Research Article

Synergistic Antibacterial Activity of Ceftriaxone–Clavulanic Acid and Ceftazidime–Clavulanic Acid Combinations Against Selected Bacterial Pathogens

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Abstract

Combination therapy using a β-lactam antibiotic and a β-lactamase inhibitor may enhance effectiveness against resistant bacteria. This study examined the pharmacology and potential synergism of ceftriaxone-clavulanic acid and ceftazidime-clavulanic acid against Escherichia coli and Pseudomonas aeruginosa. Antibacterial efficacy was evaluated using the disk diffusion method across 32 Petri dishes — 16 per bacterial strain. Each strain's dishes were divided equally among four treatments: ceftriaxone (CX), ceftriaxone-clavulanate (CXC), ceftazidime (CT), and ceftazidime-clavulanate (CTX). Plates were incubated at 37°C for 18–24 hours, then assessed for zones of bacterial inhibition. Against E. coli, ceftriaxone alone showed greater activity than ceftazidime alone (mean: 12.5 vs. 1.75). Clavulanic acid enhanced both, with ceftazidime-clavulanate achieving the highest inhibition (mean = 20). Both combinations proved equally effective overall. Against P. aeruginosa, ceftriaxone again outperformed ceftazidime alone (mean: 17.25 vs. 4.00). Clavulanic acid did not significantly enhance ceftriaxone, but dramatically potentiated ceftazidime (mean: 4.00 to 21.5). Both clavulanate combinations were equally effective against this strain as well. These findings reinforce the value of β-lactam/β-lactamase inhibitor combination therapy for infections caused by E. coli and P. aeruginosa. Despite differences in standalone potency, clavulanic acid effectively equalized the performance of both antibiotics, highlighting the importance of synergy testing in guiding optimal antibiotic treatment.

Keywords: E. coli, P. aeruginosa, MDR, Combination therapy and β-lactamase inhibitor

1. Introduction

Infections due to multidrug-resistant (MDR) Gram-negative pathogens have become a major public health threat worldwide (Atoom et al., 2025; Zhang et al., 2023). Ceftriaxone–clavulanic acid and ceftazidime–clavulanic acid are two promising combinations to combat this threat, especially against Escherichia coli and Pseudomonas aeruginosa (Dave & Mittal, 2025; Holger et al., 2022). Ceftriaxone is in the WHO Model List of Essential Medicines as a second-choice drug for severe infections caused by E. coli, and ceftazidime is a priority drug for P. aeruginosa infections (Balcazar-Ochoa et al., 2024; Sudharsan et al., 2024). Despite this significance, the detailed antibacterial mechanisms of these combinations are poorly understood (Aslan & Akova, 2022; Cusumano et al., 2022). Combination therapy is a promising strategy to prolong the lifespan of existing antibiotics. Various antibiotics, such as β-lactams, are often combined with β-lactamase inhibitors to resuscitate their activity against resistant pathogens (Edyedu et al., 2025; Xiao et al., 2023). Ceftriaxone and ceftazidime are broad-spectrum, time-dependent antibiotics whose combination with clavulanic acid has a well-defined clinical rationale (Corbella et al., 2022; Nasomsong et al., 2022). E. coli and P. aeruginosa remain particularly vulnerable to both combinations, prompting a systematic examination of the pharmacodynamics and pharmacokinetics of each pair (Filby et al., 2022; Kalatharan et al., 2023). Understanding the anticipated antibacterial interactions will guide experimental investigations (Longhi et al., 2022; Pokharel et al., 2023). Clavulanic acid is the first discovered β-lactamase inhibitor, and its paired combination with aztreonam has been established in vitro and in vivo against MDR E. coli (Esposito et al., 2022; Naidoo & Zishiri, 2025). Consequently, ceftriaxone and ceftazidime are also investigated,

as both can potentially benefit from clavulanic acid co-treatment (Biswas et al., 2024; Di Gregorio et al., 2024).
Combination therapy offers multiple advantages in the treatment of infectious diseases. Although single agents may be insufficient to achieve the required therapeutic concentration or optimal bactericidal effect, two drugs used in conjunction may produce an overall clinical response better than that obtainable with either agent alone (Biswas et al., 2024; Rahim Khorasani et al., 2023). Combination therapy improves the likelihood of treatment efficacy against pathogens exhibiting hetero-resistance or variable antibiotic susceptibility. Furthermore, the top1 clinical problem is the widespread emergence of antibiotic-resistant pathogens (Ali Salman et al., 2022; Ferreres et al., 2023). Many β-lactam antibiotics have been rendered ineffective against resistant pathogens. Cationic surfactant β-lactams such as ceftriaxone and ceftazidime are widely substituted with co-administration of β-lactamase inhibitors (Kamel et al., 2022; Zinad et al., 2024).

