Antibiotic Resistance of Klebsiella Pneumoniae Against Antibiotics Ciprofloxacin

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**Abstract:** *Klebsiella pneumoniae* is a Gram-negative bacterium commonly linked to hospital-acquired infections, such as *pneumonia*, UTI, and bacteremia. This study investigated the characteristics of a *K. pneumoniae* isolate through biochemical tests, which confirmed its non-motility, positive results for methyl red and citrate utilization tests, and variable lactose fermentation. Haemolytic activity was assessed at different concentrations of cell lysate, showing a concentration-dependent increase in red blood cell lysis, reaching a peak activity of 100% at 1000 µg/ml. The cell viability assay demonstrated a significant reduction in bacterial survival following ciprofloxacin treatment, with complete eradication at concentrations of 750 µg/ml and above. Additionally, the antibiofilm activity of ciprofloxacin was evaluated, revealing substantial disruption of biofilm integrity at 1000 µg/ml, with a marked decrease in biofilm density compared to the control group. These results highlight ciprofloxacin’s effectiveness in combating K. pneumoniae infections by significantly reducing bacterial viability and disrupting biofilm formation.

**Keywords:** Klebsiella pneumoniae; Ciprofloxacin; Haemolysis; Biofilm

# Introduction

*Klebsiella pneumoniae* is a gram-negative and non-motile *Enterobacteriaceae bacillus* with a polysaccharide capsule that plays an important role in pathogenesis and phagocytosis prevention [(Lee et al., 2017; P et al., 2024)](https://paperpile.com/c/owEX2y/YX4j+xHnm). This bacterium is an opportunistic pathogen that causes a number of nosocomial infections, including pneumonia, urinary tract infection, liver abscess, meningitis, and wound infection, as well as bacteremia and sepsis [(Martin & Bachman, 2018)](https://paperpile.com/c/owEX2y/R5Ud). *Klebsiella pneumoniae* strains are often classed as opportunistic, hypervirulent (hyKp) and multidrug resistant (MDR) [(Wang et al., 2020)](https://paperpile.com/c/owEX2y/7rpk). Capsules, lipopolysaccharide (LPS), siderophores, and fimbriae are the primary contributors to hypervirulence [(Parrott et al., 2021)](https://paperpile.com/c/owEX2y/7ncE). *Klebsiella pneumoniae* infections are caused through plasmid horizontal transfer [(Wyres & Holt, 2018)](https://paperpile.com/c/owEX2y/EEH2). The World Health Organization has identified extended-spectrum β-lactam (ESBL)-producing and carbapenem-resistant *K. pneumoniae* (CRKP) as a significant public health hazard [(Shrivastava et al., 2018)](https://paperpile.com/c/owEX2y/0J0N). *Klebsiella pneumoniae* is also known for its biofilm-forming abilities, which includes virulence factors such as type 1 and type 3 fimbriae, lipopolysaccharides, & outer membrane proteins that may contribute in immune system evasion during infection and biofilm formation [(Murphy & Clegg, 2012)](https://paperpile.com/c/owEX2y/vCz2). *Klebsiella pneumoniae* biofilm development is a complex process that contributes significantly to pathogenicity and antibiotic resistance [(Li & Ni, 2023)](https://paperpile.com/c/owEX2y/4E6t). Biofilms are structured bacterial colonies encased in a self-generated matrix that protects them from external threats such as antibiotic treatments [(Babu et al., 2021; Guerra et al., 2022)](https://paperpile.com/c/owEX2y/fe0a+MgA5). The presence of iron has been shown to increase biofilm density, resulting in increased concentrations of proteins and polysaccharides in extracellular polymeric substances (EPS), while succinic acid may reduce this effect [(Liu et al., 2021)](https://paperpile.com/c/owEX2y/Sb5G). Notably, clinical isolates of *K. pneumoniae* that produce extended-spectrum β-lactamases exhibit a greater tendency for biofilm formation, with a significant presence of fimbrial genes that facilitate this process [(Mohamed et al., 2020)](https://paperpile.com/c/owEX2y/cbg7). Environmental factors, including nutrient composition, oxygen availability, and temperature, also play a role in biofilm development, with aerobic conditions at 37ºC being particularly favorable [(Ignatova et al., 2020)](https://paperpile.com/c/owEX2y/Zbee). The formation of biofilms has been associated with increased expression of efflux pump genes, which can be suppressed by efflux pump inhibitors [(Tang et al., 2020)](https://paperpile.com/c/owEX2y/5aId). The critical role of type 3 fimbriae in promoting biofilm formation has been highlighted, while type 1 fimbriae seem to have no effect [(Schroll et al., 2010)](https://paperpile.com/c/owEX2y/JU4c).Antibiotic resistance in *Klebsiella pneumoniae*, particularly against the fluoroquinolone drug ciprofloxacin, is becoming a major issue in clinical environments. This resistance reduces the efficacy of ciprofloxacin, a second-generation antibiotic used to treat bacterial infections, including *pneumonia*, skin, bone, joint, infectious diarrhea, prostate, abdominal,  kidney, sinus,  urinary tract infections, and bronchitis [(Fauzi et al., 2022; Singh et al., 2020)](https://paperpile.com/c/owEX2y/kmEL+z4si). Resistance mechanisms include efflux pumps such as AcrAB and OqxAB, which actively remove antibiotics from bacterial cells, lowering intracellular concentrations and hence decreasing effectiveness [(Razavi et al., 2020)](https://paperpile.com/c/owEX2y/R0Is). Additionally, mutations in genes encoding target enzymes can also contribute to the decreased susceptibility of *Klebsiella pneumoniae* to ciprofloxacin [(Vijayakumar et al., 2024)](https://paperpile.com/c/owEX2y/8kSL). Interestingly, while efflux pump inhibitors have shown promise in restoring ciprofloxacin sensitivity in resistant strains (Ruolun, 2007), the emergence of cross-resistance to other antibiotics in bacteriophage-insensitive mutants suggests a complex interplay of resistance mechanisms [(Uddin et al., 2019)](https://paperpile.com/c/owEX2y/RxuA). Furthermore, the presence of resistance genes on plasmids highlights a significant potential for horizontal gene transfer, further complicating the resistance landscape [(Long et al., 2018)](https://paperpile.com/c/owEX2y/PHcR).

