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COLLATERAL SENSITIVITY PROFILING OF ANTIBIOTICS IN DRUG-RESISTANT ESCHERICHIA COLI: A COMPARATIVE PHARMACOLOGICAL ANALYSIS

Muhammad Auwal Sule[1], Eko Otakwu[2]
[1]Centre for Civil-Military Cooperation (CIMICO), Abuja, Nigeria. Email: albalagu1@gmail.com
[2]RCCG, Ebonyi State, Nigeria. Email: civilsocietyofnigeria@gmail.com

***CorrespondingAuthor:** MuhammadAuwalSule, albalagu1@gmail.com*

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ABSTRACT

Antimicrobial resistance in Escherichia coli continues to limit the effectiveness of commonly used antibiotics and has increased interest in collateral sensitivity as a potential strategy for exploiting resistance-associated trade-offs. Comparative minimum inhibitory concentration (MIC) profiling can help distinguish collateral sensitivity from cross-resistance patterns. To compare MIC-based antibiotic susceptibility between susceptible and drug-resistant E. coli and identify fold-change patterns consistent with cross-resistance or potential collateral sensitivity. A secondary comparative pharmacological analysis was performed using publicly available phenotypic antimicrobial susceptibility data. E. coli ATCC 25922 served as the susceptible reference strain and E. coli LSI-770 as the resistant comparator. MIC values, susceptibility classifications, MIC fold changes, $\log_2$ fold changes, and agreement between BLAST-derived and reference broth microdilution measurements were evaluated. The reference strain remained susceptible to all 11 evaluated antibiotics. Direct comparison was available for doxycycline, levofloxacin, and cefazolin. The resistant strain showed marked MIC elevation for all three agents. Levofloxacin demonstrated the greatest MIC increase, followed by doxycycline, while cefazolin showed off-scale resistance. No negative MIC fold change was observed, indicating cross-resistance rather than detectable collateral sensitivity. BLAST measurements showed generally strong agreement with reference broth microdilution. The resistant E. coli strain exhibited broad reduced susceptibility across matched antibiotics, supporting a cross-resistance profile. Larger strain panels and broader antibiotic matrices are needed to identify reproducible collateral-sensitivity relationships.

Keywords: Escherichia coli; collateral sensitivity; cross-resistance; minimum inhibitory concentration; antimicrobial resistance

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1. Introduction

Antimicrobial resistance has emerged as a major problem in the treatment of bacterial infections especially those which are caused by multidrug resistant Gram-negative organisms. Escherichia coli is a clinically significant organism due to its capability to cause urinary tract, bloodstream, gastrointestinal, and other types of infections, as well as gradually develop resistance to various classes of antimicrobials. The rise of extensively and multidrug-resistant strains has decreased the use of traditional treatments and raised the necessity of approaches that would help to conserve the remaining antibiotics (Almutairy, 2024). Other antimicrobial strategies, such as antimicrobial peptides, have been considered in targeting extensively drug-resistant bacteria due to the possibility of an increased restriction of conventional drug options (Askari et al., 2021). Other such efforts have comprised engineered antimicrobial peptides active against resistant ESKAPE pathogens, emphasizing the more general hunt of effective treatments against challenging bacterial infections (Chaudhary et al., 2023).

Phenotypic antimicrobial susceptibility testing continues to be crucial in the identification of whether strains of bacteria are susceptible to certain antibiotics. The minimum inhibitory concentration measures are considered to have a quantitative estimate of the lowest concentration of antimicrobial that could inhibit the visible bacterial growth, thus making it possible to compare the susceptibility of different strains to different drugs. Alteration of drug targets, efflux, reduced permeability, enzymatic inactivation or acquisition of mobile genetic elements can all lead to resistance. It has been shown that resistance can be gradually acquired during experimental exposure of E. coli ATCC 25922 to sub-inhibitory concentrations of antimicrobials (Gu et al., 2020). Phenotype-based methods have thus continued to be useful in monitoring clinically significant resistance phenotypes, such as the fluoroquinolone resistance in E. coli (Marzouk & Almuzaini, 2025). Pharmacodynamic and pharmacokinetic studies have also provided increased reasons to believe that the optimization of therapeutic combinations is more important when the activity of antibiotics is optimized against multidrug-resistant E. coli (Kroemer et al., 2024).