The present study examined the antimicrobial interaction of ceftriaxone-clavulanic acid and ceftazidime-clavulanic acid against E. coli and P. aeruginosa with contrasting susceptibility patterns. An overview of possible synergistic mechanisms among these antibiotic combinations is also emphasized.

2. Methodes

2.1. Materials which were used in the research

The materials used in this study included antibiotic discs of ceftriaxone (10 µg; CX) and ceftriaxone combined with clavulanic acid (30 µg + 10 µg; CXC), as well as ceftazidime (30 µg; CT) and ceftazidime combined with clavulanic acid (30 µg + 10 µg; CTC), all obtained from Bioanalyse. A McFarland turbidity standard device was supplied by Biosan. Microbiological media included Mueller–Hinton agar (MHA) and Mueller–Hinton broth (MHB), both sourced from Neogen. Additional laboratory supplies such as swabs, test tubes, and Petri dishes were also utilized throughout the experimental procedures.

2.2. Preparation of agar plates and Bacterial strains

Mueller-Hinton agar was prepared for microbial growth, following the manufacturer's instructions. The prepared agar medium was poured into 50 sterile Petri dishes, ensuring even distribution. Allow the agar to solidify at room temperature. As directed by the manufacturer, Mueller-Hinton agar was produced for microbial growth. To ensure uniform distribution, the produced agar medium was transferred into 100 sterile Petri plates. Leave the agar at room temperature to solidify. The microorganisms were obtained from medical laboratories in Koya university, Erbil City, and they possess the following coding: *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. Before culturing, we prepared a MacFarland 0.5 standard using fresh cultures of the target microbial strains, which were subsequently injected into sterile nutrient broth medium. A sterile swab was employed to distribute the bacteria evenly throughout the surface of the solidified agar plates to guarantee consistent growth.

2.3. Antimicrobial Assays

The antibacterial efficacy was assessed utilizing 32 Petri plates, with 16 dishes allocated for each bacterial strain. From these 16 Petri dishes, four were designated for each Antibiotics: CX, CXC, CT, and CTC respectively. The efficacy was assessed by the disk diffusion method. The plates were incubated at 37°C for 18 to 24 hours for bacterial cultures. Following incubation, the agar plates were examined for zones of inhibition surrounding the disks, indicating areas where microbial growth was inhibited. The diameter of the inhibitory zones was measured around the disks with a caliper in millimeters. This will demonstrate the degree of antibacterial activity.

2.4. Determination of MIC

A total of thirty-two sterile tubes were each prepared with 2 ml of Mueller Hinton Broth (MHB). These tubes were allocated into two distinct sets: sixteen tubes were designated for *Escherichia coli* (*E. coli*) and the remaining sixteen for *Pseudomonas aeruginosa* (*P. aeruginosa*). For each bacterial species, the sixteen tubes were organized into four experimental groups (n=4 per group), with each group assigned to a specific antibiotic or antibiotic combination. Within each group, a serial dilution was established to test a range of concentrations for the primary antibiotic.
Group 1: Ceftriaxone (CX). The four tubes in this group received ceftriaxone at final concentrations of 30 µg, 60 µg, 120 µg, and 240 µg, respectively. Group 2: Ceftriaxone in combination with Clavulanic Acid (CXC). The four tubes in this group received ceftriaxone at the concentrations listed for Group 1. Additionally, a fixed concentration of the β-lactamase inhibitor clavulanic acid was incorporated into each corresponding tube at concentrations of 10 µg, 20 µg, 40

µg, and 80 µg, respectively. Groups 3 & 4: Ceftazidime and Combination. This procedural pattern was replicated for the third and fourth antibiotic groups. Group 3 tubes received ceftazidime (CT) at concentrations identical to those used for ceftriaxone. Group 4 tubes received ceftazidime at these same concentrations, each combined with clavulanic acid at the corresponding concentrations (10, 20, 40, and 80 µg) as described for Group 2.