# Materials and methods

*Klebsiella pneumoniae* has been collected from hospitals and. On MacConkey agar, the culture was grown for 24 hours at 37°C. *Klebsiella pneumoniae* colony morphology was examined under a microscope after incubation. A biochemical characterization of the bacterial pathogen Klebsiella pneumoniae was carried out using clinical samples collected from. For preliminary identification, the isolate was streaked onto MacConkey agar medium. A number of biochemical assays were then carried out using the methods described in Bergey's Manual (1974). These tests included indole production, methyl red, Voges-Proskauer, citrate utilization, lactose fermentation, catalase activity, hydrogen sulfide (H₂S) production, urease activity, inositol fermentation, as well as assessments using triple sugar iron (TSI) agar, and tests for maltose, sucrose, xylose, and starch utilization.The haemolytic activity of *Klebsiella pneumoniae* was determined using the technique described by [(Greco et al., 2020)](https://paperpile.com/c/owEX2y/JFoc). The entire blood sample was centrifuged for five minutes at 5000 rpm. After centrifugation, the plasma fraction was discarded and the pellets were washed three times with an equivalent volume of saline. After washing, PBS was added to the pellets to dilute them further until the samples had a concentration of 1:10. Using different quantities of cell lysate (from 250 µg/ml to 1000 µg/ml) obtained from well-grown *Klebsiella pneumoniae*, the experiment was carried out in sterile Eppendorf tubes. The activity of ciprofloxacin in inhibiting Klebsiella pneumoniae biofilm formation was assessed using the technique published by [(Suzuki et al., 2015)](https://paperpile.com/c/owEX2y/eeVq). Bacteria were initially cultivated in a 96-well microplate with turbidity adjusted to 0.5 McFarland standard. After biofilm development, cells were treated with ciprofloxacin concentrations ranging from 250 to 1000 µg/mL. The plate was then incubated at 37 °C for 48 hours. After incubation, the wells were rinsed with PBS to eliminate any non-adherent cells, and biofilm development was measured by staining with 0.1% crystal violet for 15 minutes. The stain was then removed, and the plate dried. The bound crystal violet was solubilized in 95% ethanol, and its optical density (OD) was measured at 595 nm.

