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Review Article

Antimicrobial Peptides from Plants: Structural Diversity, Modes of Action, and Antimicrobial Potential

Aroosa Maqsood*[1], Masooma[1,2]

[1]Atta-ur-Rahman School of Applied Biosciences, National University of Sciences & Technology, Islamabad, Pakistan
[2]Department of Biotechnology, Sardar Bahadur Khan Women's University, Quetta, Pakistan
***Correspondence:** aroosamaqsood@yahoo.com

Abstract

Antimicrobial resistance (AMR) has emerged as one of the most prominent global public health crises of the 21st century. As traditional antibiotics face declining efficacy against multidrug-resistant (MDR) pathogens, plant antimicrobial peptides (AMPs) have gained significant attention as potent, multi-targeted alternatives. This review provides a comprehensive analysis of the major plant AMP families, including thionins, defensins, lipid transfer proteins (LTPs), hevein-like peptides, snakins, and cyclotides. These peptides are defined by their small size, cationic nature, and cysteine-rich scaffolds stabilized by complex disulfide bond networks. The structure–activity relationships (SARs) that govern their function, specifically the roles of cationicity, amphipathicity, and glycosylation in pathogen discrimination. The review also provides insights of the multifaceted mechanisms of action employed by plant AMPs, ranging from physical membrane disruption to the sequestration of cell wall precursors and the interference with intracellular metabolic processes, including transcription and translation. The review also discusses the current challenges in clinical translation of use of AMPs, such as metabolic instability and host toxicity, and highlights the role of emerging technologies such as AI-driven design, nanoparticle-based delivery systems, and combinatorial therapies in accelerating the development of plant-inspired AMPs as next-generation tools for sustainable infectious disease management.

Keywords: Antimicrobial resistance, Antimicrobial peptides, Thionins, Defensins, Cyclotides

1. Introduction

Antimicrobial resistance (AMR) has emerged as one of the most challenging global public health threats in the 21st century. AMR manifests when microorganisms such as bacteria, fungi, parasites, and viruses, undergo evolutionary processes leading to resistance against antimicrobial medications, such as antibiotics. AMR is largely attributed to the consequences of antibiotic overuse or irresponsible utilization across diverse contexts, predominantly in clinical treatment, agricultural practices, animal healthcare, and the food system. Labelled as a silent pandemic, AMR requires immediate and effective intervention (Ahmed et al. 2024). It has been projected that by 2050 AMR could potentially surpass all other causes of mortality worldwide. Globally, estimates show that mortality linked to AMR surpassed 1.2 million in 2019, with a projected increase to approximately 10 million deaths annually by 2050 if adequate measures are not taken. While mortality has decreased among children younger than five, it has increased by over 80% for adults 70 years and older, highlighting a shifting but persistent global,

burden (Naghavi et al. 2024). This crisis has shifted the focus and interest in investigating natural compounds as potential substitutes for synthetic antibiotics. While alternative therapies such as human monoclonal antibodies, antibody-antibiotic conjugates, bacteriophages, and CRISPR-based gene therapies show promise, they face significant challenges regarding specificity, cost, and delivery (Ho et al. 2025). Consequently, there is an urgent need to develop a different drug to treat and control multidrug-resistant (MDR) infections. Plants, having existed for more than 400 million years, have developed unique characteristics to protect themselves from infections. Unlike animals, plants lack a mobile, adaptive immune system involving antibodies. Instead, they rely entirely on the innate immune system where the production of secondary metabolites and antimicrobial peptides (AMPs) serves as the primary line of defense (Abdallah et al. 2023). The field of plant-derived antimicrobial substances dates to centuries where medicinal values have been known to traditional practitioners for ages. Scientific discovery of specific plant AMPs began in between the 1940s and 1970s, notably with the isolation of thionins. These peptides are now recognized as essential components of plant innate immunity, particularly in defense against biotic stressors (Alzain et al. 2025). Plant AMPs are typically small molecules ranging from 2 to 6 kDa or usually fewer than 50 amino acids, often cationic (positively charged), and amphiphilic. A defining structural feature is their cysteine-rich nature, which allows for the formation of multiple intramolecular disulfide bonds. These bonds provide exceptional stability against proteolysis and environmental extremes, a necessary trait for peptides extracted from diverse vegetative and generative plant parts (Angelini 2024).

This review focuses on the structural diversity, mechanisms, and therapeutic potential of major plant AMP families. Given the vast molecular diversity, where each species within a specific taxon displays distinct peptides, this review is selective rather than exhaustive. The review explores how these peptides target membrane integrity and cell wall biosynthesis and discusses their potential for clinical translation as novel pharmaceuticals or biological agents for plant protection.