Following the preparation of antibiotic gradients, each tube was inoculated with 200 µL of a standardized bacterial suspension (0.5 McFarland standard) of *Escherichia coli* (*E. coli*). Appropriate controls were included for each experimental run: a positive control tube containing MHB inoculated with bacteria but no antibiotic, and a negative control tube containing sterile MHB only. The entire procedure, encompassing tube preparation, antibiotic dilution, and inoculation, was subsequently repeated in an identical manner using the sixteen tubes allocated for *Pseudomonas aeruginosa*.

2.5. Statistical Analysis

Statistical analysis was performed using GraphPad Prism (version 8). The Shapiro–Wilk test was used to assess the normality of data distribution. Based on the distribution results, appropriate tests were applied. For comparisons between two independent groups, the student's t-test was used for normally distributed data. For comparisons among more than two groups, one-way analysis of variance (ANOVA) was used for parametric data, followed by appropriate post-hoc tests, when necessary.

All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Levels of significance were denoted as follows: $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***) and $p < 0.0001$ (****).

3. Results

3.1. Multiple Comparisons between (CX, CT, CXC, CTC) against two types of bacteria

Table (1) Descriptive statistics for all antibiotics against both bacteria

		No. of Petri dish	Mean	Std. Deviation	Std. Error of Mean	Min	Max
CX	E. coli	4	12.5	2.38	1.19	9	14
	P. aeruginosa	4	17.25	0.9574	0.4787	16	18
CT	E. coli	4	1.75	0.9574	0.4787	1	3
	P. aeruginosa	4	4	3.916	1.958	0	9
CXC	E. coli	4	19	1.414	0.7071	17	20
	P. aeruginosa	4	21.25	0.9574	0.4787	20	22
CTC	E. coli	4	20	0.8165	0.4082	19	21
	P. aeruginosa	4	21.5	5.066	2.533	15	26

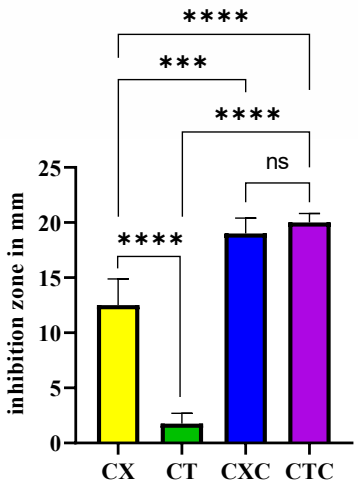

Fig (1) Means of inhibition zone in mm for (CX, CT, CXC and CTC) against *E. coli*

Ceftazidime (CT) alone demonstrated the lowest mean inhibitory effect (1.75), while Ceftriaxone (CX) alone showed a significantly higher, yet still moderate, effect (12.5). The direct comparison between these two third-generation cephalosporins was highly significant (Mean Diff.=10.75, p<0.0001), indicating superior intrinsic activity of CX against this specific *E. coli* isolate under the test conditions. The most striking finding is the profound and statistically significant enhancement of activity upon the addition of clavulanic acid, a β-lactamase inhibitor. The combination of Ceftazidime + Clavulanic Acid (CTC) yielded the highest mean inhibition (20). The combination Ceftriaxone + Clavulanic Acid (CXC) also showed a very high and statistically significant increase compared to its corresponding antibiotic alone (19 vs. 12.5, p=0.0003). The dramatic improvement for CT when combined with clavulanate (from 1.75 to 20, p<0.0001) far exceeds that seen for CX (from 12.5 to 19). This suggests that the resistance mechanism in this *E. coli* isolate is likely mediated primarily by β-lactamase enzymes that are more effectively inhibited by clavulanate in the context of ceftazidime, or that ceftazidime is more susceptible to hydrolysis by the present enzymes than ceftriaxone. Notably, there was no statistically significant difference between the two clavulanate-potentiated combinations (CXC vs. CTC, Mean Diff.=-1, p=0.7897). Despite starting from vastly different baselines, both combinations achieved a similarly high and maximal level of inhibitory efficacy against this strain.