% 𝐼𝑛ℎ𝑖𝑏𝑡𝑖𝑜𝑛 = Control − Test/Control 𝑥 100%

The biofilm was allowed to grow for 48 hours and gently rinsed twice with phosphate buffer saline (pH 7.4) to remove planktonic cells. The biofilm was then treated with 1000 mg/ml of ciprofloxacin for 24 hours. After incubation the biofilm was fixed with 70% ethanol for 15 minutes, and then stained with 0.1ml of acridine orange. The slides were observed under a light microscope.

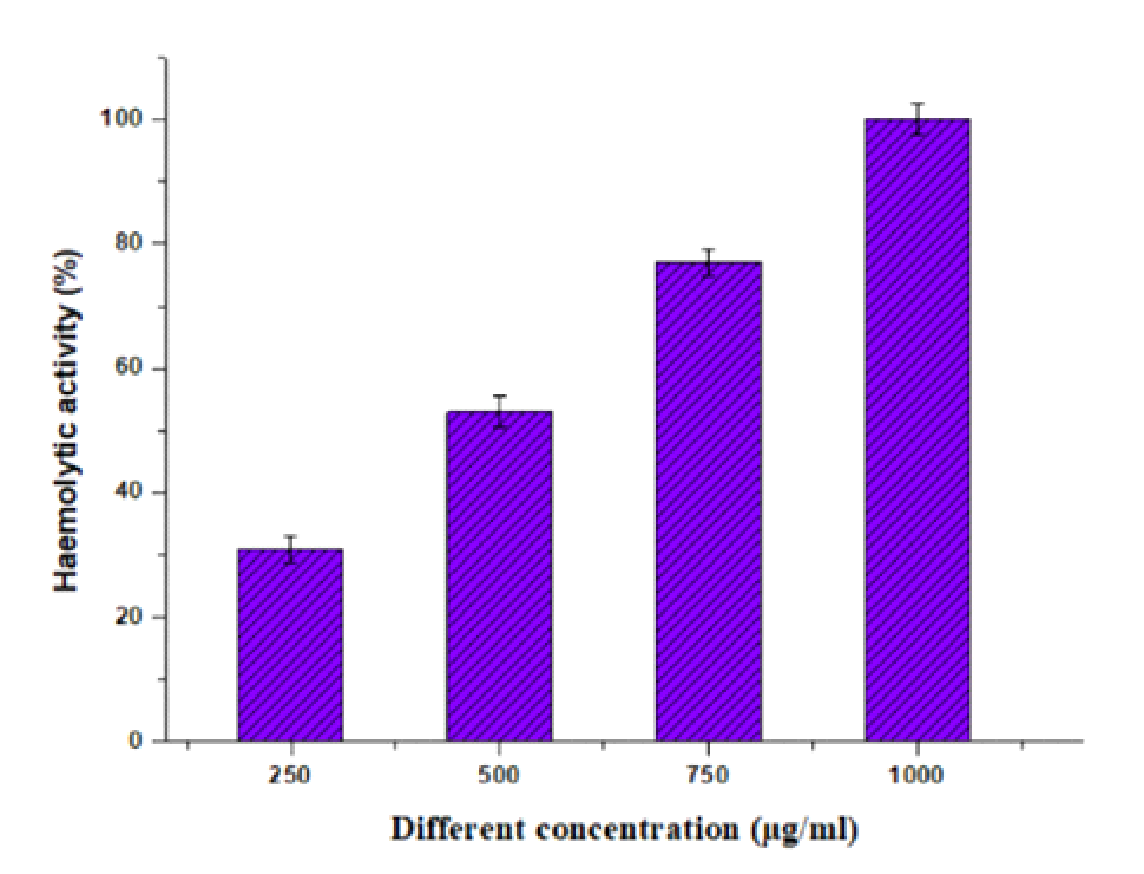
# Results

*K. pneumoniae* is a Gram-negative bacterium that commonly causes hospital-acquired infections, including pneumonia,UTI, and bloodstream infections. Based on the biochemical tests it was found to be rod shaped and non-motile, indicating it lacks flagella, a common trait among *Klebsiella* strains (Table 1). The positive methyl red (MR) test, coupled with a negative Voges-Proskauer (VP) test, suggests that the isolate ferments glucose to produce mixed acids rather than butanediol. The positive citrate utilization test confirms that the isolate can utilize citrate as