Collateral sensitivity is an evolutionary trade-off where the development of resistance against one antimicrobial agent results in an increase in susceptibility to another, but cross-resistance is when the development of resistance against one drug is associated with a decrease in susceptibility to more than one drug. Genetic background, resistance mechanism, and antimicrobial class are factors that affect these relationships. Multidrug resistance reviews have highlighted the evolutionary significance of collateral sensitivity as a possible vulnerability that can be used to aid in therapy (Fodor et al., 2020). The change in the susceptibility to unrelated antibiotics by resistance plasmids also indicates that mobile genetic elements can be involved in collateral patterns of sensitivity (Cristina et al., 2021). Mechanisticer detailed similar trade-offs of plasmid-associated susceptibility have been described (Herencias et al., 2021). Expansive studies have also characterized collateral sensitivity as a resistance trade-off that has the potential to be useful in antibiotic sequencing and treatment design (Mahmud and Wakeman, 2024).

The sensitivity of collateral is not always steady and constant. It has been demonstrated, using experimental evolution experiments, that varying patterns of resistance may produce divergent patterns of susceptibility and this has been demonstrated in the case of vancomycin selection in Staphylococcus aureus (Card et al., 2025). Similar evolutionary trade-offs were also found in fungal infectors, with collateral sensitivity having an antifungal resistance antifungal resistant Candida auris (Carolus et al., 2024). The dynamic profiles can evolve with time, making it hard to design effective antibiotic sequences (Maltas et al., 2021), with future research pointing to the opportunities and constraints that come with taking advantage of such temporal profiles in therapy (Maltas et al., 2025). Combination therapy resistance mechanisms can also interact to influence the change of treatment response and development of cross-resistance (Morales-Durán et al., 2024).

The value of systematic susceptibility profiling has been supported by evidence in particular with regard to drug resistant E. coli. Cephalosporin resistance Suppression by compounds has been determined by collateral sensitivity screening in resistant E. coli, showing the pharmacological

usefulness of comparing processes of MIC responses on antimicrobial agents (Liu et al., 2023). Other modelling methods have analysed whether the older antibiotics can be active against the multidrug-resistant Gram-negative pathogens (Paranos et al., 2022). Defined genomic changes can also result in collateral susceptibility, as can be seen with heteroresistant bacterial populations, which bear a given resistance-related change (Sancak et al., 2026). In spite of these improvements, comparative MIC-based analysis of corresponding susceptible and resistant E. coli strains is still significant to sort out possible collateral-sensitivity indicators and cross-resistance. Thus, the current work compared the profiles of MIC, measured antibiotic-specific fold changes, and assessed the pattern of phenotypic susceptibility of the chosen pharmacological classes.

Objectives of the study

1.To compare MIC-based antibiotic susceptibility between susceptible and resistant E. coli.
2.To identify MIC fold-change patterns indicating cross-resistance or potential collateral sensitivity.

2. Methodology

2.1 Study Design

A secondary comparative pharmacological analysis was done by using publicly available phenotypic antimicrobial susceptibility data. The comparison was based on the variations in the response of the antibiotic on a susceptible model strain of Escherichia coli and a drug-resistant isolate of E. coli. The main pharmacological outcome was the measurements of minimum inhibitory concentration. The experiment compared the susceptibility patterns among the available antibiotics, and measured the change in MIC magnitude, resistance state, and potential collateral-sensitivity/cross-resistance reactions between matched antimicrobial observations of the source data.

2.2 Data Source

Data were obtained from the publicly available A Rapid Bacterial Labeling Method for Phenotypic Antimicrobial Susceptibility Testing collection available in Mendeley Data (Kittle & Lwande, 2025). The source included the BLAST-derived MIC values of E. coli ATCC 25922 against 11 antimicrobial agents along with reference broth microdilution values and CLSI quality-control data. A starting inoculum of around 5 × 106 CFU/mL had already been tested on bacteria isolates and the files were downloaded in Microsoft Excel format to be analyzed.

