Infection and Drug Resistance

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ORIGINAL RESEARCH

# Repurposing the Anticancer Drug Cisplatin for Antibacterial Therapy: Evaluating Its Efficacy Against *Pseudomonas aeruginosa* Infections

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**Background:** The rising global threat of antimicrobial resistance, particularly among multidrug-resistant pathogens like *Pseudomonas aeruginosa*, has prompted research into repurposing existing drugs with established safety profiles. Cisplatin, a well-known anticancer agent, has shown preliminary antimicrobial activity but its efficacy against *P. aeruginosa* has not been thoroughly explored. This study aims to evaluate the antimicrobial potential of cisplatin against clinical strains of *P. aeruginosa* by determining the minimum inhibitory concentration (MIC).

**Methodology:** This study assessed whether cisplatin could serve as a novel therapeutic option for treating infections caused by *P. aeruginosa* via broth microdilution assay, especially as the pathogen shows increasing resistance to last-resort antibiotics such as meropenem, colistin, and tigecycline. Findings from this research could contribute to expanding the arsenal of treatments for resistant *P. aeruginosa* infections.

**Results:** The study found that 54.9% of isolates had an MIC of 16 µg/mL, 26.8% had 32 µg/mL, 12.7% had 64 µg/mL, and 5.6% had 8 µg/mL. While cisplatin demonstrated antibacterial activity, no statistically significant difference ($p = 0.089$) was observed between sensitive and resistant strains. A key limitation of this study is the small number of both resistant and sensitive strains, which limits statistical power. Increasing the sample size in future studies will allow for a more robust assessment of cisplatin's efficacy and validate the observed MIC similarities. Additionally, further studies including resistance assays, time-kill kinetics, and in vivo models are needed to explore its bactericidal potential and efficacy in combination with β-lactams.

**Conclusion:** Although cisplatin exhibited activity against *P. aeruginosa*, its clinical potential remains uncertain, and further investigation is necessary to optimize its use and overcome resistance.

**Keywords:** *Pseudomonas aeruginosa*, cisplatin, antimicrobial resistance, MIC, repurposing drugs



Received: 16 March 2025
Accepted: 25 June 2025
Published: 19 August 2025

## Introduction

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health threats of the 21st century, contributing to an alarming increase in mortality rates worldwide.[1] The World Health Organization (WHO) has highlighted the escalating prevalence of resistant pathogens, which are rendering many existing antibiotics ineffective.[2,3] Projections suggest that by 2050, AMR could claim over 10 million lives annually, potentially surpassing cancer as a leading cause of death.[4,5] This crisis is further intensified by the rapid pace at which resistance develops, outstripping the discovery of new antibiotics.[6,7] The growing threat underscores an urgent need for innovative strategies to combat drug-resistant infections and avert the catastrophic consequences of a "post-antibiotic" era. To address this challenge, innovative strategies such as antibiotic adjuvants (eg, β-lactamase and efflux pump inhibitors), lytic transglycosylase inhibitors, bacteriophage therapy, and green synthesis nanoparticles are being explored. Host-directed therapy, which targets host pathways essential for pathogen survival, also holds promise. Understanding resistance mechanisms and enhancing stewardship programs are crucial for validating these emerging alternatives and ensuring the effective treatment of resistant infections.[8]

*P. aeruginosa* is a highly adaptable and opportunistic pathogen known for its remarkable ability to develop resistance to antimicrobial agents.[9,10] It is associated with a wide spectrum of infections, including respiratory tract infections such as ventilator-associated pneumonia, bloodstream infections, urinary tract infections, and chronic wound infections.[11,12] *P. aeruginosa* is prevalent in both healthcare and community settings, particularly in immunocompromised individuals, and is a major cause of hospital-acquired infections (HAIs).[13] Its intrinsic resistance mechanisms, combined with its ability to acquire additional resistance through horizontal gene transfer, have made it a significant contributor to the global AMR crisis.[14,15]

