



Antimicrobial resistance and antimicrobial activity of plant-based antimicrobial peptides against bacteria

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Abstract

Antimicrobial peptides (AMPs) are a class of short, usually positively charged, polypeptides which are widely used to overcome the threat of the antimicrobial resistance. The potential of the AMPs is increasing as a new class of antibiotics. They have a broad range of activity against the gram positive bacteria, gram negative bacteria, and fungi. Different kinds of plant based AMPs like thionins, defensins, cyclotides, knottins, snakins and some others are discussed in this review with their potential as antimicrobials – such as regulating plant growth and development and treating many human diseases with a great efficacy. Use of AMPs in agriculture and disease treatment is gaining interest. This review also focuses on the mechanism of action of the AMPs and their potential applications in agriculture and human health.

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1. Introduction

Diverse and widespread bacteria are essential to preserve our surroundings (Sharma et al. 2018). Infections and diseases are caused by just a small percentage of the microbes on Earth (Salimi and Zare 2023). Public health is significantly affected by these bacterial diseases (Janik et al. 2020). Bacteria are categorized as Gram-positive or Gram-negative depending on the properties of their cell walls. Regarding clinical applications, gram-negative bacteria are distinguished from gram-positive organisms primarily by their propensity to create endotoxins, which have the potential to induce tissue damage, shock, and deadly outcomes (Xiao 2023). Every organ in the human body is vulnerable to bacterial infection. Most of the bacterial infections are specific but they can travel to other organs through blood circulation or tissue fluid and infect more than one organ (Di Franco et al. 2021). For example, *Neisseria meningitidis*, normally infecting the meninges of the central nervous system and causing meningitis, can also infect the lungs and cause pneumonia. It is not, however, a cause of skin

infection (Mikucki et al. 2022). People often carry *Staphylococcus aureus* on their skin or mucous membranes, which can lead to infections of the skin and soft tissues. However, the bacteria can also easily spread throughout the body through the bloodstream and cause infections in the abdomen, lungs, heart valves, and nearly any other part of the body (Linz et al. 2023). Both gram-positive and gram-negative bacteria cause infectious but gram-negative bacteria have significant public health concerns due to their high resistance to antibiotics (Xiao 2023). They are responsible for a range of diseases, including pneumonia, urinary tract infections, and sepsis (Wilson and Wilson 2021). In a study conducted in 2015-17, Gram-negative bacteria were isolated from 67.1% of patients in intensive care units (Islam 2023).

Two major groups of gram-negative bacteria cause trouble in hospitals which include *Escherichia coli* and *Pseudomonas*, while *pseudomonas* causes a wider range of infections (Oliveira and Reygaert 2023). Antibiotics are used to control these bacteria by killing them or inhibiting their growth. However incorrect doses and continuous use of antibiotics to