2.3 Bacterial Strains and Antibiotic Selection

It was analyzed with E. coli ATCC 25922 as antimicrobial susceptible control strain and E. coli LSI-770 as the drug-resistant comparison. They were nitrofurantoin, meropenem, ceftriaxone, ciprofloxacin, cefuroxime, amoxicillin/clavulanate, ampicillin, cefoxitin, doxycycline, levofloxacin, and cefazolin. Only doxycycline, levofloxacin, and cefazolin were directly compared resistant-versus-susceptible due to the availability of respective MIC measurements in both strains. Antibiotics were also categorized based on their pharmacological classes to aid the interpretation of susceptibility patterns based on classes.

2.4 MIC Processing and Susceptibility Classification

The values of minimum inhibitory concentration were obtained in µg/mL and categorized on the basis of the susceptible, intermediate, or resistant categories found in the source files. Precise numeric values of MIC were left unaltered, but off-scale measurements, which were represented in terms of inequality signs, were considered as censored observations. Any value that was more than 142 µg/mL was not regarded as an exact measurement and was only used to estimate the minimum fold changes. The consistency of susceptibility classifications and reference-strain measurements were checked by means of available CLSI breakpoint and quality-control information.

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2.5 Comparative Pharmacological and Collateral-Sensitivity Analysis

The susceptible and resistant E. coli strains were matched in terms of MIC values. The fold change of MIC was determined by dividing the resistant-strain MIC by the reference-strain MIC and precision values were converted to log2 fold changes. Changes in positive log2 were considered as decreased susceptibility or cross-resistance, and changes in negative log2 as possible collateral-sensitivity signals. Near-zero changes denoted low susceptibility changes. Since no antibiotic-specific evolved resistant lineages were present, any reduction in MIC would have been seen as a potential, but not definitive, collateral-sensitivity response.

2.6 Statistical Analysis

Antimicrobial susceptibility and MIC patterns were summarized using descriptive analyses. The maximum, minimum, median, arithmetic and geometric mean were used to summarize MIC values where necessary. The susceptibility classifications were computed in frequencies and percentages. MIC fold change and log2 fold change were used to assess matched antibiotics and censored MIC values were reported with minimum possible fold-change estimates. Two-fold differences in dilution were assessed to determine agreement between BLAST and reference broth microdilution measurements. There was no inferential comparison done since the observations of the resistant versus reference were small.

3. Results

3.1 Baseline Antimicrobial Susceptibility Profile of E. coli ATCC 25922

The reference strain E. coli ATCC 25922 was tested on 11 antibiotics that represent 10 pharmacological classes. All antibiotics that were tested were found to be susceptible and the total susceptibility rate was 100%. MIC values ranged from 0.015625 to 8.00 µg/mL, with a median of 2.00 µg/mL and a geometric mean of 0.50 µg/mL. Meropenem and ciprofloxacin had the lowest MICs, with nitrofurantoin having the highest value. The entire susceptibility profile is shown in Table 1.

Table 1. Antimicrobial susceptibility profile of E. coli ATCC 25922

Antibiotic	Pharmacological class	Susceptibility	MIC (µg/mL)	CLSI breakpoint(s)	CLSI QC range
Nitrofurantoin	Nitrofuran	S	8.000	32, 64, 128	4.0–16.0
Meropenem	Carbapenem	S	0.015625	1, 2, 4	0.008–0.06
Ceftriaxone	Third-generation cephalosporin	S	0.0625	1, 2, 4	0.03–0.12
Ciprofloxacin	Fluoroquinolone	S	0.015625	0.25, 0.5, 1	0.004–0.016
Cefuroxime (oral)	Second-generation cephalosporin	S	4.000	4, 8–16, 32	2.0–8.0
Amoxicillin/clavulanate 2:1	Penicillin + β-lactamase	S	2.000	8/4, 16/8, 32/16	2/1–8/4

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	inhibitor				
Ampicillin	Aminopenicillin	S	4.000	8, 16, 32	2.0–8.0
Cefoxitin	Cephamycin	S	4.000	8, 16, 32	2.0–8.0
Doxycycline	Tetracycline	S	0.500	4, 8, 16	0.5–2.0
Levofloxacin	Fluoroquinolone	S	0.031	0.5, 1, 2	0.008–0.06
Cefazolin	First-generation cephalosporin	S	2.000	16, –, 32	1.0–4.0

The differences in the antimicrobial activity of the pharmacological classes of antibiotics are depicted in Figure 1.

