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

Asif Ali [1], Silla Ambrose* [2], Dilawar Hussain [1], Faisal Hafeez [2], Tayyaba Asghar [3], Syed Noraiz Arif Shah [2], Momina Ahsan [2], Muhammad Shakir [3], Arsam Ali [4], Arslan Muhammad Ali Khan [2], Muhammad Usama Javed [2]

[1] *University of Layyah, Layyah, Pakistan*
[2] *University of Agriculture, Faisalabad, Pakistan*
[3] *University of Veterinary and Animal Sciences, Lahore, Pakistan*
[4] *Livestock and Dairy Development Department, Punjab, Pakistan*

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* *Corresponding author:*
Silla Ambrose
Email: ambrosesilla99@gmail.com

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Zain-un-Nisa
Govt. College University, Faisalabad, Pakistan

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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

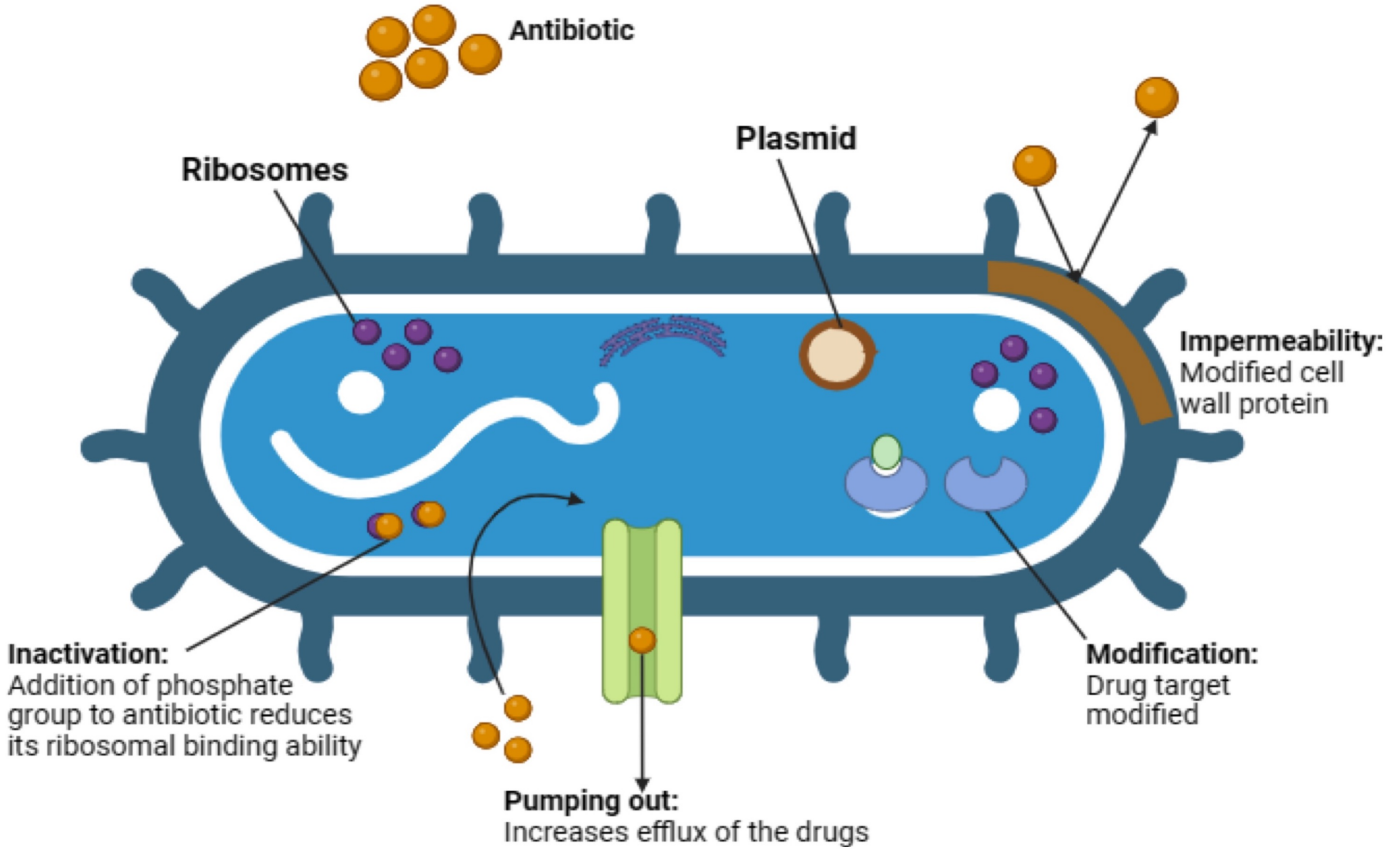

***Fig. 1**: Different resistance mechanisms against the antibiotics (Created in BioRender.com)*

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 bio-compatibility, 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 (αβ). 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