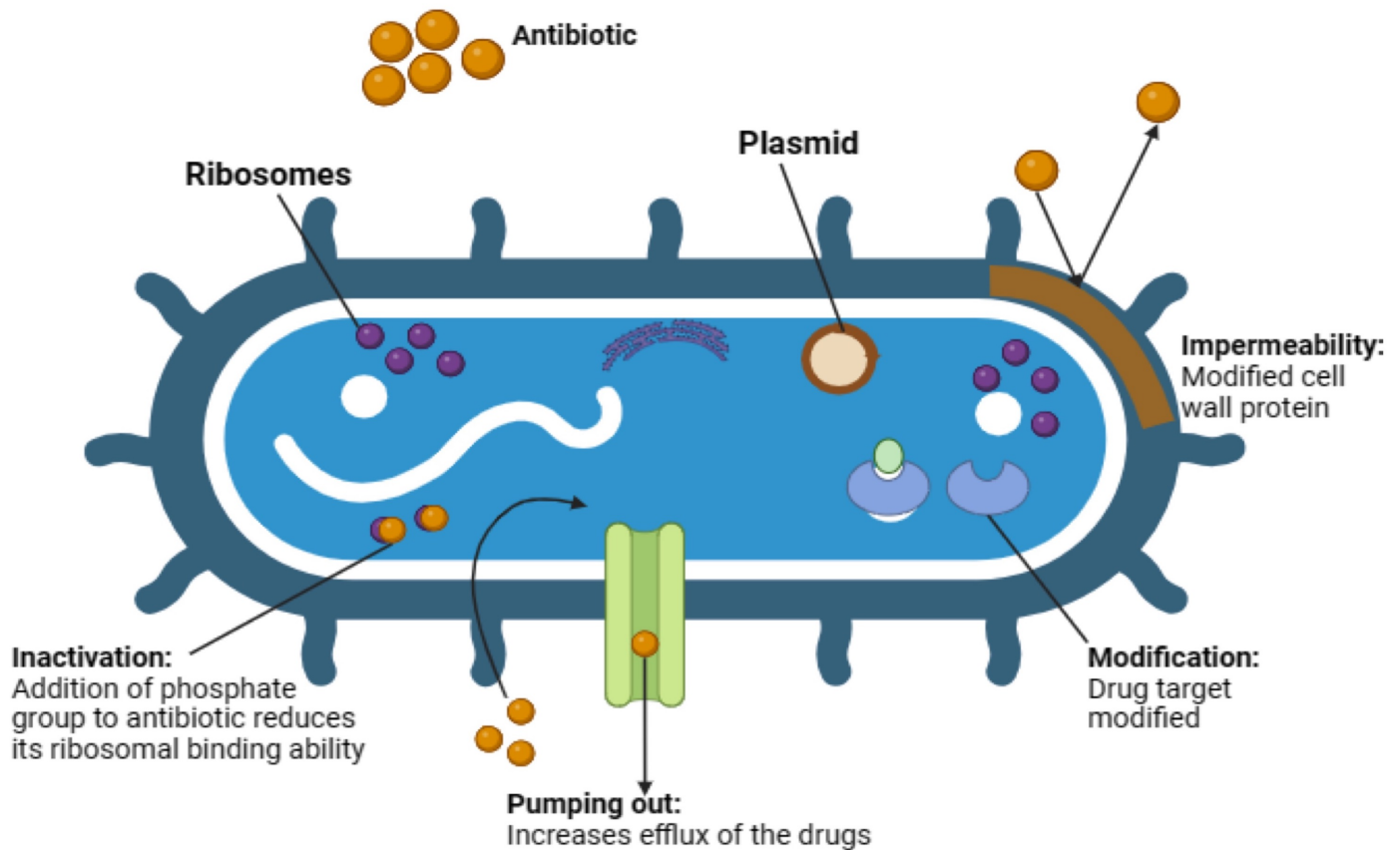


Fig. 1: Different resistance mechanisms against the antibiotics (Created in BioRender.com)

control bacteria have led to antimicrobial resistance (AMR) which is nowadays a global concern (Tang et al. 2023). It has emerged as a serious threat and has caused massive difficulty in the treatment of persistent diseases (Dadgostar 2019). It is a major concern and despite many efforts made to control the resistance it still emerges as a great global threat (Mattar et al. 2020). The bacteria can acquire AMR either due to modification of the already existing genes or mainly by acquiring genes that are resistant to various antibiotics. Apart from the acquisition of genes overuse and misuse of antibiotics are also rendering antibiotics ineffective against some bacteria (Bennani et al. 2020). By 2050, antimicrobial resistance (AMR) might overtake all other causes of mortality as the greatest hazard (Inoue 2019). A global "One Health Approach" joins different entities to reduce the impact of AMR. For improved control, the World Health Organization (WHO) has devised strategies to monitor and manage AMR (Tang et al. 2023). Antibiotic resistance poses a significant risk to human health. It makes treating infections more difficult, particularly for those with weakened immune systems or long-term medical conditions. Due to their limited availability and severe side effects, harsher antibiotics are used by doctors as a result (Dadgostar 2019). Bacteria have various mechanisms to spread and develop resistance. Plasmids, transposons and integrons are mobile genetic elements that allow bacteria to share and acquire resistance genes. Other mechanisms include toxin-antitoxin systems and swarming motility. Biofilms also play a role in protecting bacteria from antibiotics (Palma et al. 2020; Begum and Mir 2023). Antibiotic

overuse in agriculture and livestock is a major contributor to human antibiotic resistance. In the US alone, 80% of antibiotics are sold for livestock and are often used for growth promotion rather than just treating sick animals. The overuse of these medications puts human health at risk by fostering the growth and spread of resistant microorganisms (Dadgostar 2019). Some innate mechanisms in bacteria allow them to escape the effect of the antibiotics, these include impenetrable cell walls, lack of target molecules, and enzymes that break down antibiotics. These intrinsic resistances are essential for bacterial survival and are not caused by antibiotic misuse (Palma et al. 2020). There are five main antibiotic classes with different ways of attacking bacteria. They can block protein synthesis (tetracyclines, aminoglycosides), disrupt DNA replication (fluoroquinolones), mess with cell wall building (beta-lactams, glycopeptides), interfere with folate production (sulfonamides), or damage the cell membrane (lipopeptides) (Vikesland et al. 2019).

