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Research Article

Exploring Multi-drug Resistance Patterns in *Escherichia coli* Isolated from the Gut of Healthy Individuals: A Comprehensive Analysis

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A B S T R A C T

Introduction: Antibiotic resistance is a global health concern that must be addressed immediately. To combat antibiotic resistance, we need to understand the origins and transmission of resistant bacteria in both community and clinical settings. Commensal *Escherichia coli* (*E. coli*) can operate as resistance gene repositories in the human gut.

Objective: To determine the prevalence of resistance in isolated *E. coli* from the gut of reportedly healthy individuals, towards commonly used antibiotics.

Methods: E. coli isolates from 100 stool samples were subjected to routine identification and susceptibility testing by the Kirby-Bauer method. The *E. coli* isolates confirmed by biochemical tests were then stored for genotypic correlation using the PCR method.

Results: Out of 100 isolates, 18 showed resistance to multiple groups of drugs. Out of this, 15 were found to be Extended Spectrum Beta Lactamase (ESBL) producers (83%) and 2 were carbapenem-resistant (CR) (11%). The highest sensitivity was observed to meropenem (98%) followed by imipenem (86%) and gentamicin (86%). It showed highest resistance to ampicillin (36%) and cefazolin (31%). The prevalence of the *TEM* gene was higher in ESBL producers (35%) followed by NDM and KPC in CR MDR E. coli (50% each). None of the CR isolates exhibited *VIM* and *IMP* genes.

Conclusion: Antibiotic use should be judicious, and modern diagnostic tools should be used to detect MDR isolates early in order to curb the emergence and spread of these bacteria in the gut of healthy individuals.

Keywords: Escherichia Coli, Multi-Drug Resistance, ESBL, CR

Introduction

Enterobacterales constitute a diverse family of bacteria widely distributed in the environment, accounting for 80% of gram-negative bacterial isolates obtained from clinical samples. Within this family, several notorious pathogens, including Escherichia coli, Klebsiella species, and Salmonella species, have garnered significant attention due to their capacity to induce a wide spectrum of disorders in humans.

Escherichia coli, often abbreviated as E. coli, stands out as a particularly intriguing member of the *Enterobacteriaceae* family. It is a gram-negative, facultative anaerobic bacteria residing in the genus Escherichia. E. coli establishes its presence shortly after birth in the human gut. In doing so, it contributes to the depletion of oxygen along the gastrointestinal mucosal surface, thus creating an environment conducive for strict anaerobes to colonise and dominate.[1]

The human gut harbours the largest population of commensal bacteria, and these inhabitants are not immune to the effects of antibiotics, whether administered orally or through parenteral routes.[2,3] Infections caused by antibiotic-resistant bacteria, particularly multidrug-resistant (MDR) species, pose significant challenges, leading to prolonged hospitalisation, treatment failures, and even fatalities.[4]

One striking example of gram-negative bacteria's adaptability in the face of new antimicrobial challenges is the emergence of Extended-Spectrum Beta-Lactamases (ESBLs). These enzymes can be produced by various members of the *Enterobacteriaceae* including E. coli, and serve as a testament to the bacteria's ability to develop novel antibiotic resistance mechanisms. More recently, it has been identified that carbapenemase production contributes significantly to drug resistance in *Enterobacteriaceae*.[5,6]

Colonisation by MDR bacteria in the intestinal tract carries profound implications for both individuals and communities.[1,4] Researchers have recently explored the potential of non-antimicrobial compounds, such as proanthocyanidin, in preventing MDR bacterial infections.[7]

This present study aims to ascertain the existence of critical genes responsible for antibiotic resistance, including bla_{CTX-M}, bla_{TEM}, bla_{NDM}, bla_{KPC}, bla_{VIM}, and bla_{IMP}, within clinical isolates derived from stool specimens collected at the Laboratory of Microbiology in a tertiary care hospital.

Materials and Methods

This study was a prospective investigation conducted from January 2023 to August 2023 at Chettinad Academy of Research and Education (CARE), situated in Kelambakkam, Chengalpattu, Tamil Nadu. Ethical approval for this study was obtained from the Institutional Human Ethics Committee (IHEC) of CARE (IHEC-I/1913/23). One hundred stool samples were collected from healthy individuals after their consent was obtained for the study.

