Next-Generation Antimicrobial Peptides: Mechanistic Insights and Delivery Strategies against ESKAPE Pathogens

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Abstract : The present global health concerns of deaths of patients with diseases caused by Multidrug-Resistant (MDR) bacterial pathogens like *P. aeruginosa* and *S. aureus* result in 1.27 million deaths annually and could lead to an estimated 10 million annual deaths in 2050,which is higher than number of deaths due to cancer, if no action is taken. This situation is the emergence of resistant genes from industrial effluents, residential waste, and hospital management waste, and the evolution of a new immune response in bacteria. Traditional antibiotics in the face of a failure approach in combating MDR bacteria. Some of the most threatening bacterial strains identified by the WHO, known as the ESKAPE pathogens, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*, use their survival mechanisms to counteract conventional drug treatments. The aim of this review is to highlight these Host Defense Peptides (HDPs) which target the electrostatic charge of the outer membrane and the lipid bilayer, creating a multifaceted assault through the dissipation of the proton motive force (PMF) and the induction of reactive oxygen species (ROS). Through the transition from simple extraction to the construction of high-fidelity databases and the use of machine learning architectures like dsAMPGAN and HydrAMP, researchers can now optimize synthetic-natural peptides for minimal hemolytic effect on human red blood cells. Exploration of the synergistic approach with animal derived peptides with traditional β-lactam antibiotics , to help traditional antibiotics reach their targets, alongside the integration of advanced delivery systems such as gold nanoparticles (AuNPs) using plant-derived antimicrobial peptides nanoemulsions to solve problems associated with proteolytic resistance. New applications of the plant-derived antimicrobial peptides in environmental and agricultural biotechnology sectors other than pharmaceutical biotechnology.

Index terms **- Biofilms, ESKAPE pathogens, peptides, β-lactamase, defensins, *Moringa oleifera*.**

I. INTRODUCTION

INTRODUCTION

Multidrug-Resistant (MDR) Bacteria are those bacteria that display non-susceptibility to at least one antimicrobial drug from at least three classes of antimicrobial medicines. Bacterial pathogens have evolved in industrial effluents discharged into water bodies , sanitary human wastes from households, improper hospital waste management , the overuse of antibiotics for higher animal growth and the yield of animal products in animal husbandry in agriculture and prescription of antibiotics against diseases caused by microorganisms other than bacteria. This creates a situation whereby there is a concentration of antibiotics in water, and this becomes a new training ground for the emergence of a new immune response in bacteria against the traditional antibiotics. Through plasmid-mediated gene transfer, conjugation and chromosomal gene mutation are the primary reasons for the development of multidrug resistance mechanism [1,2]. Globally, the Antimicrobial Resistance (AMR) bacterial diseases were directly responsible for 1.27 million deaths in 2019, with a prediction to reach 10 million annual deaths by 2050 [3,4]. If no innovation is done in research for the development of multipathway mechanism of action of drugs, then the number of deaths because of multidrug resistant bacterial diseases will be more than cancer-related deaths by 2050. Among the most isolated MDR pathogens world-wide (ESKAPE pathogens according to WHO report) are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

NEED OF THE STUDY.

This failure of traditional antibiotics has led to the development of new classes of therapeutics. Antimicrobial Peptides (AMPs), also known as host defense peptides, are a promising alternative approach as they target more than one target to attack the bacteria at a time [5]. Traditional antibiotics target metabolic pathways, replication pathways, and basic cell wall synthesis at a time that is one target pathway at a time. Antimicrobial peptides, on the other hand, target the cell wall of bacteria, which is a basic physiological characteristic of bacteria and a secondary target of metabolic pathways, inhibiting quorum sensing for biofilm formation and blocking mutant enzymes for cell wall synthesis and β-lactam ring disruption of antibiotics [6]. The antimicrobial peptides target the electrostatic charge of the outer membrane and the pore formation in the lipid bilayer . It is evolutionarily very costly for the bacteria to change the outer layer in order to develop a resistance mechanism against the antimicrobial peptides compared to traditional drugs [7].

The aim of this review is to highlight the recent developments in the engineering of hemolytically safe antimicrobial peptides for use in the management of drug-resistant *P. aeruginosa* and *S. aureus*. An analysis of the current epidemiological data on last-resort resistance, the molecular mechanism by which these AMPs circumvent the traditional hurdles, and the use of nanotechnology-based delivery systems for improving peptide stability will be discussed.