*P. aeruginosa* is a prime example of a pathogen with remarkable adaptability and persistence that can rapidly develop resistance to multiple antibiotics.[16,17] Initially, *P. aeruginosa* exhibited resistance to beta-lactam antibiotics through the production of beta-lactamases, enzymes that break down the antibiotic structure.[18,19] Over time, the bacterium acquired additional mechanisms of resistance, including alterations to its outer membrane porins, which limit the entry of antibiotics into the cell. *P. aeruginosa* also developed efflux pumps that actively expel antibiotics from the cell, further contributing to its resistance profile.[20,21] As a result, this pathogen has become resistant to a broad range of antibiotics, including carbapenems, cephalosporins, and aminoglycosides.[20,22] More concerning is the emergence of multidrug-resistant strains, which pose significant challenges in clinical settings, particularly in patients with compromised immune systems or those requiring intensive care.[23,24] The continued evolution of *P. aeruginosa* underscores the need for novel therapeutic strategies and vigilant surveillance to combat its growing resistance.

*P. aeruginosa* has demonstrated resistance to several last-resort antibiotics, including meropenem, colistin, and tigecycline. Initially, meropenem, a carbapenem, was considered a critical option for treating multidrug-resistant infections.[25–27] However, resistance has emerged through mechanisms such as the production of carbapenemases, which degrade the antibiotic, and alterations in porin channels that limit drug entry.[28,29] Similarly, colistin, once regarded as a last-line treatment for resistant *P. aeruginosa* infections, has seen growing resistance due to modifications in the bacterial outer membrane, which reduce the binding affinity of colistin.[30] Tigecycline, a broad-spectrum antibiotic used for complicated infections, has also faced resistance from *P. aeruginosa*, primarily through efflux pump overexpression and ribosomal modifications.[31] The development of resistance to these critical antibiotics has raised significant concerns in clinical settings, emphasizing the urgent need for alternative therapeutic strategies and the development of new antimicrobial agents to combat these resistant strains.[32]

The increasing prevalence of bacterial resistance due to antibiotic overuse has intensified the need for alternative antimicrobial strategies. One promising avenue involves targeting bacterial metal acquisition systems, particularly through the study of *metallophores*—small, high-affinity metal-chelating molecules produced by bacteria to sequester essential metal ions such as iron, zinc, and manganese.[33,34] These metal ions are crucial for bacterial growth, survival, and virulence. Metallophores play a key role in overcoming host-imposed nutritional immunity and are vital for the pathogenesis of many bacterial infections.[35] Recent research highlights their potential as innovative targets in antimicrobial therapy, either by disrupting metal acquisition or by employing metallophore-based drug delivery systems such as siderophore-antibiotic conjugates.[36,37]

In response to the growing challenge of antimicrobial resistance, researchers are increasingly exploring drugs with established indications for other conditions, hoping to repurpose them as treatments for resistant pathogens.[38,39] The advantage of repurposing these drugs lies in their established safety profiles, which could expedite the approval process and allow for quicker deployment against infections that are otherwise difficult to treat.[40,41] The FDA's "fast track" approval process offers a pathway for such drugs, providing a potential boost to the arsenal of available treatments.[42]

One such drug under investigation is cisplatin, a platinum-based chemotherapeutic agent widely used for treating various malignancies, including testicular and ovarian cancers.[43] While traditionally employed in oncology, emerging evidence suggests cisplatin also exhibits antibacterial activity. For instance, it has shown inhibitory effects against several Gram-negative bacteria, including *Aerobacter aerogenes, Alcaligenes faecalis, Proteus mirabilis, Pseudomonas aeruginosa*, and *Serratia marcescens*.[44] These studies indicate that cisplatin may exert its antimicrobial action via DNA cross-linking and induction of oxidative stress, mechanisms similar to those in cancer therapy. However, the extent of cisplatin's activity specifically against clinical isolates of *P. aeruginosa*, including resistant and sensitive strains, remains insufficiently characterized. Given the increasing resistance of *P. aeruginosa* to critical antibiotics such as meropenem, colistin, and tigecycline, exploring alternative strategies is imperative. This study addresses this critical gap by evaluating the minimum inhibitory concentration (MIC) of cisplatin against both resistant and sensitive clinical strains of *P. aeruginosa*, aiming to determine whether cisplatin could be repurposed as a potential therapeutic agent against this formidable pathogen.