Various methods are being adopted to overcome AMR which include the development of combination therapies, bacteriophage therapy, antimicrobial adjuvants therapy, and new kinds of antimicrobial agents such as antimicrobial peptides (Moo et al. 2020). Nanoparticles (NPs) have gained attention in the recent years due to their various benefits including increased durability, conductivity, enhanced biocompatibility, and low toxicity. Examples include Zinc oxide NPs, Gold NPs, Silver NPs, Silica NPs, Iron oxide NPs, Graphene oxide NPs, and Selenium NPs (Kausar et al. 2023).

Despite of the advantages various demerits are seen such as neuropsychiatric problems due to ZnO NPs, colitis like symptoms associated with use of Ag NPs, higher doses of Cu NPs causing liver necrosis, and Au NPs disrupting the normal gut flora; this leads to utilization of some other strategies (Khan et al. 2023). Antimicrobial peptides are used significantly instead of antibiotics because they act on the bacterial membrane and target general areas instead of specific ones (Wang et al. 2023).

2. Antimicrobial peptides (AMPs)

AMR, which poses a major risk to human health, has been worrisome for developing nations in particular. AMPs derived from natural sources present a possible alternative to the critically required new medications (Sinha and Shukla 2019). AMPs are excellent contenders to replace existing antibiotics in the future (Tiwari et al. 2023) because they are effective against a broader spectrum of microorganisms and can circumvent drug resistance in bacteria. Therefore, they present a viable substitute for upcoming antibiotics (Shanmugaraj et al. 2021). These artificial or natural compounds having a low molecular weight have a variety of antibacterial effects (Fry 2018). Even though research has advanced our understanding of AMPs, more work needs to be done before these compounds are routinely employed as therapeutics (Tiwari et al. 2023). These short and positively charged proteins are determined by genes and possess certain structures that aid in the destruction of bacteria (Lei et al. 2019). AMPs can target internal structures or damage cell wall and membrane to kill bacteria in a variety of ways. Although this reduces the likelihood of broad resistance, some AMPs may still face resistance by bacteria through mutations in particular protein targets which can be fixed by changing the structure of the AMPs (Bechinger and Gorr 2017). Based on their structural characteristics, AMPs are categorized into four main groups: extended AMPs, β -sheet, amphipathic α -helical, and β -hairpin or loops. Amphipathic α -helical AMPs include dermaseptin, pardaxin, and the well-researched LL-37 AMP (Mhlongo et al. 2023). Disulfide bond formation stabilizes β -sheet AMPs. This class covers defensins with α , β , and θ positions. Loops, also known as β -hairpin AMPs, are extremely stable peptides with a hairpin structure linked by a type II β -turn (Deplazes et al. 2020). The disulfide bonds that form between the β -strands are what give them their stability. Among the AMPs in this class are tachyplesins, dodecapeptides, and bentenecins (Lipkin and Lazaridis 2015). Last but not least, peptides with a high histidine, arginine, or glycine content but no secondary structure are known as extended AMPs. Among others, indolicidin, histatins, and drosogenin are examples (Decker et al. 2022).

The need to create novel antimicrobial drugs developed from the advent of multi-drug resistant super-bacteria. However, eukaryotic peptides work on bacterial membranes and other broad targets, like DNA, unlike most antibiotics that are target specific proteins (Lopez-Cano et al. 2023). As a result, it is unlikely that microbial resistance will arise. The term "host defense peptides" is another common word for AMPs in higher eukaryotic organisms, and it emphasizes their additional immunomodulatory activities (Mhlongo et al. 2023). AMPs are

not only effective against bacteria but also have anti-tumor and wound-healing qualities. They have some anticancer abilities too (Datta et al. 2023). Researchers are trying to figure out ways to enhance AMPs so they work better and can be used in clinical settings (Zhang et al. 2021). AMPs have many advantages over antibiotics which include increased efficacy, high specificity, decreased drug interaction, low toxicity, biological diversity, and direct attacking properties (Boparai and Sharma 2020). Their stability, water solubility, and lower cost for production and use make them the best alternative to antibiotics against which various organisms have become resistant (Lei et al. 2019). Based on amino acid sequence, net charge, protein structure, and their activity the AMPs have been classified into various groups (Zhang et al. 2021) including mammalian AMPs (Cathelicidins and defensins), amphipathic AMPs, insect-derived AMPs, antibacterial peptides, antiviral peptides, antifungal peptides, and plant-based AMPs. Plant-based AMPs have been used over the years and they are not very expensive and play much role in boosting the economy of the agriculture sector.

