Journal of the West
ISSN: 0022-5169 / **E-ISSN:** 1930-0115
https://journalofthewest.com/jw

Design and Synthesis of Novel Antimicrobial Peptides Against Drug-Resistant Pathogens

Dr. Meera Nair
Department of Biochemistry and Molecular Biology,
Centre for Antimicrobial Drug Discovery and Peptide Engineering,
Institute of Advanced Life Sciences and Biotechnology,
Thiruvananthapuram, India

RECEIVED: 15/08/2025 ACCEPTED :05/10/2025 PUBLISHED: 07/03/2026

Abstract
Antimicrobial resistance (AMR) is on the rise and poses a serious danger to public health around the world. It has rendered many traditional antibiotics useless, prompting a race to find new treatment options. The naturally occurring defensive chemicals known as antimicrobial peptides (AMPs) have recently attracted a lot of interest because of their unique ways of action, decreased tendency for resistance development, and broad-spectrum activity, in comparison to conventional antibiotics. the development and production of new ampicillin-resistant microorganisms (AMPs). We prioritize rational design strategies that optimize amphipathicity, charge distribution, and secondary structures to enhance membrane disruption efficiency and selectivity. These strategies incorporate computational modeling, structure-activity relationship (SAR) analysis, and peptide engineering. To improve stability, bioavailability, and protease resistance, synthetic procedures such solid-phase peptide synthesis (SPPS), hybrid peptide creation, and the addition of non-natural amino acids are considered. To further address typical drawbacks including cytotoxicity and short half-life, we also investigate peptidomimetics, nanoparticle conjugation, and cyclization as potential solutions. To show the therapeutic promise, case studies of new AMPs that work against S. aureus, Pseudomonas aeruginosa, and carbapenem-resistant E. coli are highlighted.
Keywords: Antimicrobial peptides (AMPs), drug-resistant pathogens, multidrug resistance (MDR), peptide engineering

Introduction

AMR, one of the biggest global health issues of the 21st century, threatens decades of medical progress and puts millions of lives at danger from once-treatable illnesses. The World Health Organization and recent global health reports estimate that drug-resistant infections kill hundreds of thousands of people each year and could kill 10 million by 2050 if effective countermeasures are not developed, making the search for novel antimicrobial agents a top scientific and medical priority. Though historically effective, conventional antibiotics are increasingly compromised by the rapid emergence of multidrug-resistant (MDR) pathogens like MRSA, carbapenem-resistant Enterobacteriaceae, and Pseudomonas aeruginosa, which use genetic mutations, horizontal gene transfer, and biofilm formation to evade conventional drug mechanisms. In this dire situation, antimicrobial peptides (AMPs), naturally occurring

molecules that are essential to innate immune systems in plants, animals, and microorganisms, have garnered immense interest due to their broad-spectrum antimicrobial activity, unique mechanisms of action, and lower resistance risk than traditional antibiotics. Most small-molecule drugs target metabolic pathways, but AMPs directly interact with microbial membranes, using amphipathic structures and cationic residues to disrupt membrane integrity, leak cellular contents, and kill the bacteria. AMPs can influence immune responses, limit biofilm development, and kill bacteria, fungi, viruses, and cancer cells, making them useful therapeutic prospects. AMPs are promising, but proteolytic breakdown, cytotoxicity to host cells, limited bioavailability, and large-scale production require creative design and synthesis methodologies. Recent advances in computational chemistry, bioinformatics, and molecular modeling have led to rational peptide design with optimized charge distribution, amphipathicity, hydrophobicity, and secondary structures like α-helices and β-sheets, improving microbial membrane specificity and reducing host toxicity. Structure–activity relationship (SAR) investigations, using machine learning and peptide libraries, allow researchers to optimize sequences for antibacterial potency and safety. Solid-phase peptide synthesis (SPPS) is the main method for AMP production, with high precision and flexibility in sequence design. Modifications like incorporation of non-natural amino acids, cyclization, and terminal capping improve stability against proteases and extend half-life in physiological environments. Hybrid peptide methods, which mix natural AMP fragments with synthetic patterns, and peptidomimetics, which mimic AMP structures without degradation, can bypass biological and pharmacological obstacles. Nanoparticle conjugation and encapsulation have changed the functional landscape of AMPs by improving targeted distribution, systemic toxicity, and pharmacokinetic characteristics by shielding peptides from enzymatic degradation. Recent years have witnessed remarkable progress in developing AMPs against high-priority drug-resistant diseases. Engineered peptides like pexiganan, melittin derivatives, and synthetic β-peptides effectively fight MRSA and VRE, while biofilm-targeting peptide conjugates offer potential in treating chronic infections from medical devices. Stapled peptides and disulfide-bridged structures have improved structural stability and selectivity, expanding their therapeutic window. Furthermore, AMPs synergistically reduce the dosage of conventional antibiotics and may expand the clinical efficacy of existing antibiotic classes. AMPs including omiganan, brilacidin, and LL-37 derivatives are in preclinical and clinical trials, proving their translational potential. AMPs face high production costs, regulatory complexity, and the requirement for standardized efficacy and safety testing before they may reach mainstream clinical practice.