THE MECHANISM OF RESISTANCE DEVELOPMENT

3.1 *Pseudomonas aeruginosa*: A Fortress of Permeability and Efflux

3.1.1 Biofilm formation and suppression of Porin gene expression

The main line of defense in *P. aeruginosa* is its low outer membrane permeability, which is 12 to 100 times lower than in *E.coli* [8].
OprD Loss: The most important porin-mediated mechanism is the loss of OprD porin. OprD is a transmembrane protein channel for the entry of carbapenems and essential amino acids; therefore, when lost, the bacteria acquire resistance to imipenem and meropenem, which eventually causes therapeutic failure [9].

3.1.2 Active Efflux Systems (RND Family)

The cell employs Resistance-Nodulation-Division (RND) family efflux pumps to actively transport a wide range of antibiotics such as β-lactams and fluoroquinolones out of the bacterial cell.
MexAB-OprM: The cell expresses this system constitutively which provides a baseline resistance to penicillins and cephalosporins.
MexXY-OprM: Aminoglycoside exposure often induces this pump and hence it acts as a primary driver of resistance against that specific antibiotic class where the drug is pumped out faster than it can reach the ribosome [10].

3.1.3 Enzymatic Inactivation AmpC β-lactamase

P. aeruginosa possesses a chromosomally encoded ampC gene and although it is not expressed by the bacteria under normal conditions, it is hyper-produced in the presence of β-lactams and this results in the rapid hydrolysis of cephalosporins. Through the process of horizontal gene transmission, the infecting agent is able to acquire Metallo-beta-lactamases (MBLs) such as VIM and IMP that enable the bacteria to hydrolyze all forms of β-lactams including carbapenems [9].

3.2 *Staphylococcus aureus* : The Master of Target Modification

On the other hand, unlike Gram-negative bacteria, *S. aureus* heavily depends on the strategy of modifying the particular molecular target to be attacked by antibiotics, a different approach altogether.

3.2.1 β-lactam Resistance and the mecA Gene

The characteristic attribute of *Methicillin-Resistant S. aureus* (MRSA) is the acquisition of the SCCmec mobile genetic element, which consequently results in the possession of the mecA gene, as documented in a recent review on *S. aureus* [11].
PBP2a Production: The mecA gene codes for PBP2a, a penicillin-binding protein, which has a low affinity for antibiotics, meaning that whereas normal PBPs fail to perform, PBP2a continues to perform its function of synthesizing the bacterial cell wall, making the antibiotics ineffective even at high concentrations [12].

3.2.2 Glycopeptide Resistance (VISA and VRSA)

The bacteria manage to evade vancomycin, a "last-resort" antibiotic, through two different routes of evolution.
***Vancomycin-Resistant S. aureus* (VRSA):** By acquiring the vanA operon the bacteria modify the terminal peptidoglycan precursor from D-Ala-D-Ala to D-Ala-D-Lac which prevents binding entirely.
***Vancomycin-Intermediate S. aureus* (VISA)**: This resistance mechanism involves adaptive mutations causing a thickened cell wall, which produces surplus D-Ala-D-Ala that trap vancomycin molecules before they can reach the cytoplasmic membrane [13].

3.2.3 Efflux-Mediated Resistance

S. aureus has also developed Major Facilitator Superfamily pumps, such as NorA, to eject fluoroquinolones, and finally, plasmid-encoded QacA/B pumps to eject antiseptics, thus helping the pathogen survive in a harsh environment, such as a hospital, where antiseptics are commonly used [14].

3.3 OVERVIEW OF ANTIMICROBIAL PEPTIDES

3.3.1 The Biological Journey: Defining the Nature of Antimicrobial Peptides

The story of modern antimicrobial history is incomplete without mentioning Antimicrobial Peptides (AMPs), also called Host Defense Peptides (HDPs).It is a group of polypeptides with average amino acid length 10-50 [7]. Antimicrobial peptides are a form of evolutionary chemical defense that is ubiquitous across the domains of life. It is inherited from the prokaryotes immune system to the human immune system with immunomodulation activity to trigger the adaptive immune system [15].

The nature of these compounds is generally cationic with a charge range of +2 to +9. The balance of amphipathic nature is an important trait for the disruption of lipid bilayer of bacterial membrane. The nature of these compounds is such that they can selectively bind with the negatively charged moieties of microbial membranes, including lipopolysaccharides (LPS) of Gram-negative bacteria and teichoic acids of Gram-positive bacteria [6].

