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A review on Diversity, Mechanism of Action and Evolutionary Significance of Antimicrobial Peptides

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ABSTRACT

Antimicrobial peptides (AMPs) are small, evolutionarily main peptides that widely exist in rich diversity across nature and play a significant role in the innate immunity of various taxa from invertebrates to vertebrates. They are equally targeted as the newest discovered antibiotics against various prokaryotes, including bacteria, viruses, fungi, and parasites. AMPs show broad-spectrum potential with high efficacy and low toxicity via in vivo studies. Undoubtedly, this also confers their specific mechanism of action (MOA) and unique but distinct structures. Already, many studies have reported that AMPs possess diverse MOA against various pathogenic microbes. AMPs also encourage the cells to enhance wound healing, programmed cell death, angiogenesis, and produce chemokines. However, the associated risk is the evolution of resistance to AMPs could lead to possible danger to inherent immunity. From an evolutionary perspective, they are usually considered nonspecific with redundant functions due to the fact that they are easily duplicated and produce pseudogenes, thus showing less evolution at the primary amino acid level. However, the microbial resistance risk against conventional antibiotics can be minimized by using AMPs efficiently and sustainably. Understanding the nature and evolution of AMPs will be beneficial as well. The current review focused on antimicrobial peptides' diversity, history, MOA, and evolutionary significance.

INTRODUCTION

In recent years, microbes' resistance has increased due to the absence of new antimicrobial agents and the reduced ineffectiveness of antibiotics. Thus, the discovery and approval of novel drugs for therapeutic use are of great importance. Among these new drugs, antimicrobial peptides are one of the excellent members for the discovery of new antimicrobial agents [1]. Antimicrobial peptides are peptide-based effectors of the innate immune system in prokaryotic and eukaryotic organisms. AMPs are categorized into various subgroups according to amino acid substitution [2]. They usually contain 12-50 amino acids. Practically, AMPs are part of microorganisms, humans and other living organisms' innate immune system and have been known for an age. Skin infections and wounds are treated by using these peptides [3]. No matter the origin, almost all peptides share some similar characteristics, such as peptides have a net positive charge, they all have amphiphilic activity (both hydrophobic and hydrophilic), and, in some cases, they are also membrane activators [4]. The positive charge of peptides shows more attraction towards negatively charged microorganisms than the host cell because host cells have comparatively less negative charge than prokaryotic cells. Therefore, the antimicrobial peptides bind with the microbes. The ability of AMPs to accumulate at the target location, i.e., the infection site in microbes, makes them more toxic, and their toxicity is more harmful to microorganisms than the host cells; due to this ability, they

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may be called attractive targeting vectors [5].

The AMPs interfere with the synthesis of cytoplasmic and cell membranes. By inhibiting their synthesis, they can kill the microbe and reduce the growth of bacterial cells. The AMPs also hinder the enzymes production in the microbial cell. Thus, weakening the defense of cells [6]. AMPs offer clear and prominent advantages over conventional antimicrobial agents, as they do not tend to induce multidrug resistance in the host. Additionally, AMPs not only exhibit antimicrobial activity but also assist the host's immune system [7]. Biofilms are the communities of surface associated sessile microorganisms and bound in a self-produced extracellular matrix, thus developing the resistance against antimicrobial agents and giving rise to these chemotherapeutic problems [8]. More particularly, these bacterial colonies are physiologically different from those colonies which are planktonic but belong to the same group. They have embedded in a self-secreted matrix that can increase the antimicrobial resistance by one thousand folds by blocking the penetrance of antimicrobial agents [9]. Usually, AMPs were recommended to tackled biofilms because they have broad-spectrum bactericidal action. AMPs are frequently synergistically used with antimicrobial drugs to inhibit the molecular pathways involved in formation of biofilm [10].

AMPs have demonstrated remarkable effectiveness and efficiency in laboratory settings, particularly in cultural tubes. They exhibit significant efficacy against a wide range of bacteria, including both Gram-negative and Gram-positive strains. Moreover, AMPs have shown efficacy against many drug-resistant bacteria, highlighting their ability to overcome microbial resistance mechanisms [11]. The AMPs possess hydrophilic and hydrophobic parts, i.e., they are amphipathic, and they are a-helical peptides. Therefore, they can easily attach themselves to the cell membrane and the proteins in serum. This property helps them remain intact in circulation [12].