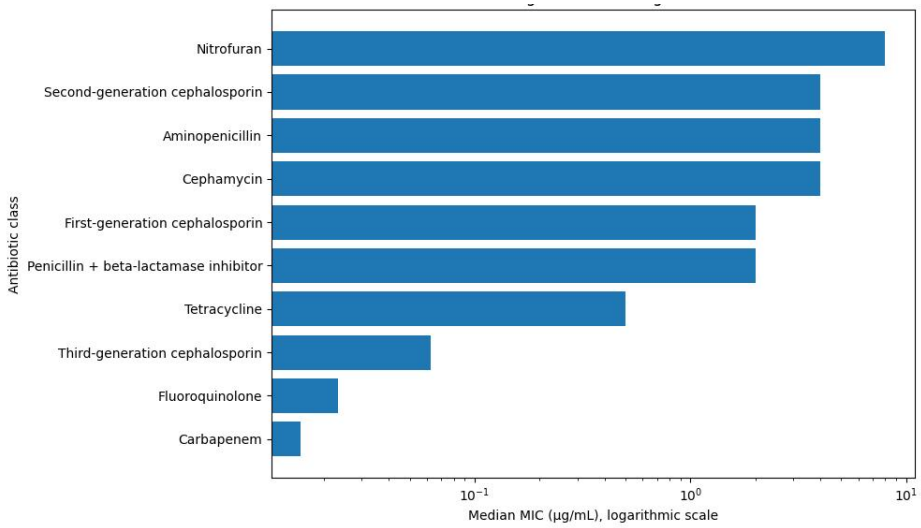

Figure 1. MIC profile according to pharmacological antibiotic class

The figure shows a definite difference in median MIC values depending on the classes. Increased MIC levels were noted in nitrofuran and some of the classes of β-lactams, but fluoroquinolone and carbapenem classes had relatively lower MICs in the susceptible reference strain.

3.2 Resistant-Strain MIC Elevation Across Matched Antibiotics

Doxycycline, levofloxacin and cefazolin could be directly compared between the susceptible E. coli ATCC 25922 and the resistant E. coli LSI-770. The resistant was carrying the increase in the MIC of all the three antibiotics. Doxycycline rose to 0.14 to 71 µg/ml whereas levofloxacin rose to 0.01 to 35.6 µg/ml. Cefazolin rose to over 142 µg/mL, as opposed to 4.44 µg/mL. The alterations were associated with the transition between vulnerable and resistant positions as summarized in Table 2.

Table 2. Comparative MIC profile of susceptible and resistant E. coli

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Antibiotic	Pharmacological class	Reference MIC (µg/mL)	Resistant MIC (µg/mL)	Reference status	Resistant status	MIC fold change	log_2 fold change
Doxycycline	Tetracycline	0.14	71.0	Susceptible	Resistant	507.14	8.99
Levofloxacin	Fluoroquinolone	0.01	35.6	Susceptible	Resistant	3560.00	11.80
Cefazolin	First-generation cephalosporin	4.44	>142	Susceptible	Resistant	>31.98*	-

The relative MIC pattern between susceptible and resistant strains of E. coli is shown in Figure 2.

