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CORRESPONDENCE

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AI-driven drug discovery: Exploring Abaucin as a promising treatment against multidrug-resistant *Acinetobacter baumannii*

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Abstract

Background and Aims: This study presents a comprehensive overview of a well-recognized critical pathogen *Acinetobacter baumannii* and demonstrates the potential of artificial intelligence (AI) in discovering new antibiotics. It is well-known for causing serious infections, especially in patients admitted to intensive care units, which is further compromised by bacterium's resistance to even last-resort antibiotics like carbapenems, posing critical challenges in its treatment and eradication. This article discusses Abaucin, a revolutionary antibiotic created from artificial intelligence, as a creative and potential treatment for *A. baumannii*.

Methods: A comprehensive literature search was conducted using various databases including PubMed, Google Scholar, Cochrane, Science Direct, MEDLINE. Only articles written in English were considered. This correspondence was written after a thorough evaluation of all the articles that discussed Abaucin's discovery, potency against *A. baumannii*, and the potential of AI in discovering new antibiotics. In addition, references from the selected articles were also examined to ensure a comprehensive review of the literature.

Results: This article highlights the discovery of a novel AI-derived antibiotic, Abaucin that offers a promising solution for *A. baumannii* infections. Abaucin has a narrow range of action that minimizes the risk of inter-pathogen spread of resistance, making the drug more appealing and effective. Its potential to suppress wound infections caused by multidrug-resistant *A. baumannii* paves a hope for the eradication of superbugs. Further investigation and trials are needed to determine its effectiveness in human subjects and its integrity in the clinical workflow. machine learning (ML) and precision approach could revolutionize treatment strategies.

Conclusion: The discovery of Abaucin as an antibiotic to combat drug-resistant *A. baumannii* bacteria showcases AI and ML's potential to uncover novel antibiotics, thereby offering alternative treatment options. This novel inception of the AI-derived antibiotic, Abaucin marks the first step in introducing an innovative

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treatment option and represents a substantial leap in the treatment of drug-resistant illnesses and the use of AI in medical advancements.

KEYWORDS

Abaucin, *Acinetobacter baumannii*, artificial inteligence, carbapenem-resistant isolates, machine learning

Acinetobacter baumannii is designated as a high-priority pathogen by the World Health Organization (WHO) owing to its broad spectrum of antimicrobial resistance and severe clinical manifestations. This opportunistic pathogen is known to cause severe and invasive nosocomial infections, including bloodstream infections, pulmonary infections, meningitis, wound infections, and ventilator-associated pneumonia, associated with a significantly high mortality rate of approximately 42.6%.[1,2] As reported, it affects approximately 1 million people globally, with the rate of multidrug-resistant strain being four times higher, accounting for 45% of all the *A. baumannii* isolates.[3]

The treatment for multidrug-resistant *A. baumannii* (MDRAB) poses significant challenges due to its broad spectrum of resistance even against the last resort antibiotics. Current pharmacologic treatment for MDRAB includes minocycline, eravacycline, cefiderocol, ampicillin, sulbactam and colistin (polymyxin E).[4] However, it has been demonstrated that efflux pump overexpression and porin loss linked to carbapenem-resistance may also confer cross-resistance to other antibiotic classes such as tigecycline. Additionally, there is anecdotal information on the effectiveness of minocycline and eravacycline against carbapenem-resistant isolates. While cefiderocol exhibits activity against the majority of *A. baumannii* strains, the emergence of cefiderocol-resistant strains has already been documented. ampicillin/sulbactam and trimethoprim/sulfamethoxazole have been utilized in the treatment of carbapenem-resistant *A. baumannii*; however, their role and efficacy against carbapenem-resistant isolates are still not well-defined.[4] Colistin, a polymyxin antibiotic, is often used as a last-resort treatment option owing to its relatively lower rates of resistance. However, the emergence of colistin-resistant *A. baumannii* strains has become a global concern, further complicating treatment strategies. Recent studies have suggested that polymyxin B, another polymyxin antibiotic, may serve as an alternative to colistin. However, polymyxin B has traditionally been associated with dose-dependent nephrotoxicity, which poses challenges in its clinical use.[1,4]

