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A systematic review of Antimicrobial peptides and their current applications

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ABSTRACT

In present days, drug resistance is a major emerging problem in the healthcare sector. Novel antibiotics are in considerable need because present effective treatments have repeatedly failed. Antimicrobial peptides are the biologically active secondary metabolites produced by a variety of microorganisms like bacteria, fungi, and algae, which possess surface activity reduction activity along with this they are having antimicrobial, antifungal, and antioxidant antibiofilm activity. Antimicrobial peptides include a wide variety of bioactive compounds such as Bacteriocins, glycolipids, lipopeptides, polysaccharide-protein complexes, phospholipids, fatty acids, and neutral lipids. Bioactive peptides derived from various natural sources like bacteria, fungi, and algae in higher eucaryotic animals offer novel possibilities to identify potential lead compounds for treating a variety of diseases. The antimicrobial activity, various properties, mechanisms, and applications of AMPs are the focus of this systematic study.

Keywords: *Antibiotics, Antioxidant, Antifungal, Bacteria*

INTRODUCTION

Sir Fleming discovered penicillin [1]and in the 1940s, along with Howard Florey and Ernst Chain, he brought the therapeutic use of penicillin to fruition, which led these three men to share the 1945 Nobel Prize for Medicine [2]. The advent of penicillin and streptomycin in 1943, began the "Golden Age of antibiotics," which led to a rapid loss of interest in the therapeutic potential of natural host antibiotics such as lysozyme and the importance of this immune defense strategy [3,4]. Antimicrobial peptides (AMPs) have been recognized in prokaryotic cells since 1939 when antimicrobial substances, named gramicidins, were isolated from Bacillus brevis and were found to exhibit activity both in vitro and in vivo against a wide range of Gram-positive bacteria. "Golden Age of antibiotics" had ended and with the rise of multidrug-resistant microbial pathogens in the early 1960s, an awakened interest in host defense molecules was prompted [5,6]. It is this point in time that some sources consider being the true origin of research into AMPs, beginning with studies that were conducted in the 1950s and 1960s when it was shown that cationic proteins were responsible for the ability of human neutrophils to kill bacteria via oxygen-independent mechanisms – clearly not an activity associated with the adaptive immune system [7,8]. In 1962, in what some consider to be the first description of an animal

AMP [9], bombinin was reported in the orange-speckled frog Bombina variegate [10].

Now a days bacteria act as a good source for antimicrobial peptide production. The majority of bacteria produce ribosomally synthesized antimicrobial polypeptides generally called bacteriocins, and non-ribosomally synthesized peptides, such as lipopeptides, gramicidin, polymixins, bacitracin, and others (11, 12). AMPs have different classifications such as; biosynthetic machines, biological sources, biological functions, molecular properties, covalent bonding patterns, three-dimensional structures, and molecular targets.

Structure of AMPs

The secondary structures of the AMPs were revealed to consist of a variety of -helices, -strands with one or more disulfide bridges, loops, and extended structures. For Amps to exhibit such broad-spectrum antimicrobial activity, it is completely essential that they present in a wide variety of structural configurations [13]. In addition to these properties, other essential elements that contribute to their broad-spectrum antimicrobial activity include size, charge, hydrophobicity, amphipathic stereo geometry, and peptide self-association to the biological membrane. Because of their smaller size, AMPs make it easier for peptides to diffuse and secrete quickly outside of cells, which is necessary for triggering a fast defence reaction against pathogenic microbes. [14]. Currently, more than 2,000 AMPs have been reported in the antimicrobial peptide database (http://aps.unmc.edu/AP/main.php/). Most of them are cationic peptides, and only a few of them are anionic, which shared the ability to fold into amphipathic conformation upon interacting with the membranes [15]. Besides antimicrobial function, AMPs also serve as drug delivery vectors, antitumor agents, mitogenic agents, contraceptive agents, and signaling molecules in signal transduction pathways [16].

Most AMPs reported to date can be characterized as one of the following four types based on their secondary structures: β-sheet, α-helix, extended, and loop. Among these structural groups, α-helix and β-sheet structures are more common [17] and α-helical peptides are the most studied AMPs to date. The best-known examples of such AMPs are protegrin, magainin, cyclic indolicin, and coiled indolicin. β-sheet peptides are composed of at least two β-strands with disulfide bonds between these strands [18]. Unlikely antibiotics, which target specific cellular activities (e.g., synthesis of DNA, protein, or cell wall), AMPs target the lipopolysaccharide layer of the cell membrane, which is ubiquitous in microorganisms. Having a high level of cholesterol and low anionic charge puts eukaryotic cells out of the target range of many AMPs [19].

