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Chemical insights into antimicrobial peptides: Mechanisms and potential in combating antimicrobial resistance

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Abstract
Antimicrobial resistance (AMR) presents a critical global health challenge, with multidrug-resistant (MDR) pathogens rendering many antibiotics ineffective. This crisis is exacerbated by excessive antibiotic usage and limited advancements in new antimicrobial therapies. Antimicrobial peptides (AMPs) have emerged as a promising solution due to their unique mechanisms of action, which make them less prone to resistance. Derived from natural sources, AMPs target pathogens through membrane disruption and intracellular interference, offering broad-spectrum activity against bacteria, fungi, and viruses. However, bacterial adaptations such as reduced permeability, efflux pump overexpression, and protease secretion pose challenges to AMP efficacy. Recent research has focused on enhancing AMP stability, specificity, and resistance to bacterial defenses using advanced peptide engineering and bioinformatics tools. This review explores AMR mechanisms, the structure-function relationship of AMPs, and their therapeutic potential in combating resistant pathogens. It also highlights the integration of AMPs in combination therapies and predictive resistance models to optimize their clinical application. Despite their promise, widespread AMP adoption requires strategic management to prevent resistance development. Addressing AMR in developing countries through public education, healthcare reform, and equitable AMP access is critical to mitigating its global impact. By leveraging advances in biotechnology and resistance prediction, AMPs represent a vital avenue in the fight against AMR.

Keywords: Antimicrobial resistance (AMR), antimicrobial peptides (AMPs), multidrug-resistant pathogens, therapeutic potential, bioinformatics and biotechnology integration

Introduction
The emergence of infections caused by multidrug-resistant (MDR) bacterial pathogens has become a critical challenge for global public health. Over the past three decades, excessive and often inappropriate use of antibiotics has led to the evolution of various resistant bacterial species, including Staphylococcus aureus, Escherichia coli, and Mycobacterium tuberculosis (Penchovsky and Traykovska, 2015) [22]. Unfortunately, the development of new antimicrobial agents has not kept pace with the emergence of these resistant pathogens. To mitigate this growing threat, it is essential to minimize antibiotic usage, implement robust antibacterial immunization programs, and invest in the development of novel therapeutic classes to combat MDR bacterial infections. Antimicrobial peptides (AMPs) have emerged as a promising alternative to conventional antibiotics due to their diverse mechanisms of action and ability to circumvent traditional resistance pathways (Nuti *et al*., 2017) [19]. Found abundantly in nature, AMPs exhibit broad-spectrum antimicrobial activity, and advances in synthetic chemistry have facilitated the creation of semi-synthetic AMP analogs with enhanced efficacy and stability.

Antimicrobial Resistance and Its Mechanisms
Antimicrobial resistance (AMR) occurs when microorganisms evolve strategies to counteract the effects of antimicrobial agents.

This growing issue poses a serious challenge to global health, diminishing the effectiveness of treatments for critical diseases such as tuberculosis, malaria, HIV/AIDS, and pneumonia (Hwang & Gums, 2016) [12].

Global Impact of AMR

AMR has far-reaching consequences, both economically and medically. Resistant infections lead to increased healthcare costs due to extended treatment durations, additional diagnostic procedures, and higher rates of morbidity and mortality. Globally, drug-resistant infections are estimated to cause over 500,000 deaths annually. The burden of AMR is disproportionately higher in low- and middle-income countries, where surveillance and healthcare infrastructure are limited. For example, between 2004 and 2007, studies from India revealed high resistance rates in *E. coli* isolates to antibiotics such as ampicillin (75%), nalidixic acid (73%), and cotrimoxazole (59%) (World Health Organization, 2009) [28].

Mechanisms of Antimicrobial Resistance

Microorganisms employ various mechanisms to evade antimicrobial agents, enabling their survival and proliferation despite drug exposure.

1. **Reduced Drug Permeability:** A significant factor in resistance is reduced permeability to antimicrobial agents. Gram-negative bacteria, characterized by their outer membrane, inherently restrict drug entry through porin channels. Additionally, alterations or downregulation of these channels further limit the penetration of antibiotics (Zgurskaya *et al*., 2015) [29].
2. **Drug-Inactivating Enzymes:** Certain bacteria produce enzymes, such as β-lactamases, that neutralize antibiotics by breaking down their core β-lactam ring structure. These enzymes have been identified in several pathogens, including *Staphylococcus* and *Neisseria* species, significantly compromising the effectiveness of β-lactam antibiotics (Kong *et al*., 2010) [13].
3. **Increased Efflux of Antimicrobial Agents:** Efflux pumps are another common mechanism that bacteria use to resist drugs. These systems actively expel antibiotics from the cell, thereby lowering their intracellular concentrations and reducing their efficacy. Overexpression of efflux pumps is a major contributor to multidrug resistance (Sun *et al*., 2014) [27].
4. **Modification of Antimicrobial Targets:** Mutations in the genes encoding antimicrobial target proteins can hinder drug binding, thereby conferring resistance. Additionally, "mosaic genes," which result from horizontal gene transfer events, can modify these targets further, enhancing the bacteria's ability to withstand treatment (Nuti *et al*., 2017) [19].