a sole carbon source. Additionally, the positive urease test indicates that the isolate can hydrolyze urea to produce ammonia and carbon dioxide. The triple sugar iron (TSI) test showed an acid alkaline but with gas production but no hydrogen sulfide (H₂S), demonstrating the isolate ability to ferment sugars and produce gas. The isolate was negative for oxidase but positive for catalase. It exhibited variable lactose fermentation (±), reflecting the diversity within the genus. Furthermore, the isolate was negative for maltose, sucrose, and inositol fermentation but positive for xylose and starch hydrolysis.

**Table 1.** Biochemical analysis of *klebsiella pneumoniae*

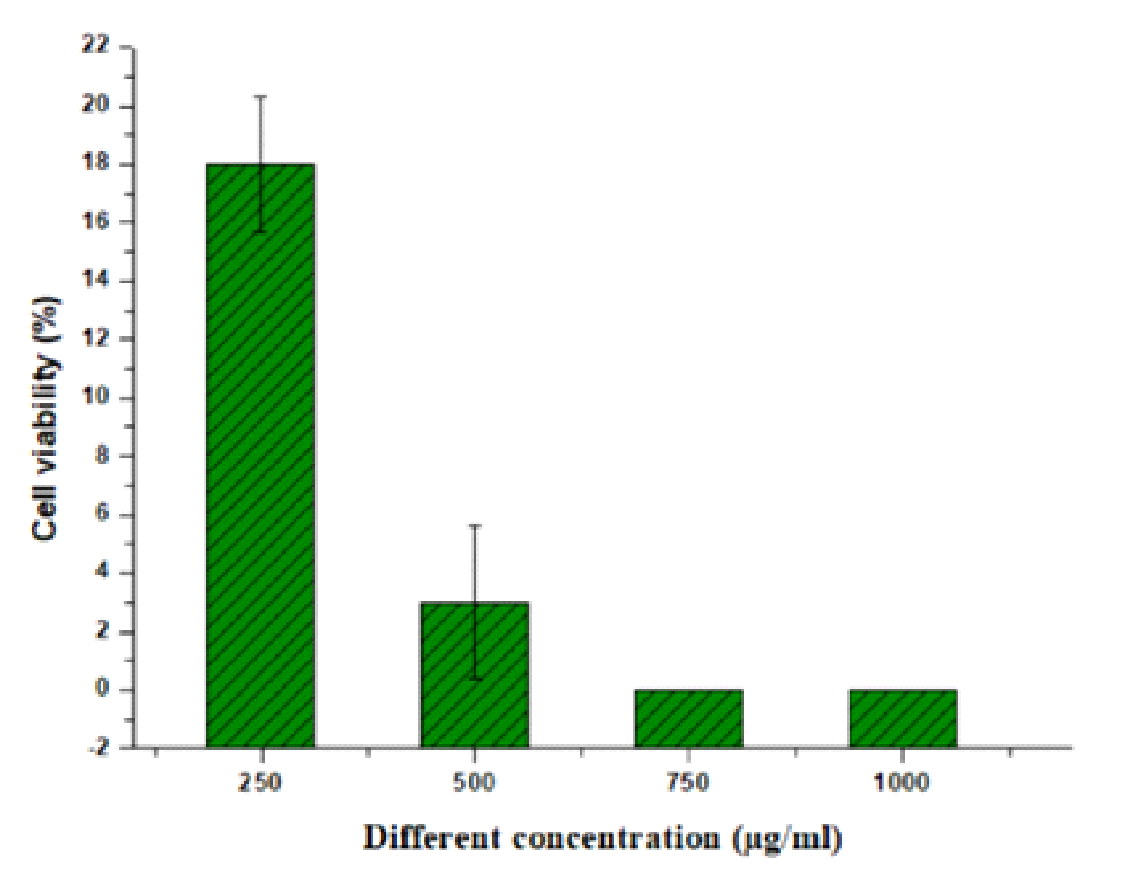
|  |  |
| --- | --- |
| **Biochemical characteristics** | **Results** |
| Gram stain | - |
| Shape | Rod |
| Motility | - |
| Indole | - |
| MR | + |
| VP | - |
| Citrate | + |
| TSI | + |
| Oxidase | - |
| Catalase | + |
| Urease | + |
| Lactose | ± |
| Maltose | - |
| Sucrose | - |
| Xylose | + |
| Starch | + |
| Inositol | - |