Types of antimicrobial peptides

1) Anionic antimicrobial peptides (AAMPs) were first discovered during the 1980s and have since been recognized as a necessary element of the natural immune systems of vertebrates, invertebrates, and plants. These peptides possess antimicrobial, fungicidal, and antiviral activity. examples of Anionic antimicrobial peptides are Maximin H5 from amphibians, and Dermicidin obtained through humans [20].

2) Cationic antimicrobial peptides: These peptides antimicrobial potential has been well studied, and many of these have a broad range of actions not only against Gram-negative and Gram-positive bacteria but also against bacteria that are resistant to antibiotics, fungi, viruses, and parasites. To kill bacteria, such cationic antimicrobial peptides can also be combined with conventional antibiotics, other cationic peptides and proteins, and lysozyme. For example, honeybee apidaecins, prophenin from pigs, and indolicidin from cattle [21], Surfactin from Bacillus velenzensis strain SK.(22)

3) Cationic amphipathic peptide: mainly these Peptides were synthesized chemically from the N-terminal domain of human lactoferrin (LFh 18–31 and LFh 20–38) and bovine lactoferrin (LFb 17–30 and LFb 19–37) that includes an amphipathic alpha-helix. Because many positively charged amphipathic helices have antimicrobial properties [23].

4)Linear cationic α-helical peptides – it is one of the most widely distributed AMPs, α-helical antimicrobial peptides (aAMPs) have been thoroughly investigated. Numerous studies have been performed to optimize their potential for clinical applications, i.e., to improve antimicrobial activity and reduce toxicity against human cells. E.g. Cecropins, andropin, moricin, ceratotoxin, and melittin from insects, Magainin, dermaseptin, bombinin, brevinin-1, esculentins and buforin II from amphibians, CAP18 from rabbits, LL37 from humans.[24,25].

Mechanisms of Action of Antimicrobial Peptides

The interaction of antimicrobial peptides with membranes

The traditional mode of action of AMPs is their ability to damage cell membranes. cell membrane disruption depends on various factors like peptide concentration, and potency of antimicrobial peptides. potent biomembrane permeabilization is often associated with AMP activity. The interaction and action of AMPs with their target cells depend largely on the cell surface as well as on the amino acid composition of these peptides. This idea is supported by the high conservation of positively charged amino acid residues among peptide sequences from various organisms [26]. In addition, the secondary structure adopted by the peptide is essential for the binding to negatively charged compounds in the target membrane, such as anionic phospholipids [27]. Depending on the peptide/lipid's ratios and affinity, these peptide molecules can be oriented perpendicularly, allowing their insertion into the lipid bilayer and the formation of transmembrane pores [28]. The mechanisms by which AMPs can traverse microbial membranes are not common to all peptides and seem to depend on the molecular properties of both, the peptide addressed and lipid membrane composition. Several membrane defects can be induced by AMPs, among them we can highlight the formation of pores, phase separation, and promotion of non-lamellar lipid structure or disruption of the membrane bilayer. Some models that may explain membrane disruption by AMPs have been proposed, such as barrel-stave, toroidal, and carpet models. [29].

Intracellular target

Inhibition Of Cell Wall Synthesis

The cell wall prevents cell lysis due to the high cytoplasmic osmotic pressure and allows the anchoring of membrane components and extracellular proteins, such as adhesins. In Gram-positive organisms, the main component of the cell wall is the peptidoglycan, present in multiple layers. In Gram-negative bacteria, an outer membrane, composed mainly of LPS, overlaps a thin layer of peptidoglycan. Since peptidoglycan is not found in eukaryotic cells, compounds that inhibit its synthesis are interesting targets for therapeutics. E.g - Class I bacteriocins, also known as lantibiotics [30].

Inhibition Of Nucleic Acid And Protein Synthesis

Some AMPs have the ability to naturally penetrate both the outer and inner membranes of microorganisms, aiming for intracellular biomolecules like proteins and nucleic acids. One class of mammalian proteins with such a broad range of antibacterial activity is cathelicidins. Another example is PR-39, which plays a role in a variety of biological functions such as anti-inflammatory, angiogenesis, wound healing, and chemoattraction [31,32]. This AMP rapidly enters the cell without harming the membrane and prevents bacterial DNA and protein synthesis [33,34,35].

