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Antimicrobial peptides: A promising alternative to traditional antibiotics

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Abstract

Antimicrobial resistance (AMR) is becoming an emerging global threat, causing the reduced effectiveness of traditional antibiotics and the growing problem of multi-resistant pathogens. Under these circumstances, the attention given to antimicrobial peptides (AMPs) as a promising alternative to conventional antibiotics is considerable. AMPs are endogenous molecules present in any organism: mammals, amphibians, insects, plants, and microorganisms. AMPs play the most significant role in the innate immunity of bacteria, viruses, fungi, and even cancer cells. In this review, structural diversity, mechanisms of action, and therapeutic potential of AMPs are discussed. AMPs are divided into α -helical, β -sheet, loop, and extended peptides based on secondary structures that provide unique modes of action including membrane disruption and inhibition of intracellular targets. Despite the merits of a rapidly responding mechanism and lower resistive propensity, therapeutic use of AMPs suffers from numerous disadvantages, including poor stability and high production costs, cytotoxicity. The latest advancements of nanotechnology and synthetic biology along with computational tools provide solutions to the latter steps toward developing more effective AMP-based therapeutics. The future prospects for AMPs lie in overcoming the current challenges through innovative research and technological advancement. As the search for effective alternatives to traditional antibiotics intensifies, AMPs are a versatile and potent class of molecules with the promise to answer this ever-mounting problem of antimicrobial resistance.

Keywords: Antimicrobial resistance (AMR), antimicrobial peptides (AMPs), therapeutic potential, mechanisms of action, nanotechnology, antibiotic alternatives

Introduction

Antimicrobial Peptides (AMPs) are small peptides of natural occurrence and are crucially involved in wide ranges of organism's innate immune defense systems, including humans and animals, plants, and microorganisms. Of late, these peptides have been of great interest because they can exert antimicrobial effects and can be used as a new replacement for antibiotics. The intensive research and development of AMPs have been prompted by the need to combat multidrug-resistant pathogens, declining potency of traditional antibiotics, and a decline in the production of new antibiotics with novel mechanisms of action (Ventola, 2015) [13]. AMPs generally vary from a few to a hundred amino acids in size, are amphipathic, and contain a net positive charge that is necessary for the interactions and disruption of microbial membranes (Jenssen *et al.*, 2006) [6]. They depict wide-spectrum activities against classes of pathogens, which include bacteria, fungi, and viruses to cancerous cells. Contrasting with the traditional antibiotics that usually target almost singular biochemical pathways, AMPs target the integrity of cell membranes in microorganisms that is very rapidly translated into cell lysis and death. Such a mechanism of action has thus reduced the possibility of microbial resistance, which is of paramount necessity at this rising age of antibiotic resistance (Baltzer and Brown, 2011) [1]. Historically, the discovery of AMPs goes way back to a period when gramicidin from the bacteria *Bacillus brevis* was found in the early 1930s as the start of research on peptides-based antimicrobials (Phoenix *et al.*, 2013) [9]. Many AMPs have since been discovered in vast sources of nature including mammals, amphibians, insects, plants, and microorganisms. For instance, magainins from African clawed frog and human defensins are some of the best-known natural AMPs that

demonstrated very good antimicrobial activity (Huan *et al.*, 2020) [5]. One of the most promising features of AMPs is multifunctionality. AMPs will not only result in antimicrobial action but will also have immunomodulatory effects in addition to facilitating wound healing and an anti-inflammatory effect, thus greatly increasing the potential value of AMPs as therapeutic drugs (Reddy *et al.*, 2004) [10]. Additional properties in AMPs make these valuable candidates not only for treating infections but also for inflammatory and immune-related conditions. However, these promising attributes of AMPs still raise challenges in developing them into useful therapeutic agents with the major issues concerning instability, poor bioavailability, and even systemic toxicities of cytotoxicity when administered. However, breakthroughs in peptide engineering, nanotechnology, and synthetic biology defeat these challenges and allow the easy clinical translation of AMPs (Kumar *et al.*, 2020) [7]. The rapid and highly emerging challenge of AMR required novel approaches to treating infections. AMPs are an exciting frontier in antimicrobial therapy because of various mechanisms and rapid killing alongside very low propensity to develop resistance. With more research, the applications of AMPs will drastically revolutionize clinical practices involved in dealing with infectious diseases and their control.