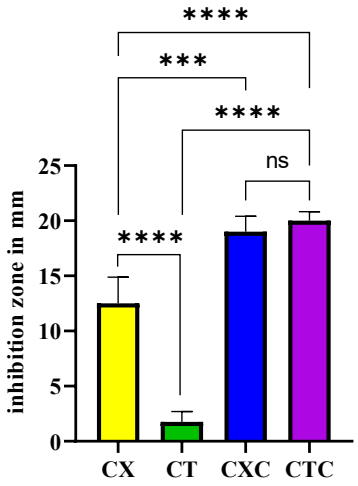

Fig (2) Means of inhibition zone in mm for (CX, CT, CXC and CTC) against *P. aeruginosa*

A clear and significant difference exists between the two cephalosporins when used alone. Ceftriaxone (CX) demonstrates a substantially higher mean inhibitory effect (17.25) compared to ceftazidime (CT, mean=4), with a mean

difference of 13.25 (p=0.0005). This indicates that, against this particular *P. aeruginosa* strain, ceftriaxone possesses superior intrinsic activity. In stark contrast to the results with *E. coli*, the addition of clavulanic acid did not result in a statistically significant enhancement of ceftriaxone's activity. The comparisons between CX and its potentiated form CXC (17.25 vs. 21.25, p=0.3518), and between CX and CTC (17.25 vs. 21.5, p=0.3042), were non-significant. This suggests that β-lactamase-mediated resistance is not a primary mechanism limiting ceftriaxone's efficacy against this strain. For ceftazidime, however, the addition of clavulanic acid resulted in a dramatic and highly significant increase in inhibitory effect, from a mean of 4 to 21.5 (p<0.0001). This indicates that while ceftazidime alone is poorly effective, its activity is severely hampered by a clavulanate-sensitive resistance mechanism (likely a specific β-lactamase) in this isolate. Mirroring the finding with *E. coli*, there was no significant difference between the two clavulanate-containing combinations (CXC vs. CTC, p=0.9995). Both achieved a similarly high level of efficacy (means ~21.5).

3.2. The effect of each antibiotic alone against two types of bacteria

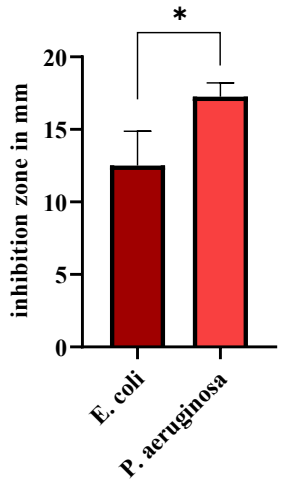

Fig (3) Means of inhibition zone in mm for CX against two types of bacteria

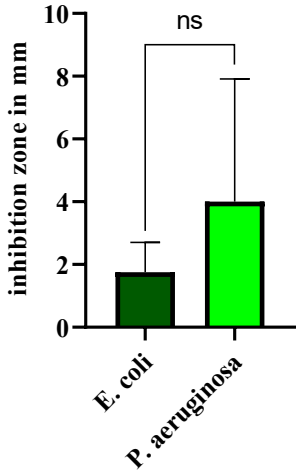

Fig (4) Means of inhibition zone in mm for CT against two types of bacteria

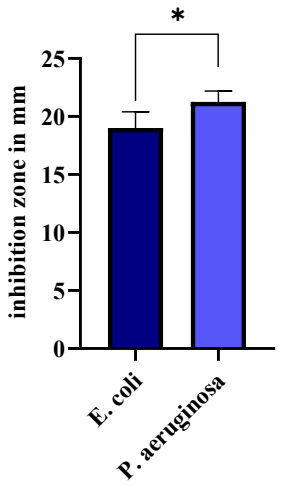

Fig (5) Means of inhibition zone in mm for CXC against two types of bacteria

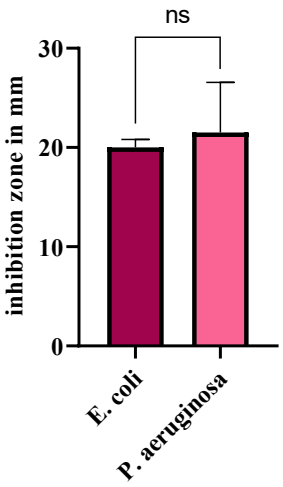

Fig (6) Means of inhibition zone in mm for CTC against two types of bacteria

Figures (3,4,5,6) presents the results of the independent t-test comparing the antibacterial activity (mean values) between *E. coli* and *P. aeruginosa* for the tested antibiotics and their combinations. For ceftriaxone (CX), there was a statistically significant difference between the two organisms (t = 3.703, p = 0.0101), with *P. aeruginosa* showing a higher mean value (17.25) compared to *E. coli* (12.5), indicating greater susceptibility. Similarly, the combination of ceftriaxone with clavulanic acid (CXC) demonstrated a significant difference (t = 2.635, p = 0.0388), with higher activity observed against *P. aeruginosa* (mean = 21.25) than *E. coli* (mean = 19), suggesting that the addition of clavulanic acid enhanced the antibacterial effect, particularly against *P. aeruginosa*.