Antimicrobial Peptides (AMPs): An Overview

Antimicrobial peptides (AMPs) are small molecules, typically consisting of 12 to 50 amino acids, that play a crucial role in the innate immune defense mechanisms of various organisms (Nawrot *et al*., 2014) [17]. These peptides, often referred to as host defense peptides, are potent against a wide range of pathogens, including bacteria, fungi, and viruses. Due to their low toxicity to eukaryotic cells, high thermal stability, solubility, and small molecular size, AMPs hold great promise for therapeutic applications (Li *et al*., 2019) [16].

Structure and Mode of Action of AMPs

AMPs can be categorized into different structural types, including α-helical, β-sheet, linear, and mixed α-helix/β-sheet peptides (Huan *et al*., 2020) [11]. Their mechanisms of action vary depending on the target pathogen.

Structure of antimicrobial peptides

Antimicrobial peptides can be divided into four categories based on their structures including linear α-helical peptides, β-sheet peptides, linear extension structures, and both α-helix and β-sheet peptides (Huan *et al*., 2020) [11].

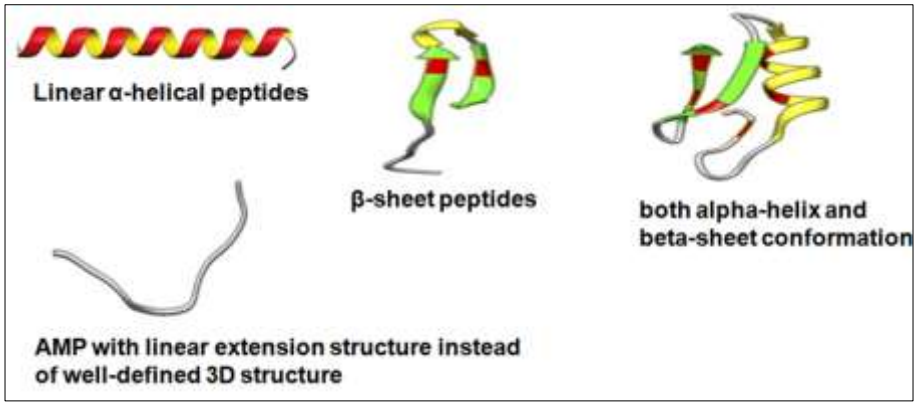


Fig 1: Different structures of antimicrobial peptides

AMP's general mode of action

Each antimicrobial peptide (AMP) exhibits a specific mode of action and can be categorized based on its target organism.

Antiviral Action

Antiviral AMPs are classified according to their mechanisms of action and are effective against both RNA and DNA viruses:

i) **Viral Membrane-Targeting AMPs:** These peptides integrate into the viral envelope, destabilizing its structure. This disruption prevents the virus from entering host cells by compromising the membrane's integrity (Bastian and Schäfer, 2001) [2].
ii) **AMPs Targeting Viral Receptors:** These peptides act on viral adsorption mechanisms, blocking the virus from attaching to and penetrating the host cell by

interfering with receptors on the target cells (Robinson *et al*., 1998) [23].

iii) **Intracellular Targeting AMPs:** Certain AMPs inhibit viral processes within the host cell. For instance, NP-1, an alpha-defensin found in rabbit neutrophils, prevents Herpes simplex virus type 2 (HSV-2) from reaching the nucleus by obstructing the function of the virion protein VP16 (Andersen *et al*., 2004) [1].

2. Antibacterial Action

Antibacterial AMPs can be classified into two main types based on their mechanisms of action: (i) membrane-disrupting peptides and (ii) non-membrane-targeting peptides (Cooper and Williams, 1999) [7]. Notably, some AMPs can employ both mechanisms.