Inclusion Criteria

In this study, all non-duplicate *Escherichia coli* isolates obtained from the stool culture of samples collected from healthy individuals were included for analysis.

Exclusion Criteria

E. coli isolates obtained from various clinical samples, including blood, exudates, urine, and stool from patients with infections of the gastrointestinal tract as well as other bacterial colonies isolated from stool samples of healthy individuals were excluded from this study.

Study Procedure

Sample Processing and Identification

Stool samples, collected in sterile containers, underwent a meticulous laboratory process for the isolation and identification of E. coli. Initially, the samples were streaked onto MacConkey's agar (Figure 1), a specialised medium designed for the selective growth and differentiation of members of the *Enterobacteriaceae* family, with a particular emphasis on gram-negative bacteria. Following the streaking process, the agar plates were incubated for 12 to 24 hours at 37 °C. To establish the identity of these gram-negative isolates as Escherichia coli, a battery of biochemical reactions was performed (Figure 2). Finally, the confirmed E. coli species were preserved by storing them in a Brain Heart Infusion (BHI) glycerol broth at a frigid -20 °C for future reference and research.

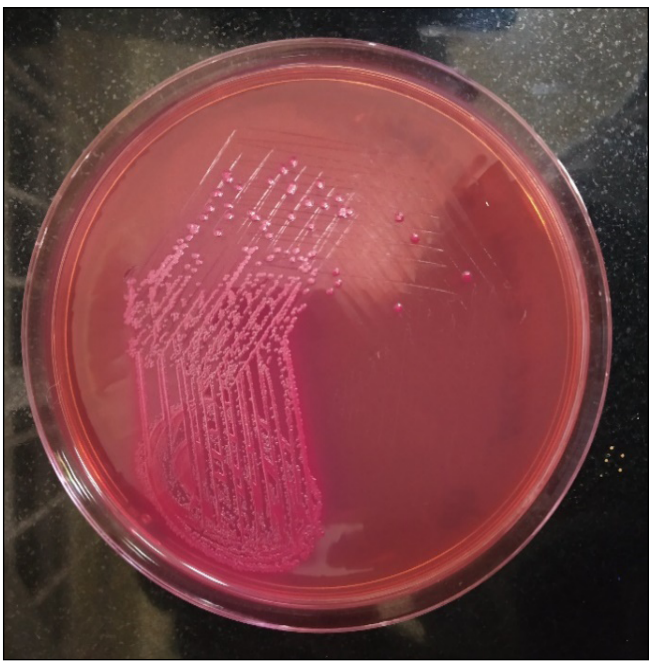

Figure 1.Lactose Fermenting Colonies Seen on Mac-Conkey Agar After 24 Hours of Growth

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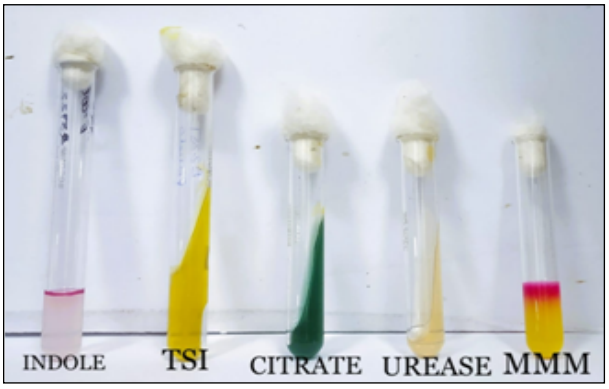

Figure 2.Various Tests Conducted to Identify *Escherichia coli* within the *Enterobacteriaceae* Family (Indole, TSI, Citrate, Urease, and MMM Tests)

Antibiotic Sensitivity Testing

The colonies confirmed as E. coli were then inoculated into peptone water and were incubated at 37 °C for 1 hour; its turbidity was set with 0.5 Mc Farland standard. The Kirby–Bauer disc diffusion method was used to detect the antibiotic sensitivity pattern.