Using artificial intelligence (AI) technology, an antibiotic named Abaucin previously called RS102895 has been discovered that has proven to be highly efficient against the superbug, *A. baumannii*.[5] A machine-learning model was first trained to assess inhibition of bacterial growth based on molecular structures by exposing MDRAB to 7500 known chemical compounds. Using this, the model evaluated 6680 unknown compounds, identifying 240 hits for experimental testing through which nine antibiotics were discovered, the most potent being Abaucin.[5] Similar artificial neural networks that can screen chemical libraries can be deployed to explore novel antibiotics based on their antibacterial properties. One such discovery identified as an atypical antibiotic capable of inhibiting the growth of *Escherichia coli* is Halicin, the c-Jun N-terminal kinase inhibitor SU3327 sourced from the Drug Repurposing Hub. Notably, it has demonstrated effectiveness against *Clostridioides difficile* and pan-resistant *A. baumannii* in experiments involving mice. Further studies are required to compare the efficacy of Abaucin and Halicin against *A. baumannii*.[6] Additionally, AI has helped to identify molecules that target *Helicobacter pylori's* XGHPRT enzyme, which will potentially speed up the process of drug delivery and optimization to combat *H. pylori* infections.[7]

Abaucin works by obstructing lipoprotein trafficking. Lipoprotein trafficking is a process used by cells to transport proteins from the inside of cells to the cell's envelope. This drug appears to inhibit the lipoprotein-releasing system transmembrane protein LolE specifically which is involved in this process.[8] This interferes with the LolE-mediated accommodation and transport of lipoproteins, inhibiting the growth of *A. baumannii*. Because of this inhibition, bacterial cells enlarge significantly and lose their ability to condense nuclei, resulting in abnormal cell morphology.

Unlike other antibiotics that are mostly broad-spectrum acting against many bacterial species, this drug was found to be effective only against *A. baumannii*. In antimicrobial assays, Abaucin showcased potent antimicrobial activity, exhibiting minimal inhibitory concentration (MIC) values ranging from 2 to 64 $\mu g\,mL^{-1}$ against all 42 strains of *A. baumannii* tested, including clinical isolates from the ARIsolate Bank—a unique repository of antibiotic-resistant isolates provided by the US Center for Disease Control and Prevention. Abaucin was investigated for growth inhibitory activity against other bacterial species that is, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and carbapenem-resistant bacteria. Contrary to what was observed with *A. baumannii*, this drug did not exhibit any growth inhibitory action against these pathogenic species up to 20 times the MIC in *A. baumannii* which provided strong evidence of Abaucin's "narrow spectrum" activity. This "narrow spectrum" killing ability is desirable as it minimizes inter-pathogen spread of resistance,[5] making the drug more appealing and effective, and not imposing the universal selective pressure. Furthermore, Abaucin was not reported to have a growth inhibitory effect against the commensal species in contrast to the currently employed antibiotics like ampicillin and ciprofloxacin, thereby safeguarding against opportunistic diseases. Additionally, *A. baumannii* is a key contributor to multidrug resistance infections in wounded patients but surprisingly, it was demonstrated that Abaucin can suppress wound infections caused by *A. baumannii*, thereby

aiding in the eradication of superbugs. In a clinical trial on mice, the effectiveness of the drug Abaucin for treating wound infections brought on by the bacterium *A. baumannii*, ATCC 17978 was examined using an inoculum of 6.5×10^6 CFU of the bacterium. Abaucin was found to effectively suppress the wound infection, consistent with its impact on *A. baumannii* viability in vitro, as evidenced by the fact that Abaucin-treated mice carried 4.0×10^7 CFU g^{-1}, similar to the pretreated infection control mice, and Abaucin-treated tissues displayed noticeably less inflammation.[5]