3. Plant-based antimicrobial peptides (PAMPs)

AMPs produced by plants are called PAMPs which have the potential to ward off bacteria, fungi, and insects. PAMPs vary from other antimicrobial peptides due to their distinct structure and higher cysteine residue count (Bakare et al. 2022). Many plant components, like phenolics and terpenes, have antimicrobial properties. These work in various ways, such as breaking down bacterial cell membranes or causing them to leak contents. The specific structure of the plant compound can significantly affect its antibacterial capacity. This suggests that there is a potential to develop new antimicrobials from plant by-products based on their natural chemical properties (Tiwari et al. 2023). PAMPs are positively charged molecules with different disulfide bonds. These elements make them steady and hard to arrange because of their different design and functions (Li et al. 2021). Plant AMPs are classified into various classes like thionins, defensin, hevein-like peptides, knottins, stable-like peptides, lipid transfer proteins, snakins, and cyclotides (Lima et al. 2022). PAMPs are found throughout various plant parts like stems, roots, flowers, and leaves and can kill a wide range of microbes. This makes them interesting as they could help protect crops from disease and they have potential as new antibiotics to fight human infections (Tang et al. 2018). Plant AMPs are characterized by a variety of folds and forms like alpha helices (α) or beta sheets (β) and some have a combination of both ($\alpha\beta$). Disulfide bridges stabilize these folds, increasing the resistance to heat, chemicals, and enzyme degradation (Santos-Silva et al. 2020).

3.1 Thionins

Thionins are a family of plant AMPs that are characterized by their small molecular size, typically composed of 45-48 amino acid residues, and their cysteine-rich nature, containing 6 or 8 cysteine residues and 3 or 4 disulfide bonds (Tam et al. 2015). They are found in various plant species and are expressed in different tissues, including seeds, leaves, and roots. They can be induced by infection with microbes and are related to the