In contrast, ceftazidime (CT) showed no statistically significant difference between *E. coli* (mean = 1.75) and *P. aeruginosa* (mean = 4) (t = 1.116, p = 0.307), indicating comparable and relatively low activity against both organisms. Likewise, the combination of ceftazidime with clavulanic acid (CTC) did not produce a significant difference (t = 0.5846, p = 0.5801), despite slightly higher mean values in *P. aeruginosa* (21.5) compared to *E. coli* (20). Overall, these findings suggest that ceftriaxone and its combination with clavulanic acid exhibit significantly different antibacterial effects between the two bacteria, whereas ceftazidime and its combination do not show statistically meaningful differences.

3.3. MIC tests for all antibiotecs against *E.coli* and *P. aeruginosa*

Table (2) MIC test for CX and CXC against *E.coli*				
	Tube 1	Tube 2	Tube 3	Tube 4
Ceftriaxone	30 µg	60 µg	120 µg	240 µg
	Turbidity	Turbidity	Turbidity	Turbidity
Ceftriaxone + Clavulanic acid	30 µg + 10 µg	60 µg + 20 µg	120 µg + 40 µg	240 µg + 80 µg
	Turbidity	Clarity	Clarity	Clarity
Interpretation: Turbidity = Bacterial Growth. Clarity = No Bacterial Growth				

Table (3) MIC test for CT and CTC against *E.coli*				
	Tube 1	Tube 2	Tube 3	Tube 4
Ceftazidime	30 µg	60 µg	120 µg	240 µg
	Turbidity	Turbidity	Turbidity	Turbidity
Ceftazidime + Clavulanic acid	30 µg + 10 µg	60 µg + 20 µg	120 µg + 40 µg	240 µg + 80 µg
	Turbidity	Turbidity	Clarity	Clarity
Interpretation: Turbidity = Bacterial Growth. Clarity = No Bacterial Growth				

The highest concentration tested (240 µg) was not sufficient to inhibit the growth of this *E. coli* isolate. Therefore, the MIC for CX alone is >240 µg. This indicates a very high level of resistance to ceftriaxone. the MIC for the CXC combination is 60 µg of ceftriaxone (in the presence of 20 µg of clavulanic acid). Even at 240 µg, ceftazidime alone could not inhibit growth. The MIC for CT alone is >240 µg. This confirms very high-level resistance to ceftazidime. The MIC for the CTC combination is 120 µg of ceftazidime (in the presence of 40 µg of clavulanic acid).

Table (4) MIC test for CX and CXC against *P. aeruginosa*				
	Tube 1	Tube 2	Tube 3	Tube 4
Ceftriaxone	30 µg	60 µg	120 µg	240 µg
	Turbidity	Turbidity	Turbidity	Clarity
Ceftriaxone + Clavulanic acid	30 µg + 10 µg	60 µg + 20 µg	120 µg + 40 µg	240 µg + 80 µg
	Turbidity	Turbidity	Clarity	Clarity
Interpretation: Turbidity = Bacterial Growth. Clarity = No Bacterial Growth				

Table (5) MIC test for CT and CTC against *P. aeruginosa*				
	Tube 1	Tube 2	Tube 3	Tube 4
Ceftazidime	30 µg	60 µg	120 µg	240 µg
	Turbidity	Turbidity	Turbidity	Turbidity

Ceftazidime + Clavulanic acid	30 µg + 10 µg	60 µg + 20 µg	120 µg + 40 µg	240 µg + 80 µg
	Turbidity	Turbidity	Turbidity	Clarity
Interpretation: Turbidity = Bacterial Growth. Clarity = No Bacterial Growth				

Adding clavulanic acid lowered the MIC of ceftriaxone from 240 µg to 120 µg. This is only a 2-fold reduction, which is minor and often not considered biologically significant. It suggests that β-lactamase inhibition plays a very small role, if any, in the resistance to ceftriaxone in this *P. aeruginosa* strain. The primary resistance mechanism is likely something else (e.g., efflux pumps, porin mutations). Adding clavulanic acid did not lower the MIC of ceftazidime; it remained at 240 µg (the combination just happened to show growth inhibition at that top concentration). The MIC is still >240 µg for practical purposes. This shows that clavulanic acid provides no meaningful potentiation of ceftazidime against this strain. The resistance is not mediated by clavulanate-sensitive β-lactamases.