## Materials and Methods

Cisplatin used in this study was obtained from Sigma-Aldrich (USA). A stock solution was prepared by dissolving cisplatin in 5% dimethyl sulfoxide (DMSO) from Sigma-Aldrich (USA), chosen for its compatibility and solubility. A 5% dimethyl sulfoxide (DMSO) solution was prepared using 5 mL of DMSO and 95 mL of distilled water. All preparations were performed under sterile conditions to maintain experimental integrity and prevent contamination.

### Bacterial Isolates

This study investigated *P. aeruginosa* isolates to compare antibiotic-resistant and antibiotic-sensitive strains. This study included 71 *Pseudomonas aeruginosa* strains, of which 40 were resistant to β-lactams and meropenem, while 31 were sensitive to β-lactams. The isolates were sourced from the Microbiology Culture Collections maintained by the Clinical and Molecular Microbiology Laboratories at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, ensuring high-quality standards in bacterial collection, identification, and preservation.

The isolates were stored in sterile glycerol stocks at −80°C to maintain their viability and genetic stability. Prior to experimentation, the frozen isolates were thawed and sub-cultured on sheep blood agar plates (Saudi Prepared Media Laboratory Company) to ensure optimal growth. The cultures were incubated aerobically at 35–37°C for approximately 20 hours, allowing the bacteria to recover and display typical morphological and biochemical traits.

For identification and antibiotic susceptibility testing, the Vitek 2 automated system (BioMérieux, France) was utilized. Gram-negative bacteria were identified using the GN Identification Card, while susceptibility testing was performed with the AST-N419 and AST-N417 cards, designed for clinically significant aerobic Gram-negative bacilli. All procedures were conducted according to the manufacturer's guidelines to ensure data accuracy and reproducibility.

### MIC Assay

The broth microdilution method was employed to determine the MIC of the tested compounds, a standard and reliable technique for antimicrobial susceptibility testing. A stock solution at 512 µg/mL was prepared using the formula C1V1=C2V2 ensuring precision. Mueller-Hinton Broth (MHB) (Sigma-Aldrich (USA) served as the medium, providing optimal conditions for bacterial growth. To prepare the stock solution, 100 mg of the compound was dissolved in 10 mL of 5% DMSO, resulting in a final stock concentration of 10 mg/mL. To achieve an initial working concentration of 256 µg/mL, the dilution was calculated using the formula:

$C_1V_1 = C_2V_2$,

where:

$C_1$ = 10 mg/mL (stock concentration), $V_1$ = volume to be calculated, $C_2$ = 256 µg/mL (desired concentration), $V_2$ = 10 mL (final volume).

By substituting the values and converting units appropriately, the required volume ($V_1$) was determined. This calculated volume of stock solution was then diluted with water to reach the desired concentration. Following this, a series of two-fold serial dilutions were performed to obtain the final concentrations required for the assay.

Serial two-fold dilutions were performed in 96-well microtiter plates to create a gradient of concentrations. A standardized bacterial inoculum, adjusted to 0.5 McFarland standards (~$10^8$ CFU/mL) and diluted to the required density, was added to each well. The plates were incubated at 35−37°C for 18–20 hours under aerobic conditions.[45]

The MIC was determined as the lowest concentration of the compound that completely inhibited visible bacterial growth, validated against positive (bacteria without compound) and negative (broth only) controls. All experiments were conducted in triplicate, and average MIC values were calculated to ensure consistency and reproducibility.[46]

## Statistical Analysis

To compare the sensitive and resistant strains of *Pseudomonas aeruginosa*, a *t*-test was conducted to evaluate statistical significance in their differences. The analysis was performed using GraphPad Prism version 8, chosen for its accuracy and user-friendly interface. Data were verified for completeness, consistency, and normal distribution to meet the *t*-test assumptions.

The *t*-test provided a p-value to assess whether observed differences were due to random chance. A significance threshold of $p<0.05$ indicated meaningful differences, while $p\geq0.05$ suggested no significant variation. Results were visualized with graphs such as bar charts or scatter plots, aiding interpretation and communication. This rigorous process ensured reliable and valid conclusions about the differences between sensitive and resistant strains.

