Prevalence and Resistance Patterns of Ceftazidime in Carbapenemase-Producing Klebsiella Pneumoniae from Oral Sample

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**Abstract:** *Klebsiella pneumoniae*, a gram-negative bacterium commonly found in the human body, is responsible for a range of infections, including urinary tract infections, liver abscesses, sepsis, pneumonia and wound infections, particularly in healthcare settings. The treatment of *Klebsiella infections* is complicated by antibiotic resistance, notably due to the production of ESBLs and carbapenemases. This study explores the biochemical characteristics of *K. pneumoniae* and investigates the anti-biofilm activity of seagrass extract compared to ceftazidime. Biochemical tests revealed that *K. pneumoniae* is non-motile, rod-shaped, and positive for citrate utilization, methyl red, catalase, triple sugar iron, urease, lactose fermentation, xylose fermentation, and starch hydrolysis, while negative for indole, Voges-Proskauer, oxidase, maltose fermentation, sucrose fermentation, and inositol fermentation. The quantification of histamine release from cell lysates indicated a dose-dependent increase with seagrass extract. Anti-biofilm assays demonstrated that seagrass extract at 1000 mg/ml significantly inhibited biofilm formation of *K. pneumoniae*, showing greater effectiveness than ceftazidime. These findings suggest the potential of seagrass extract as an alternative or complementary treatment for managing biofilm-associated infections in *K. pneumoniae*.

**Keywords:** *Klebsiella pneumoniae*; Antibiotic resistance; Histamine; Anti-biofilm activity; seagrass extract; Ceftazidime

# Introduction

Klebsiella pneumoniae, a Gram-negative bacterium, can cause severe infections, especially in immunocompromised people. The proliferation of carbapenemase-producing K. pneumoniae (CPKP), which produces enzymes such as KPC, NDM, VIM, and OXA-48, offers a substantial concern because of their ability to breakdown carbapenems, resulting in multidrug resistance [(P et al., 2024; Yuan et al., 2022)](https://paperpile.com/c/mnzf1m/Pu5nR+0M41y). Resistance to ceftazidime, a third-generation cephalosporin, is typically caused by carbapenemases and other β-lactamases, as well as efflux pumps and porin mutations [(Edwards et al., 2022; Noufal et al., 2021)](https://paperpile.com/c/mnzf1m/13NgR+FumHC). The genes encoding these resistance mechanisms are usually found on mobile genetic elements, which aids their dissemination [(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/mnzf1m/MJwYq+rRihQ+YJ7Aj)[(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/mnzf1m/MJwYq+rRihQ+YJ7Aj+kpZsj). CPKP infections are difficult to treat and frequently need the use of less effective or more toxic antibiotics such as polymyxins, tigecycline, and Fosfomycin [(Karaiskos et al., 2022)](https://paperpile.com/c/mnzf1m/jxcOV). In recent years, the health of people is now seriously threatened by carbapenem-resistant Enterobacterales (CRE), a result of limitations on antibiotic alternatives [(Yahav et al., 2020)](https://paperpile.com/c/mnzf1m/NZfLI). The US Food and Drug Administration authorized ceftazidime/avibactam, a novel beta lactam antibiotic combination (2 g ceftazidime and 0.5 g avibactam), in 2015 to treat CRE-caused infections. Enterobacteria that produce A-, C-, and D-type β-lactamases, such as AmpC, OXA-48 and KPCs, could be efficiently inhibited by CZA [(Jiang et al., 2022)](https://paperpile.com/c/mnzf1m/J9Xor). Klebsiella pneumoniae (CRKP) that is resistant to carbapenems is still a health concern [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/mnzf1m/hIklq+n0aYd+CYdF7). High mortality rates are linked to CRKP infections, although the best antimicrobial therapy is still up for debate and frequently relies on nephrotoxic medications like tigecycline and colistin [(Subbalakshmi et al., 2023; P. Zhang et al., 2020)](https://paperpile.com/c/mnzf1m/1gxJ1+DBJyM). Carbapenem-resistant Enterobacteriaceae (CRE) infections have become much more common in recent years [(Ramakrishnan et al., 2023; Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/mnzf1m/3rEzB+HjRlP+wICH4). Patients who have this illness frequently have a high death rate since the CRE strain is typically resistant to the majority of antibacterial treatments [(W. Zhang et al., 2018)](https://paperpile.com/c/mnzf1m/OzrfO). According to clinical research, bloodstream infections with CRKP have a mortality rate of over 50%, which is two to three times higher than that of K. pneumoniae that is sensitive to carbapenem [(Fu et al., 2023)](https://paperpile.com/c/mnzf1m/iTqRS). The WHO listed CRKP as one of the antibiotic-resistant bacteria for which there is an urgent need for new treatments in 2017 [(J. Zhou et al., 2024)](https://paperpile.com/c/mnzf1m/HrxqJ). The use of ceftazidime–avibactam (CZA) as an antibiotic for the treatment of CRE has been approved. However, as CZA was widely used to treat CRE infections, the crisis of CZA resistance quickly emerged [(Chen et al., 2023; Shields et al., 2016)](https://paperpile.com/c/mnzf1m/JCzIs+V9qhh). Nowadays, CZA appears to be one of the only viable pharmacological alternatives for treating CRKP in clinical practice [(N. Zhou et al., 2022)](https://paperpile.com/c/mnzf1m/UdJXR). Fascinatingly, a significant fraction of the CRKP that is common in China produces KPC, which means that CZA is the best treatment for infections with KPC resistance [(G. & Ganapathy, 2022; Kumar & Ramesh, 2021)](https://paperpile.com/c/mnzf1m/Jw6sL+6syFf)). Reports of CZA opposition have surfaced, nevertheless. Numerous investigations have discovered KPC variations, including KPC-33, KPC-86, KPC-87, and KPC-88 [(D. Li et al., 2021; Qiao et al., 2024)](https://paperpile.com/c/mnzf1m/yVBmr+Kmggs). The aim of this study is to investigate the mechanisms and prevalence of ceftazidime resistance in carbapenemase-producing Klebsiella pneumoniae (CPKP) isolates, with a focus on understanding the genetic and phenotypic factors contributing to this resistance [(Sakthi et al, 2021)](https://paperpile.com/c/mnzf1m/MGKb6+4LAvH+nWCpE). The study is to assess the impact of ceftazidime resistance on treatment outcomes, and explore potential strategies for mitigating the spread of resistant strains in clinical settings [(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/mnzf1m/0BRcr+y5JVv+8rfCd).