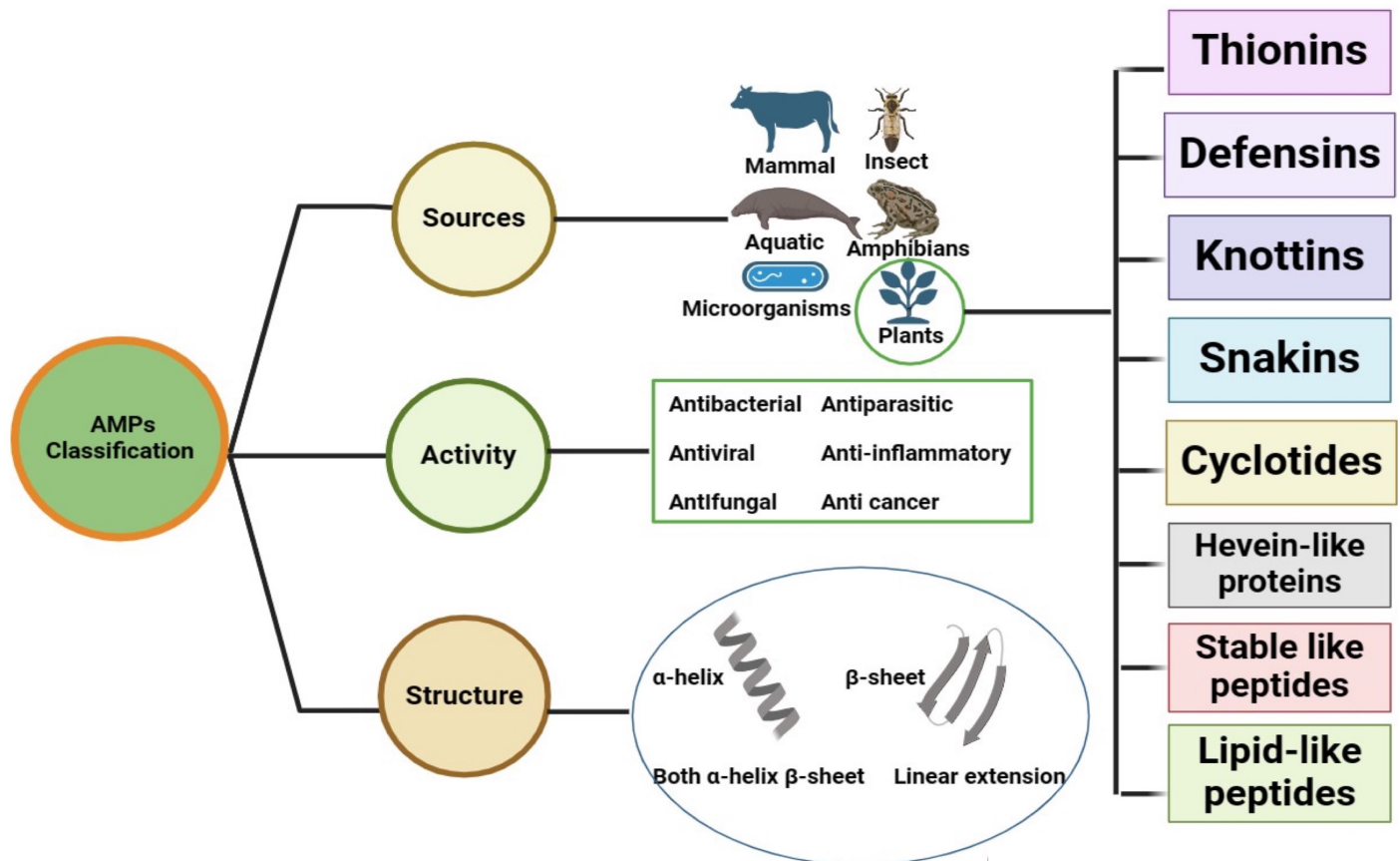


Fig. 2: Classification of the AMPs (Created in BioRender.com)

release of the hormone methyl jasmonate upon plant wounding or microorganism invasion (Li et al. 2021). Thionins exhibit an amphipathic nature and possess a ring structure topology due to an end-to-end disulfide bond, making them categorized as cyclic peptides (Tam et al. 2015). Thionins have been shown to have antimicrobial properties and potential therapeutic applications, including their inhibitory effects on breast cancer cells and their ability to reduce cholesterol levels and reverse metabolic disorders in animal models (Li et al. 2021).

3.2 Defensins

Defensins are a well-known family of plant AMPs that play a crucial role in plant defense against pathogens, including bacteria, fungi, and viruses. They are widely distributed in the plant kingdom and are found in various plant species, including *Arabidopsis thaliana*, wheat, barley, and *Medicago truncatula* (Olga et al. 2020). Plant defensins are small cationic peptides with 45-54 amino acids and contain four to five disulfide bonds, which contribute to their stability and antimicrobial activity. These AMPs exhibit broad-spectrum antimicrobial activity, inhibiting the growth of bacteria, fungi, and viruses by disrupting microbial cell membranes (Sathoff et al. 2019). Plant defensins perform a variety of biological functions in addition to their antibacterial capabilities. These functions include modulating abiotic stress, influencing self-incompatibility, suppressing the action of α -amylase and trypsin, and serving as epigenetic factors (Ishaq et al. 2019). Plant defensins have potential therapeutic applications,

including their use as antimicrobial agents, anti-cancer agents, and in the development of transgenic plants with enhanced resistance to pathogens (Lima et al. 2022).

3.3 Hevein-like proteins

Hevein-like proteins are a family of PAMPs that exhibit antifungal activity by binding to chitin, a component of fungal cell walls (Odintsova et al. 2020). These peptides belong to the type-1 chitin-binding domain superfamily and are characterized by the presence of a chitin-binding domain (CBD). Hevein-like peptides, such as HEV-CANN and HEV-PHYT00231, have been isolated from bell pepper leaves and *Hevea brasiliensis*, respectively, and have shown antimicrobial activity against fungi and bacteria (Games et al. 2016). The binding of CBD to chitin reduces or stops the elongation of the fungal cell wall, contributing to its anti-fungal activity. Hevein-like AMPs have potential applications in plant defense, biotechnology, and agriculture, including the development of transgenic plants with enhanced resistance to pathogens (Azmi et al. 2021).