Structure and Classification of AMPs

Many organisms possess small, naturally occurring molecules of various structural types as components of their innate immunity system. Such small molecules, given their unique structures and physicochemical properties, are able to target and destroy a wide range of pathogens. Their structural features have much potential for further understanding mechanisms of action of these peptides and potential applications in therapy.

1. Structure of AMPs

In general, AMPs vary in length and comprise several amino acids ranging from few to hundreds, and they have several characteristic structural features:

Amphipathic Nature: AMPs are amphipathic molecules having both hydrophilic and hydrophobic segments. They thus have easy access to the lipid bilayer of the microbial cell membrane; this is followed by cell membrane disruption (Jenssen *et al.*, 2006) [6].

Cationic Charge: AMPs, mainly the major ones, carry a high cationic charge since they have positively charged amino acids such as lysine and arginine. Such charge helps in offering an attractive force toward the negatively charged constituents of the microbial membranes like lipopolysaccharide in Gram negative bacteria and teichoic acids in Gram positive bacteria (Baltzer and Brown, 2011) [1].

Disulfide Bridges: Most AMPs contain disulfide bridges to make them have more stabilized secondary structures with high resistance to degradation of structural integrity even at harsh conditions (Broekaert *et al.*, 1997) [2].

2. Classification of AMPs based on their Structure

AMPs can be broadly classified into several groups based upon their secondary structure and plays a vital role in determining their mechanism of action as well as in interaction with microbial cells. The main three types of structural classes of AMPs are:

- a. **α -Helical Peptides:** These are α -helical in nature and make up the largest percentage of all AMPs that are most widely studied. The α -helical structure enables them to get inserted into the membrane of the microbes; such an insertion causes membrane destabilization, eventually to cell lysis. Examples include Magainins from the skin of African clawed frog and LL-37, in humans (Huan *et al.*, 2020) [5]. Due to the ease of modification and greater flexibility, α -helical peptides are highly adaptable for the synthesis of stable AMPs with high antimicrobial activity (Storici *et al.*, 1994) [12].
- b. **β -Sheet Peptides:** The β -sheet AMPs are structurally stabilized by two or more disulfide bridges, hence making the structure relatively rigid. Consequently, the peptide is less prone to conformational changes, which makes it stable and increased its ability to interact with the cell membranes of microbes. Human α - and β -defensins, and also Protegrins are some of the most common β -sheet peptides from porcine leukocytes (Kumar *et al.*, 2020) [7]. The β -sheet peptides are stable; thus, they are best suited for retention of their structure and function even under changing physiological conditions (Wang *et al.*, 2016) [15].
- c. **Loop Peptides:** Loop peptides have loop topology due to a disulfide bond which cross-links two cysteine residues and hence, has nearly cyclic nature. Due to this loop topology they have inherent protection against proteolytic degradation and are more stable in nature. The most highlighted bacteriocin secreted by the *Lactococcus lactis* is Nisin, which is a compound of this class (Wang *et al.*, 2016) [15]. Loop peptides have been applied as drugs and for preserving food because they have strong antimicrobial activities and stability in nature (Huan *et al.*, 2020) [5].
- d. **Extended Peptides:** In general, extended peptides do not form α -helix and β -sheet type of secondary structure. Mostly they contain some particular amino acids, such as proline, arginine, and tryptophan. Their flexible structures enable them to pass through the microbial cell walls and interfere with such intracellular events such as protein and nucleic acid synthesis. Indolicidin is a linear peptide isolated from bovine neutrophils that encompasses both antimicrobial and anti-inflammatory properties (Wang *et al.*, 2016) [15]. Linear peptides have been referred to as effective against even resistant bacteria and are less likely to induce resistance compared to common antibiotics (Huan *et al.*, 2020) [5].

3. Classification of AMPs by Source

They can also be categorized according to their source:

- **Mammalian AMPs:** Fundamentally of man and other vertebrates with the defensins and cathelicidin that are critical in innate immunity (Reddy *et al.*, 2004) [10].
- **Amphibian-Derived AMPs:** The best-characterized example is magainins from frog skin secretions, known for their strong antibacterial and antifungal activity (Chen *et al.*, 2008) [3].
- **Insect-Derived AMPs:** The insect steals AMPs, like Cecropins and Drosomycin, for the survival against microbial infections and shows remarkable antimicrobial activities (Vilcinskas *et al.*, 2013) [14].