# Materials and methods

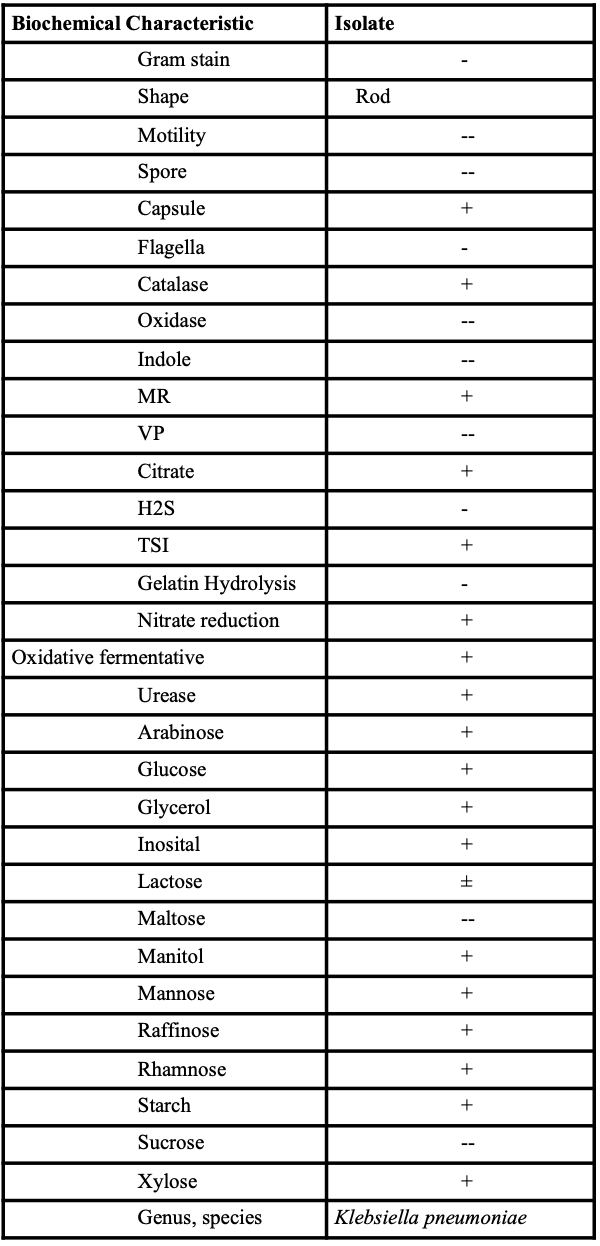
Oral swab samples were collected from the clinic of Swabs were streaked in the Nutrient agar media then incubated at 24 hours at 37ºC for bacterial growth. The next morning, we observed the 3 bacterial stains which are Streptococcus mutans, Staphylococcus aureus and Klebsiella pneumoniae. The bacterial pathogen K. pneumoniae was subjected to biochemical analysis utilizing samples sourced from. In order to identify the pathogen, it was streaked on MacConkey agar medium and its numerous biochemical features were evaluated in accordance with the guidelines supplied by (Buchanan, 1974). Tests for the production of indole, specifically the triple sugar iron agar and other maltose test, the Methyl Red test, the Voges-Proskauer test, the citrate utilization test, the lactose test, the catalase test, the hydrogen sulfide (H2S) production test, the urease test, the inositol test, the sucrose test, the xylose test, and the starch test were conducted.Genomic DNA was isolated from well grown carbapenamase producing Klebsiella pneumoniae and amplified with universal primer 27F (5′-AGA GTT TGA TCC TGG CTC AG-3′) and 1492R (5′-TAC GGY TAC CTT GTT ACG ACT T-3′) primer previously described method [(Sokhi et al., 2020)](https://paperpile.com/c/mnzf1m/UnYwN).