2. Major Families of Plant Antimicrobial Peptides

According to the Antimicrobial Peptide Database (APD), AMPs are broadly classified into four families based on their three-dimensional structure: alpha (α), beta (β), alpha-beta ($\alpha\beta$), and non-alpha-beta (non$\alpha\beta$) (Wang 2010). The α family consists of helical structures; the β family contains at least one β sheet; the $\alpha\beta$ family combines both elements; and the non$\alpha\beta$ family contains neither defined helices nor sheets (Wang 2010). Plant AMPs exhibit high genetic variability and structural complexity, often possessing positive charges fundamental for interacting with anionic pathogen membrane lipids. Their composition facilitates protection through membrane rupture, pore formation, and microbial processes (Sinha and Shukla 2019). The most studied families include thionins, defensins, lipid-transfer proteins (LTPs), hevein-like proteins, snakins, and cyclotides **(Table 1)**.

2.1 Thionins

Thionins are the prototypic plant AMP family, originally recognized as plant toxins due to their potent activity against bacteria, fungi, insect larvae, and animal cells (de Oliveira et al. 2024). These short peptides (approximately 5 kDa) typically consist of 45 to 48 amino acid residues and are characterized as amphipathic molecules with a distinct structural fold. While historically grouped together, structural analysis has shown that $\alpha\beta$ thionins are distinct from γ thionins, with the latter now classified as plant defensins. Thionins are further categorized based on their cysteine content specifically as 8C-thionins (eight cysteines) or 6C-thionins (six cysteines) and are

divided into five types (I–V) based on their source, charge, and disulfide bridge patterns (Odintsova et al. 2018). For example, Type I thionins like the wheat-derived purothionin are highly basic and found in seeds, whereas Type IV thionins are neutral (Colilla et al. 1990).

The biological utility of thionins is extensive, ranging from traditional antimicrobial defense to complex cellular interactions. Since the discovery of purothionin in 1942, various members of this family have demonstrated remarkable efficacy. CaThi from *Capsicum annuum* shows high antifungal activity against *Fusarium solani* by inducing membrane permeability and apoptosis, often working synergistically with conventional drugs like fluconazole (Taveira et al. 2017). Other thionins, such as those from mistletoe e.g., ligatoxin B and foratoxins, exhibit cytotoxic effects on human tumor cell lines and act as DNA-binding proteins (Höng et al. 2021; Li et al. 2002). Furthermore, transgenic applications have shown that overexpressing thionin genes in plants like tobacco and *Arabidopsis* confers robust resistance against pathogenic fungi and insects (Charity et al. 2005). Peptides from black cumin seeds (*Nigella sativa*) have demonstrated potent inhibitory effects against filamentous fungi such as *Aspergillus ochraceus* and *Aspergillus fumigatus*, as well as Gram-positive bacteria like *Bacillus subtilis* and *Staphylococcus aureus* (Kul'Ko et al. 2016).

The primary mode of action for thionins involves direct interaction with the cell membrane. As hydrophobic and cationic peptides, they target negatively charged phospholipids to disrupt membrane fluidity, leading to lysis. This structure-function relationship is highly specific; conserved residues like Lys1 and Tyr13 are critical for toxicity, while Arg10 ensures folding stability (Tam et al. 2015). Recent transcriptomic analyses continue to expand this family, having identified over 130 new thionin sequences. Some of these new findings suggest the existence of a class with an uneven number of cysteines, indicating that the structural and functional diversity of thionins is even more vast than previously understood (Höng et al. 2021).

2.2 Plant defensins

Plant defensins are the most abundant and well-studied superfamily of plant AMPs. These typically range from 45 to 54 amino acid residues and are characterized by a highly conserved structural scaffold known as the cysteine-stabilized α-helix β-sheet motif. This fold consists of three antiparallel β-sheets and one α-helix, stabilized by four to five intramolecular disulfide bonds that form a robust "cystine knot." This configuration renders them exceptionally stable against proteolysis and environmental extremes of pH and temperature (Khan et al. 2019; Odintsova et al. 2020). Initially identified as γ-thionins due to their isolation alongside purothionins in cereal grains, they were reclassified in 1995 as defensins based on structural homology with mammalian and insect counterparts. A critical functional region within this structure is the γ-core motif, a hairpin loop between the β2 and β3 strands that serves as a primary determinant for antimicrobial activity (Tam et al. 2015).

Found across diverse tissues including seeds, flowers, and fruits, plant defensins are classified into two groups based on their precursor structure. Class I peptides, which provide a first line of extracellular defense, and Class II peptides, which possess a C-terminal prodomain associated with vacuolar sorting and host protection. Their biological functions are remarkably diverse; beyond their potent activity against fungi and bacteria, they inhibit α-amylase and trypsin activity, mediate abiotic stress, and even exhibit anticancer properties (Aguieiras et al. 2021; Lay et al. 2014). For instance, PaDef from the Mexican avocado (*Persea americana*) has shown cytotoxic potential against chronic myeloid leukemia and breast cancer cell lines without damaging normal membranes (Flores-Alvarez et al. 2018). In clinical contexts, defensins like Dm-AMP1 from *Dahlia merckii* and VuDef2 from *Vigna unguiculata* have shown potent inhibition of *Bacillus subtilis* and

Staphylococcus aureus at very low concentrations (Thevissen et al. 2003; Dos Santos et al. 2010).