However, some limitations in the use of AMPs exist that may be disastrous. These limitations can finish the game of AMPs if serious steps are not taken. These limitations include high cost of discovering the peptides, the synthesis, and the management with screening. Moreover, peptides are toxic for both host and microbial cells; therefore, this is also a limitation in AMPs. In addition, the activity of AMPs is affected by factors such as salt concentration, pH levels, and exposure to serum. Furthermore, they are also sensitive to proteolysis, which can reduce their effectiveness. Additionally, repeated application of AMPs may lead to reduced sensitivity and potential allergic reactions [13].

HISTORY

The first AMP was discovered in 1939, followed by the discovery of some important antimicrobial peptides in the 1980s, initially in insect hemolymph, mammalian neutrophil granules, and the skin secretions of frogs. These peptides, such as defensins and cathelicidins, are key components of the innate immune system and play a crucial role in defending against microbial pathogens. They are typically small, cationic molecules with amphipathic properties, allowing them to interact with microbial membranes and disrupt their integrity [14]. The discovery of antimicrobial peptides has sparked significant interest in their therapeutic potential, particularly in the face of increasing antibiotic resistance. Research continues to uncover new antimicrobial peptides in various organisms, highlighting their diversity and potential for novel antimicrobial therapies [15]. There are almost thousands of AMPs that have been found naturally in microorganisms, plants and from different sources. In addition, several AMPs are synthesized in the laboratory artificially by mimicking the original sequence or with the help of computer design [16]. Since the start of this field, the AMPs have been promoted. From the discovery to some time, these AMPs failed to seek the attraction of scientists and pharmacists. When antimicrobial drug resistance occurs, these peptides become important and promoted well because antimicrobial drug resistance is the leading health crisis in morbidity and mortality globally [17]. In recent times, the significance of AMPs has grown due to the development of some into powerful antimicrobial agents. Several antimicrobial peptides are currently undergoing trials to assess their effectiveness against a wide array of microorganisms and microbial activities [18].

DIVERSITY OF ANTIMICROBIAL PEPTIDES

Antimicrobial peptides are present in great diversity based on their structures (Figure 1), sequences and mechanism of action.

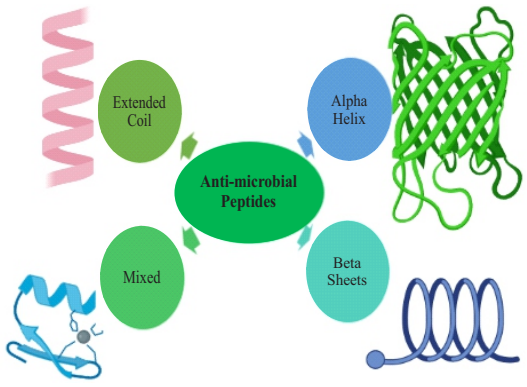

Figure 1: The figure showed types of antimicrobial peptides which are categorized according to their structures. The AMPs are known to have four main types, i.e., extended coil, alpha helix, beta-sheets, and mixed AMPs.

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Diversity Based on the Structure

Based on the structure, the AMPs are categorized into three general subclasses.

1. Antimicrobial Peptides with Alpha-Helical Structure

Antimicrobial peptides present in this subgroup have an alpha-helical structure and these are common in insects and frogs and found in their extracellular matrix.

In Alpha helical peptides, mostly amide groups are present at the C-terminal, enhancing the antimicrobial activity. In addition, the presence of the amide group at the C-terminal increases the electrostatic interaction among the peptide which is charged positively and the bacterial membrane which is negatively charged. This contact helps in stabilization of helical structure at the membrane surface [19].

Few Examples of antimicrobial peptides with α helical cathelicidins [20], LL-37 [21], α helical magainin [22], Aurein [23], pexiganan [18], Mellitin [21], Brevinin [24], Maculatins [25] and Citropin [26].

1. Antimicrobial Peptides with β Sheet Structure

This class comprises Cathelicidin family AMPs [20], such as Protegrins found in pigs, and Bactenecin found in bovine, which contain an arginine-rich disulfide loop. Arginine is crucial in the disulfide loop of Cathelicidin AMPs because it contributes to their antimicrobial activity. Arginine is positively charged, allowing it to interact with negatively charged microbial membranes, disrupting their integrity. This interaction is vital for the peptides' ability to penetrate and destabilize the membranes, leading to microbial cell death. Additionally, the arginine-rich nature of the disulfide loop enhances the peptide's overall cationic charge, which is important for its interaction with microbial membranes and subsequent antimicrobial effects. Defensins are the chief group of β sheet antimicrobial peptides, further divided into three subgroups [27]. Defensins also show antibacterial, antifungal, antiviral, and inflammatory and immune reactions [21, 28]. Tachyplesins and polyphemusins peptides, derived from the hemocytes of horseshoe crabs, are rich in arginine, making up 30% of their sequence [24].