Haemolytic activity assays are employed to evaluate a bacterium's ability to lyse red blood cells, indicating the presence of haemolysis or other lytic factors. Evaluating haemolytic activity at different concentrations of cell lysate helps determine the bacterium’s capacity for producing these lytic substances (Fig. 1). At 250 µg/ml, the haemolytic activity of 31% indicates a baseline level of red blood cell lysis by *Klebsiella pneumoniae*. This baseline provides a reference for evaluating the haemolytic effects at higher concentrations. The increase in haemolytic activity to 53% at 500 µg/ml indicates that higher concentrations of cell lysate contain more haemolytic factors, which contribute to a greater lytic effect. At 750 µg/ml, haemolytic activity rose to 77%, peaking at 1000 µg/ml with an activity of 100%. This consistent increase indicates that higher lysate concentrations result in greater haemolytic activity. Haemolysis and lytic proteins can be either cell wall components or secreted products of the bacteria. At higher concentrations, these factors are more likely to interact with and disrupt the red blood cell membranes, thereby increasing the extent of haemolysis observed.



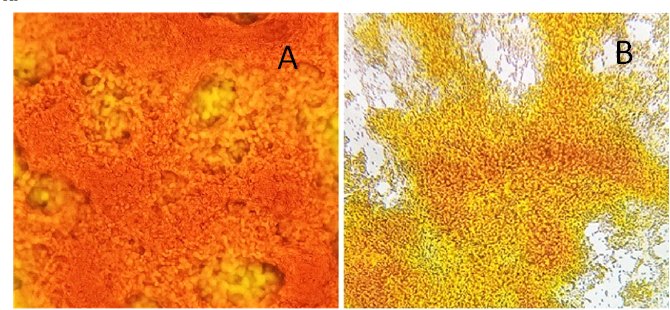
**Figure 1.** Haemolytic activity of *klebsiella pneumoniae* cell lysate.