3.4 Knottins

Knottins are a class of peptides characterized by a unique structural motif known as the cysteine knot, which consists of a knotted arrangement of disulfide bonds. They are found in various sources, including plants, and have been identified in phytomedicines used in traditional medicine (Attah et al. 2022). Among plant AMPs, they are the smallest in size and perform a

variety of biological operations, such as fostering disease resistance, accelerating root development, and serving as signaling molecules (Lima et al. 2022). Synthetic biology techniques, such as site-directed mutagenesis, can be used to address the limitations of knottin plant AMPs, such as hemolytic potential and target non-selectivity. Knottin plant AMPs have potential applications as peptide therapeutics, nutraceuticals, and in biotechnology due to their stability and selectivity for biomolecular targets and bioengineering applications (Li et al. 2021).

3.5 Snakins

Snakins are a class of plant antimicrobial peptides (AMPs) that have been identified in various plant species and for the first time in potatoes (*Solanum tuberosum*) (Santos-Silva et al. 2020). Snakins have antibacterial action against many different types of pathogens, including viruses, fungi, and bacteria. These peptides are characterized by a conserved structural motif, consisting of a signal peptide, a pro-peptide region, and a mature peptide region (Li et al. 2021). They control the bacteria by causing aggregation of gram-positive and gram-negative bacteria. Their mechanism of action is not properly known but unlike other peptides, they do not interact with the lipid membranes (Yili et al. 2014). Snakins can potentially inhibit bacteria (*Micrococcus luteus*, *Staphylococcus cohnii*), as well as fungi (*Pichia pastoris*, *Fusarium solani*). They are particularly effective against Gram-negative bacteria. They can also help prevent the spread of pathogens in damaged plants. Because of these properties, snakins are being studied for their potential use in plant disease control (Lima et al. 2022).

3.6 Lipid transfer proteins (LTPs)

Tiny proteins – LTPs have a stable structure due to multiple disulphide bonds. They are available in two varieties (LTP1 and LTP2), each with a hydrophobic cavity but slightly in different forms. LTPs can interact with lipids due to the cavities into them which is probably crucial to their activity (Maximiano and Franco 2021). Plant LTPs have great antimicrobial activity against various bacteria and fungi (Finkina et al. 2016). They play their role in various processes like development, stress response, and fighting pathogens. LTPs can bind and move lipids around within the plant, and may even help break down pathogen membranes. The exact way they kill microbes is still being studied, but it likely involves disrupting their cell membranes (Maximiano and Franco 2021). They likely target the cell membrane of the pathogen through electrostatic interactions, causing it to break down and leak. They have antiviral and antiproliferative properties; and may cause inhibition of some enzymes (Finkina et al. 2016).

3.7 Cyclotides

Plant compounds known as cyclotides have a stable structure because of three disulfide bridges made up of six cysteine residues. Six loops, each with a different size, allow for a greater degree of variation in the amino acid sequence than the others (Weidmann and Craik 2016). They are present in various plant families like Rubiaceae, Violaceae, Apocynaceae, Cucurbitaceae, and Poaceae. Their unique structure makes

them resistant to heat, chemicals and breakdown by enzymes (Matkawala et al. 2019). They have been identified in multiple families of flowering plants and are present in a variety of plant tissues. These compounds have activity against bacteria, viruses, cancers, and insects which is why researchers are looking at using them as possible medications. They function by rupturing the membranes of viruses and bacteria (Lima et al. 2022).

4. Mechanism of action of AMPs

AMPs have a unique mechanism of action on microorganisms. They interact with the bacterial cell membrane, disrupting its construction and leading to cell death. This interaction is facilitated by electrostatic forces between the cationic AMPs and the negatively charged bacterial surface (Li et al. 2021). AMPs can impair membrane integrity, inhibit protein, DNA, and RNA synthesis, and interact with specific intracellular targets (Zhang et al. 2021). The AMPs can form pores in bacterial membranes resulting in channels which leak cell contents and there are two main pore models (barrel-stave and toroidal) describing this mechanism of AMPs' action. Secondly, in the carpet model and detergent-like model, AMPs disrupt the membrane structure without forming pores, causing the membrane to collapse. They have some intracellular effects that enable them to enter the cell and interfere with internal processes like protein/DNA synthesis, affecting the cell cycle (Luo and Song 2021). AMPs can punch holes in bacterial membranes using a method called the toroidal pore model. This approach falls between carpet-like disruption and well-defined pores. In this mechanism AMPs first latch onto the membrane and transform their shape. This triggers the membrane to bend inwards. Finally, the AMPs themselves insert into the membrane, creating a pore with a ring-like (toroidal) shape (Li et al. 2021). Additionally, AMPs play a role in the immune system by recruiting and activating immune cells to fight the infection. They can also help control inflammation, which is a damaging side effect of the immune response (Kumar et al. 2018). They can also prevent infections by hindering the formation of biofilms, the sticky communities bacteria form on surfaces. AMPs achieve this by interfering with bacterial communication and limiting their ability to build the structures needed for biofilms (Yasir et al. 2018). Even against established biofilms, AMPs can disrupt the bacterial membranes, effectively dissolving these harmful structures. This multi-pronged approach makes AMPs highly promising candidates for future antibiotics (Talapko et al. 2022). Bacteria inside and outside of cells are targets for AMPs. They are comparable to peptides that can penetrate cells, known as cell-penetrating peptides (CPPs). AMPs are primarily focused on combating bacterial infections, whereas CPPs are usually employed for drug delivery in mammalian cells (Luo and Song 2021).