Membrane-Targeting AMPs: Many antibacterial AMPs target bacterial cell membranes. Initially, these peptides electrostatically interact with the negatively charged bacterial surface and the positively charged peptide molecules. This interaction is followed by hydrophobic interactions with membrane phospholipids (Hollmann *et al*., 2018) [10]. The subsequent pore formation can occur via various proposed mechanisms, including the barrel-stave, carpet-like, and toroidal pore models (Shai and Oren, 2001) [26], as well as the aggregated channel model (Rozek *et al*., 2000) [24] and clustering of anionic lipids (Sengupta *et al*., 2008) [25]. Additionally, certain AMPs may utilize more than one of these mechanisms to exert their antibacterial effects.

The barrel-stave model of anti-microbial peptide

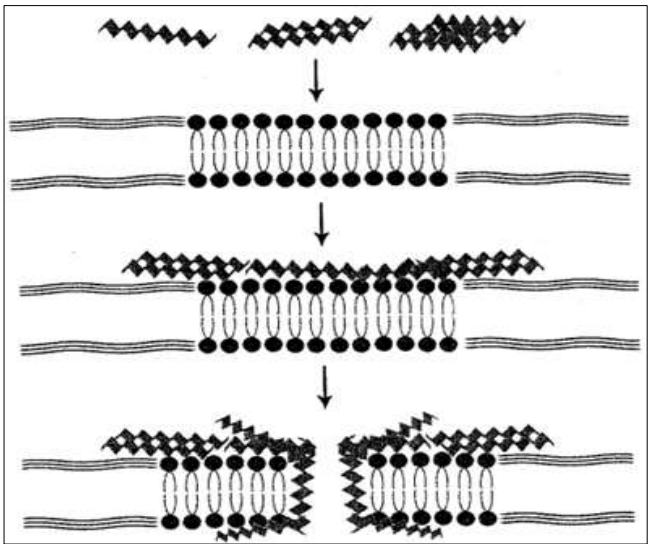


Fig 2: In this model, the attached peptides aggregate and insert into the membrane bilayer, aligning their hydrophobic regions with the lipid core while the hydrophilic regions form the inner surface of the pore (Park and Hahm, 2005) [21].

a) Carpet model of anti-microbial peptide

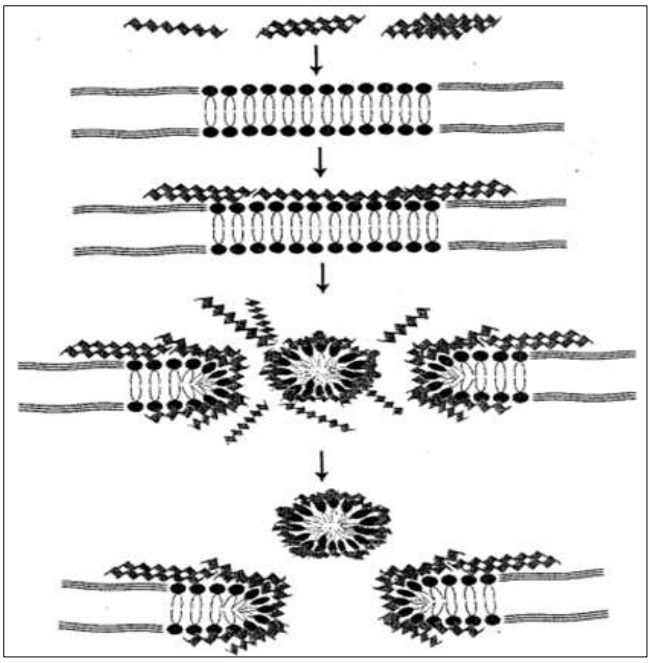


Fig 3: In this model, the peptides disrupt the membrane by positioning themselves parallel to the surface of the lipid bilayer and forming a dense, carpet-like layer (Park and Hahm, 2005) [21].

