold at 4°C was maintained indefinitely. The amplified products were directly analysed in a PCR system, and the resulting graphs were assessed for final interpretation and reporting.

2.6 Extraction and Sample Preparation

Plant material of *A. indica* was collected from DMIMS MGAC and H, Wardha and identified and authenticated. Further, the collected material was shade dried at room temperature and ground into powder. Soxhlet Extraction using 50% methanol was carried

out to extract the water-soluble and alcohol soluble bioactive phytochemicals. The filtrate, i.e. sample, was concentrated using a rotary evaporator and stored at 4°C for further use.

2.7 Assessment of Antibacterial Activity

The Kirby-Bauer disc diffusion method was used for the determination of the antibacterial activity of the sample at two different concentrations (100 % and 50 %). Bacterial culture of ESBL and carbapenemase-producing *E. coli* was adjusted to 0.5 McFarland turbidity standards and inoculated on Nutrient Agar (NA). The sterile filter paper discs (6 mm), impregnated with plant extract, were placed on a culture plate seeded with genetically confirmed *E. coli*. The disc impregnated with Methanol (50 %) was used as a control. The standard antimicrobial disc of Gentamicin (10 µg/ml) was used as a standard. The plates were further incubated for 24 hr., and zones of inhibition were recorded. To ensure the reliability of results, the experiment was performed in triplicate.

3. Results and Discussion

3.1 Isolation, Purification and Identification of *E. coli*

Antibiotic Susceptibility test showed prominent zones (Figure 1). Further, the Phenotypic Confirmation of ESBL and Carbapenemase producing *E. coli* by Modified Double Disc Synergy (Figure 2A) Test and the Modified Hodge Test (Figure 2B) respectively showed remarkable results.

3.2 Prevalence of ESBL and Carbapenemase Genes

It was found that among all ESBL-producing isolates, the CTX-M gene was found to be most prevalent (39%), whereas, SHV gene was found to be less common (13%).

In case of Carbapenemase genes, the NDM gene was found to be most frequently detected (37%), followed by VIM as well OXA-48 genes (33% each). The KPC gene was identified in only 4% of isolates, whereas IMP, OXA-23, OXA-51, and OXA-58 genes were absent. (Figure 3 and Figure 4) Findings on the prevalence of ESBL and Carbapenemase genes revealed the significant

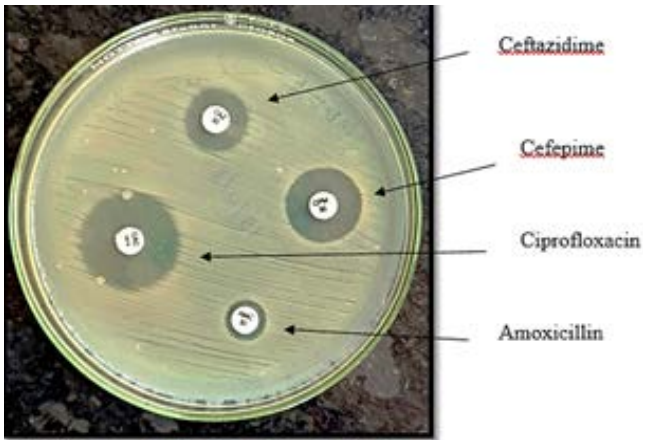


Figure 1. Antibiotic susceptibility test.

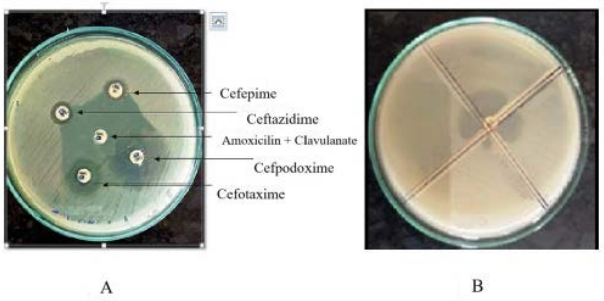


Figure 2. Phenotypic Confirmation of ESBL and Carbapenemase-producing *E. coli*; **A.** ESBL production; **B.** Carbapenemase production.

presence of CTX-M and NDM genes, both of which are strongly associated with multidrug resistance. The absence of certain Carbapenemase genes indicated the variability in resistance gene distribution, which could influence the treatment strategies and infection control measures. These results not only align with global resistance trends but also reflect the regional variations, underlining the need to focus on prevalent genes like CTX-M and NDM for efficient control of UTI and associated therapeutic interventions[10].