5. Plant AMPs and human diseases

The pharmaceutical sector is the most significant application area for additive manufacturing proteins. Since antibiotics are capable of curing a wide range of infectious and deadly illnesses, they have always been essential for treating

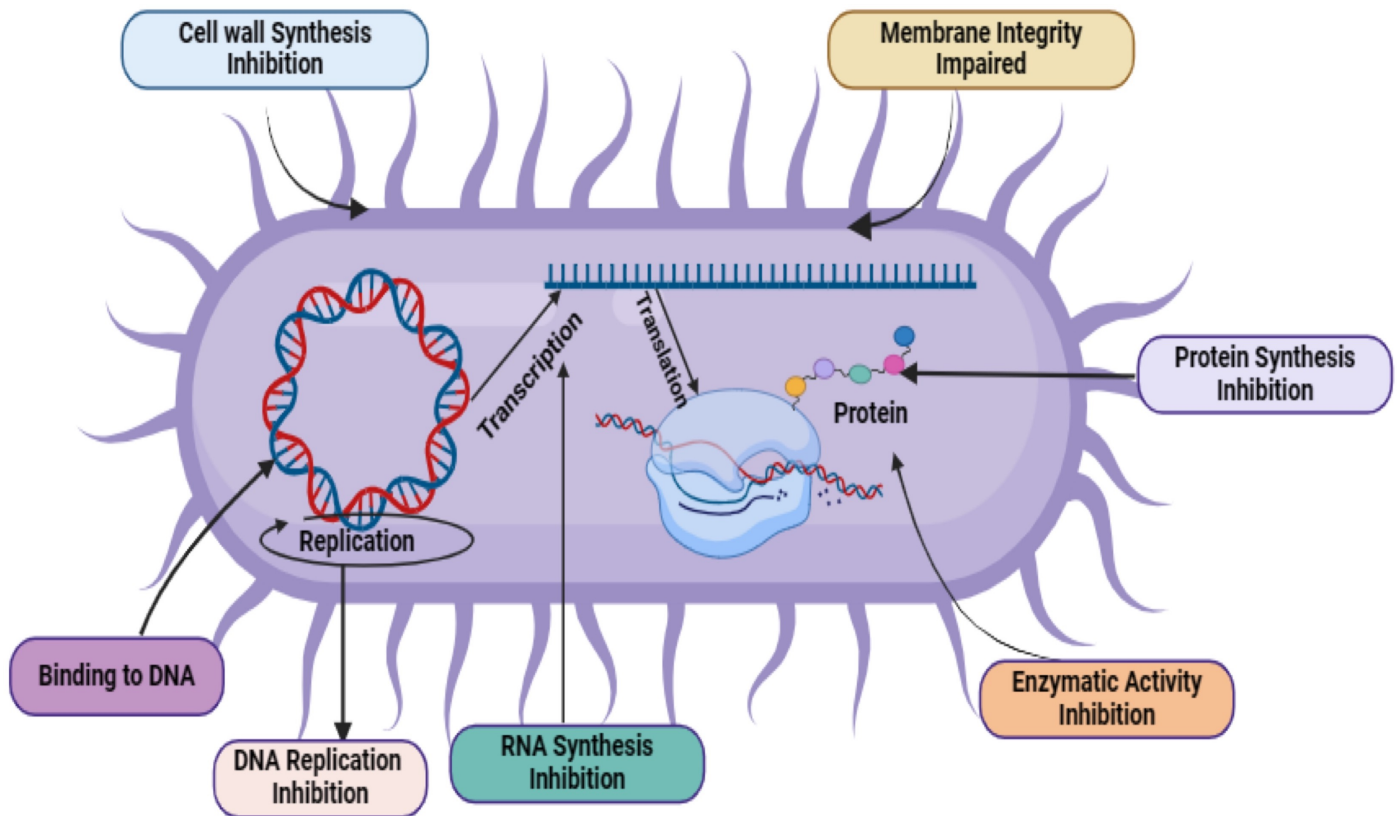


Fig. 3: Antimicrobial mechanism of action of AMPs (Created in BioRender.com)