- **Plant-Derived AMPs:** Thionins and defensins endogenous to plants confer resistance to both pathogens and insect pests (Broekaert *et al.*, 1997)^[2].
- **Microbial-Derived AMPs:** Bacteriocins or Nisin and Gramicidin are produced by microorganisms, but they inhibit the growth of other competitive microbial species (Huan *et al.*, 2020)^[5].

Mechanism of Action of AMPs

AMPs exhibit diverse mechanisms of action that target microbial cells, making them potent agents against a broad range of pathogens, including bacteria, fungi, viruses, and even cancer cells. The activity of AMPs can be broadly divided into membrane-targeting mechanisms and non-membrane-targeting mechanisms. These unique modes of action not only disrupt microbial cell integrity but also inhibit vital cellular processes, reducing the chances of resistance development.

1. Membrane-Targeting Mechanisms: The primary mechanism of action for many AMPs involves interactions with the microbial cell membrane. Due to their amphipathic nature, AMPs can easily bind to and disrupt the lipid bilayer of microbial membranes, leading to cell lysis and death. Several models describe how AMPs interact with the microbial membrane:

- Carpet Model:** In the carpet model, AMPs align parallel to the surface of the bacterial membrane like a "carpet." They accumulate on the membrane until a threshold concentration is reached, leading to the disintegration of the lipid bilayer into micelle-like structures. This disruption causes leakage of intracellular contents and ultimately cell death (Moretta *et al.*, 2021)^[8].
- Toroidal Pore Model:** In the toroidal pore model, AMPs insert themselves into the membrane, causing the lipid molecules to bend continuously through the pore, resulting in a "wormhole-like" structure. This pore formation leads to a significant disruption of membrane integrity, causing ion imbalance and leakage of essential cellular components, leading to microbial death (Moretta *et al.*, 2021)^[8].
- Barrel-Stave Model:** The barrel-stave model involves the formation of pore-like structures within the microbial membrane. In this model, the AMPs insert perpendicularly into the membrane and arrange themselves in a barrel-like fashion, with their hydrophobic sides facing the lipid bilayer and their hydrophilic sides forming the interior of the pore. This pore allows the uncontrolled flow of ions and molecules, resulting in cell death (Moretta *et al.*, 2021)^[8].

2. Non-Membrane-Targeting Mechanisms: In addition to targeting cell membranes, AMPs can also affect intracellular components of microbial cells, disrupting vital cellular functions. These non-membrane-targeting mechanisms are crucial for the versatility and effectiveness of AMPs against a wide range of pathogens.

- Inhibition of Cell Wall Synthesis:** AMPs can inhibit the synthesis of cell walls in bacteria by interacting with precursor molecules necessary for cell wall formation. This action compromises the integrity and strength of the cell wall, making bacteria more susceptible to

external stress and osmotic pressure (Jenssen *et al.*, 2006)^[6].

- Inhibition of Protein Synthesis:** Certain AMPs can penetrate microbial cells and bind to ribosomes, thereby interfering with the process of protein synthesis. By binding to ribosomal subunits, AMPs inhibit the translation process, preventing the production of essential proteins required for cell growth and survival (Huan *et al.*, 2020)^[5].
- Inhibition of Nucleic Acid Synthesis:** Some AMPs can directly target nucleic acids, such as DNA and RNA, within microbial cells. By binding to these molecules, AMPs disrupt the processes of DNA replication and RNA transcription, thereby halting cell division and preventing microbial proliferation (Moretta *et al.*, 2021)^[8].
- Inhibition of Enzyme Activity:** AMPs can inhibit various microbial enzymes critical for survival, such as proteases and enzymes involved in metabolic pathways. This inhibition interferes with essential metabolic processes, leading to a reduction in microbial viability and growth (Moretta *et al.*, 2021)^[8].

Immunomodulatory Effects of AMPs: Apart from their direct antimicrobial actions, AMPs also play a significant role in modulating the host immune response. They can enhance the innate immune system by promoting the production of cytokines, chemokines, and other immune mediators. This immunomodulatory property not only aids in clearing infections but also reduces inflammation and promotes tissue repair and healing (Kumar *et al.*, 2020)^[7].

Limitations and Challenges in the Therapeutic Use of AMPs

Despite their potential as alternatives to traditional antibiotics, antimicrobial peptides (AMPs) face several limitations and challenges that have slowed their progress towards widespread clinical and commercial application. Understanding these barriers is crucial for developing strategies to overcome them and successfully utilize AMPs in therapeutic settings.