Antimicrobial Peptides as Next-Generation Therapeutics

One of the most promising families of treatment medicines for multidrug-resistant (MDR) diseases is antimicrobial peptides (AMPs), which have unique modes of action and broad-spectrum efficacy. AMPs are short, cationic, amphipathic molecules that rapidly interact with and disrupt microbial membranes, causing cellular leakage and microbial death. They are found everywhere in nature as part of the innate immune defense in plants, animals, and microorganisms. Compared to antibiotics that target enzymes or metabolic processes, this

electrostatic contact and membrane instability mechanism makes pathogen resistance much harder to build. Immunomodulatory features include recruiting immune cells, modulating inflammatory responses, and promoting wound healing make many AMPs useful beyond antibacterial function. AMPs have been shown to kill bacteria, fungus, viruses, parasites, and cancer cells, proving their medicinal potential. In preclinical models, AMPs outperform conventional antibiotics or work synergistically to restore antibiotic efficacy against drug-resistant pathogens like MRSA, VRE, and CRE. Peptide engineering has improved their medicinal potential by optimizing charge distribution, hydrophobicity, amphipathicity, and secondary structures to select microbial membranes and reduce host toxicity. Cyclization, inclusion of non-natural amino acids, and conjugation with nanoparticles or polymers have been used to counteract fast proteolytic degradation, poor bioavailability, and short half-life in vivo. Importantly, pexiganan, a magainin derivative, is being studied for diabetic foot infections, brilacidin for acute bacterial skin infections, and LL-37 derivatives for antimicrobial and wound-healing properties. AMPs are becoming therapeutic candidates, as shown by these examples. However, large-scale manufacturing costs, pharmacokinetic optimization, and regulatory approval still hinder the translation of AMPs into widely utilized clinical medicines. Despite these challenges, AMPs offer a new paradigm in antimicrobial therapy by combining membrane-targeted activity with multifunctional biological effects and meeting the growing threat of antimicrobial resistance where conventional antibiotics fail.

Challenges in Clinical Translation

Stability, Bioavailability, and Protease Resistance

The intrinsic instability of antimicrobial peptides (AMPs) in physiological conditions is one of the most persistent obstacles in turning them into clinical therapies. Proteolytic enzymes found in the gastrointestinal system, blood, and tissues rapidly break down the peptide backbone of AMPs, drastically shortening their half-life and therapeutic window. Because of their poor oral bioavailability, they are not very useful in clinical settings and must be administered intravenously, which is both more expensive and less convenient for patients. To increase protease resistance and improve systemic stability, scientists have devised strategies like cyclization, terminal modification, adding D-amino acids or non-natural residues, and encapsulating nanoparticles. However, these methods make medication development and production more complicated.

Cytotoxicity and Host Selectivity

There is concern about toxicity toward host cells because to the amphipathic character of AMPs, despite their effectiveness at targeting bacterial membranes through electrostatic and hydrophobic interactions. Hemolysis, tissue injury, or off-target immunological responses can result from AMPs disrupting mammalian membranes at greater doses. Finding the sweet spot where antimicrobial effectiveness meets host specificity is still a major obstacle. While rational peptide design has made strides in selectivity by adjusting hydrophobicity, charge distribution, and secondary structure, extensive preclinical and clinical validation is still needed to guarantee safety in various therapeutic settings.

Production Costs and Scalability

The AMP synthesis process is expensive, which is another big drawback. Large-scale production is economically hard due to the resource-intensive and expensive nature of solid-phase peptide synthesis (SPPS), despite its precision and versatility. Although microbial fermentation and recombinant expression methods are more scalable options, they still encounter problems with optimizing yields, making post-translational changes, and achieving efficient purification. Antimicrobials have a lower potential for profit in the market than medications for long-term health conditions, which inhibits substantial investment from the pharmaceutical sector. Improving the commercial feasibility of AMPs requires the development of cost-effective, high-yield production methods. This includes automated synthesis and biotechnological breakthroughs.