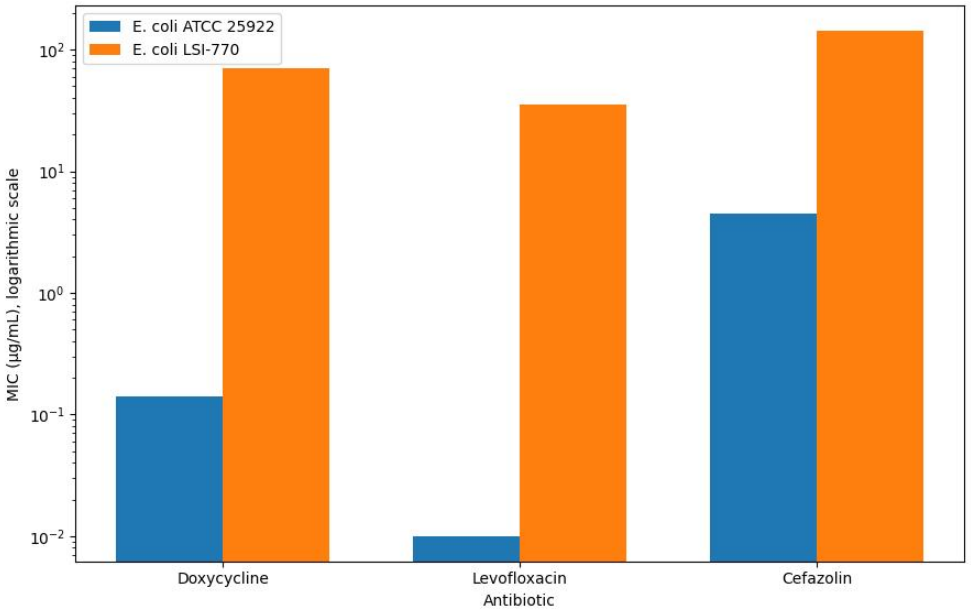

Figure 2. Comparative MIC profiles of susceptible and resistant Escherichia coli

The figure indicates a steady rise in MIC of all resistant strains in all matched antibiotics over the susceptible reference strain. This visual image substantiates significant decreases in antimicrobial susceptibility and shows a resistant pharmacological reaction that is cross-dominant.

3.3 Cross-Resistance Dominated the Comparative Susceptibility Pattern

Fold-change analysis revealed a steady decreased susceptibility in the resistant strain to all the matched antibiotics. Levofloxacin demonstrated the most significant change with 3560-fold increase in its MIC and a log2 fold change of 11.80. Doxycycline was increased 507.14-fold with a log2 fold change of 8.99. Cefazolin generated the lowest estimated increase of over 31.98-folds since its resistant MIC was above the assay range. No MIC shift was found to be negative, which means that a collateral-sensitivity signal is not detected in Table 3.

Table 3. Antibiotic-specific susceptibility shifts in drug-resistant E. coli

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Antibiotic	Reference MIC (µg/mL)	Resistant MIC (µg/mL)	MIC fold change	log_2 fold change	Minimum fold change	Pharmacological response
Doxycycline	0.14	71.0	507.14	8.99	-	Reduced susceptibility / cross-resistance
Levofloxacin	0.01	35.6	3560.00	11.80	-	Reduced susceptibility / cross-resistance
Cefazolin	4.44	>142	-	-	>31.98	Reduced susceptibility / cross-resistance

Figure 3 shows the relative change in the antimicrobial susceptibility between resistant and reference E. coli strains.