pathogenic bacterial infections in humans. However, as time goes on, the pathogens become more resistant to them (French 2005). The extensive use of antibiotics in both humans and animals is a major contributing factor to the prevalence of antibiotic resistance; as was previously mentioned in the sections above, overuse causes spontaneous mutations in antibiotic targets and the exchange of plasmids encoding resistance genes (Shoaib et al. 2023). In response to the antimicrobial resistance the alternatives are being used all over the world (Breithaupt 1999). Accordingly, AMPs are gaining interest in the medical field. AMPs can work by direct interaction with the biofilm of the pathogenic bacteria increasing the antibiotic permeability in biofilm, which can increase its synergistic use with the antibiotics (Mhlongo et al. 2023). Meanwhile, the main advantage of the AMPs lies in their universal mechanism of action which is different and much advantageous than the antibiotics (Cassone and Otvos 2010). The mammalian cell surface contains amphoteric phospholipids, sphingomyelin, and cholesterol whereas the bacterial cell surface contains lipopolysaccharides and teichoic acids which impart a negative charge to the cell (Caudill et al. 2020). Generally, AMPs that are positively charged can easily interact with the negatively charged biofilms of bacteria (Hilchie et al. 2013). This suggests that the AMPs have reduced negative effect on the human cells but can specifically target the cell membrane of the pathogens. In support of this, the Ep-AMP1 from *Echinopsis pachanoi* was reported to have low human-cell cytotoxicity compared to the human antimicrobial

peptide LL-37 (Li et al. 2021).

A number of studies have confirmed that AMPs can act as multifunctional effectors of the innate immune system and hence can regulate the immune functions in addition to their direct antimicrobial function (Seyfi et al. 2020). It is evident that AMPs can influence the immune responses to a variety of diseases by influencing the signaling in the body which also highlights their potential to treat fatal diseases (Bruno et al. 2022). For example, AMPs have the ability to regulate multiple signaling pathways, including inhibiting the synthesis of signaling molecules, nitric oxide (NO) and reactive oxygen species (ROS), altering wound and vascular healing and modification of nitrogen-activated kinase (MAPK) (Hurley et al. 2006; Shahrour et al. 2019). According to recent research, peptides found in chickpeas considerably reduce the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) and fatty acid synthase (FAS) (Andrade-Pavon et al. 2014). Chickpea peptides have the ability to decrease serum levels of triglycerides (TG), total cholesterol (TC), and low density lipoprotein cholesterol (LDL-C). Additionally, chickpea peptides were found to increase serum levels of high density lipoprotein cholesterol (HDL-C) in rats that were fed a high-fat diet. Furthermore, these peptides have been shown to effectively treat liver and blood metabolic disorders in these obese rats (Shi et al. 2019). The root tissues of *Pombalia calceolaria* yield cyclotide AMPs, such as Poca A and Poca B, which have potent inhibitory effects on MDA-MB-231 breast cells (Pinto et al. 2018). Furthermore, potential for tumor

treatment and immune stimulation has been shown by peptide fractions of agglutinin and abrin from *Abrus* spp (Shah et al. 2023), but the plant itself shows some toxic effects on mammalian cells like apoptosis of the cells (Banger et al. 2019). This indicates that both medicinal and even toxic plants are able to produce AMPs and help fight against various pathogens (Barashkova and Rogozhin 2020).

6. Conclusions

Among plant AMPs, a notable characteristic is that most of them are cysteine rich peptide families and every family has a distinctive theme. Through sequence diversity of non-cysteine residues encased in an identical scaffold within a specific family, these cysteinyl motifs allow plant AMPs to organize into distinct groups with conserved structural folds, allowing them to play diverse functions. The extended family of knottins and, to a limited extent, the defensins exhibit this evolvable behavior. Knottins are known to have a variety of functions, including those of an agonist or antagonist to hormones, insecticidal, antibacterial, and enzyme inhibitory. In certain respects, the capacity of plant AMPs to withstand hypervariable sequences through the use of a conserved scaffold mimic is comparable to the capacity of immunoglobulins to identify a variety of targets by altering the sequence of complementary binding domains.

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