Therefore, to limit the spread of multidrug-resistant organisms among high-risk patients, there urgent need for robust infection control measures and judicious antimicrobial use in hospital environments.

3.3 Assessment of Antibacterial Activity

During the assessment of the antimicrobial activity of *A. indica* extract against ESBL-producing UPEC, it was observed that the *A. indica* sample exhibited a remarkable zone of inhibition of 20.18 ± 0.89 mm

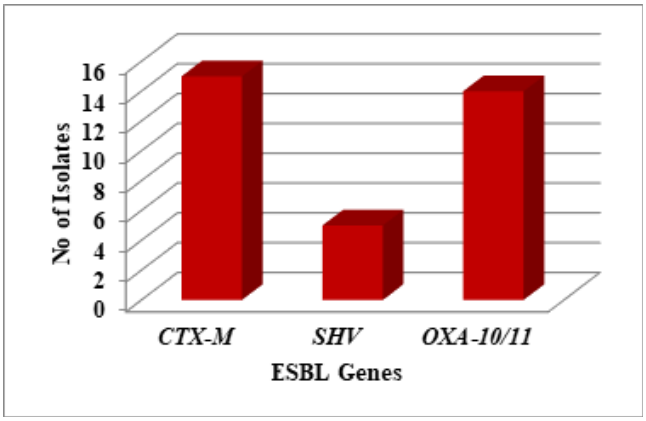


Figure 3. Prevalence of ESBL genes.

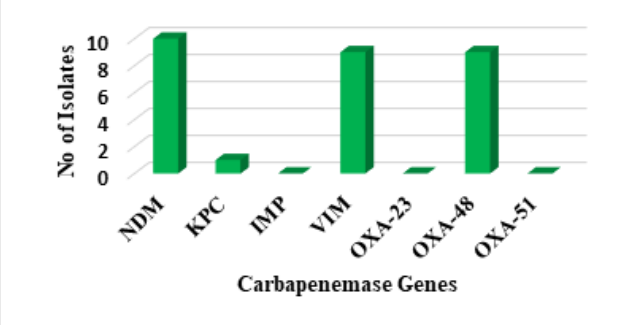


Figure 4. Prevalence of carbapenemase genes.

at 100%, which was statistically comparable to the standard antibiotic Gentamicin (21.28 ± 1.6 mm). However, the inhibition zone was found to decrease to 14.93 ± 2.4 mm at 50 % (Figure 5 and Table 1).

In the case of Carbapenemase-producing UPEC, *A. indica* extract showed a zone of inhibition of 20.91 ± 1.3 mm at 100%, which was slightly higher than the inhibition zone of Gentamicin (20.81 ± 1.6 mm), signifying the superior activity of this extract against these resistant strains.

Whereas the inhibition zone was reduced to 16.6 ± 2.2 mm at a concentration of 50 % (Figure 6 and Table 1).

Statistical analysis confirmed that at 100% concentration of the sample, the zone of inhibition did not significantly differ from Gentamicin ($p > 0.05$), whereas at 50% concentration of the sample, the reduction in inhibition was statistically significant ($p < 0.05$). Based on these findings, *A. indica* shows remarkable antimicrobial potential against both ESBL- and carbapenemase-producing UPEC. Although the efficacy was found to decrease at lower concentrations, the sample has shown considerable activity, justifying further exploration for its therapeutic applications. The antimicrobial activity of *A. indica* demonstrates a strong dose-dependent effect, signifying its potential as a promising antibacterial agent comparable to conventional antibiotics. This activity is due to the bioactive compounds of *A. indica,* which could disrupt bacterial cell walls and inhibit critical enzyme systems, particularly in ESBL- and Carbapenemase-producing UPEC.