The cell viability of *Klebsiella pneumoniae* was assessed after exposure to varying concentrations of ciprofloxacin, revealing a significant reduction in bacterial survival as the antibiotic concentration increased (Fig. 2). At 250 µg/ml, the cell viability was reduced to 18%, indicating that ciprofloxacin effectively killed a substantial portion of the bacterial population at this concentration. This suggests that the antibiotic exerts strong bactericidal activity, even at lower concentrations. As the concentration was increased to 500 µg/ml, cell viability dropped sharply to 3%, demonstrating that only a small fraction of the bacterial cells could withstand this higher dose, highlighting the potency of ciprofloxacin in inhibiting bacterial growth. At the concentrations of 750 µg/ml and 1000 µg/ml, cell viability was completely abolished, with no detectable viable cells remaining. This complete eradication of *Klebsiella pneumoniae* at higher concentrations of ciprofloxacin confirms the antibiotic’s efficacy in killing the bacteria and suggests that these concentrations exceed the minimum inhibitory concentration necessary to eliminate the bacterial population.



**Figure 2.** Cell viability activity of *Klebsiella pneumoniae* treated with ciprofloxacin antibiotic.

Biofilm formation is a critical survival strategy employed by *Klebsiella pneumoniae*, allowing the bacteria to adhere to surfaces and create a protective barrier that enhances their resistance to environmental stresses, including antibiotic treatment. In this study, the antibiofilm activity of ciprofloxacin at a (Nikalje et al., 2024) (Chehelgerdi et al., 2023) concentration of 1000 µg/ml against *Klebsiella pneumoniae* was assessed by comparing the biofilm integrity of a control group with that of a treated group (Fig. 3). In the control group, *Klebsiella pneumoniae* was able to form a dense and cohesive biofilm. This biofilm was characterized by a thick and uniform structure, indicating the bacteria’s successful adherence and production of an extracellular matrix that provides protection and stability to the bacterial community. The presence of such a robust biofilm in the control group underscores the bacterium's natural ability to thrive in a biofilm mode, which is known to contribute to its persistence and resistance to antibiotics. in the treated group, where *Klebsiella pneumoniae* was exposed to 1000 µg/ml of ciprofloxacin, there was a marked disruption in biofilm formation. The biofilm in the treated group appeared significantly less dense and cohesive compared to the control group. The reduction in biofilm density and the disintegration of the biofilm structure suggest that ciprofloxacin at this concentration effectively interferes with the biofilm matrix, possibly by disrupting the production of extracellular polymeric substances or by killing the bacterial cells embedded within the biofilm. The significant reduction in biofilm integrity and density in the treated group compared to the control group demonstrates the antibiotic's ability to prevent biofilm formation and disrupt existing biofilms, thereby potentially enhancing the efficacy of treatment against this pathogen.



**Figure 3.** Antibiofilm activity of *Klebsiella pneumoniae* treated with ciprofloxacin. (A) Control: Untreated biofilm showing dense bacterial colony, (B) Ciprofloxacin treatment at 1000 µg/ml significantly reduced biofilm formation.

# Discussion

Haemolysis enhances the bacterium's ability to break down red blood cell membranes, releasing haemoglobin, which serves as a nutrient source, especially for iron acquisition [(M. Sharma, 2019)](https://paperpile.com/c/owEX2y/yllq). [(Zaghloul et al., 2021)](https://paperpile.com/c/owEX2y/wfEi)found that 25% of K. pneumoniae strains had haemolytic activity, indicating that these bacteria might lyse red blood cells, potentially causing tissue damage and assisting in infection transmission. The capacity to lyse host cells plays an important role in the infection process, and knowing this mechanism may assist in the development of targeted therapeutics or preventative methods against K. pneumoniae infections [(Pu et al., 2024)](https://paperpile.com/c/owEX2y/MQP3).