## Ethical Statement

This study strictly adhered to ethical standards at all stages. Sample collection and research activities were conducted in full compliance with the guidelines set by the Research Ethics Committee (REC) of the Faculty of Medicine at King Abdulaziz University (Ethics Reference No. 301–24). These protocols were in full alignment with the Declaration of Helsinki, ensuring respect for participants' rights, privacy, and ethical responsibility. The clinical isolates used in this study were obtained as part of routine diagnostic procedures at the hospital. The study's careful attention to ethical oversight, along with the meticulous handling, cultivation, and identification of isolates, reflects a strong commitment to both scientific integrity and ethical principles.

# Results

## Cisplatin Activity Against Sensitive *P. aeruginosa* Strains

In this study, the antibacterial activity of cisplatin was assessed against sensitive *Pseudomonas aeruginosa* strains using MIC determination. The MIC values for these strains ranged from 8 to 16 µg/mL, while one strain showed inhibition at 64 µg/mL. These results indicate a consistent inhibitory effect of cisplatin against sensitive strains, suggesting that it may serve as a potential antimicrobial agent. Cisplatin's known mechanisms—DNA cross-linking and induction of oxidative stress—could contribute to this observed activity, independent of conventional antibiotic pathways.

## Cisplatin Activity Against Resistant *P. aeruginosa* Strains

For resistant *P. aeruginosa* strains, MIC values ranged from 8 to 64 µg/mL. It is indicating that reduced susceptibility compared to sensitive strains. However, statistical analysis revealed no significant difference between the two groups ($p$ = 0.089). This finding implies that cisplatin's antibacterial effect may not be significantly influenced by established resistance mechanisms (Table 1).

**Table 1** MIC Distribution of *P. aeruginosa* Isolates Against Cisplatin. The Table Presents the Number of Isolates, Corresponding MIC Values (μg/mL), and Their Respective Percentage Distributions

| MIC (μg/mL) | Number of Isolates | Percent (%) |
|---|---|---|
| 8 | 4 | 5.6% |
| 16 | 39 | 54.9% |
| 32 | 19 | 26.8% |
| 64 | 9 | 12.7% |
| **Total** | **71** | **100%** |

## Discussion

For the first time, we have evaluated the in vitro efficacy of cisplatin against a collection of 71 *P. aeruginosa* strains, encompassing both resistant and sensitive isolates. Our findings revealed that the MICs of cisplatin ranged from 8 to 64 μg/mL, indicating that this drug exhibits promising antimicrobial activity against the notoriously challenging pathogen *P. aeruginosa*. This suggests that cisplatin has the potential to serve as an effective therapeutic agent against this "superbug", which is known for its significant resistance to many conventional antibiotics. This study presents novel findings by evaluating the antimicrobial activity of cisplatin—a widely used anticancer drug—against *Pseudomonas aeruginosa* clinical isolates, including both sensitive and resistant strains. While prior studies have noted cisplatin's potential antibacterial effects, this research specifically focuses on its efficacy against *P. aeruginosa*, a WHO-prioritized multidrug-resistant pathogen, an area that remains underexplored. The value of this study lies in its potential to repurpose an existing FDA-approved drug as an alternative antimicrobial agent, which could help address the growing challenge of antibiotic resistance. A major limitation is the relatively small number of resistant isolates, which limits statistical power and generalizability. Future research should incorporate a larger and more diverse set of clinical isolates and include mechanistic studies, combination therapy evaluations, and in vivo models to further validate and expand upon these preliminary findings.

Interestingly, our analysis showed no significant differences in MIC values between resistant and sensitive strains of *P. aeruginosa*. This observation implies that, to date, there may not be a specific resistance mechanism within *P. aeruginosa* capable of counteracting the effects of cisplatin. This is a particularly important finding, as it suggests that cisplatin might circumvent common resistance pathways that compromise the efficacy of other antibiotics. Also, more assays are needed to study this observation.

However, while these in vitro results are encouraging, further research is needed to assess the efficacy of cisplatin in vivo. Studies in animal models or clinical trials would be essential to determine its therapeutic potential, optimal dosing, and safety profile when used to treat *P. aeruginosa* infections. These findings provide a strong foundation for further exploration of cisplatin as a novel antimicrobial agent against multidrug-resistant pathogens.