The ineffectiveness of 50% methanol against MDR *E. coli* in UTIs might be attributed to a combination of various factors, such as membrane impermeability, as *E. coli* has a complex cell membrane, impermeable to certain solvents, including methanol[11]. Besides, the MDR *E. coli* can possess efflux pumps that actively remove toxic substances, including methanol, from the cell[12]. Methanol could also show its solvent effects on the agar medium, potentially reducing its effectiveness against bacterial growth[13]. The MDR *E. coli* also form biofilms, which could help protect these bacteria from the antimicrobial effects of methanol[14]. Moreover, the MDR *E. coli* can possess various antimicrobial resistance mechanisms, such as enzymatic inactivation

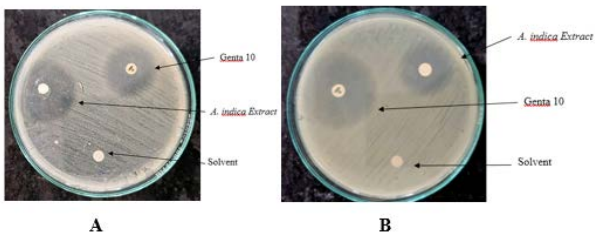


Figure 5. Antibacterial potential of *A. indica* with concentration of 100% (A) and 50% (B) against Uropathogenic ESBL-producing *E. coli.*

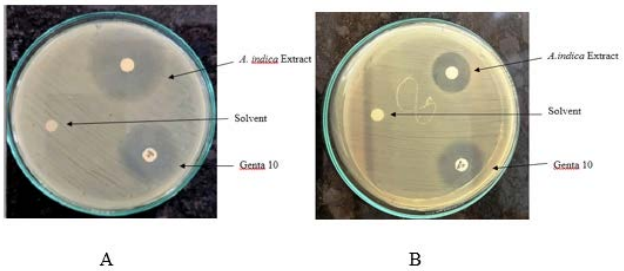


Figure 6. Antibacterial potential of *A. indica* with concentration of 100% (A) and 50% (B) against Uropathogenic Carbapenemase-producing *E. coli.*

Table 1. Antibacterial activity of *A. indica* against genetically confirmed ESBL and carbapenemase-producing UPEC

Sample Concentration (%)	Zone of inhibition of *A. indica extract (mm)*	Zone of inhibition of Standard Gentamicin (mm)
ESBL-producing UPEC		
100	20.18 ± 0.89	21.28 ± 1.6
50	14.93 ± 2.4	21.28 ± 1.6
Carbapenemase-producing UPEC		
100	20.91 ± 1.3	20.81 ± 1.6
50	16.6 ± 2.2	20.81 ± 1.6

or target modification, that can render methanol ineffective[15-17].

4. Conclusion

The rising prevalence of antibiotic-resistant *E. coli*, particularly ESBL- and Carbapenemase-producing UPEC strains, is a major challenge in UTI management. This study highlights the alarming resistance rates, with 70% of UPEC isolates exhibiting multidrug resistance. The detection of key resistance genes, such as *CTX-M-15* and *NDM*, underscores the increasing difficulty in treating UTIs with conventional antibiotics. Consequently, this suggests the urgent need for alternative or complementary treatment strategies. During the study, *A. indica* has demonstrated significant antibacterial properties against MDR UPEC strains. The crude extract exhibited inhibition zones of 20.18 ± 0.89 mm against ESBL-producing UPEC and 20.91 ± 1.3 mm against Carbapenemase-producing UPEC, comparable to standard Gentamicin. These findings suggest that *A. indica* holds considerable antibacterial potential and may serve as an effective complement or alternative to conventional antibiotics in UTI treatment. The results of this study emphasise the necessity of exploring plant-based therapies as viable solutions for combating MDR bacterial infections. Given the dose-dependent antibacterial activity of *A. indica*, further research is essential to optimise its formulation by assessment of its synergistic potential with conventional antibiotics, and to evaluate its clinical applicability. Implementing such complementary/alternative approaches in resource-limited settings could offer a sustainable and cost-effective strategy to combat the antibiotic-resistant *E. coli*, particularly ESBL- and Carbapenemase-producing UPEC strains.

5. Acknowledgement

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6. Ethics Statement

Although no human or animal subject was directly involved in this research, ethical approval was obtained from the Institutional Ethics Committee (IEC) of DMIHER (DU) Wardha, Maharashtra, India. (Ref No: DMIMS (DU)/IEC/2022/02 dated 15th July 2022).

7. Author Contribution

N. P. Khairnar: Conducted Research experiments; P. Dawande: Supervision, Project administration; N. J. Bankar: Mentoring; S. S. Ghangale: Formal analysis; P. S. Musale: Writing draft, Data curation; A. V. Handore: Conceptualization, writing and editing. All authors have read and agreed to the published version of the manuscript.

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