The presence of cysteine residues in almost all β-sheet antimicrobial peptides is of significant importance. Cysteine residues are crucial because they enable the formation of disulfide bonds. These bonds play a critical role in stabilizing the peptide's tertiary structure, enhancing its resistance to degradation by proteases and other enzymes. Additionally, disulfide bonds can contribute to the peptide's antimicrobial activity by facilitating interactions with microbial membranes or other targets. Therefore, cysteine residues are essential for the structural integrity and functional efficacy of β-sheet antimicrobial peptides [29].

2. Antimicrobial Peptides with Extended Coil Structure

The last subclass of antimicrobial peptides has an exceptional extended coil structure. This subclass includes hesitatin, which is found in humans and is known for its antimicrobial properties. Hesitatin contains histidine residues, which are important for its activity. Additionally, this subclass includes members of the Cathelicidin family [20], such as PR-39b, Tritrpticin, Indolicidin, and Crotalicidin, which also exhibit an extended coil structure [30]. Diversity of some antimicrobial peptides is shown in table 1.

Table 1. Diversity of Antimicrobial Peptides

Category	Peptides	Structure	Source	Reference
A Helix	Aurein1-2	Amidated C-Terminus	Frogs	[31]
	Brevinin 1	-	Frogs	[24]
	Mellitin	Amidated C-Terminus	Bees	[21]
	Maculatins	Amidated C-Terminus	Frogs	[32]
	Buforin II	-	Toad	[33]
	Citropin	Amidated C-Terminus	Frogs	[34]
	BMAP-27,28,34	-	Bovine	[20]
	LL-37	Amidated C-Terminus	Humans	[20]
	Cecropin	Amidated C-Terminus	Insect	[20]
	Magainins	-	Frogs	[20]
ß-Sheets	Protegrins	Cysteine Rich	Pigs	[20]
	Bactenecin	Arginine Rich	Bovine	[20]
	α defensins	Disulfide Bonds	Mammals	[27]
	β defensins	Disulfide Bonds	Mammals	[27]
	θ defensins	Disulfide Bonds	Gorilla	[27]
	Tachyplesins	Arginine Rich	Horse Crab	[28]
	Polyphemus	C-Terminus	Horse Crab	[30]
Extended Coil	PR-39	Arginine Rich	Pigs	[20]
	Indolicidin	Tryptophan C-Terminus	Bovine	[20]
	Histatins	Histidine Rich	Humans	[30]
	Tritrpticin	Arginine Rich	Pigs	[20]

HOW ANTIMICROBIAL PEPTIDES WORK/ACT

Antimicrobial peptides act in two different ways. Following are the mechanisms;

Direct Killing: The Membrane-Targeting Mechanism

The antimicrobial peptides with membrane targeting mechanisms have two types of interactions; receptor and non-receptor mediated interactions.

1. Receptor-Mediated Pathway

The pathway involving bacterially produced antimicrobial peptides represents a critical defense mechanism against microbial threats. These peptides, such as nisin, exhibit remarkable activity even at extremely low concentrations in laboratory conditions, typically in the nanomolar range [35]. Nisin, a well-studied antimicrobial peptide, consists of two primary domains, each serving a distinct function. One domain demonstrates a strong affinity for the lipid II molecule, a crucial component involved in bacterial cell wall synthesis. This interaction occurs within the bacterial

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membrane, specifically with the precursor of the cell wall [36]. The second domain, known as the pore-developing domain, becomes embedded within the bacterial membrane. This embedding facilitates the formation of pores in the membrane, which compromises its integrity and leads to microbial cell death. This dual-domain structure and mechanism of action underscore the effectiveness of antimicrobial peptides in combating bacterial infections [37].

2. Non-Receptor-Mediated Pathway

Antimicrobial peptides of vertebrates and invertebrates target the membrane without combining with the receptors [38]. Antimicrobial peptides demonstrate potent activity *in vitro* at micromolar concentrations against various microbes. Their broad-spectrum effectiveness extends to bacteria, fungi, viruses, and some parasites, making them valuable in combating infections. These peptides' ability to act at low concentrations highlights their potential as safe and effective therapeutic agents. Ongoing research aims to enhance their efficacy and develop novel peptide-based treatments, underscoring the importance of antimicrobial peptides in addressing the challenge of antimicrobial resistance.