The following antibiotics manufactured by HI Media Labs, Mumbai, India were used (Figure 3): ampicillin (10 µg), amikacin (30 µg), cefazolin (30 µg), cefuroxime (30 µg), ciprofloxacin (5 µg), cefotaxime (30 µg), cotrimoxazole (1.25 µg/ 23.75 µg), tobramycin (10 µg), gentamicin (10 µg), cefepime (30 µg), meropenem (10 µg) imipenem (10 µg), and piperacillin/ tazobactam (100 µg/ 10 µg).

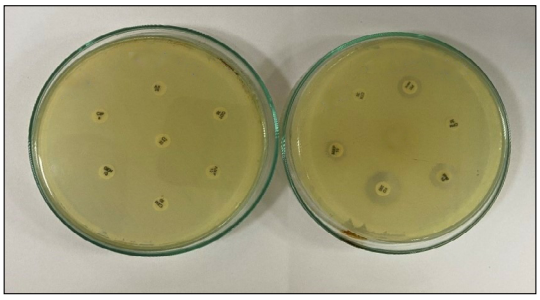

Figure 3.Kirby–Bauer Disc Diffusion Method Employed to Determine the Resistance Pattern of the Isolated *E. coli*

The sensitivity zone was measured using a measuring scale and compared with the standard zone size according to the recent CLSI guidelines (2023).[8] The zones that were interpreted as ESBL and Carbapenem-Resistant (CR) were taken for further genotypic characterisation.

Genotypic Characterisation of Genes Responsible for MDR

In order to isolate genomic DNA from bacterial isolates, nutrient agar culture plates were incubated overnight with a pure culture of the isolated bacteria.

Cell Lysis and Extraction of DNA

Isolated MDR colonies of E. coli were aseptically transferred to 1.5 ml centrifuge tubes. Within each tube, sterilised double-distilled water was added up to 1 ml, and the mixture was carefully handled using a sterilised loop wire (4 mm). The isolated colonies were subsequently subjected to a heat treatment process, placed in a water bath, and boiled at 95 °C for 15 minutes. After this thermal treatment, the samples were centrifuged for 10 minutes at 15,000 rpm to separate cellular components.

Primer Designing

In this study, we meticulously selected the primers (forward and reverse) from the 2019 second edition of the ICMR's Standard Operating Procedures for Bacteriology and Antimicrobial Resistance Surveillance[9] (Table 1).

Table 1.Primer Sequences used in this Study

Target Gene	Primer Sequence (5' to 3')	Amplicon Size (kbp)
CTX-M	Forward - ATGTGCAGYACCAGTAARGT Reverse - TGGGTRAARTARGTSACCAGA	593
TEM	Forward - ATGAGTATTCAACATTTCCG Reverse - GACAGTTACCAATGCTTAATCA	862
NDM	Forward – TAAAATACCTTGAGCGGGC Reverse - AAATGGAAACTGGCGACC	439
KPC	Forward - TGTTGCTGAAGGAGTTGGGC Reverse - ACGACGGCATAGTCATTTGC	340
VIM	Forward - CGCGGAGATTGARAAGCAAA Reverse - CGCAGCACCRGGATAGAARA	247
IMP	Forward - GAGTGGCTTAATTCTCRATC Reverse - CCAAACYACTASGTTATCT	183

Master Mix

For this study, we utilised a commercially available SYBR Green PCR master mix. For each of the six genes under investigation, both forward and reverse primers were added.

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The PCR reaction mixture was prepared for 25 µl and contained the following:

- Master Mix (12.5 µl) that was prepared by adding selected genes, H_2O, and a pre-mix
- Nuclease-free water (8.5 µl)
- Forward primer (1 µl)
- Reverse primer (1 µl)
- Test sample DNA (2 µl)

This mixture was stored at -20 °C for future use.

Conventional PCR Method

We employed the conventional PCR method for this study (Table 1).[10–12] The conditions of cycles were as follows: 95 °C for 15 minutes initially followed by 30 cycles of amplification of 30 seconds each at 94 °C, 59 °C, and 72 °C. In the final step of PCR amplification, the temperature was raised to 72 °C for 10 minutes.