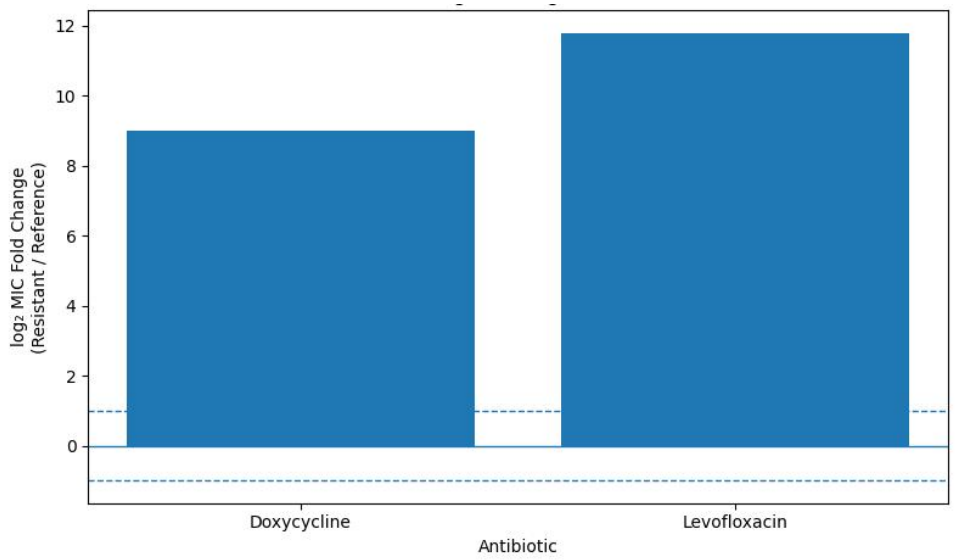

Figure 3. MIC fold-change profile in drug-resistant Escherichia coli

The figure demonstrates high positive log2 MIC fold changes to all the antibiotics being tested, which implies that there is a significant decrease in susceptibility to the resistant strain. The lack of negative fold changes indicates that the observed response is due to cross-resistance not collateral sensitivity.

3.4 Concordance Between BLAST and Reference MIC Measurements

There was a general high degree of agreement between BLAST-derived measurements of MIC and reference broth microdilution. Measurements of BLAST in urine indicated 100% agreement at a

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single two-fold dilution but 80% agreement in colony-grown BLAST measurements. Precision was found to be exact at resistant LSI-770 when compared to doxycycline and levofloxacin in which both tests varied at zero dilution steps. The highest variation was noted between colony-grown doxycycline in ATCC 25922 which varied by 2 dilutions. Table 4 shows that Cefazolin in LSI-770 had a higher value than the measurable range in both the assays.

Table 4. Agreement between BLAST and reference broth microdilution measurements

Strain	Antibiotic	BLAST urine MIC	BLAST colony MIC	rBMDMIC	Urine dilution difference	Colony dilution difference
E. coli ATCC 25922	Doxycycline	0.28	0.14	0.50	-1	-2
E. coli ATCC 25922	Levofloxacin	0.01	0.01	0.016	-1	-1
E. coli ATCC 25922	Cefazolin	1.11	4.44	2.00	-1	1
E. coli LSI-770	Doxycycline	71	71	64	0	0
E. coli LSI-770	Levofloxacin	35.6	35.6	32	0	0
E. coli LSI-770	Cefazolin	>142	>142	>256	Both off-scale	-

4. Discussion

The study revealed a significant decrease in the levels of antibiotic susceptibility of drug-resistant Escherichia coli LSI-770 in comparison to the susceptible ATCC 25922 reference strain. The resistant isolate was found to have significant MIC increase in doxycycline, levofloxacin and cefazolin with the greatest proportional increase in levofloxacin. All the directly matched antibiotics that changed to susceptible were resistant, and none of them indicated a negative MIC fold change. Such results showed that the most common trend in the comparison available was that of cross-resistance and not

of collateral sensitivity which was measurable. The findings thus indicate that resistance in this strain was linked with a wide loss of susceptibility among a number of pharmacological classes as opposed to an apparent trade-off that predisposed it to a different antibiotic.