The bioassay was carried out according to the reports of [(Abd Rani et al., 2019)](https://paperpile.com/c/mnzf1m/UBSir) and [(Shahari et al., 2017)](https://paperpile.com/c/mnzf1m/4kMmw). Klebsiella cells were grown in 400 µL/well of 24-well plates. After an overnight incubation period, the cells reached 80% confluency. Before being treated with 320 µL of enriched medium, the cells were twice washed with 500 µL of enriched media. Following a 10-minute incubation period, 40 µL of several concentrations of seagrass crude extract were added to the cells, and they were let to incubate for an additional 10-minute period. After applying 20 µL of the allergen, DNP-BSA (10 mg/mL), to the cells, they were incubated for an additional half-hour. After that, the produced supernatant was put into a microcentrifuge tube and centrifuged at 1000× g for 20 minutes at 8 °C. After transferring the supernatant to the Histamine ELISA kit, the ELISA manufacturer's protocol was followed to quantify the histamine. The blank well correlated with 0% histamine release, whereas the control cells treated with ceftazidime were thought to have 100% histamine release when allergen was added without any treatment. Six-well plates were injected with well-grown K. pneumoniae (104 cells/ml), which was allowed to form a biofilm for 24 hours. The biofilm was then treated with ceftazidime for a duration of 12 to 48 hours. The biofilm was stained with propidium iodide and acridine orange after 48 hours of incubation to reveal the dead and live cells.