Results

In the present study, we isolated 100 clinically confirmed E. coli strains from stool samples obtained from healthy individuals at a tertiary care hospital. Among these healthy individuals, 71% were female, while 29% were male. Regarding the age distribution, 25% of the healthy individuals were in the age groups of 31–40 and 41–50 years, 18% were in the age group of 51–60 years, 15% were in the age group of 61–70 years, and 10% were less than 30 years old. The remaining 7% of healthy individuals were aged over 70 years.

Antimicrobial Susceptibility

Among the 100 clinical samples, we observed varying sensitivity patterns to different antibiotics. Notably, higher sensitivity was found towards the following drugs: meropenem (98%), imipenem (86%), cefepime (81%), cefotaxime (80%), and gentamicin (86%). On the other hand, the highest amount of resistance patterns were observed in ampicillin (36%) and cefazolin (31%) (Figure 4).

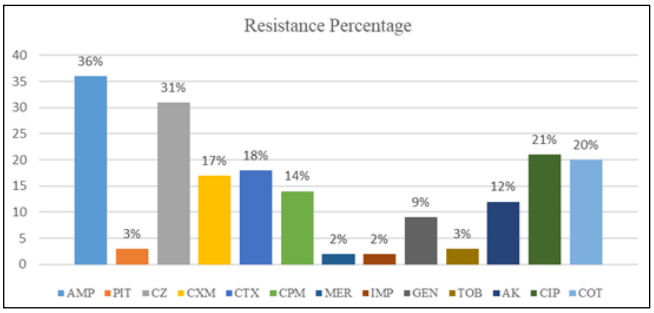

Figure 4.Antibiotic Resistance Observed in Isolated *E. coli*

AMP: ampicillin, PIT: piperacillin/ tazobactam, CZ: cefazolin, CXM: cefuroxime, CTX: cefotaxime, CPM: cefepime, MER: meropenem, IMP: imipenem, GEN: gentamycin, TOB: tobramycin, AK: amikacin, CIP: ciprofloxacin, COT: cotrimoxazole

Out of the 100 isolates, 18% of the *Escherichia coli* strains exhibited multidrug resistance (MDR). Among these 18 MDR samples, 15 (83%) were identified as the strains of ESBL producers, while the remaining 2 (11%) were characterised as carbapenemase producers.

Gene Detection

A conventional PCR method was employed to detect the presence of ESBL resistance genes in 15 isolated E. coli strains, specifically targeting the $bla_{CTX\text{-}M}$ and bla_{TEM} genes. Additionally, the presence of carbapenem resistance genes, namely bla_{NDM}, bla_{KPC}, bla_{VIM}, and bla_{IMP}, was assessed in the remaining 3 isolates.

Among the ESBL isolates, it was observed that the majority (33%) carried the bla_{TEM} gene within their plasmid DNA, while only a minority (7%) encoded the $bla_{CTX\text{-}M}$ gene within their plasmid DNA (Figure 5). Out of the 3 CR isolates, 1 (33%) was found to encode both the bla_{NDM} and bla_{KPC} genes within their plasmid DNA. Interestingly, none of the carbapenemase isolates was found to harbour the bla_{VIM} or bla_{IMP} genes within their plasmid DNA (Figure 6).

Figure 5.*bla*TEM and *bla*CTX-M Genes Detected in ESBL-isolated MDR *E. coli*

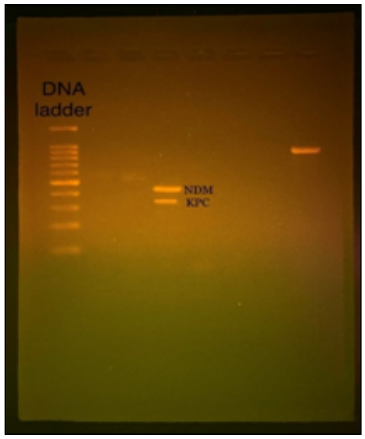

Figure 6.*bla*NDM and *bla*KPC Genes Detected in CR-isolated MDR *E. coli*

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Discussion

The majority of *E. coli* isolates in our study were obtained from females, constituting 71% of the total isolates, while males accounted for 29%. These findings align with a study conducted by Magliano et al. in 2012 in Italy, which reported a similar gender-based distribution of E. coli isolates.[13]