The findings can be regarded in the framework of the prior research on trade-offs in collateral sensitivity and resistance. It has also been suggested that collateral sensitivity is an evolutionary vulnerability that can be exploited in resistant bacteria, but its frequency is heavily determined by the resistance mechanism under consideration and the antimicrobial pair (Yekani et al., 2023). Equally, Yang et al. (2025) pointed out that antibiotic resistance has the potential to introduce certain genetic susceptibilities, but these susceptibilities are not uniformly manifested in all resistance backgrounds. Unlike those reports, the signal of collateral-sensitivity was not observed in the matched antibiotics in the current analysis, which implies that the present resistant phenotype could have evolved a larger cross-resistant pattern. This trend is also aligned with the fact that collateral responses are very context specific and may differ among organisms and resistance mechanisms (Singh et al., 2025). Experimental evidence has demonstrated that collateral sensitivity can be developed by the way intracellular drugs are handled, metabolism, or it can be a compensatory mechanism. The example of a mechanism that leads to collateral sensitivity that is promoted by the accumulation of intracellular antibiotics in ciprofloxacin-resistant Streptococcus suis was presented (Zhang et al., 2024). Elsewhere, augmented glutamine metabolism augmented antibiotic absorption and augmented the executing of multidrug-unresponsive uropathogenic microbes, illustrating that resistance-related physiology can be sometimes taken advantage of pharmacologically (Zhao et al., 2021). The lack of a similar susceptibility turnaround in the current analysis could be taken to mean that the resistant E. coli strain did not have such trade-offs in the three antibiotics that have been assessed. This supports the argument that the evaluation of collateral effects should be conducted empirically and not based on the idea that resistance to a particular drug will automatically result in susceptibility to another drug.

The practical implications of the findings to the development of antimicrobial strategies are also provided. The large MIC increases of various agents imply that the mere replacement of one agent with an unrelated antibiotic class might not necessarily result in regaining activity against resistant E. coli. Alternative strategies might thus necessitate more extensive phenotypic screening, mechanistically guided drug sequencing or adjunctive compounds which reestablish antibiotic uptake or action. In vitro collateral-sensitivity techniques have been suggested as one of the possible methods to combat multidrug-resistant bacteria, although the success of these methods is conditional upon the ability to find reproducible drug-pair interactions (Youseha et al., 2023). Similarly, new antimicrobial platforms, including evolved host-compatible peptides, have also been shown to have activity against drug-resistant and biofilm-forming bacteria and can be used in combination with conventional methods when standard antibiotics no longer work (Starr et al., 2020).

There are a number of restrictions to be counted on. Vital comparison was done with a single susceptible reference strain, a single resistant E. coli isolates and three directly matched antibiotics. Hence, the pattern of cross-resistance that was observed cannot be considered as general to all the resistant strains of E. coli and all types of the antibiotics. The resistant isolate did not arise in a controlled experiment of antibiotic-specific evolution; thus, the analysis was unable to determine which of the resistance mechanisms generated each shift in MIC. Also, there was a report on cefazolin resistance as an off-scale censored value, which did not allow calculating a specific fold change. In subsequent research, more extensive panels of resistant E. coli isolates, antibiotic-specific evolved lineages, and full-fledged MIC matrices with a variety of drug classes should be involved. The genomic and transcriptomic characterization may assist in correlating the changes in susceptibility with the specific resistance mechanisms. Sequential-exposure experiments would also be useful in determining stable and clinically useful collateral-sensitivity relationships that can aid either antibiotic cycling or precision antimicrobial therapy.

5. Conclusion

This research showed the definite variation in the susceptibility to antimicrobial agents between the

susceptible Escherichia coli ATCC 25922 and the drug-resistant E. coli LSI-770. The reference strain was still vulnerable in the tested antibiotic panel, but the resistant strain exhibited significant MIC increase in doxycycline, levofloxacin and cefazolin. Levofloxacin, doxycycline, and cefazolin were the best-matched antibiotics in the increase in MIC relative, with cefazolin exhibiting a significant off-scale response to resistance. The positive MIC fold variances among all matched agents were indicative of a pattern of less susceptibility and cross resistant instead of classical collateral sensitivity. The results indicate that resistance in the tested E. coli strain was linked with widespread pharmacological loss of susceptibility of various antibiotic classes. This reduces the chances of the mere replacement of the tested drugs to re-establish antimicrobial activity. Simultaneously, the relatively high correlation between BLAST-obtained MICs and the reference broth microdilution indicated the accuracy of the phenotypic measurements employed in the analysis. The interpretation was however limited by the limited number of matched antibiotics and use of one resistant isolate. Future research ought to consider bigger sets of resistant E. coli isolates, wider combinations of antibiotics and full MIC panels to determine reproducible collateral-sensitivity connections and elucidate their potential utility in resistance-guided antibiotic choice and sequencing.

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