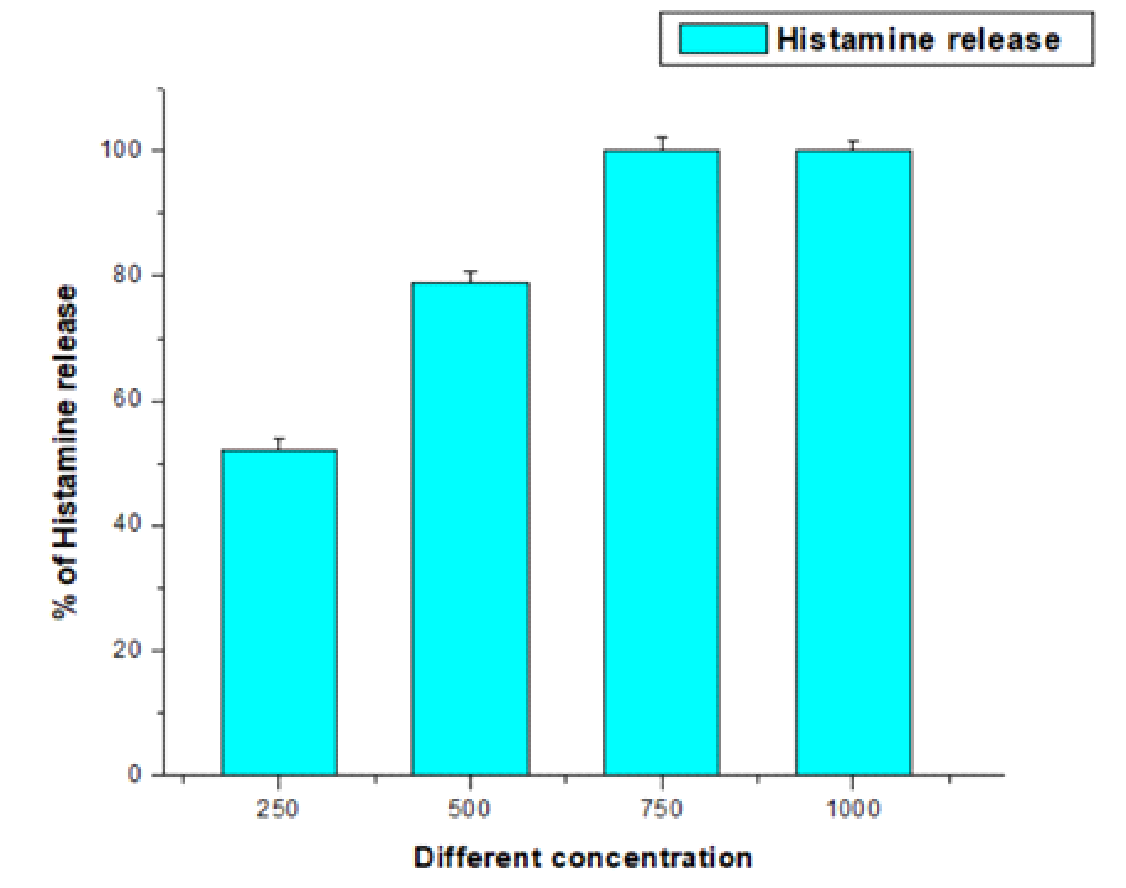
# Results

A frequent gram-negative bacterium in the human body is *Klebsiella sp*. Particularly in hospital environments, it can result in a number of illnesses, such as liver abscesses, pneumonia, urinary tract infections, sepsis, and wound infections(Saadh et al., 2024).The treatment of *Klebsiella* infections is often complicated by antibiotic resistance, notably to beta-lactam antibiotics due to the production of ESBLs and carbapenemases. This resistance limits effective treatment options. Biochemically, *Klebsiella pneumoniae* is a non-motile, rod-shaped bacillus with a diameter of 0.5–0.8 μm, and it grows optimally at 37°C. It is notable for its positive reactions in a series of biochemical tests, including methyl red (MR), indicating mixed acid fermentation(Almatrafi et al., 2024); citrate utilization, demonstrating its ability to use citrate as a sole carbon source; and triple sugar iron (TSI), showing acid production in slant and butt with gas but no hydrogen sulfide production. The bacterium also tests positive for catalase, which breaks down hydrogen peroxide into water and oxygen; urease, which hydrolyzes urea into ammonia and carbon dioxide; and lactose fermentation, xylose fermentation, and starch hydrolysis, which indicate its ability to metabolize these carbohydrates. Conversely, *Klebsiella pneumoniae* tests negative for several other biochemical assays. It does not produce indole, which means it cannot convert tryptophan into indole; it is negative for Voges-Proskauer (VP), indicating it does not produce acetoin from glucose metabolism; and it lacks oxidase activity, confirming the absence of cytochrome c oxidase. Additionally, the bacterium does not ferment maltose, sucrose, or inositol, further narrowing its identification profile (**Table 1**). These combined biochemical characteristics are definitive for *Klebsiella pneumoniae*, a significant pathogen responsible for various infections such as pneumonia, UTI, and septicemia, particularly in individuals with compromised immune systems.