Our findings align with previous research demonstrating that the antitumor agent cisplatin possesses a broad antimicrobial spectrum. The growth of all 29 tested microorganisms, including seven Gram-negative bacterial strains, eight Gram-positive bacterial strains, seven yeast strains, and seven mold strains, was inhibited.[47] However, while their study utilized the disc diffusion assay, our investigation employed the broth microdilution method to evaluate antimicrobial activity.

Cisplatin is a widely utilized anticancer agent renowned for its significant role in cancer therapy. Its mechanism of action involves binding to DNA, inducing cross-linking between adjacent intrastrand purines, and disrupting the DNA repair process. These actions result in effective DNA damage, making cisplatin a powerful tool in the treatment of various cancers.[43] Studies have demonstrated that cisplatin treatment triggers the expression of various genes associated with energy metabolism. This finding aligns with earlier proteomics research, which revealed that cisplatin can disrupt stress response pathways and interfere with energy metabolism in *Escherichia coli*.[48] Additionally, transcriptomic analysis has shown that cisplatin exposure leads to the downregulation of numerous secretion-related genes in Gram negative bacteria, including those associated with the type III secretion system (T3SS).[49] This effect is similar to the impact observed with ciprofloxacin exposure. Furthermore, another study showed that qRT-PCR analysis confirmed that

the expression of two key T3SS genes, *exoS* and *pscG*, was significantly downregulated in response to cisplatin treatment compared to the control.[50] Collectively, these findings may provide a mechanistic explanation for the notable efficacy of cisplatin against *P. aeruginosa*, but further assays are needed.

Cisplatin's adverse effects include renal toxicity, neurotoxicity, emesis, bone marrow suppression, anemia, and hearing loss. Due to these toxicities, cisplatin is administered intravenously at low doses to minimize harm while maintaining therapeutic efficacy.[47] This paves the way for future strategies involving the combination of cisplatin with other antibiotics to harness the synergistic effects of both drugs, aiming to enhance therapeutic efficacy while minimizing toxicity.[51] One key limitation of this study is the relatively limited number of both resistant and sensitive *P. aeruginosa* strains, which may have affected the statistical power of the analysis. Although similar MIC values were observed among resistant and sensitive strains, the small sample size limits the ability to draw definitive conclusions regarding cisplatin's comparative efficacy. Increasing the number of clinical isolates in future studies would strengthen the statistical analysis and allow for a more comprehensive evaluation of cisplatin's antibacterial potential. A larger, more diverse sample set would also help clarify whether the observed MIC similarities are consistent or merely coincidental, thereby providing deeper insight into cisplatin's mechanism of action and clinical applicability.

Future studies should focus on further evaluating the antibacterial potential of cisplatin against *Pseudomonas aeruginosa*, particularly in resistant strains. To comprehensively assess its bactericidal activity, time-kill assays should be conducted to determine the kinetics of bacterial eradication. Given cisplatin's known cytotoxicity, evaluating its therapeutic feasibility is essential. Future studies should include cytotoxicity assays, such as MTT or LDH, to compare its MIC with its toxic effects on human cell lines including epithelial or macrophage cells. This will help determine a safe and effective therapeutic window. To better understand cisplatin's antibacterial mechanism, future studies should investigate reactive oxygen species (ROS) generation and DNA fragmentation to confirm whether its antimicrobial effect parallels its known anticancer activity. Moreover, future studies will investigate the potential synergistic effects between cisplatin and β-lactam antibiotics using methods such as checkerboard assays and calculation of fractional inhibitory concentration indices (FICI) to better understand their combined antibacterial activity. In addition, future study will focus on evaluating the potential for resistance development to cisplatin by performing serial passage experiments and assessing the spontaneous mutation frequency, which will help determine the risk of resistance emergence during treatment. These investigations will provide deeper insights into the clinical applicability of cisplatin as an alternative or adjunctive treatment for multidrug-resistant infections.

## Conclusion

This study highlights the potential antimicrobial activity of cisplatin against clinical strains of *Pseudomonas aeruginosa*, including both sensitive and resistant isolates. The MIC testing revealed moderate activity, with the majority of strains showing MIC values ranging from 8 to 64 μg/mL. However, no statistically significant difference was found between sensitive and resistant strains, suggesting a uniform response across phenotypes. A key limitation of this study is the limited number of clinical isolates, particularly resistant strains, which may affect the generalizability of the findings. Future studies with larger sample sizes are essential to validate these results. Additional investigations such as time-kill assays, resistance mechanism analysis, combination therapies with β-lactams, and in vivo models are recommended to better understand cisplatin's antimicrobial potential and optimize its application. These findings contribute to the growing body of evidence supporting drug repurposing as a promising strategy to combat multidrug-resistant pathogens.