3.3.2 Antimicrobial peptides as the Sentinels of the Innate Immune System

Antimicrobial peptides acts as non-specific antibiotics in the innate immune system before the action of adaptive immune system.
In the Animal Kingdom, Antimicrobial peptides acts as chemoattractor and cytokine expression regulator which signals the adaptive immune cells such as neutrophils and T-cells, modulate the production of pro-inflammatory cytokines, and accelerate wound healing through the stimulation of angiogenesis [16].
In the Plant Kingdom, Plants do not have a specialised circulatory system like animals . Antimicrobial peptides are expressed in seeds, tubers, and leaves such as Thionins, Hevenins and Defensins which protects the plants from systemic spread of phytopathogens through the apoplastic and vascular spaces [15].
The host organism ensures the strategic storage and secretion strategy against microbial invasion as shown in the Table1.

Table 3.3.2: Summary of Antimicrobial Peptide secretion site.

Host Type	Primary Cells/Tissues	Intracellular/Extracellular Localization
Animals	Neutrophils, Monocytes, Macrophages, Epithelial cells (Skin, Gut, Lungs).	The cell stores these molecules within specialized cytoplasmic granules before secreting them into phagosomes or the extracellular space during the activation phase of the immune response. [17]
Plants	Epidermal cells, Vascular tissues, and Storage organs (Seeds)	The plant localizes these defenses within the cell wall, vacuoles, or the apoplast, ensuring they are positioned to intercept invading fungal hyphae or bacteria at the point of contact. [15]
Bacteria	All bacterial cells	The bacteria synthesize these peptides in the cytoplasm as precursors before they are modified and secreted via specialized ABC transporters to eliminate microbial competitors in the surrounding environment. [16]

3.4 RECENT ADVANCES IN AMPs AGAINST MDR BACTERIAL PATHOGENS

The story of the search for novel antimicrobial agents begins with a global crisis—the rapid dissemination of multidrug-resistant (MDR) bacterial pathogens which have evolved in environments ranging from industrial effluents discharged into water bodies to the improper management of hospital wastes.

3.4.1 Animal-Derived Peptide Discovery: The Narrative of AMP-17

As for different candidates, animal-derived peptides have received considerable attention in literature and exhibit a discovery logic that relies on exploiting innate immunity in various animals. AMP-17 isolated from houseflies (*Musca domestica*) has shown antimicrobial activity against WHO reported priority pathogens, including carbapenem-resistant *P. aeruginosa* and MRSA [18]. This breakthrough peptide was discovered through a complex transcriptome screening process. Its mechanism of action creates a situation whereby the peptide kills bacteria through a multifaceted assault: the disruption of bacterial membrane integrity, the dissipation of the proton motive force (PMF) which is the electrochemical gradient essential for ATP synthesis, and the induction of intracellular reactive oxygen species (ROS) accumulation that leads to irreparable cellular damage [18]. The in vivo studies in murine models concluded that AMP-17 promotes wound healing by modulating inflammatory responses through the downregulation of pro-inflammatory cytokines (IL-6, TNF-α) and the upregulation of vascular endothelial growth factor (VEGF). [17,18]

3.4.2 Computational Design and Machine Learning Architectures

How did the idea of "machine-designed" peptides come into being?.The transition from simple extraction of AMPs to synthesis of novel molecules starts with the construction of high-fidelity databases of peptides with manually curated data such as APD6 (containing over 6,300 AMP sequences by 2026) and dbAMP 3.0 annotated with functions of inhibiting quorum sensing [19,20]. Scientists have been able to utilize in silico tools to produce synthetic-natural peptides that are better in pharmacology through dsAMPGAN compared to peptides produced using HydrAMP that make use of conditional variational autoencoders to improve their amphipathic nature and reduce host cell toxicity [21,22].Utilizing silicon frameworks, researchers can optimize the peptide for the highest affinity to bacterial membranes with minimal hemolytic effect on human red blood cells.

3.4.3 Synergistic and Combinatory Approaches

There are two main drivers for combinatory therapy – collateral sensitivity of a pathogen to another substance and ability of one substance to enhance the efficiency of traditional medicines. Thus, antimicrobial peptides act as synergistic adjuvants for conventional treatment regimes.