The antimicrobial mechanisms of plant defensins are complex and often involve specific receptor interactions rather than non-specific membrane insertion. While many defensins induce membrane permeability and the production of reactive oxygen species (ROS), others are internalized to target intracellular processes (Tam et al. 2015). For example, NaD1 from tobacco flowers enters the cytoplasm to trigger oxidative stress, while MtDef5 from *Medicago truncatula* binds to DNA to inhibit replication and gene expression. Some, like the radish defensin Rs-AFP2, interact specifically with fungal glycosylceramides to induce apoptosis. This versatility is underscored by numerous studies where recombinant defensins from alfalfa, adzuki bean, and fenugreek have been successfully expressed in transgenic tomato, rice, and cotton, conferring significant resistance against economically devastating pathogens like *Fusarium oxysporum* and *Magnaporthe grisea* (Sathoff et al. 2019; de Oliveira et al. 2024).

2.3 Lipid transfer proteins (LTPs)

Lipid transfer proteins (LTPs) were first isolated from potato tubers. These represent a unique class of cationic AMPs known for their relatively larger size (approximately 70 to 100 amino acid residues) compared to other families. These AMPs are characterized by a compact, barrel-like structural fold stabilized by eight conserved cysteine residues forming four intramolecular disulfide bonds. This architecture creates a central hydrophobic cavity or "cleft" that allows LTPs to bind and transport various lipids, including fatty acids, phospholipids, and acyl-coenzyme A (Douliez et al. 2001; Wong et al. 2017; Edqvist et al. 2018). LTPs are divided into two major subfamilies based on their molecular weight: LTP1 (approximately 9 kDa) and LTP2 (approximately 7 kDa), however modern classification groups them into five types (LTP1, LTP2, c, d, and g) depending upon their sequence identity and cysteine spacing. Their compact folding provides stability against heat, denaturing agents, and proteolysis by enzymes like pepsin and trypsin (Edqvist et al. 2018).

The antimicrobial potential of LTPs is extensively documented across numerous plant species. LTPs from rice leaves demonstrate potent activity against the rice blast fungus *Pyricularia oryzae* and the bacterium *Xanthomonas oryzae* (Ge et al. 2003). Similarly, LTPs isolated from onion seeds (Ace-AMP1) and radish exhibit high broad-spectrum activity, while those from mung bean seeds (*Phaseolus mungo*) confer resistance against *Staphylococcus aureus* and *Fusarium oxysporum* (Tassin et al. 1998; Wang et al. 2004). Studies on LTPs from coffee (*Coffea canephora*) and motherwort (*Leonurus japonicus*) confirm that this membrane-disrupting activity is effective against a wide range of filamentous fungi, yeasts like *Candida albicans*, and Gram-positive bacteria such as *Bacillus subtilis* (Zottich et al. 2011). LTPs also exhibit antiviral properties. LTPs from the daffodil (*Narcissus tazetta*) significantly inhibit plaque formation of Respiratory Syncytial Virus (RSV) and the H1N1 influenza virus (Ooi et al. 2008).

The mechanism of action for LTPs primarily involves the permeabilization of pathogen membranes. Evidence suggests that they interact directly with specific membrane components to induce pore formation and cellular imbalance. This process facilitates the extraction of lipids from the pathogen membrane or the reinsertion of lipids in a manner that disrupts membrane fluidity and integrity (Regente et al. 2005; Tam et al. 2015).

2.4 Havein-like peptides

Hevein-like peptides are small, basic molecules comprising 29 to 45 amino acids, distinguished by a high content of glycine, cysteine, and aromatic residues. These peptides adopt a compact fold stabilized by three to five disulfide bonds, a structural motif known as a "cystine knot" (Slavokhotova et al. 2017; Odintsova et al. 2020). Historically identified as the most abundant protein in the latex of the rubber tree (*Hevea*

brasiliensis), these peptides contain a conserved chitin-binding domain that facilitates specific interactions with fungal cell walls. Based on their cysteine count, they are categorized into 6C, 8C, and 10C subgroups. This conformation ensures exceptional stability against thermal, chemical, and proteolytic degradation, making them ideal candidates for biotechnological applications (Slavokhotova et al. 2017; Odintsova et al. 2020).