c) Toroidal model of anti-microbial peptide

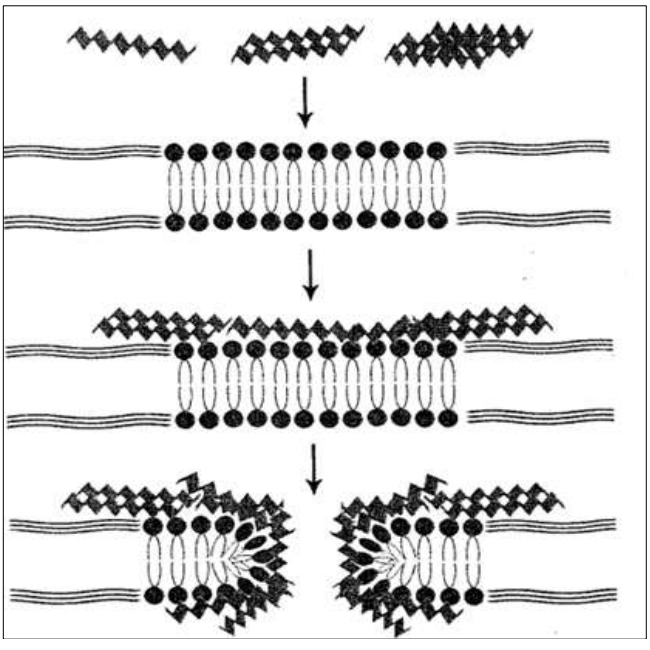
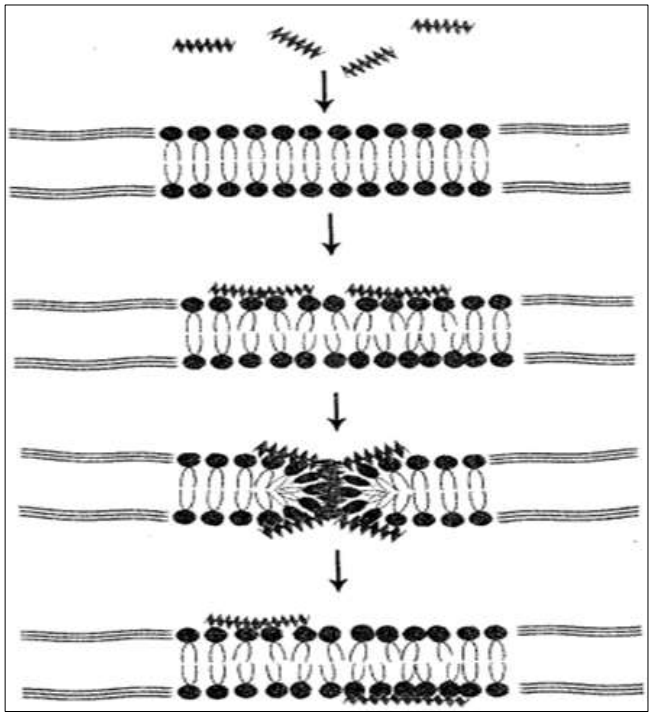


Fig 4: In this model, the lipid head groups and embedded peptides align along the water core, facilitated by the peptides' aggregation, which induces continuous bending of the lipid monolayers through the pore structure (Park and Hahm, 2005) [21].

d) Membrane translocation mechanism of AMPs



Non-Membrane Targeting/Intracellular AMPs

Certain AMPs exert antibacterial effects without compromising membrane stability. These peptides penetrate bacterial cells directly, disrupting critical processes such as DNA replication, transcription, translation, protein folding, and cell division, all of which are essential for bacterial survival (Park *et al*., 1998) [20].

Nucleic Acid-Targeting AMPs: Buforins I and II are examples of AMPs that penetrate the bacterial membrane without causing permeabilization and bind to intracellular targets such as DNA and RNA, as demonstrated in *E. coli* (Bustillo *et al*., 2014; Birkemo *et al*., 2003) [5, 4].

AMPs Affecting Cell Division: These peptides inhibit bacterial growth by disrupting DNA replication or damaging DNA. This prevents the cell cycle from progressing and hinders chromosome segregation. They also interfere with DNA damage responses, such as the SOS repair system (Chileveru *et al*., 2015) [6].

Protein Synthesis Inhibition: AMPs targeting protein synthesis achieve antibacterial effects by impacting transcription, translation, or protein assembly (Le *et al*., 2016) [15].

Proline-Rich Peptides: Derived from insects, these peptides inhibit bacterial DNA replication and protein folding, further impairing cellular functions.

Protease Inhibition: Certain AMPs inhibit proteases, disrupting vital cellular processes necessary for bacterial survival (Bin *et al*., 2021) [3].