- Instability and Short Half-life:** One of the major limitations of AMPs is their poor stability in biological environments. AMPs are prone to degradation by proteolytic enzymes present in the bloodstream and tissues, which significantly reduces their half-life and therapeutic efficacy. This instability limits their potential as systemic treatments and necessitates high or frequent dosing to maintain effective concentrations *in vivo* (Kumar *et al.*, 2020)^[7].
- Poor Bioavailability:** AMPs often suffer from low bioavailability when administered orally or through other non-invasive routes. Their susceptibility to enzymatic breakdown in the gastrointestinal tract and poor absorption through mucosal barriers restrict their use to topical or localized applications. This issue significantly hampers their development as broad-spectrum systemic antibiotics (Moretta *et al.*, 2021)^[8].
- Potential Cytotoxicity:** While AMPs are designed to target microbial cells, some can also exhibit cytotoxic effects on mammalian cells. The non-selective action of certain AMPs can lead to the disruption of host cell membranes, causing adverse effects and limiting their therapeutic index. Developing AMPs that maintain high

specificity for microbial targets without affecting host cells remains a significant challenge (Baltzer and Brown, 2011)^[1].

4. **High Production Costs:** The manufacturing of AMPs can be costly due to the complexity of peptide synthesis and purification processes. Producing AMPs at a large scale while maintaining their structural integrity and functional activity requires significant investment in technology and resources. This economic constraint poses a barrier to the commercial viability of AMPs compared to small-molecule antibiotics (Huan *et al.*, 2020)^[5].
5. **Regulatory Challenges:** AMPs face stringent regulatory requirements that complicate their path to market approval. The need to demonstrate safety, efficacy, and stability through well-designed clinical trials is often a lengthy and expensive process. Moreover, the lack of standardized guidelines specific to AMP-based therapeutics further complicates regulatory compliance, delaying their progression into clinical use (Kumar *et al.*, 2020)^[7].
6. **Potential for Resistance Development:** Although AMPs are less likely to induce resistance compared to traditional antibiotics, the risk of resistance development cannot be entirely ruled out. Prolonged exposure to sub-lethal doses of AMPs could potentially lead to the evolution of resistant strains, reducing the efficacy of these peptides over time. Understanding and mitigating the factors that contribute to resistance is essential for the long-term viability of AMP-based therapies (Rima *et al.*, 2021)^[11].
7. **Limited Penetration in Complex Biofilms:** Biofilms, which are protective layers formed by microbial communities, present a significant barrier to antimicrobial treatments. AMPs often have limited ability to penetrate these biofilms effectively, reducing their antimicrobial activity against biofilm-associated infections. Enhancing the biofilm-disrupting properties of AMPs is necessary to treat chronic and persistent infections (Dijksteel *et al.*, 2021)^[4].

Overcoming the Challenges: To address these challenges, many ongoing research focuses on improving the stability, specificity, and delivery of AMPs through advanced techniques like:

Nanotechnology: Using nanoparticles as carriers to protect AMPs from degradation and enhance their delivery to infection sites.

Peptide Engineering: Designing synthetic AMPs with modifications that increase their resistance to enzymatic breakdown and reduce cytotoxicity.

Combination Therapies: Employing AMPs in combination with conventional antibiotics to reduce the required dosage and minimize the risk of resistance development.

Future Prospects of Antimicrobial Peptides (AMPs)

In the near future, AMPs are perspectives to replace the classic antibiotics on which all hopes and expectations are placed. Their main challenge rests in reducing the current limitations to further expand their application in therapy. AMPs are an area of critical importance in today's world

facing a global threat because of antimicrobial resistance, and research in these areas can pave the way for innovative solutions on both health care and agriculture grounds.