Table 1. Biochemical identification of *Klebsiella pneumoniae*

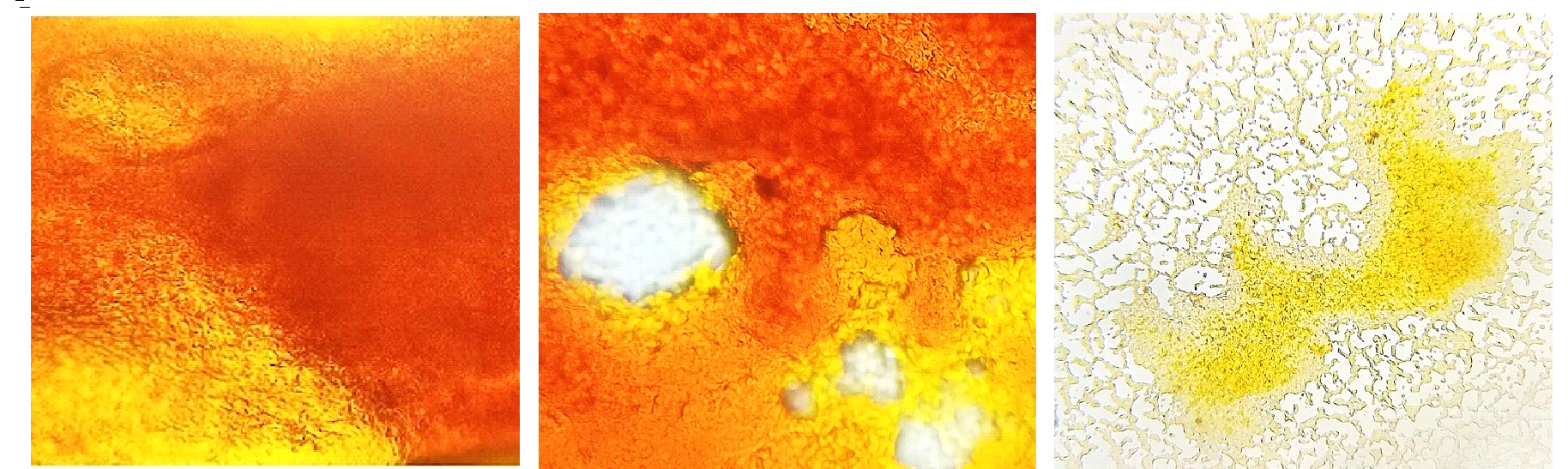


The experiment using seagrass extract at varying concentrations demonstrated a dose-dependent increase in histamine release from cell lysates. At the lowest concentration tested, 250 µg/ml, the extract induced a moderate histamine release of 52% with a standard deviation of 2.1, indicating some variability in the response. As the concentration of the seagrass extract increased to 500 µg/ml, histamine release significantly rose to 79%, with a slightly lower standard deviation of 1.7, suggesting a more consistent response among the samples. At 750 µg/ml, histamine release reached 100%, the maximum possible level, indicating that all cells were releasing histamine at their full potential, albeit with some variation in the extent of release. Similarly, at the highest concentration of 1000 µg/ml, histamine release remained at 100%, reflecting a consistent maximal response across the samples (**Graph 1**). In this study, highlight the potent effect of the seagrass extract in stimulating histamine release from cell lysates, with higher concentrations yielding a more pronounced and uniform response. Recent research has brought attention to the function of histamine in inter-domain communication as a bacterial signal molecule.



**Figure 1.** Quantification histamine release.

Anti-biofilm activity of *Klebsiella pneumoniae* using ceftazidime and seagrass extract, with seagrass extract serving as the biofilm-inhibiting agent at a concentration of 1000 mg/ml (**Figure 1**). Image A, the untreated control exhibits a dense and extensive biofilm, indicated by the strong and uniform coloration, showing robust biofilm formation by *Klebsiella pneumoniae*. Image B, representing the ceftazidime-treated sample, shows disruption in the biofilm structure with areas of decreased density and some clear patches, suggesting partial inhibition by the antibiotic. Image C, depicting the effect of the seagrass extract, reveals a significantly reduced biofilm formation, characterized by much lighter coloration and large clear areas. This indicates that the seagrass extract at 1000 mg/ml effectively inhibits biofilm formation of *Klebsiella pneumoniae*, likely more effectively than ceftazidime, as evidenced by the greater reduction in biofilm density and extent. These results highlight the potent anti-biofilm activity of the seagrass extract, suggesting its potential as an alternative or complementary treatment to traditional antibiotics like ceftazidime in managing biofilm-associated infections. The rise of antibiotic-resistant forms of bacteria propelled bacterial biofilms to the attention of medical professionals.