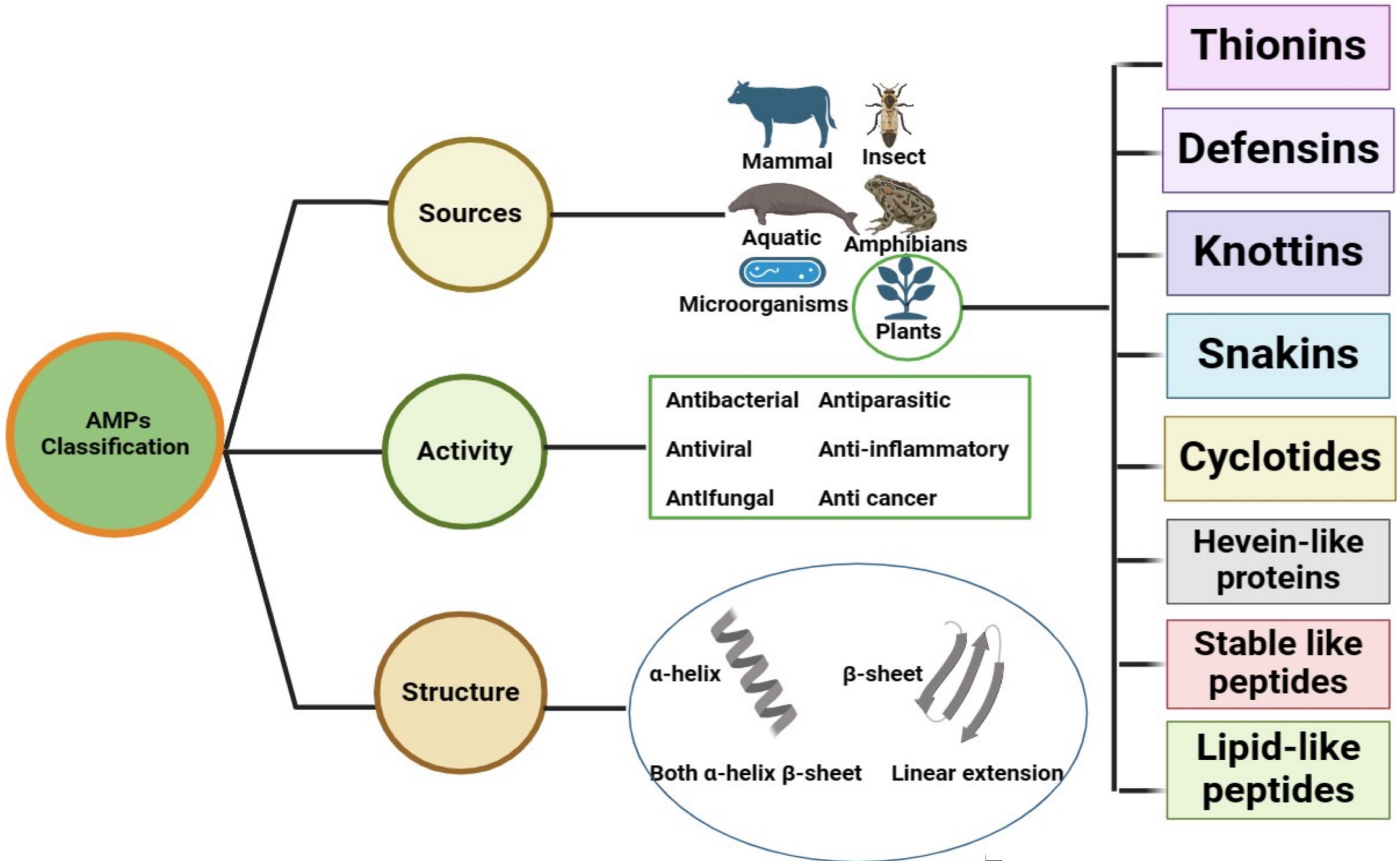

***Fig. 2**: Classification of the AMPs (Created in BioRender.com)*

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

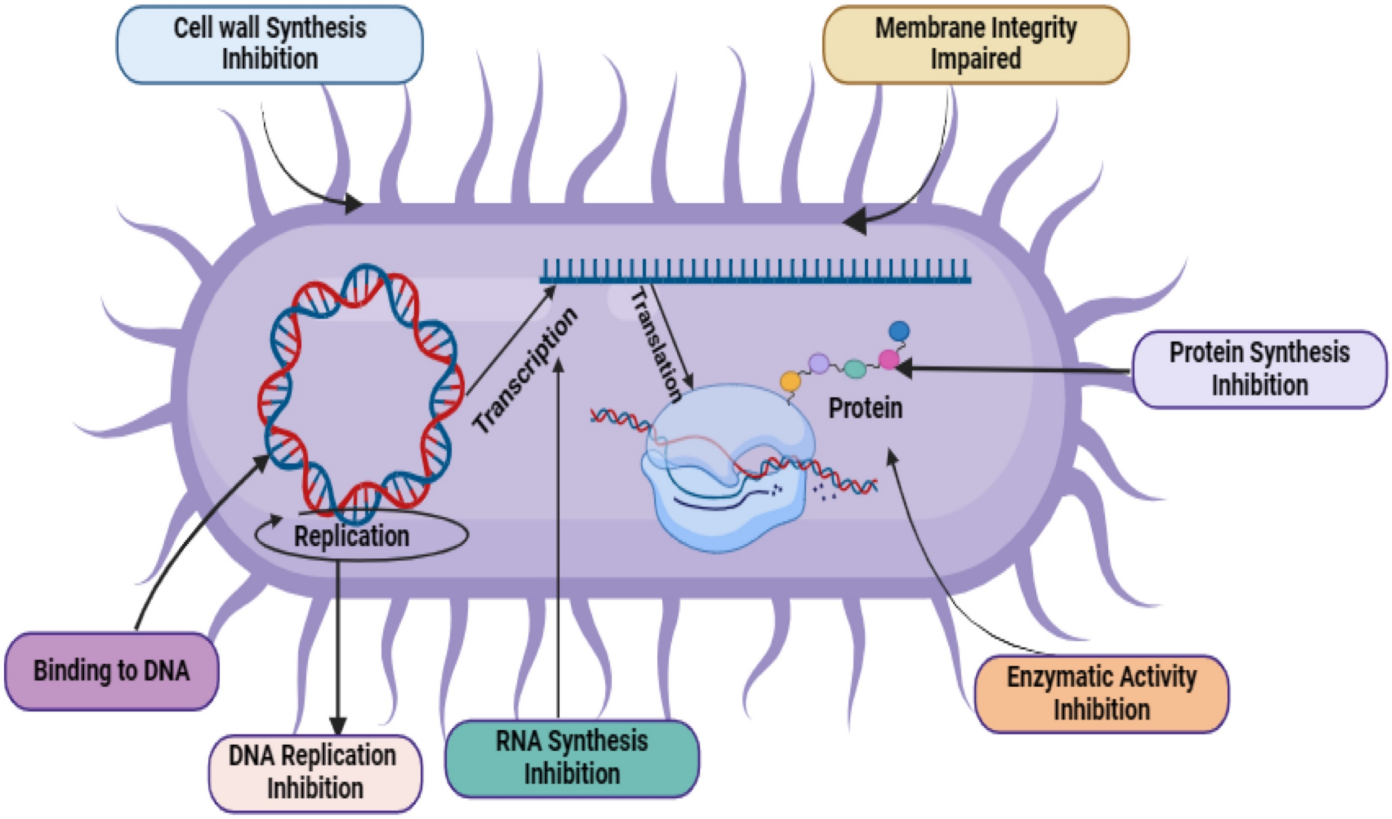

***Fig. 3**: Antimicrobial mechanism of action of AMPs (Created in BioRender.com)*

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 lipopolysacharrides 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-cyseine 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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References