3. Antifungal Action

Antifungal AMPs are produced by various archaea, bacteria, plants, and animals (Henzler *et al*., 2003) [9]. These peptides typically target the fungal cell wall, primarily composed of chitin, and their mechanisms are comparable to those of antibacterial AMPs. The primary modes of action include:

i) **Barrel-Stave Model:** This mechanism involves peptides like Amphotericin B, which binds to membrane ergosterol, creating transmembrane pores.
ii) **Carpet-Like Model:** Peptides like Dermaseptin disrupt fungal membranes by forming a dense layer that destabilizes the lipid bilayer.
iii) **Toroidal Pore Model:** AMPs such as LL-37 and Protegrin-1 interact with fungal cell wall carbohydrates, forming toroidal pores, as observed in *Candida* species.
iv) **Inhibition of 1,3-β-Glucan Biosynthesis:** Peptides like echinocandins, pneumocandins, and aculeacins block the synthesis of 1,3-β-glucan, a vital fungal cell wall component.
v) **Inhibition of Chitin Biosynthesis:** Aureobasidins interfere with chitin synthesis, a key structural component of the fungal cell wall.
vi) **Intracellular Target Interference:** Certain peptides, such as DNA-binding actinomycins, intercalate with fungal DNA, disrupting vital intracellular processes (Bin *et al*., 2021) [3].

Combating Antimicrobial Resistance with Antimicrobial Peptides (AMPs)

Antimicrobial peptides (AMPs) have emerged as a promising solution in the fight against antimicrobial resistance (AMR). AMPs are considered difficult for pathogens to resist due to several inherent characteristics. First, they induce rapid microbial killing, leaving limited time for bacteria to mutate and adapt. Second, AMPs often target multiple sites within microbial cells, ensuring that even if resistance develops to one mechanism, others remain effective (Kristian *et al*., 2003) [14].

Mechanisms of Resistance Against AMPs

While AMPs offer many advantages, bacteria have evolved strategies to reduce their efficacy:

1. **Reduced Permeability and Altered Membrane Properties:** Changes in the net negative charge of bacterial membranes can reduce the binding efficiency of AMPs, which rely on electrostatic interactions for initial contact. These alterations hinder AMP penetration, particularly for AMPs targeting intracellular components like nucleic acids or proteins (Kristian *et al*., 2003) [14]. Such modifications have been observed across several bacterial species, with genetic mutations driving these physiological changes extensively documented (Nizet, 2006) [18].
2. **Protease Secretion:** The secretion of proteases is another bacterial strategy to inactivate AMPs. For example:

- *Salmonella* species utilize the outer membrane protease PgtE to cleave and neutralize AMPs.
- *Staphylococcus aureus* produces aureolysin, a metalloproteinase capable of degrading human antimicrobial peptide LL-37 (Guina *et al*., 2000) [8].

These mechanisms highlight the increasing adaptability of bacteria to AMPs, emphasizing the need for innovative solutions to mitigate resistance.

Challenges in addressing AMR in developing countries: Developing countries face a higher prevalence of AMR due

to factors such as incomplete antibiotic courses, overuse of antibiotics, and limited access to healthcare resources. Educating healthcare providers and the public on the importance of adhering to prescribed treatments is critical. Additionally, robust surveillance systems must be established to monitor resistance trends.

Advancements in AMP Research and Development

Recent advancements in AMP research, peptide synthesis, and biotechnology provide renewed hope for overcoming AMR. Databases such as the Collection of Anti-Microbial Peptides (CAMP) and Antimicrobial Peptide Database (APD) offer extensive data on peptide sequences, activity, mechanisms, source organisms, and target organisms. These resources expedite the discovery of novel AMPs and streamline the drug development process.

Future Directions: Enhancing AMP Utility

1. **Developing Resistance Prediction Model:** Creating specialized databases and software that integrate resistance mechanisms into predictive algorithms can aid in identifying potential resistance in newly synthesized peptides. This proactive approach could optimize AMP design, reducing the likelihood of resistance development.
2. **Combating Resistance to AMPs**: While AMPs are currently less prone to resistance than traditional antibiotics, widespread and indiscriminate use could lead to resistance. Strategic use, combined with continuous research to understand and counteract resistance mechanisms, will ensure their long-term efficacy.
3. **Integrating AMPs into Combination Therapies:** Combining AMPs with existing antimicrobials or adjuvants can enhance their effectiveness while minimizing the risk of resistance development. This approach leverages synergistic effects to overcome resistant strains.
4. **Advancing Biotechnology for AMP Design:** Innovations in peptide engineering, such as incorporating unnatural amino acids or modifying peptide structures, can improve AMP stability, specificity, and activity against resistant pathogens.

Conclusion

Antimicrobial peptides represent a powerful tool in combating AMR, but their utility requires careful management to avoid resistance development. By integrating advancements in bioinformatics, biotechnology, and resistance prediction tools, AMPs can be optimized for therapeutic use. Furthermore, raising awareness and ensuring equitable access to AMP-based therapies will be critical to addressing the global AMR crisis effectively.,

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