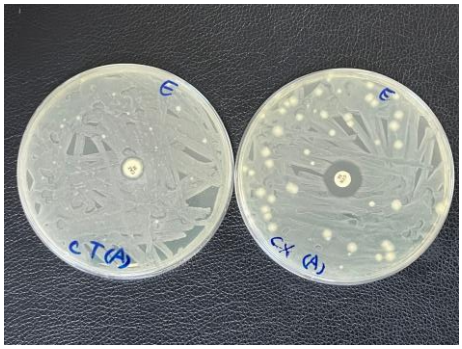

Fig (7) inhabitation zone for (CX and CT) against *Escherichia coli*

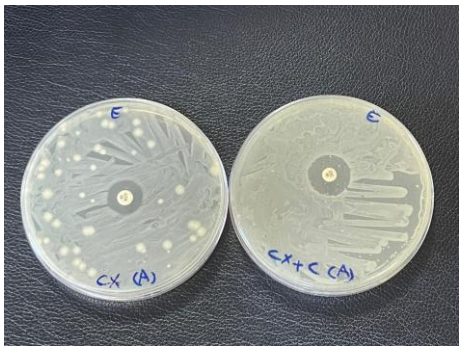

Fig (8) inhabitation zone for (CX and CXC) against *Escherichia coli*

Fig (9) inhabitation zone for (CT and CTC) against *Escherichia coli*

Fig (10) inhabitation zone for (CXC and CTC) against *Escherichia coli*

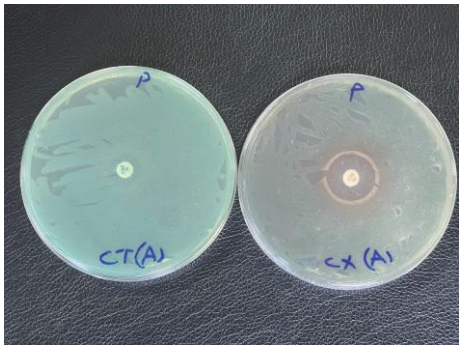

Fig (11) inhabitation zone for (CX and CT) against *P. aeruginosa*

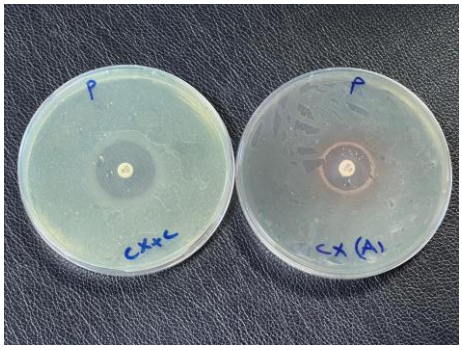

Fig (12) inhabitation zone for (CX and CXC) against *P. aeruginosa*

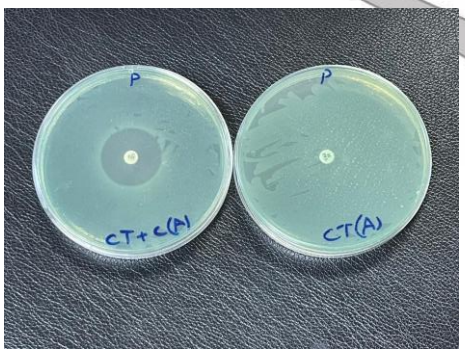

Fig (13) inhabitation zone for (CT and CTC) against *P. aeruginosa*

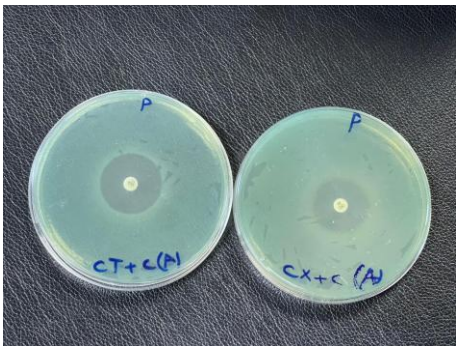

Fig (14) inhabitation zone for (CXC and CTC) against *P. aeruginosa*

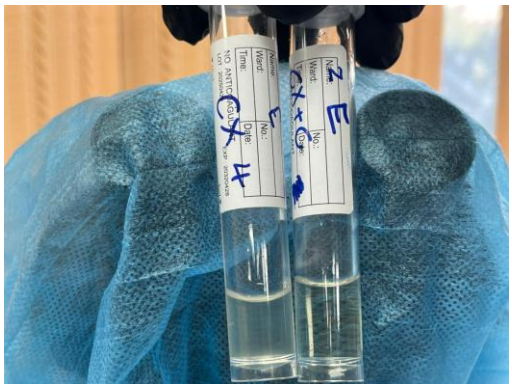

Fig (15) MIC for (CX and CXC) for *Escherichia coli*

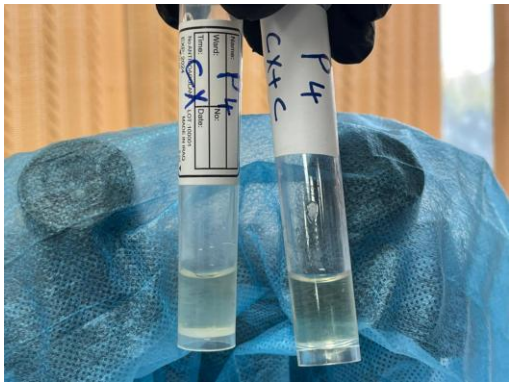

Fig (16) MIC for (CX and CXC) for *P. aeruginosa*

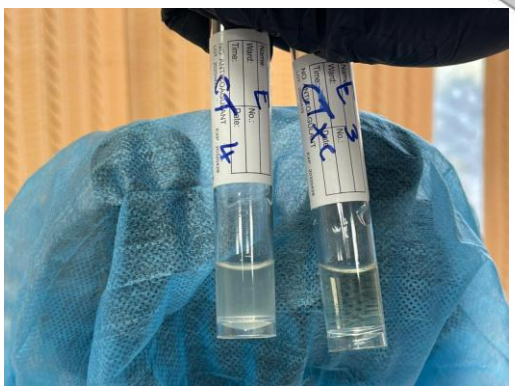

Fig (17) MIC for (CT and CTC) for *Escherichia coli*

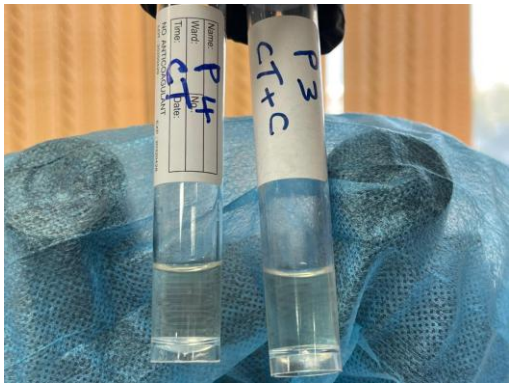

Fig (18) MIC for (CT and CTC) for *P. aeruginosa*

4. Discussion

The data strongly indicate that the test *E. coli* isolate possesses significant resistance to ceftazidime and, to a lesser extent, ceftriaxone, which is likely due to the production of clavulanate-sensitive β-lactamases (e.g., ESBLs or other plasmid-encoded β-lactamases). The resistance was effectively reversed by the addition of clavulanic acid, restoring high susceptibility. For this isolate, the choice between ceftriaxone or ceftazidime is less critical if a β-lactamase inhibitor is co-administered, as both combinations achieve equivalent high efficacy. These findings underscore the importance of combination therapy with β-lactamase inhibitors for treating infections caused by resistant *E. coli* and highlight the utility of synergy testing to guide effective antibiotic selection. The resistance profile of this *P. aeruginosa* isolate differs fundamentally from that of the *E. coli*. The primary finding is that ceftriaxone alone is moderately effective, and its activity is not limited by clavulanate-sensitive β-lactamases. In contrast, ceftazidime alone is poorly effective due to hydrolysis by such an enzyme, as evidenced by its complete restoration of activity with clavulanic acid. Ultimately, both clavulanate-potentiated combinations are equally and highly effective. This highlights the strain-specific and drug-specific nature of resistance mechanisms: the same inhibitor (clavulanate) is critically important for one drug (CT) but inconsequential for another (CX) against the same bacterial species. These results emphasize that susceptibility can vary significantly even within a species and that the choice of a β-lactam/β-lactamase inhibitor combination should be informed by the specific drug-bug interaction.