Despite its remarkable benefits, there are certain aspects that warrant further investigation and exploration. The clinical trial has exclusively been conducted on mice until now, therefore it is crucial to test the effectiveness of Abaucin along with its in-depth toxicity assessment on human subjects to investigate its superior efficacy and confirm the drug's safety profile. Similarly, there is anecdotal information regarding its drug–drug interaction, so Abaucin's interaction with other drugs must also be investigated to know about any unexpected side effects or interactions with other drugs that may emerge over time. Furthermore, a cost-effectiveness analysis is required to determine the effectiveness of its implementation as the empiric treatment or its integrity in the clinical workflow. We believe that in this era of superbugs which are prevalent in many countries throughout the world, this targeted approach could pave the way for precision medicine, where specific antibiotics are developed to target drug-resistant pathogens, reducing the impact on beneficial bacteria and minimizing side effects. Through analysis and investigation of specific antibiotics belonging to certain classes, machine learning (ML) can predict the mechanisms of action of different antibiotics belonging to the same class and estimate antibiotic potency, thus speeding up the process of identifying potential treatment options even in the presence of resistance mechanisms and introducing efficient therapeutic strategies against the critical pathogens.[9]

In conclusion, the discovery of Abaucin as an antibiotic against drug-resistant *A. baumannii* bacteria showcases AI and ML's potential to uncover novel antibiotics, thereby offering alternative treatment options. This novel inception of the AI-derived antibiotic, Abaucin marks the first step in introducing an innovative treatment option. Modern medicine is dealing with the difficulty of handling a lot of information to solve such complicated health problems. AI in the dynamic field of medicine can serve as a powerful tool to assist doctors in treating critically ill patients affected by superbugs worldwide.

AUTHOR CONTRIBUTIONS

Roshanay E. Awan: Conceptualization; writing—original draft; writing—review and editing. **Syeda Zainab**: Conceptualization; writing—original draft; writing—review and editing. **Fizza J. Yousuf**: Writing—original draft; writing—review and editing. **Sanila Mughal**: Writing—review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author Roshanay E. Awan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Reina R, León-Moya C, Garnacho-Montero J. Treatment of *Acinetobacter baumannii* severe infections. *Med Intens*. 2022;46:700-710. doi:10.1016/j.medine.2022.08.007
2. Mohd Sazlly Lim S, Zainal Abidin A, Liew SM, Roberts JA, Sime FB. The global prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia and its associated mortality: a systematic review and meta-analysis. *J Infect*. 2019;79:593-600. doi:10.1016/j.jinf.2019.09.012
3. Cavallo I, Oliva A, Pages R, et al. *Acinetobacter baumannii* in the critically ill: complex infections get complicated. *Front Microbiol*. 2023;14:1196774. doi:10.3389/fmicb.2023.1196774
4. Karakonstantis S, Kritsotakis EI, Gikas A. Treatment options for *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* co-resistant to carbapenems, aminoglycosides, polymyxins and tigecycline: an approach based on the mechanisms of resistance to carbapenems. *Infection*. 2020;48:835-851. doi:10.1007/s15010-020-01520-6
5. Liu G, Catacutan DB, Rathod K, et al. Deep learning-guided discovery of an antibiotic targeting *Acinetobacter baumannii*. *Nat Chem Biol*. 2023;19:1342-1350. doi:10.1038/s41589-023-01349-8
6. Stokes JM, Yang K, Swanson K, et al. A deep learning approach to antibiotic discovery. *Cell*. 2020;180:688-702. doi:10.1016/J.CELL.2020.01.021
7. Alabbas AB. Targeting XGHPRT enzyme to manage *Helicobacter pylori* induced gastric cancer: a multi-pronged machine learning, artificial intelligence and biophysics-based study. *Saudi J Biol Sci*. 2024;31:103960. doi:10.1016/j.sjbs.2024.103960
8. Peters JM, Colavin A, Shi H, et al. A comprehensive, CRISPR-based functional analysis of essential genes in bacteria. *Cell*. 2016;165:1493-1506. doi:10.1016/j.cell.2016.05.003
9. David L, Brata AM, Mogosan C, et al. Artificial intelligence and antibiotic discovery. *Antibiotics*. 2021;10:1376. doi:10.3390/antibiotics10111376

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