Wimley and Hristova [39] reported that these antimicrobial peptides play their role by interacting with the membrane's components. For example, Gram-positive and Gram-negative bacteria's outer surface has teichoic and lipopolysaccharide. Surfaces of both contain net negative charge due to which electrostatic attraction with cationic AMPs is possible.

Guilhelmelli *et al.*, [40] reported that AMPs act differently in the bacterial membrane and animals' membrane. The outer leaflet of the lipid bilayer in bacterial membranes is made of lipids that contain head groups, for example, PG and cardiolipin which are negatively charged. They further reported that in animal membranes, zwitterionic phospholipids is present, for example, sphingomyelin, PC, and cholesterol. Guilhelmelli *et al.*, [40] reported that in animal membranes, head groups containing anionic lipids are present in the inner leaflet.

Andersson *et al.*, [41] found that antimicrobial peptides (AMPs) exhibit a stronger electrostatic attraction to the outer leaflet of bacterial membranes compared to animal membranes. AMPs accumulate on the surface through a series of electrostatic and hydrophobic interactions. Once a critical concentration is reached, they begin to self-assemble on the bacterial membrane.

At this stage, various models define the AMPs action. These models are divided into two categories:

- Transmembrane pore which are further divided into two categories: barrel-stave pore and toroidal pore models
- Carpet model (Non-pore models)

Barrel-Stave Pore Model

In the barrel stave model, Kumar *et al.*, [38] reported that the AMPs are oriented parallel to the membrane at the start and then inserted in a perpendicular direction in the lipid bilayer. Wimley [42] reported that it gives rise to lateral peptide-peptide interactions. Ramamoorthy *et al.*, [43] reported another example that is pardaxin. Brogden [44] reported that protegrins also exhibit barrel stave channels.

Toroidal Pore Model

In the toroidal pore model, Wimley [42] reported that the peptides perpendicularly inserted in the lipid bilayer, but no any specific peptide-peptide interactions exist.

However, the peptides cause a local curvature of the lipid bilayer with pores produced in part by peptides and in part by the phospholipid head group. The "toroidal pore" is a dynamic and transient lipid-peptide supramolecule. The distinctive characteristic of this model with the barrel-stave pore model is the net arrangement of the bilayer. In the barrel-stave pore model, the arrangement of the lipids either hydrophilic or hydrophobic is maintained but not maintained in the toroidal pore model, due to which alternative surfaces for the interaction with the lipid's head and tail group arises. As the toroidal pore is transient so, after the disintegration, these peptides move towards the inner cytoplasmic leaflet, so after entering the cytoplasm, they strongly target the components within the cell . The toroidal pore has a discrete size. It exhibits ion selectivity [45].

Lee *et al.*, [29] reported that AMPs such as magainin 2 and lacticin Q exhibit this model activity.

Both toroidal pore and barrel which are pore forming models cause membrane depolarization and lead to cell death.

Carpet Model

Lee *et al.*, [29] reported the model in which antimicrobial peptides act without the formation of specific pores. Wimley and Hristova [39] reported that antimicrobial peptides oriented parallel to the lipid bilayer. They cover the surface of the membrane which looks like a "carpet" when they reached threshold concentration. This is disapproving of interactions on the surface of the membrane. As a result, membrane integrity is lost. The same happened in the detergent model, in which the membrane disintegrates at last by forming micelles. The peptide doesn't have to put into the hydrophobic core for the formation of trans-membrane channels. The membrane-bound peptide monomers' relations to one another are not shown in the carpet model.

Direct Killing: Mechanisms of Action without Targeting Membrane

The non-membrane targeting antimicrobial peptides

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classified into two groups

- Bacterial cell wall target
- Intracellular targets

1. Bacterial Cell Wall Target

Malanovic and Lohner [46] reported that, like antibiotics (which were used conventionally), AMPs obstruct the synthesis of cell wall. These antibiotics attach to particular proteins which involved in synthesis of cell wall's components. On the other hand, AMPs show interaction with a variety of precursor molecules used to synthesize the cell wall. Highly conserved lipid II is one of the molecules which is a major target. Münch and Sahl [47] reported that AMPs like defensins bind with negatively charged pyrophosphate sugar precursor of the lipid II molecule.