The hevein-like AMPs are primarily geared toward antifungal defense, protecting plants from a wide array of chitin-containing pathogens. Peptides isolated from the bark of *Euonymus europaeus* and *Eucommia ulmoides* demonstrate potent inhibitory effects against *Botrytis cinerea*, *Phytophthora infestans*, and *Fusarium oxysporum* (Van den Bergh et al. 2002). Their antimicrobial spectrum also extends to bacteria; peptides from *Stellaria media* and *Wasabia japonica* inhibit the growth of *Escherichia coli*, *Bacillus subtilis*, and several *Pseudomonas* species (Kiba et al. 2003). The efficacy of these peptides has been further validated through transgenic expression. For instance, rubber tree hevein-like genes expressed in rice successfully regulated infections of the rice blast fungus *Magnaporthe grisea*, while transgenic tobacco and tomatoes expressing morning glory (*Pharbitis nil*) peptides showed enhanced resistance against *Phytophthora* and *Fusarium* species (Pujade-Renaud et al. 2005).

The primary mechanism of action for hevein-like peptides is linked to their high affinity for chitin which is the major component of fungal cell walls. This interaction is mediated by hydrogen bonding and van der Waals forces between the carbohydrate's hydrophobic groups and the π-electron systems of conserved aromatic residues, such as tryptophan and tyrosine. Binding to fungal chitin leads to hyphal tip bursting and the subsequent leakage of cytoplasmic material, effectively inhibiting fungal growth. Additionally, some hevein-like peptides, known as WAMPs (wheat antimicrobial peptides), exhibit an innovative secondary defense mechanism. They can inhibit fungal proteases like fungalysin, which pathogens use to degrade plant chitinases. By binding to these proteases, WAMPs protect the plant's own enzymatic defenses, ensuring they remain active to digest the invading fungus, thereby showcasing a sophisticated layer of plant innate immunity.

2.5 Snakins

Snakins are a highly complex family of plant AMPs, characterized by the largest number of cysteine residues and disulfide bonds among all known plant peptide classes. Typically comprising 63 to 66 amino acids with 12 conserved cysteines forming six intramolecular disulfide bonds, these peptides possess exceptionally stable structure predicted to consist of two long α-helices. The first identified members, snakin-1 and snakin-2, were isolated from potato tubers (*Solanum tuberosum*) and were named for their subtle sequence similarities to motifs found in certain snake venoms (Segura et al. 1999; Padovan et al. 2010).

The antimicrobial potential of snakins is robust, particularly regarding their ability to agglutinate or aggregate microorganism cells. Snakin-1 and snakin-2 exhibit significant activity against a variety of pathogens at low micromolar concentrations, including the fungi *Fusarium solani* and *Pichia pastoris*, and bacteria such as *Staphylococcus cohnii* and *Agrobacterium tumefaciens*. Their bactericidal activity is particularly prominent against Gram-negative bacteria. A unique feature of snakins is their ability to induce the aggregation of both Gram-positive and Gram-negative bacteria, a property that helps prevent the spread of pathogens in damaged plant tissues (Meneguetti et al. 2017).

While the precise mechanism of action for snakins remains under investigation, their high positive charge density is believed to be central to their function. The cationic nature of these peptides facilitates the initial attraction and interaction with the negatively charged membranes of pathogens, leading to membrane destabilization (Oliveira-

Lima et al. 2017).

2.6 Cyclotides

Cyclotides are a class of macrocyclic peptides, typically comprising of 28 to 37 amino acids, and have a unique "head-to-tail" cyclic backbone. This structure is stabilized by a structural motif known as the cyclic cystine knot (CCK), formed by six conserved cysteine residues that create an exceptionally rigid and stable conformation. This configuration grants cyclotides remarkable resistance to thermal and chemical denaturation, as well as high stability against proteolytic degradation by gastrointestinal enzymes like trypsin and pepsin. While true cyclotides are predominantly found in dicotyledonous families, including Rubiaceae, Violaceae, Cucurbitaceae, Fabaceae, and Solanaceae, acyclic variants have been observed in monocots such as the Poaceae family (Weidmann and Craik 2016; De Veer et al. 2019).

The antimicrobial potential of cyclotides is due to their ability to target and disrupt lipid-rich microbial membranes, leading to pore formation and cellular destabilization (De Veer et al. 2019). This activity is potent against both Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, and Gram-positive bacteria like *Staphylococcus aureus* (Pränting et al. 2010; Wong et al. 2011; Fu et al. 2021). Their antiviral capabilities are notably restricted to viruses with lipid envelopes, where cyclotides cause membrane disruption to inhibit viral entry and replication within host cells (Gran et al. 2008). Furthermore, cyclotides serve a vital role in plant defense as natural insecticides and nematicides; for instance, they significantly reduce the growth of moth larvae (*Helicoverpa armigera*) and exert lethal effects on *Caenorhabditis elegans* larvae. From the traditional use of *Oldenlandia affinis* medicinal tea to modern applications in crop protection, the extreme stability and multifaceted biological activity of cyclotides make them prime candidates for the development of resilient, peptide-based therapeutics and innovative anti-microbial drug strategies (Gran et al. 2008).