## Funding

This study did not receive any external funding. All expenses were covered by the authors.

## Disclosure

The authors declare that there are no conflicts of interest related to this study. No financial, personal, or professional relationships have influenced the findings or interpretations presented in this work.

## References


1. Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. *Perspect Medicin Chem*. 2014;6(1):25–64. doi:10.4137/PMC.S14459
2. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. *Bull World Health Organ*. 1980;2(1):129–139.
3. Tripathy S, Sahu SK. FtsZ inhibitors as a new genera of antibacterial agents. *Bioorg Chem*. 2019;91(7):103169. doi:10.1016/j.bioorg.2019.103169
4. Inoue H. Strategic approach for combating antimicrobial resistance (AMR). *Glob Heal Med*. 2019;1(2):61–64. doi:10.35772/ghm.2019.01026
5. Ahmed SK, Hussein S, Qurbani K, et al. Antimicrobial resistance: impacts, challenges, and future prospects. *J Med Surgery Public Heal*. 2024;2 (January):100081. doi:10.1016/j.glmedi.2024.100081
6. Alkuwaity KIAEK, Mokhtar JA, Abujamel T, et al. Evaluation of the antibacterial activity of 3-hydrazinoquinoxaline-2-thiol compound against extended-spectrum beta-lactamases producing bacteria. *Eur Rev Med Pharmacol Sci*. 2024;28(10):3548–55.
7. Sultan I, Rahman S, Jan AT, Siddiqui MT, Mondal AH, Haq QMR. Antibiotics, resistome and resistance mechanisms: a bacterial perspective. *Front Microbiol*. 2018;9(Sep). doi:10.3389/fmicb.2018.02066
8. Aggarwal AK, Mahajan R, Pandiya P. Antibiotic resistance: a global crisis, problems and solutions. *Crit Rev Microbiol*. 2024;50(5):896–921. doi:10.1080/1040841X.2024.2313024
9. Meto A, Colombari B, Meto A, et al. Propolis affects pseudomonas aeruginosa growth, biofilm formation, eDNA release and phenazine production: potential involvement of polyphenols. *Microorganisms*. 2020;8(2):243. doi:10.3390/microorganisms8020243
10. Rezzoagli C, Archetti M, Mignot I, Baumgartner M, Kümmerli R. Combining antibiotics with antivirulence compounds can have synergistic effects and reverse selection for antibiotic resistance in pseudomonas aeruginosa. *PLOS Biol*. 2020;18(8):1–27. doi:10.1371/journal.pbio.3000805
11. Streeter K, Katouli M. Pseudomonas aeruginosa: a review of their pathogenesis and prevalence in clinical settings and the environment. *Infect Epidemiol Med*. 2016;2(1):25–32. doi:10.18869/modares.iem.2.1.25
12. Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage Pseudomonas aeruginosa infections. *Drugs Context*. 2018;7:1–18. doi:10.7573/dic.212527
13. Restrepo MI, Babu BL, Reyes LF, et al. Burden and risk factors for pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *Eur Respir J*. 2018;52(2):1701190. doi:10.1183/13993003.01190-2017
14. Masadeh MM, Alzoubi KH, Masadeh MM, Aburashed ZO. Metformin as a potential adjuvant antimicrobial agent against multidrug resistant bacteria. *Clin Pharmacol Adv Appl*. 2021;13:83–90.
15. Botelho J, Grosso F, Peixe L. Antibiotic resistance in pseudomonas aeruginosa – mechanisms, epidemiology and evolution. *Drug Resist Updat*. 2019;44(April):100640. doi:10.1016/j.drup.2019.07.002
16. Nasrin F. Study of antimicrobial and antioxidant potentiality of anti-diabetic drug metformin. *Int J Pharm Drug Anal*. 2014;2(3):220–224.
17. Andersson DI, Balaban NQ, Baquero F, et al. Antibiotic resistance: turning evolutionary principles into clinical reality. *FEMS Microbiol Rev*. 2021;44(2):171–188. doi:10.1093/femsre/fuaa001