The E. coli isolate exhibited high-level resistance to both ceftriaxone and ceftazidime alone, with MICs >240 µg/mL for each. The addition of clavulanic acid restored susceptibility, reducing the MICs to 60 µg/mL and 120 µg/mL for the ceftriaxone-clavulanate (CXC) and ceftazidime-clavulanate (CTC) combinations, respectively. This ≥4-fold reduction in MIC for both drugs confirms the production of an extended-spectrum β-lactamase (ESBL). The CXC combination demonstrated a 2-fold greater in vitro potency compared to CTC against this isolate. The MIC profile for P. aeruginosa differed markedly from that of E. coli. For ceftriaxone, the MIC was 240 µg/mL alone and 120 µg/mL with clavulanate,

a non-significant 2-fold reduction. For ceftazidime, the MIC was >240 µg/mL both alone and in combination with clavulanate. The lack of significant potentiation by clavulanic acid indicates that resistance in this P. aeruginosa isolate is not mediated by clavulanate-sensitive β-lactamases (e.g., ESBLs) but is likely due to intrinsic mechanisms such as chromosomal AmpC expression, efflux pumps, or porin mutations.

Previous studies consistently demonstrate that combining cephalosporins with β-lactamase inhibitors enhances antibacterial activity against β-lactamase–producing organisms. Fiol et al. showed, using both in vitro assays and an animal model, that the addition of clavulanic acid significantly improved the efficacy of cephalosporins against Staphylococcus aureus strains producing β-lactamase, suggesting clinical usefulness in staphylococcal infections (De Sá Del Fiol et al., 2000). Similarly, Petit et al. reported a clinical isolate of Klebsiella pneumoniae with resistance to ceftazidime but clear synergism when ceftazidime was combined with clavulanic acid, highlighting the role of β-lactamase inhibition in overcoming resistance associated with high-level SHV-type enzyme production (Petit, 1992). In vitro evidence from Bonnefoy and colleagues further confirmed that combining ceftazidime with the novel β-lactamase inhibitor markedly reduced minimum inhibitory concentrations across a wide range of Enterobacteriaceae, including ceftazidime-resistant strains, indicating broad-spectrum activity against Ambler class A and C β-lactamase producers (Bonnefoy, 2004). In a clinical laboratory context, Bhandari et al. demonstrated that the ceftazidime/clavulanate combination is particularly effective for phenotypic confirmation of extended-spectrum β-lactamase (ESBL) production among uropathogens, supporting its routine use alongside standard antibiograms for early and appropriate management of urinary tract infections (Bhandari et al., 2016).

5. Conclusion

This study demonstrates that the antibacterial efficacy of ceftriaxone and ceftazidime is significantly influenced by the presence of clavulanic acid and varies markedly between *E. coli* and *P. aeruginosa*. The *E. coli* isolate exhibited high-level resistance to both antibiotics alone; however, the addition of clavulanic acid resulted in a pronounced restoration of antibacterial activity, confirming the role of clavulanate-sensitive β-lactamases (likely ESBLs) as the primary resistance mechanism. In contrast, *P. aeruginosa* showed a distinct resistance profile, where ceftriaxone retained moderate intrinsic activity and was minimally affected by clavulanic acid, while ceftazidime activity was significantly enhanced only in disk diffusion assays but not meaningfully improved in MIC testing. This suggests that resistance in *P. aeruginosa* is predominantly mediated by non–β-lactamase mechanisms such as efflux pumps or porin alterations.

Importantly, both ceftriaxone–clavulanic acid and ceftazidime–clavulanic acid combinations achieved similarly high inhibitory effects in agar diffusion assays against both organisms, despite differing underlying resistance mechanisms. These findings highlight that the success of β-lactam/β-lactamase inhibitor combinations is highly strain-specific and dependent on the dominant resistance pathways. Overall, this study underscores the critical importance of tailored antimicrobial therapy guided by susceptibility testing and supports the strategic use of clavulanic acid–based combinations in overcoming β-lactam resistance, particularly in *E. coli* infections.

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