3. Structure–Activity Relationships and Biophysical Properties

Owing to the remarkable diversity of the structural conformations of plant AMPs, drawing common Structure–Activity Relationships (SARs) is critical. Biophysical properties such as hydrophobic patches and the distribution of positively charged residues are the most typical features of effective agents. The ability of these peptides to discriminate between host and pathogen cells depends on a delicate balance of these characteristics (Nyembe et al. 2023).

Intra-molecular disulfide bridges are essential post-translational modifications that provide the structural framework for biological activity. In plant defensins, the presence of these bonds is mandatory for antibacterial function, specifically, two to three disulfide bridges are required to preserve the β structure. These bridges change the peptide conformation, ensuring extremely stable structures that increase the affinity for specific targets (Liu et al. 2019). Besides stability, the disulfide bond is critical in the development of antimicrobial conjugates. For example, some antimicrobial peptides conjugated with aminoglycosides (like Kanamycin) via disulfide bonds demonstrate enhanced Minimum Inhibitory Concentration (MIC) values against certain pathogens (Mohamed et al. 2017).

The repetition and abundance of specific amino acids influence biological activity of the AMPs. Lysine (Lys) and Arginine (Arg) residues are primarily responsible for the cationicity of plant AMPs at physiological pH. Clusters of Lys residues confer bactericidal capacity by binding to the hydrophobic core of the lipid bilayer. However, a high density of lysine can increase cytotoxicity. Polyarginine motifs function primarily by depolarizing the plasma membrane, causing immediate lysis. Unlike Lys and Arg, the activity of polyhistidine polymers is highly effective in acidic conditions, where they interact

with membrane anions and facilitate the translocation of peptides across cell boundaries (Ciulla and Gelain 2023).

Hydrophobicity is directly related to antimicrobial potential of the AMPs. It is the primary force driving antimicrobial molecules from an aqueous environment into the lipid cell membrane. Balancing the hydrophobic and polar content is crucial for the selectivity of the peptide as extreme hydrophobicity is often correlated with higher cytotoxicity and hemolytic activity (Ciulla and Gelain 2023).

Studies show that non-polar environments cause peptides to undergo conformational modifications. Hydrophobic surfaces often trigger a change from random coils to α-helices, or from α-helices to β-sheet aggregates. This transition is often driven by a charge compensatory effect; when peptides bind to anionic phospholipids, the resulting dehydrated environment favors the formation of stable β-strand aggregates (Ciulla and Gelain 2023).

Amphiphilicity refers to the spatial rearrangement of monomers and is a major determinant of potency. The rearrangement of charge clusters can result in a prominent hydrophobic character, which significantly increases activity against Gram-negative strains like *P. aeruginosa* and *E. coli*. Besides this the nature of the cationic side chains is also important. Studies that the specific chain length of the amino alkyl side chain can modulate activity (Mojsoska et al. 2015).

Glycosylation is one of the most important post-translational modifications which results in diversity and specificity to peptide functions. In many cases, antimicrobial activity decreases significantly if glycosylation is reduced, suggesting a mechanism of action distinct from simple membrane permeabilization. Recent findings suggest that glycosylated peptides may target peptidoglycan biosynthesis or specific peptide–receptor recognition pathways involved in microbial cell wall regulation (Bednarska et al. 2017).

4. Mechanism of action

The antimicrobial efficacy of AMPs is primarily attributed to their ability to disrupt the structural integrity of microbial membranes. Unlike conventional antibiotics that often target specific metabolic enzymes, most plant AMPs utilize a physical mechanism of action that makes the development of bacterial resistance significantly more challenging. Several mechanisms of action have been proposed **(Figure 1)** that are given in the section below.

4.1 Membrane-targeting and Pore-forming Mechanisms

The AMP molecules exist in a disordered or random coil conformation in the aqueous environment of the cell membrane where the interaction between plant AMPs and the bacterial cell begins. The initial binding is driven by the electrostatic affinity between the cationic (lysine and arginine) residues of the peptide and the negatively charged components of the microbial cell surface. In bacteria, these targets include the phosphate groups of lipid bilayers rich in anionic lipids such as phosphatidylglycerol (PG) and cardiolipin, as well as lipopolysaccharides (LPS) in Gram-negative bacteria and teichoic acids in Gram-positive bacteria (Ma et al. 2024).