18. Sykes RB, Matthew M. The β-lactamases of gram-negative bacteria and their role in resistance to β-lactam antibiotics. *J Antimicrob Chemother*. 1976;2(2):115–157. doi:10.1093/jac/2.2.115
19. Zango UU, Ibrahim M, Shawai SAA, Shamsuddin IM. A review on beta-lactam antibiotic drug resistance. *MOJ Drug Des Dev Ther*. 2019;3(2):52–58.
20. Seder N, Rayyan WA, Al-Fawares L, Hilmi M, Bakar A. Pseudomonas aeruginosa virulence factors and antivirulence mechanisms to combat drug resistance; a systematic review. *Sapporo Med J*. 2022;56(12):1–23.
21. Schweizer HP. Efflux as a mechanism of resistance to antimicrobials in pseudomonas aeruginosa and related bacteria: unanswered questions. *Genet Mol Res*. 2003;2(1):48–62.
22. Esposito S, De Simone G. Update on the main MDR pathogens: prevalence and treatment options. *Infez Med*. 2017;25(4):301–310.
23. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. *Curr Opin Pharmacol*. 2014;18:56–60. doi:10.1016/j.coph.2014.09.006
24. Duhaniuc A, Păduraru D, Nastase E-V, et al. Multidrug-resistant bacteria in immunocompromised patients. *Pharmaceuticals*. 2024;17(9):1151. doi:10.3390/ph17091151
25. Verkaik NJ, Wielders CCH, den Boer H, et al. O03 phenotypic antimicrobial resistance to last-resort antibiotics in carbapenemase-producing bacteria from Ukrainian patients. *JAC-Antimicrobial Resist*. 2024;6(Supplement_1). doi:10.1093/jacamr/dlad143.003.
26. Mondal AH, Khare K, Saxena P, Debnath P, Mukhopadhyay K, Yadav D. A review on colistin resistance: an antibiotic of last resort. *Microorganisms*. 2024;12(4):772. doi:10.3390/microorganisms12040772
27. Jacquier H, Le Monnier A, Carbonnelle E, et al. In vitro antimicrobial activity of "last-resort" antibiotics against unusual nonfermenting gram-negative bacilli clinical isolates. *Microb Drug Resist*. 2012;18(4):396–401. doi:10.1089/mdr.2011.0195
28. Yoon EJ, Jeong SH. Mobile carbapenemase genes in pseudomonas aeruginosa. *Front Microbiol*. 2021;12(February). doi:10.3389/fmicb.2021.614058
29. *Zeinab Breijyeh RK. Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it. *Molecules*. 2023;28(2):1340.
30. Lee JY, Park YK, Chung ES, Na IY, Ko KS. Evolved resistance to colistin and its loss due to genetic reversion in pseudomonas aeruginosa. *Sci Rep*. 2016;6(May):1–13. doi:10.1038/s41598-016-0001-8
31. Sun Y, Cai Y, Liu X, Bai N, Liang B, Wang R. The emergence of clinical resistance to tigecycline. *Int J Antimicrob Agents*. 2013;41(2):110–116. doi:10.1016/j.ijantimicag.2012.09.005
32. Ba X, Harrison EM, Lovering AL, et al. Old drugs to treat resistant bugs: methicillin-resistant staphylococcus aureus isolates with mecC are susceptible to a combination of penicillin and clavulanic acid. *Antimicrob Agents Chemother*. 2015;59(12):7396–7404. doi:10.1128/AAC.01469-15
33. Gomes AFR, Almeida MC, Sousa E, Resende DISP. Siderophores and metallophores: metal complexation weapons to fight environmental pollution. *Sci Total Environ*. 2024;932(January):173044. doi:10.1016/j.scitotenv.2024.173044
34. Neumann W, Gulati A, Nolan EM. Metal homeostasis in infectious disease: recent advances in bacterial metallophores and the human metal-withholding response. *Curr Opin Chem Biol*. 2017;176(1):100–106.
35. Murdoch CC, Skaar EP. Nutritional immunity: the battle for nutrient metals at the host–pathogen interface. *Nat Rev Microbiol*. 2022;20 (11):657–670. doi:10.1038/s41579-022-00745-6