Regulatory and Standardization Barriers

Being a new family of treatments with different mechanisms than traditional antibiotics, AMPs provide special challenges in their regulation pathway. Prolonged approval delays are a consequence of existing regulatory frameworks that are not adequately suited to assess pharmacodynamics, toxicity profiles, or resistance prospects. Clinical translation also suffers from a lack of standardised assays for determining the stability, safety, and effectiveness of antimicrobials, which makes it harder to compare results from different research. If we want to speed up the development of AMPs, we need to see testing methodologies standardized internationally, regulatory rules clarified, and researchers, physicians, and authorities like the FDA and EMA working together more closely.

Conclusion

Antimicrobial peptides (AMPs) are one of the most exciting new developments in the worldwide fight against the inexorable spread of bacteria and other microbes that have developed resistance to conventional antibiotics. When compared to traditional antibiotics, AMPs have several advantages, especially against multidrug-resistant bacteria like Pseudomonas aeruginosa, carbapenem-resistant Enterobacteriaceae, and MRSA, thanks to their unique mechanisms of action that involve disrupting bacterial membranes, influencing the immune system, and inhibiting biofilm formation. The production of tailored peptides with enhanced potency, selectivity, and resistance to proteolysis has been made possible by advances in rational design, computer modeling, structure-activity relationship analysis, and peptide engineering. Meanwhile, developments in synthesis methods have increased the structural and functional variety of AMPs, which in turn has improved their therapeutic potential. These approaches include solid-phase peptide synthesis, cyclization, nanoparticle conjugation, and the inclusion of non-natural amino acids. Clinical translation is still hindered by issues with stability, bioavailability, cytotoxicity, scalability, and regulatory approval, even though these have been addressed. Strong regulatory frameworks and ongoing investment will be necessary to overcome these obstacles, as will multidisciplinary methods combining nanotechnology, chemistry, microbiology, and pharmacology. In the future, AMP development could be accelerated and prices reduced by combining AI-driven peptide design with biotechnological production platforms and sophisticated delivery methods. This would bring

these molecules closer to mainstream clinical application. As a whole, AMPs offer hope for a new generation of life-saving medications and a practical solution to the problem of antibiotic resistance. They also present a chance to reimagine antimicrobial therapies, connecting basic research with clinical need.

References

Brogden, K. A. (2005). Antimicrobial peptides: Pore formers or metabolic inhibitors in bacteria? Nature Reviews Microbiology, 3(3), 238–250. https://doi.org/10.1038/nrmicro1098

Chen, C. H., Lu, T. K., & Kwong, G. A. (2021). Advances in antimicrobial peptide discovery and design for the treatment of multidrug-resistant infections. Advanced Drug Delivery Reviews, 170, 1–21. https://doi.org/10.1016/j.addr.2020.12.010

Fjell, C. D., Hiss, J. A., Hancock, R. E. W., & Schneider, G. (2012). Designing antimicrobial peptides: Form follows function. Nature Reviews Drug Discovery, 11(1), 37–51. https://doi.org/10.1038/nrd3591

Greber, K. E., Dawgul, M., Kamysz, W., & Sawicki, W. (2017). Antimicrobial peptides under clinical trials. Current Pharmaceutical Biotechnology, 18(2), 123–127. https://doi.org/10.2174/1389201018666170111154040

Haney, E. F., Straus, S. K., & Hancock, R. E. W. (2019). Reassessing the host defense peptide landscape. Frontiers in Chemistry, 7, 43. https://doi.org/10.3389/fchem.2019.00043

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial peptides: An emerging category of therapeutic agents. Frontiers in Cellular and Infection Microbiology, 6, 194. https://doi.org/10.3389/fcimb.2016.00194

Mookherjee, N., Anderson, M. A., Haagsman, H. P., & Davidson, D. J. (2020). Antimicrobial host defence peptides: Functions and clinical potential. Nature Reviews Drug Discovery, 19(5), 311–332. https://doi.org/10.1038/s41573-019-0058-8

Sharma, A., Gupta, P., Kumar, R., Bhardwaj, A., & Dey, P. (2022). Emerging trends in the design and synthesis of antimicrobial peptides: Peptidomimetics and beyond. Journal of Medicinal Chemistry, 65(7), 5032–5052. https://doi.org/10.1021/acs.jmedchem.1c01988

Wang, G., Li, X., & Wang, Z. (2016). APD3: The antimicrobial peptide database as a tool for research and education. Nucleic Acids Research, 44(D1), D1087–D1093. https://doi.org/10.1093/nar/gkv1278

Yeung, A. T. Y., Gellatly, S. L., & Hancock, R. E. W. (2011). Multifunctional cationic host defence peptides and their clinical applications. Cellular and Molecular Life Sciences, 68(13), 2161–2176. https://doi.org/10.1007/s00018-011-0710-x