Andrade-Pavon D, Sanchez-Sandoval E, Rosales-Acosta B, Ibarra JA, Tamariz J, Hernandez-Rodriguez C, Villa-Tanaca L. (2014). The 3-hydroxy-3-methylglutaryl coenzyme-A reductases from fungi: a proposal as a therapeutic target and as a study model. Revista Iberoamericana de Micologia 31(1): 81-85.

Attah FA, Lawal BA, Yusuf AB, Adedeji OJ, Folahan JT, Akhigbe KO, Chamcheu JC. (2022). Nutritional and pharmaceutical applications of under-explored knottin peptide-rich phytomedicines. Plants 11(23): 3271. https://doi.org/10.3390/plants11233271

Azmi S, Khatoon S, Hussain MK. (2021). Assessment of antimicrobial phytopeptides: lipid transfer protein and hevein-like peptide in the prospect of structure, function and allergenic effect. Beni-Suef University Journal of Basic and Applied Sciences 10: 1-11. https://doi.org/10.1186/s43088-021-00158-z

Bakare OO, Gokul A, Fadaka, AO, Wu R, Niekerk LA, Barker AM, Klein A. (2022). Plant antimicrobial peptides (PAMPs): features, applications, production, expression, and challenges. Molecules 27(12): 3703. https://doi.org/10.3390/molecules27123703

Banger S, Singh R, Tripathi N, Pal V, Goel A. (2019). One-step purification and characterization of Abrin toxin from *Abrus Precatorius* seeds. Defence Life Science Journal 4(4): 231-235.

Barashkova AS, Rogozhin EA. (2020). Isolation of antimicrobial peptides from different plant sources: Does a general extraction method exist? Plant Methods 16(1): 143. https://doi.org/10.1186/s13007-020-00687-1

Bechinger B, Gorr SU. (2017). Antimicrobial peptides: mechanisms of action and resistance. Journal of Dental Research 96(3): 254-260. https://doi.org/10.1177/0022034516679973

Begum J, Mir NA. (2023). Molecular mechanisms of biofilm resistance against antibiotics. Letters in Animal Biology 3(1): 17–27. https://doi.org/10.62310/liab.v3i1.107

Bennani H, Mateus A, Mays N, Eastmure E, Stark KD, Hasler B. (2020). Overview of evidence of antimicrobial use and antimicrobial resistance in the food chain. Antibiotics 9(2): 49. https://doi.org/10.3390/antibiotics9020049

Breithaupt H. (1999). The new antibiotics. Nature Biotechnology 17: 1165–1169. https://doi.org/10.1038/70705

Boparai JK, Sharma PK. (2020). Mini review on antimicrobial peptides, sources, mechanism and recent applications. Protein and Peptide Letters 27(1): 4-16. https://doi.org/10.2174/0929866526666190822165812

Bruno F, Malvaso A, Canterini S, Bruni AC. (2022). Antimicrobial Peptides (AMPs) in the pathogenesis of Alzheimer's disease: Implications for diagnosis and treatment. Antibiotics 11(6): 726. https://doi.org/10.3390/antibiotics11060726

Cassone M, Otvos L Jr. (2010). Synergy among antibacterial peptides and between peptides and small-molecule antibiotics. Expert Review of Anti-infective Therapy 8(6): 703–716. https://doi.org/10.1586/eri.10.38

Caudill MA, Obeid R, Derbyshire E, Bernhard W, Lapid K, Walker SJ, Zeisel SH. (2020). Building better babies: should choline supplementation be recommended for pregnant and lactating mothers? Literature overview and expert panel consensus. European Gynecology and Obstetrics 2(3):149-161

Dadgostar P. (2019). Antimicrobial resistance: Implications and costs. Infection and Drug Resistance 12: 3903-3910. https://doi.org/10.2147/IDR.S234610