Once the peptide approaches the target membrane, peptides accumulate on the membrane surface, often facilitated by the bacterial membrane potential. This electrical gradient assists the migration of cationic peptides toward the non-polar membrane regions, effectively lowering the energy barrier for pore formation. Upon contact with the phospholipid bilayer, many α-helical AMPs undergo a dramatic conformational shift from a random coil to a well-defined amphipathic helix. In contrast, β-sheet AMPs, such maintain their stable structure through their conserved disulfide bridges, allowing them to retain their functional fold throughout the binding process (Ma et al. 2024). As the peptide-to-lipid ratio reaches a critical threshold, the AMPs transition from a parallel

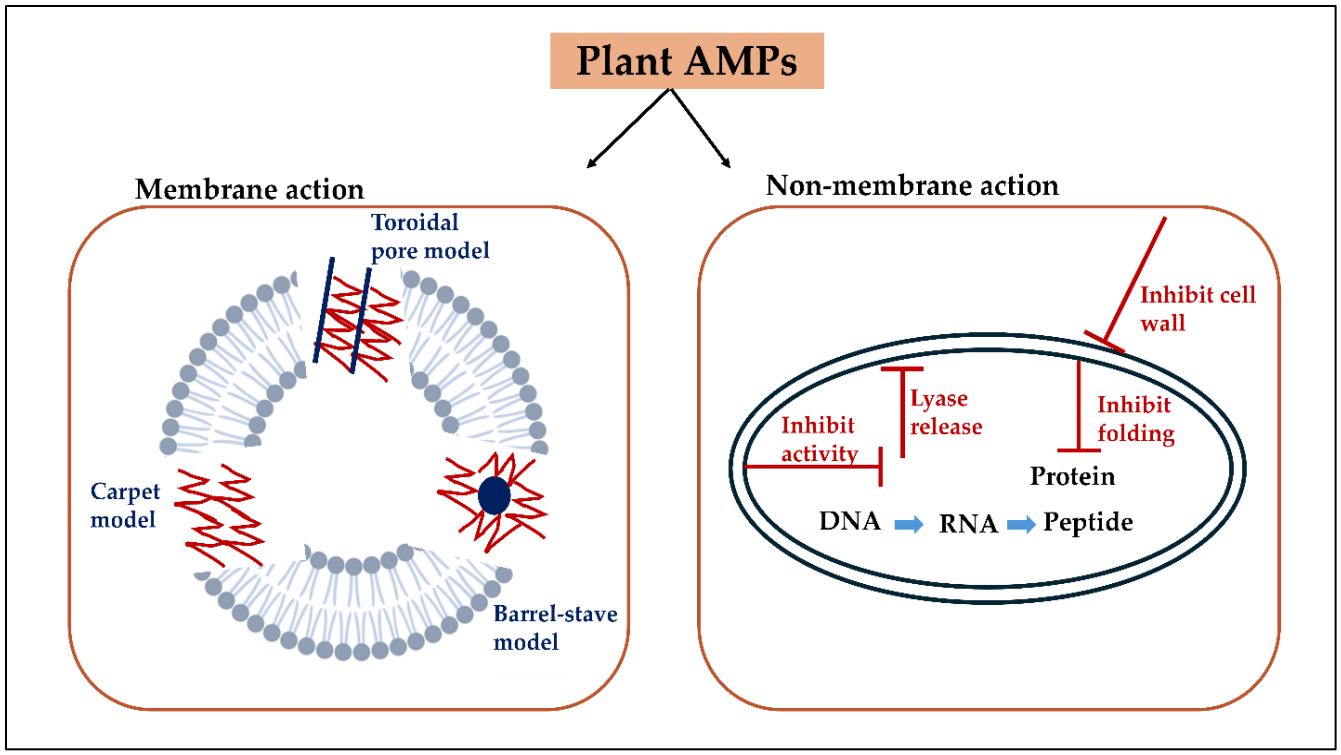

Figure 1: Schematic representation of the antimicrobial mechanisms of plant antimicrobial peptides (AMPs). **Left panel (Membrane action):** Illustrates the biophysical models of membrane permeabilization, including the **Carpet model**, the **Toroidal pore model**, and the **Barrel-stave model**. **Right panel (Non-membrane action):** Highlights the diversity of intracellular and surface targets. This includes the inhibition of cell wall biosynthesis, interference with the DNA replication and RNA transcription, disruption of protein synthesis and folding, and the induction of lethal autolytic pathways (lyase release).

orientation on the surface to a vertical insertion into the hydrophobic core, leading to membrane permeabilization through several proposed models:

1. **The Barrel-Stave Model:** In this model, AMP monomers aggregate on the membrane surface and rotate perpendicularly to insert into the bilayer. The peptides assemble such that their hydrophobic regions face the lipid acyl chains while their hydrophilic regions form the interior lining of a rigid, circular pore. This arrangement creates a permanent transmembrane channel, leading to the leakage of cytoplasmic contents and the collapse of the electrochemical gradient (Tornesello et al. 2020).
2. **The Toroidal Pore Model:** Similar to the barrel-stave model, the peptides insert vertically. However, instead of only peptide-peptide interactions, the AMPs interact directly with the lipid headgroups, causing the membrane to bend and stretch. This results in the formation of a "toroidal" or "wormhole" pore where both the peptides and the phospholipid headgroups line the channel. This dynamic supramolecular complex is often sensitive to the peptide concentration; excessive electrostatic repulsion between positively charged side chains can destabilize these pores (Ciumac et al. 2019).
3. **The Carpet Model:** In this detergent-like mechanism, peptides align parallel to the membrane surface, covering it like a "carpet" without necessarily inserting into the hydrophobic core. Once a critical concentration is reached, the peptides exert a

Table 1: Selected examples of well-studied plant AMPs.