36. Ezzeddine Z, Ghssein G. Towards new antibiotics classes targeting bacterial metallophores. *Microb Pathog*. 2023;182(I):1–19. doi:10.1016/j.micpath.2023.106221
37. Gambino D, Otero L. Metal compounds in the development of antiparasitic agents: rational design from basic chemistry to the clinic. *Met Ions Life Sci*. 2019;19(March):331–357.
38. Farha MA, Brown ED. Drug repurposing for antimicrobial discovery. *Nat Microbiol*. 2019;4(4):565–577. doi:10.1038/s41564-019-0357-1
39. Talat A, Bashir Y, Khan AU. Repurposing of antibiotics: sense or non-sense. *Front Pharmacol*. 2022;13(February):1–3. doi:10.3389/fphar.2022.833005
40. Domalaon R, Ammeter D, Brizuela M, Gorityala BK, Zhanel GG, Schweizer F. Repurposed antimicrobial combination therapy: tobramycin-ciprofloxacin hybrid augments activity of the anticancer drug mitomycin C against multidrug-resistant gram-negative bacteria. *Front Microbiol*. 2019;10(JULY):2. doi:10.3389/fmicb.2019.01556
41. Oprea TI, Mestres J. Drug repurposing: far beyond new targets for old drugs. *AAPS J*. 2012;14(4):759–763. doi:10.1208/s12248-012-9390-1
42. Cha Y, Erez T, Reynolds IJ, et al. Drug repurposing from the perspective of pharmaceutical companies. *Br J Pharmacol*. 2018;175(2):168–180. doi:10.1111/bph.13798
43. Burger H, Capello A, Schenk PW, Stoter G, Brouwer J, Nooter K. A genome-wide screening in saccharomyces cerevisiae for genes that confer resistance to the anticancer agent cisplatin. *Biochem Biophys Res Commun*. 2000;269(3):767–774. doi:10.1006/bbrc.2000.2361
44. Rosenberg B, Renshaw E, Vancamp L, Hartwick J, Drobnik J. Platinum-induced filamentous growth in escherichia coli. *J Bacteriol*. 1967;93(2):716–721. doi:10.1128/jb.93.2.716-721.1967
45. Elfadil A, Ibrahem K, Abdullah H, Mokhtar JA, Al-Rabia MW, Mohammed HA. synergistic activity of 3-hydrazinoquinoxaline-2-thiol in combination with penicillin against MRSA. *Infect Drug Resis*. 2024;17(January):355–364. doi:10.2147/IDR.S448843
46. Bazuhair MA, Alsieni M, Abdullah H, et al. The combination of 3-hydrazinoquinoxaline-2-thiol with thymoquinone demonstrates synergistic activity against different candida strains. *Infect Drug Resist*. 2024;17:2289–2298. doi:10.2147/IDR.S464287
47. Joyce K, Saxena S, Williams A, et al. Antimicrobial spectrum of the antitumor agent, cisplatin. *J Antibiot*. 2010;63(8):530–532. doi:10.1038/ja.2010.64
48. Stefanopoulou DA, Kokoschka M, Sheldrick M, Wolters DA. Cell response of Escherichia coli to cisplatin-induced stress. *Proteomics*. 2011;11(21):4174–4188. doi:10.1002/pmic.201100203
49. Cirz RT, O'Neill BM, Hammond JA, Head SR, Romesberg FE. Defining the Pseudomonas aeruginosa SOS response and its role in the global response to the antibiotic ciprofloxacin. *J Bacteriol*. 2006;188(20):7101–7110. doi:10.1128/JB.00807-06
50. Yuan M, Chua SL, Liu Y, et al. Repurposing the anticancer drug cisplatin with the aim of developing novel Pseudomonas aeruginosa infection control agents. *Beilstein J Org Chem*. 2018;14:3059–3069. doi:10.3762/bjoc.14.284
51. Hu A, Liu Y, Coates A. Azidothymidine produces synergistic activity in combination with colistin against antibiotic-resistant enterobacteriaceae. *Antimicrob Agents Chemother*. 2019;63(1):1–11. doi:10.1128/AAC.01630-18