1. **Nanotechnology for Stability and Efficacy Improvement:** One of the biggest challenges that AMP therapy presents is their instability and poor bioavailability in biological systems. Advances in nanotechnology present an opportunity for improving the stability, efficacy, and delivery of AMPs. This can be done through encapsulation of the AMPs into nanocarriers or conjugation with nanoparticles to protect these peptides from degradation, increasing their half-lives, and enhancing targeted delivery to the site of infection, thus maximizing therapeutic potential while minimizing host cell toxicity.
2. **Synthetic and Engineered AMPs:** Computational biology and synthetic biology approaches are now revolutionizing the design and development of AMPs. With tools like QSAR models and genetic algorithms, researchers can synthesize variants with optimized properties-in particular, higher potency, lower cytotoxicity, and resistance to proteolytic degradation. This approach does not only improve the therapeutic profile of AMPs but might also lead to the generation of peptides especially designed for certain pathogens.
3. **Multitarget Therapies:** AMPs Integrated into Them- The combination of AMPs with conventional antibiotics or other drugs may be an excellent opportunity for the improvement of efficacy of antimicrobial therapy with reduced incidence of resistance. It has been demonstrated that synergies exist between AMPs and other conventional drugs, and the latter can be used at lower dosages, therefore reducing side effects. It would significantly impact treatment of infections caused by multi-resistant bacteria.
4. **More Potential than Antimicrobial Activities:** The AMPs are not confined to being antibacterial; they have horizons in immunomodulation and wound healing and also have antiviral and anticancer properties. Future studies will surely look forward to these additional applications and thus open a door for AMPs to more varieties of diseases. For instance, AMPs might be produced as anti-inflammatory agents in chronic diseases or as immune system enhancers in immunocompromised patients.
5. **AMPs in Agriculture and Environmental Uses:** Besides their possible applications in medicine, AMPs are also evaluated as chemical alternatives of preservatives and pesticides in agriculture. The genetically modified crops and plants expressing AMPs might aid in a sustainable protection of crops versus pests and pathogens and at the same time decrease artificial chemicals impact in the environment. Crop yield will also be benefited as this will also prevent the enhancement of antibiotic resistance in the environment.
6. **Regulatory and Commercialization Efforts:** To move AMPs from the laboratory to the market, regulatory hurdles would have to be overcome and products demonstrated to be safe and effective through well-designed clinical trials. As more and more AMPs progress through the stages of clinical evaluation, there is a growing need to streamline the approval process to accommodate multicentered studies and to facilitate

better communication among investigators, industry, and regulatory agencies. Well-defined standards and requirements for products based on AMPs would greatly support successful commercialization efforts.

7. **Role of Computational Tools in AMP Design:** Computational and experimental biology approaches are helpful in understanding the interactions of AMPs and predicting their activity in fighting specific pathogens. Techniques like molecular docking, in silico modeling, and machine learning help identify potent peptide candidates and design AMPs with enhanced properties toward antimicrobial action. These tools will continue to drive innovation in AMP research toward the acceleration and cost-effectiveness of the development of new therapeutic agents.
8. **Innovative Research and Collaboration:** Expanded frontiers in the AMP research area will be the product of continued collaborative efforts on the part of academic institutions, biotechnology companies, and governmental organizations. Research avenues such as bio-prospecting of AMPs from a diversity of organisms and novel source exploration in nature expand this repertoire of peptides, potentially opening up new species-specific molecules with unique mechanisms of action.

Conclusion

Antimicrobial peptides (AMPs) are very promising as a new class of therapeutic agents in the war against multidrug resistant pathogens. Their broad spectrum of activity, fast acting killing mode, and capacity to kill both antibiotic-susceptible and resistant bacteria make them excellent entity for development as next generation alternatives to traditional antibiotics. AMPs novel mechanism of action, such as membrane disruption and intracellular targeting, make resistance development less likely compared to conventional antibiotics. Additionally, their multifunctional activities in immunomodulation, wound healing, and anti-inflammatory properties demonstrate their potential beyond antimicrobial activity.

Although promising, the therapeutic use of AMPs is hindered by various limitations such as low bioavailability, instability in biological systems, cytotoxicity, and high cost of production. These can be overcome by cutting-edge approaches such as nanotechnology, peptide engineering, and synthetic modifications to increase stability, efficacy, and decrease toxicity. New research in computational biology and genetic algorithms is also pushing the limits of developing synthetic AMP variants with better properties.

As the need for alternative antimicrobial strategies grows urgent due to the escalating issue of antimicrobial resistance, AMPs offer a valuable solution with their broad applicability in both clinical and agricultural settings. Continued research and development are essential to transform AMPs from promising therapeutic candidates into viable commercial products. Collaborative efforts in AMP research, regulatory advancements, and investment in innovative technologies will be crucial to unlocking their full potential and mitigating the impending antimicrobial crisis.

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