Purification of Antimicrobial peptides

Purification of the antimicrobial peptide is a very complicated task. [22] some methods discussed below [table.1.] which give an idea about the purification of antimicrobial peptides.

TABLE 1: Various methods used for antimicrobial peptide purification from fermented broth along with which chemical is used.

Sr. No	Extraction method	Chemical used	Time duration	citation
1.	Acid precipitation	HCl	12-18 hrs	Sarwar et al. 2018,[36] Das et al 2008[37]
2.	Ammonium sulfate	Ammonium sulfate salt	24 hrs	Waghamare et al 2018 [38]
3.	Isoelectric point	HCL and NaOH	24 hrs	Pergande, M. R., & Cologna, S. M. (2017).[39]
4.	HP-20	HP-20 Dianion	2 hrs	Barale et.al 2022.[22]
5.	Solvent- Solvent extraction	I)Ethanol II)Methanol III)Chloroform	2-4 hrs	Dhanrajan et al 2016.[40] Barale et.al 2022[22]

Current applications of antimicrobial peptides

Antimicrobial Peptides as Potential therapeutic agents

AMPs could be an alternative to the conventional antibiotics to which microorganisms especially opportunistic pathogens developed resistance and thus it is essential to overcome the resistance problem. AMPs are fascinating targets as novel antibiotics because of their broad-spectrum activity, which includes drug-resistant bacteria. Since the isolation of magainins from frog skin in 1987 [41], there have been many attempts to develop antibiotics from natural AMPs. Although AMPs have considerable advantages for therapeutic applications, including broad-spectrum activity, rapid onset of activity, and relatively low possibility of resistance emergence, they also have some limitations for drug development. The natural AMPs are labile, depending on the surrounding environments, such as the presence of protease, pH change, and so on [42-44]. Other obstacles to the use of peptide antibiotics are the potential toxicity of AMPs for oral application and the high cost of peptide production [45].

To overcome those obstacles, many methods have been proposed. For instance, the introduction of unusual amino acids (mainly D-form amino acids) or modification of the terminal regions (acetylation or amidation) improved the stability of peptides by preserving them from proteolytic degradation [44,46]. Also, the use of efficient drug delivery systems, such as liposome encapsulation, can be effective for the improvement of the stability and reduction of potential toxicity [47,48].

Food preservation

The use of food preservatives might be hazardous to human health. Therefore, scientists looking for use of natural food preservatives. [49] Whereas many AMPs are resistant to acids, alkaline solutions, and high temperatures, peptides are rapidly degraded by proteases in the human body. AMPs have a good inhibitory impact on common bacteria and fungi in food. AMPs are a viable replacement for preservatives as a result. A bacteriocin called nisin is produced by L. lactis subspecies. Many people utilize lactic acid bacteria for food preservation. The US Food and Drug Administration (FDA) has classified nisin as generally recognized as safe (GRAS), and it is employed as a food preservative in other nations (50). However, the FDA has only presently approved nisin and poly lysine are additives (51).

Agriculture

The majority of bacteria and fungus cause Plant disease which is the main reason for the loss of the economy for agriculture. For example, Aspergillus flavus infection of corn and peanuts, citrus green mold caused by Penicillium digitatum, gray mold disease caused by Botrytis cinerea on strawberries, and Geotrichum citri-

aurantii infection of citrus fruit all cause great harm to the growth and post-harvest of agricultural products (49,52,53). Fengycin and Itirin-A which was isolated from from Bacillus subtilis Z-14 show potent activity against Gaeumannomyces graminis Var.strain tritici This offers both a theoretical basis and a practical framework for the application of lipopeptide antibiotics in the treatment and prevention of fungal diseases. (54)

CONCLUSION

Antimicrobial peptides are a major area of research around the world, but there are still a lot of critical challenges regarding the purification, design, and application of antimicrobial peptides that need to be addressed. The use of AMPs is restricted by a number of factors. Potential AMPs can be developed further by the interaction of various fields like biology, materials science, chemistry, bioinformatics, molecular informatics, and pharmacy. The bioinformatics approach will be helpful in understanding the mechanism of action of antimicrobial peptides. Instead of performing one-sided experimental research, how to better understand of the relationship between AMPs and different targets may help experimental designs to produce more solid systematic and scientific demonstrations. As a result, further animal studies are necessary rather than straightforward cell-level investigations to examine the impact of AMPs under complex physiologic conditions. To address the issue of the structure-function relationship, more research into the reported AMPs is necessary.

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