3.4.3.1 AMP-Antibiotics Synergy: Door Opener Approach

Research studies done on synergistic antimicrobial activity of LL-37 fragments working in combination of β-lactams such as Penicillin G and Ampicillin in MRSA infections [23]. The peptide works as a "door opener" to enable access for antibiotics to act on the bacteria through the process of membrane permeabilization [24]. This combination study has concluded that the MIC for β-lactam traditional antibiotics against the multidrug resistant bacterial pathogens have drastically dropped. Synergism is measured through the Fractional Inhibitory Concentration Index (FICI) and values ≤0.5 denote synergism. [23]

3.4.4 Advanced Delivery Systems and Nano-formulations

In this era of innovation, the incorporation of peptides into advanced drug delivery system (DDS) becomes imperative to address problems associated with proteolytic resistance and system toxicity. It entails the application of nano emulsions loaded with *Moringa oleifera* seed protein as a mode of delivering the peptides specifically towards the pathogens of *S. aureus*, and the fabrication of AuNPs by employing *Capsicum annuum* extracts [25,26]. The AuNPs play a twofold role; not only do they carry the peptide, but they also carry an inherent property of anti-Quorum Sensing behaviour and can thus mitigate virulence factors such as pyocyanin and elastase of *P. aeruginosa*. [26]

3.4.5 Plant-Derived Peptides: Multi-Sectoral Applications

The story of plant-derived defenses goes back to the evolutionary absence of a specialized circulatory system, which forced plants to develop stable, cysteine-rich peptides like thionins, cyclotides, and defensins as a primary line of defense against systemic microbial invasion.[36]

3.4.6 Key Plant Sources and Their Evolutionary Roles

Moringa oleifera: Known as the "miracle tree," it contains Moringin and seed proteins that are identified through in silico genomic screening, which are used in water treatment as natural coagulants that bind to bacterial contaminants. [27,28]
***Catharanthus roseus*:** An important producer of Cyclotides that are peptide compounds characterized by thermal and chemical stability, acting as a basis for drug delivery for clinical isolates. [29,30]
***Clitoria ternatea*:** Plants that synthesize cyclotides cto1 and cto2 that resist the tough environment of human intestines; their application in agriculture in form of green pesticides and growth promoters.[31]
***Capsicum annuum*:** The story of its antimicrobial power involves Capsaicin, which inhibits the NorA efflux pump in *S.aureus*, thereby reversing antibiotic resistance through the prevention of drug expulsion. [32,33]
***Datura metel*:** Researchers have isolated the alkaloid based peptides which have shown broad spectrum antimicrobial activity against *P. aeruginosa* in the wound healing model.[34,35]

II. CONCLUSION

Conclusion

The clinical validation of antimicrobial peptides for human mass production as an antibiotic has not been done so far.In vitro validation of use of plant derived antimicrobial peptides against biofilm is in progress stage. In vivo validation of animal derived antimicrobial peptide is in progress. The flexibility of antimicrobial peptides does not stop at the boundaries of clinical medicine, being applied in numerous industrial and environmental processes that capitalize on their stability and broad spectrum of action. While AMPs such as Nisin serve as preservatives in the food industry for preventing the growth of any microorganisms causing spoilage of food products, on the other hand, plant-based peptides, especially those sourced from *Clitoria ternatea*, serve as environmentally friendly pesticides and plant growth stimulants resistant to harsh environmental factors prevailing in fields. One more instance where AMPs have been put to multiple uses is the application in environmental biotechnology where *Moringa*

oleifera seeds extracts have been used as coagulants in wastewater treatment to get rid of bacteria in water . In the end, any successful implementation from lab experiments on a huge scale in the future will require a collaborative effort.

III. ABBREVATIONS

MDR, Multidrug-Resistant; WHO, World Health Organization; HDP, Host Defense Peptides; PMF, Proton Motive Force; ROS, Reactive Oxygen Species; AuNPs, Gold Nanoparticles; AMR, Antimicrobial Resistance; AMP, Antimicrobial Peptides; RND, Resistance Nodulation Division; MBL, Metallo-beta-lactamases; MRSA, Methicillin-Resistant *S. aureus;* PBP, Penicillin-binding protein; VRSA, Vancomycin-Resistant *S. aureus*; VISA**,** Vancomycin-Intermediate *S. aureus;* VEGF, Vascular endothelial growth factor; FICI, Fractional Inhibitory Concentration Index; DDS, Drug Delivery System.

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