Münch and Sahl [47] reported that AMPs, for example, defensin 3, put heads together with the bactericidal activity by the selective binding with lipid II molecule.https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click on image to zoom&p=PMC3&id=5871973_biomolecules-08-00004-g006.jpg

2. Intracellular Targets

It was believed that AMPs have no intracellular targets. Currently it is recognized that many AMPs have intracellular targets because these AMPs lead to bacterial death without causing permeabilization of the membrane at their minimum concentration.

In this mechanism, the AMPs show interaction with the membrane of cytoplasm and then they store intracellularly, where they disrupt cellular processes like inhibition of nucleic acid or protein synthesis and block the protein as well as enzymatic activity.

3. Immune Modulation Mechanism of Action

Hilchie *et al.*, [48] Reported that antimicrobial peptides are involved in the direct killing of microbes and activating the immune cells. These cells, as a result, increase microbial killing and control inflammation.

Antimicrobial peptides are produced from certain immune cells like neutrophils and macrophages, so they are considered the first molecules interacting with the attacking microbes [41]. The examples of these antimicrobial peptides are LL-37 and β defensins that induce activation of immune cells by chemoattraction like mast cells, microglia, and monocyte. In addition, the activation of another group of immune cells (leukocytes) is also reported.

EVOLUTIONARY SIGNIFICANCE OF AMPs

AMPs are evolutionarily conserved components of innate immunity of invertebrates against pathogens. Various AMPs in invertebrates showed significant diversity in their amino acid structure, sequence, and biological activity. AMP genes have evolved rapidly, probably due to a co-evolutionary arms race among host and pathogens and allowing organisms to survive in different microbial environments. Even though AMPs have been used extensively for most of the time, they have retained their antimicrobial activity during evolution. Therefore, the sequence diversity of AMPs probably indicates organisms' ability to adapt to live in various microbial-infested environments[49].

The amino acid composition of natural AMPs plays a crucial role in their structure, function, and evolution. In higher organisms, the preference of arginines in AMPs is supposed to have performed a key part in the evolution of adaptive immune systems and provided a regulatory and integrative role to natural AMPs in host immune responses. Likewise, it appears that different natural AMP structures are directly influenced by the composition of amino acid [50].

Survival of host can significantly be affected during infection due to few evolutionary variations in composition of AMPs amino acid. In *D. melanogaster*, alleles of Diptericin A have pathogen-specific action against *Providencia rettgeri* and not show against other bacteria, including *P. rettgeri* cousins. To specifically change resistance to *P. rettgeri,* Diptericin A just to have a single polymorphic amino acid change. These findings indicate previously unrecognized AMP activity specificity [51]. Loss of gene, duplication of exon and gene and exon shuffling have all extensively occurred in AMPs. In insects, AMPs reveal the existence or lack of a gene family in general as well as lineage-specificity in copy counts within a gene family. For example, the Drosomycin family of AMPs is present in certain *Drosophila,* and coleoptericin belong to order Coleoptera [52]. Evolution of the pathogens might be restricted due to the release of multiple AMPs simultaneously during an immune response. In insects, AMPs as immune proteins evolved faster than non-immune proteins. In crustaceans, Shrimps produce AMPs in response to an infection. Shrimps have evolved and use a variety of AMPs to prevent being exposed to various harmful microbes[49].

AMPs have not lost their ability to kill the microbes totally, despite their long history of co-evolution. Microbes also have not learned to evade the lethal hit of AMPs. Therefore, AMPs can provide a significant advancement and form the foundation for a new group of antibiotics[53].

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CONCLUSIONS

It is challenging to treat biofilm-linked persistent and chronic infections with traditional antibiotics. AMPs are novel therapeutic agents that are used to treat biofilm-associated diseases. It is not easy for microbes to develop resistance against AMPs compared to conventional antibiotics. AMPs have a variety of structures and kill microbes in various ways, including interaction with biological membranes and activity at specific extracellular and intracellular targets. However, function of AMPs to control different infections is still hampered by various problems, including poor pecularity, high toxicity to animal cells, deficiency of a rational design guidelines and high expenses of production.

Nevertheless, AMPs are attractive candidates for translational application due to their potency and diversity, and many are already in clinical trials. Additionally, the research could explain both sides of a co-evolutionary arms race among host and pathogen by recognizing the alteration in microbial genes that can cause resistance to AMPs. However, to use AMPs effectively and sustainably, it will be essential to understand their evolution and natural biology to reduce the danger of collateral harm and avoid the resistance crisis that traditional antibiotics are now facing.

Authors Contribution

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Writing-review and editing: NM, WA, AU, IL, ZN

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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