Peptide Name	Family	Plant Source	Size (aa / kDa)	Net Charge	Main Activity	MIC / Activity Range
α-Purothionin	Thionin (Type I)	*Triticum aestivum* (Wheat)	45 aa / ~5 kDa	Cationic (+)	Antibacterial, Antifungal	Broad spectrum; variable
CaThi	Thionin	*Capsicum annuum* (Pepper)	~5 kDa	Cationic (+)	Antifungal (*F. solani*)	Synergistic with fluconazole
Dm-AMP1	Defensin	*Dahlia merckii* (Dahlia)	50 aa	Cationic (+)	Antifungal, Antibacterial	15 μg/mL (*B. subtilis*)
VuDef2	Defensin	*Vigna unguiculata* (Cowpea)	~50 aa	Cationic (+)	Antibacterial	15 μg/mL (*S. aureus*)
Rs-AFP2	Defensin	*Raphanus sativus* (Radish)	51 aa	Cationic (+)	Antifungal (*C. albicans*)	Induces apoptosis via ROS
Ace-AMP1	LTP	*Allium cepa* (Onion)	93 aa / ~9 kDa	Cationic (+)	Broad-spectrum Antifungal	High potency; non-specific
Ac-AMP1	Hevein-like	*Amaranthus caudatus*	29 aa	Cationic (+)	Antifungal, Gram (+) Bacteria	2–10 μg/mL
Pn-AMP1	Hevein-like	*Pharbitis nil* (Morning Glory)	40 aa	Cationic (pI 12)	Antifungal (Chitin-binding)	0.6–75 μg/mL
Snakin-1	Snakin	*Solanum tuberosum* (Potato)	63 aa	Cationic (+)	Antibacterial, Antifungal	1–20 μM (Aggregation)
Kalata B1	Cyclotide	*Oldenlandia affinis*	29 aa	Cationic (+)	Antibacterial, Insecticidal	Membrane disruption
MCoTI-II	Cyclotide	*Momordica cochinchinensis*	34 aa	Cationic (+)	Trypsin Inhibitor	Enzyme specific

Note: aa: amino acids; kDa: kilodaltons; MIC: Minimum Inhibitory Concentration; ROS: Reactive Oxygen Species

massive destabilizing pressure that leads to the disintegration of the membrane into micelles. This model is typical for peptides that lack the specific structural requirements to form discrete pores but possess enough amphipathicity to disrupt lipid packing (Lee et al. 2016).

4. **The Aggregate Model:** This model suggests that AMPs and lipids form non-specific micelle-like complexes that traverse the membrane. Unlike the more structured pore models, the aggregate model involves the dynamic creation of transient channels where the peptides do not maintain a specific orientation, allowing for both membrane disruption and the translocation of AMPs into the intracellular environment (Hale and Hancock 2007).

4.2 Intracellular targets

The changes in membrane permeability alone cannot always fully account for the potent bactericidal effects of AMPs. While permeabilization may inhibit growth, the complete destruction of the pathogen often requires the disruption of internal functional systems. Many AMPs can traverse the cell membrane via direct penetration or endocytosis to accumulate within the cytoplasm. Once inside, these peptides act on universal intracellular targets, including nucleic acids, proteins, and cellular organelles, effectively disturbing the cell cycle and energy metabolism (Bechinger and Gorr 2017).

The binding of AMPs to nucleic acids is primarily driven by electrostatic interactions between cationic regions and the negatively charged

phosphate backbone of DNA or RNA. This physical interaction can restrict replication, transcription, and translation processes. Some peptides target the non-basic regions of DNA to crosslink strands or block the activity of DNA topoisomerase I. While some tissue-factor-derived peptides, enter the cytoplasm following membrane rupture and actively break down DNA and RNA molecules, leading to irreversible cellular damage. Apart from this some peptides hinder mRNA translation or inducing premature termination, thus inhibiting microbial growth (Bechinger and Gorr 2017). The variations in peptide structure impact this interaction. Besides this, AMPs also exert significant pressure on bacterial enzyme systems and organelles. Certain peptides bind to RNA polymerase, obstructing the folding of the trigger loop and preventing substrates from entering the secondary channel, which inhibits gene transcription (Bechinger and Gorr 2017). Beyond enzymes, AMPs can damage mitochondria by inducing changes in membrane potential and triggering the release of cytochrome C. This often leads to increased reactive oxygen species (ROS) production and endoplasmic reticulum stress, resulting in necrotic cell death (Lv et al. 2019).