In our study, the highest percentage of female participants from the age group of 31–40 years accounted for 21% of the isolates, while the lowest percentages were observed from the age group of 71–80 years (5%) and less than 30 years (4%). Among males, the age group of 41–50 years had the highest number of isolates (10%), whereas the lowest was observed from the age group of 31–40 years (4%). These findings align with a study conducted by Asare et al. in 2022 in Ghana, which also reported that the majority of *Escherichia coli* isolates were obtained from individuals belonging to the age group of 21–40 years, regardless of gender.[14]

Escherichia coli exhibited the highest sensitivity to meropenem (98%), imipenem (86%), and gentamicin (86%), followed by cefepime (81%) and cefotaxime (80%). It's worth noting that in a study conducted by Joly-Guillou et al. in 2010 in France, 100% sensitivity was reported for imipenem and meropenem.[15]

In this study, a higher percentage of resistance was seen towards ampicillin (36%) and cefazolin (31%) compared to other antibiotics. Interestingly, a study by Eryılmaz et al. conducted in 2010 in Turkey reported even higher resistance percentages for *Escherichia coli* against ampicillin (56%) and lower resistance against cefazolin (12%).[16]

Furthermore, our present study identified 18% of the isolates as MDR *Escherichia coli.* This finding differs from a study by Ibrahim et al. conducted in 2010 in Saudi Arabia, where a higher proportion of isolated organisms exhibited resistance to more than two classes of drugs, estimated at 53%.[17]

In our study, of the 18 MDR strains, a substantial number of ESBL producers were identified, accounting for 83% of the total. It's noteworthy that Mahmud et al. from Bangladesh reported similar findings (71%), indicating a high prevalence of ESBL-producing *E. coli.*[18]

In our study, we found that 11% of the isolated MDR strains demonstrated carbapenemase production in *Escherichia coli* strains. Interestingly, this contrasts with the findings of Govindhaswamy et al. from New Delhi, who reported a higher prevalence of carbapenemase-producing *Escherichia coli* in their study (61.5%).[19]

In our study, the *CTX-M* gene was detected in 7% of the isolated *Escherichia coli* strains. However, this differs from the findings of Benavides et al. from Peru, who reported a higher prevalence of this gene among their isolated *Escherichia coli* strains (14%).[20]

In our study, more *TEM* genes were isolated from ESBL-producing Escherichia coli, accounting for an estimated 33% of the cases. Interestingly, Shahid et al. from Uttar Pradesh reported a lower finding that further supported the prevalence of *TEM* genes in ESBL-producing *Escherichia coli* (10.9%).[21]

In our study, a higher number of *NDM* and *KPC* genes were detected in the isolated Escherichia coli, with an estimated prevalence of 33% each. These findings align with the results reported by Flerlage et al. in 2020 and Hazen et al. in 2018, reinforcing the prevalence of *NDM* and *KPC* genes in *Escherichia coli* isolates.[22,23]

However, our study revealed no prevalence of the *VIM* and *IMP* genes in carbapenemase-producing Escherichia coli. This finding is consistent with the results reported by Mahmoud et al. in 2020 from Sudan, where they also found no prevalence of these carbapenemase-encoding genes in Escherichia coli.[24] In contrast to our own findings, the study conducted by Subramaniyan et al. in 2018 reported a 26% prevalence of bla_{VIM} genes in carbapenemase-producing organisms.[25]

Conclusion

Escherichia coli had the highest sensitivity to meropenem (98%) followed by imipenem (86%), gentamicin (86%), cefepime (81%), and cefotaxime (80%). It showed highest resistance to ampicillin (36%) and cefazolin (31%). The prevalence of multi-drug resistance was noted in 18% of the isolates of *Escherichia coli* obtained from the gut of healthy individuals, of which 15 (83%) were ESBL producers and 2 isolates (11%) were found to be carbapenemase producers. In this study, the prevalence of the *TEM* gene was higher in ESBL producers (33%) and there was no *VIM* and *IMP* gene from the CR *E. coli.*

Conflict of Interest: None

Source of Funding: None

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