[(Kim et al., 2016)](https://paperpile.com/c/owEX2y/TCSw) found that Ciprofloxacin treatments significantly reduced Klebsiella pneumoniae cell viability, with 1/4CIP-CIP achieving an additional 1 log reduction. However, these treatments also induced cross-resistance to multiple antibiotics. [(Al Marjani et al., 2022)](https://paperpile.com/c/owEX2y/GrUX) demonstrates a synergistic effect when ciprofloxacin is combined with indole, effectively eradicating persister cells of K. pneumoniae. [(Zhong et al., 2013)](https://paperpile.com/c/owEX2y/82HE) suggests that the use of ciprofloxacin can induce an increase in efflux pump (EP) activity, potentially leading to antibiotic resistance. [(Setiawan et al., 2022)](https://paperpile.com/c/owEX2y/X9aG) supports the efficacy of ciprofloxacin, showing it to have the best inhibitory effect on both non-ESBL and ESBL-producing strains of K. pneumoniae. However, [(Weniger et al., 2020)](https://paperpile.com/c/owEX2y/xCf0) presents a scenario where quinolone-resistant K. pneumoniae strains are associated with shorter progression-free survival, indicating a potential limitation in the effectiveness of ciprofloxacin due to resistance.

The combination of DNase I with ciprofloxacin enhanced biofilm eradication by eight-fold in K. pneumoniae ATCC 700603 and four-fold in a clinical isolate, achieving a 99% biofilm reduction in a mouse model [(A. Sharma et al., 2023)](https://paperpile.com/c/owEX2y/6H7e). This suggests that targeting the extracellular DNA within the biofilm matrix can be a viable strategy to potentiate the activity of ciprofloxacin. However, the overall resistance of K. pneumoniae to ciprofloxacin remains a concern, as highlighted by the high rates of resistance observed in clinical isolates, which is associated with biofilm production and decreased porin permeability [(Sulistiyawati et al., 2024)](https://paperpile.com/c/owEX2y/6q6E). High-dose oral ciprofloxacin (800 mg every 8 hours for 7 days) successfully cleared biofilm-forming multidrug-resistant Klebsiella pneumoniae bacteremia in a liver transplant patient after multiple relapses [(Jayaweera & Kothalawala, 2021)](https://paperpile.com/c/owEX2y/xEEn). Antibiotic combinations, particularly meropenem with ciprofloxacin, exhibited synergistic effects against biofilms, although at clinically insignificant concentrations [(Copur et al., 2022)](https://paperpile.com/c/owEX2y/EDuS). [(Li & Wu, 2021)](https://paperpile.com/c/owEX2y/b22k) demonstrated that while ciprofloxacin alone and in combination with BL-Ca showed limited efficacy against multi-species biofilms, the combination of ciprofloxacin with BL-Ca achieved a 99.9% eradication of the biofilm. Essential oils such as thyme oil, when combined with ciprofloxacin, have shown enhanced activity against K. pneumoniae biofilms, suggesting a potential role for natural compounds in combination therapies [(Mohamed et al., 2018)](https://paperpile.com/c/owEX2y/9cHf).

# Conclusion

This study provides critical insights into the pathogenicity and antibiotic susceptibility of *Klebsiella pneumoniae*, particularly in the context of hospital-acquired infections. The biochemical characterization confirmed the isolate's identity and highlighted key metabolic traits that contribute to its survival and virulence. The observed haemolytic activity suggests that K. pneumoniae possesses potent virulence factors capable of lysing red blood cells, which may facilitate iron acquisition and enhance its pathogenic potential. The significant reduction in bacterial viability following ciprofloxacin treatment, coupled with the antibiotic's ability to disrupt biofilm formation, underscores its potential as a therapeutic agent against *Klebsiella pneumoniae* infections. However, the high minimum biofilm inhibitory and eradication concentrations indicate that ciprofloxacin alone may be insufficient to fully eradicate biofilm-associated infections at clinically relevant doses. These results suggest a need for further investigation into combination therapies that could enhance the efficacy of ciprofloxacin, particularly in biofilm-associated infections.

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