4.3 Cell wall disruption

Many AMPs exert their antimicrobial potential by targeting the structural components of the bacterial cell wall. Like traditional antibiotics, these AMPs inhibit cell wall synthesis by interacting with essential precursor molecules. The most prominent target identified is Lipid II, a major precursor of peptidoglycan that plays a vital role in transporting cell wall subunits across the bacterial plasma membrane. AMPs sequestrate Lipid II, resulting in blocking the assembly of the peptidoglycan layer, which is especially critical for the structural integrity of Gram-positive bacteria (Lohner 2017). Certain plant-derived defensins bind specifically to the anionic pyrophosphate sugar moiety of the Lipid II molecule, resulting in inhibiting cell wall synthesis and acting as a docking mechanism that facilitates secondary pore formation and membrane disruption. Fungal peptides such as plectasin, which shares a structural fold with plant defensins target Lipid II directly without necessarily compromising the physical integrity of the membrane (Schneider et al. 2010). Similarly, the bacteriocin nisin utilizes a dual mechanism, binding to Lipid II to both inhibit synthesis and initiate the formation of stable membrane pores (Fu et al. 2023).

4.4 Cell wall disruption

In addition to direct microbicidal activity, AMPs also function as key effector and signalling molecules within the innate immune system. In mammalian models, families such as defensins and cathelicidins are responsible for systemic immunity. Among these the most important ones are α-defensins (HNPs) which account for a significant portion of neutrophil protein content and are secreted in response to microbial components.

Similarly, cathelicidins neutralize endotoxins and participate in immune regulation. Hence AMPs also play an important role mammalian homeostasis and inflammatory responses (Guryanova and Ovchinnikova 2022).

In plants, AMPs play an important role in innate immune system. While their primary mode involves membrane and intracellular targeting, their indirect effects are increasingly recognized as vital for systemic resistance. The molecular mechanisms underlying this activity are highly diverse and depend on both the physicochemical properties of the peptide and the environmental conditions of the host. This mechanistic diversity broadens the antimicrobial spectrum and significantly reduces the likelihood of pathogens developing resistance.

Furthermore, the ability of certain AMPs to translocate into microbial cells, interfering with transcription, translation, and essential metabolic pathways, amplifies their antimicrobial potency beyond simple physical membrane disruption. (Yadav et al. 2025).

5. Conclusion and future perspectives

The global problem of AMR has necessitated a paradigm shift toward multifaceted therapeutic agents. Among these plant AMPs emerge as the most important candidate for the post-antibiotic era. The primary strength of plant-derived families such as thionins, defensins, and cyclotides is their structural diversity and multiple mechanisms of action. By simultaneously targeting membrane integrity, sequestering peptidoglycan precursors, and interfering with intracellular machinery (DNA/RNA and protein synthesis), these peptides exert a potent impact on pathogens, significantly reducing the likelihood of resistance development compared to conventional antibiotics.

Despite their immense potential, several challenges constrain the widespread clinical and agricultural adoption of plant AMPs. The most important one includes toxicity and low stability of these peptides. High-potency peptides often exhibit off-target effects, such as hemolysis or nephrotoxicity, mirroring challenges seen with clinically approved agents. Furthermore, the inherent susceptibility of linear peptides to proteolytic degradation in human serum or under agricultural field conditions limits their bioavailability. Finally, the high cost of large-scale peptide synthesis and a traditionally low return on investment compared to chronic-disease medications have historically slowed industrial momentum (Ali et al. 2025).

Despite the challenges innovative approaches and emerging technologies can rapidly transform this field. Firstly, AI-driven discovery and rational design, utilizing several frameworks like UniAMP and Large Language Models (LLMs), are revolutionizing AMP research by allowing the *in-silico* prediction of potency and toxicity across an expanded chemical space, enabling the creation of synthetic analogues with non-natural amino acids or backbone-cyclization for enhanced stability (Qiu et al. 2024). Secondly, synergistic and combinatorial approaches are moving away from monotherapy, where the conjugation of AMPs with traditional antibiotics such as Vancomycin or Kanamycin can restore efficacy against certain resistant pathogens. Finally, advanced delivery systems leveraging nanotechnology, such as nanoparticle (NP) conjugation, solve issues of metabolic instability and host toxicity by providing protective scaffolds that prevent self-aggregation and facilitate targeted delivery to infection sites (Ali et al. 2025).

In conclusion, while plant AMPs are already established as essential component of the plant immune system, their transition into the clinical and commercial mainstream is now being accelerated by the convergence of biotechnology and computational intelligence. By utilizing the advanced technologies, the next generation of plant AMPs has the potential to become an important aspect in the sustainable management of global infectious diseases.

Conflict of Interest

The authors have no competing interests to declare.

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Ethical Approval

Not applicable, since the work does not involve any study with human participants or animals.

Consent Forms

NA

Author Contributions

Both authors contributed equally to this study. AM conceptualized the study, and AM and M drafted the manuscript. Both authors reviewed and approved the final version of the manuscript.

Data Availability

NA

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