**Figure 2.** shows the antibiofilm activity of *klebsiella pneumoniae* using ceftazidime and seagrass extracts at the concentration level of 1000mg/ml. A. indicates the control group (without any treatment), B. indicates pathogen treated with ceftazidime, C. indicates the biofilm inhibition of *klebsiella pneumoniae* treated with seagrass extract.

# Discussion

Histamine is produced and sensed by bacteria, and its release in the human gut affects the host's immune system [(Krell et al., 2021)](https://paperpile.com/c/mnzf1m/W6gwZ). In the human gut microbiome, 117 potential histamine-secreting bacterial species were found by a thorough investigation; these species were significantly more abundant in individuals with inflammatory bowel illness [(Mou et al., 2021)](https://paperpile.com/c/mnzf1m/nnELJ). Although the cause of histamine synthesis is yet unknown, the amount of histamine present in fermented foods like hákarl has been measured [(Belleggia et al., 2021)](https://paperpile.com/c/mnzf1m/J0QbW). By binding to the histamine 2 receptor, high quantities of histamine (10^-6 M) produced by gram-negative bacteria might hinder neutrophil phagocytosis and possibly increase bacterial pathogenicity [(Dib et al., 2023)](https://paperpile.com/c/mnzf1m/hogoq). *K. pneumoniae* is resistant to the majority of current medicines, it is especially important to address the threat that antibiotic resistance poses to world health [(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/mnzf1m/A35k+RRdd+BmbL). One important barrier that increases *K. pneumoniae's* resistance to antibiotics is the creation of biofilms. Nevertheless, little is known about the molecular mechanisms underlying biofilm development and how they relate to *K. pneumoniae's* resistance to antibiotics [(L. Li et al., 2024)](https://paperpile.com/c/mnzf1m/dkSSr). According to the current study, he *Lactobacillus helveticus* isolates G24 and G25 have the ability to generate anti-biofilms and to suppress the growth of multidrug-resistant *Klebsiella pneumoniae*, suggesting that they may be useful probiotic strains [(Raras et al., 2019)](https://paperpile.com/c/mnzf1m/ueNMH). Ursolic acid (UA) exhibited strong inhibitory effects against biofilm formation and biofilm-related gene expression in carbapenem-resistant *Klebsiella* *pneumoniae* (CRKP). Additionally, UA effectively inactivated CRKP cells encased in biofilms, highlighting its potential as an adjunct therapy for treating multidrug-resistant infections [(Qian et al., 2020)](https://paperpile.com/c/mnzf1m/44tjT). Graphene/chitosan nanoparticles (GR/CS NCs) inhibited biofilm formation by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* by up to 94% and 92%, respectively, at a concentration of 40 μg/mL. These results highlight the significant anti-biofilm potential of GR/CS NCs against multi-drug-resistant bacteria [(Muthuchamy et al., 2020)](https://paperpile.com/c/mnzf1m/iqwuf). The isolated bacteriophages ΦKpnM-vB1, ΦKpnP-vB2, and ΦKpnM-vB3 demonstrated high efficiency in reducing *Klebsiella pneumoniae* biofilms. These results suggest their potential use in controlling biofilm formation by this pathogen, making them suitable candidates for phage therapy applications [(Askoura et al., 2021)](https://paperpile.com/c/mnzf1m/1eczQ). The study underscores the critical issue of antibiotic resistance in *Klebsiella pneumoniae*, particularly due to biofilm formation, which significantly enhances the pathogen's resistance to treatment.

# Conclusion

*Klebsiella pneumoniae* presents significant challenges in clinical settings due to its robust antibiotic resistance, facilitated by biofilm formation. This study highlights the bacterium's biochemical profile and resistance mechanisms, emphasizing the need for alternative treatment strategies. The seagrass extract demonstrated potent anti-biofilm activity, outperforming the antibiotic ceftazidime in inhibiting *K. pneumoniae* biofilm formation. These results indicate that seagrass extract could serve as a promising alternative or adjunctive therapy in combating biofilm-related infections caused by multidrug-resistant *K. pneumoniae*. Further research into the mechanisms of action and potential clinical applications of seagrass extract is warranted to develop effective treatment protocols against this formidable pathogen.

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