Datta M, Rajeev A, Chattopadhyay I. (2023). Application of antimicrobial peptides as next-generation therapeutics in the biomedical world. Biotechnology and Genetic Engineering Reviews 1-39. https://doi.org/10.1080/02648725.2023.2199572

Decker AP, Mechesso AF, Wang G. (2022). Expanding the landscape of amino acid-rich antimicrobial peptides: definition, deployment in nature, implications for peptide design and therapeutic potential. International Journal of Molecular Sciences 23(21): 12874. https://doi.org/10.3390/ijms232112874

Deplazes E, Chin YKY, King GF, Mancera RL. (2020). The unusual conformation of cross-strand disulfide bonds is critical to the stability of β-hairpin peptides. Proteins 88(3): 485-502. https://doi.org/10.1002/prot.25828

Di Franco S, Alfieri A, Pace MC, Sansone P, Pota V, Fittipaldi C, Fiore M, Passavanti MB. (2021). Blood stream infections from MDR bacteria. Life 11(6): 575. https://doi.org/10.3390/life11060575

Finkina EI, Melnikova DN, Bogdanov IV. (2016). Lipid transfer proteins as components of the plant innate immune system: structure, functions, and applications. Acta Naturae 8(2): 47-61.

French G. (2005). Clinical impact and relevance of antibiotic resistance. Advanced Drug Delivery Reviews 57(10): 1514-1527. https://doi.org/10.1016/j.addr.2005.04.005

Fry DE. (2018). Antimicrobial peptides. Surgical Infections 19(8): 804-811. https://doi.org/10.1089/sur.2018.194

Games PD, daSilva EQG, Barbosa MDO, Almeida-Souza HO, Fontes

PP, deMagalhaes-Jr MJ, Baracat-Pereira MC. (2016). Computer aided identification of a Hevein-like antimicrobial peptide of bell pepper leaves for biotechnological use. BMC Genomics 17: 1-13. https://doi.org/10.1186/s12864-016-3332-8

Hilchie AL, Wuerth K, Hancock RE (2013) Immune modulation by multifaceted cationic host defense (antimicrobial) peptides. Nature Chemical Biology 9: 761–768. https://doi.org/10.1038/nchembio.1393

Hurley RL, Barre LK, Wood SD, Anderson KA, Kemp BE, Means AR, Witters LA. (2006). Regulation of AMP-activated protein kinase by multisite phosphorylation in response to agents that elevate cellular cAMP. Journal of Biological Chemistry 281(48): 36662-36672. https://doi.org/10.1074/jbc.M606676200

Inoue H. (2019). Strategic approach for combating antimicrobial resistance (AMR). Global Health and Medicine 1(2): 61-64. https://doi.org/10.35772/ghm.2019.01026

Ishaq N, Bilal M, Iqbal HM. (2019). Medicinal potentialities of plant defensins: A review with applied perspectives. Medicines 6(1): 29. https://doi.org/10.3390/medicines6010029

Islam SU. (2022). Gram-negative bacteria. Infectious Diseases 63-118. https://doi.org/10.1016/B978-0-443-18742-1.00026-9

Janik E, Ceremuga M, Niemcewicz M, Bijak M. (2020). Dangerous pathogens as a potential problem for public health. Medicina 56(11): 591. https://doi.org/10.3390/medicina56110591

Kausar M, Saleem Z, Azhar R, Rukhsar G, Ali M, Fan C, Wei Cr, Khan AMA. (2023). Role of nanoparticles in COVID-19 management. In: Sindhu ZuD, B Aslam, U Uslu, M Mohsin, editors, Complementary and alternative medicine: One health perspective, FahumSci, Lahore, Pakistan. pp: 72-80. https://doi.org/10.61748/CAM.2023/010

Khan AMA, Wei CR, Fatima K, Ali A, Akram MS, Saeed Z, Shahood SA, Ullah H. (2023). Use of various types of nanoparticles as an antioxidant for the inhibition of bacterial infections with benefits to intestinal microbiota and immune response. In: Sindhu ZuD, B Aslam, U Uslu, M Mohsin, editors, Complementary and alternative medicine: One health perspective, FahumSci, Lahore, Pakistan. pp: 81-87. https://doi.org/10.61748/CAM.2023/011

Kumar P, Kizhakkedathu JN, Straus SK. (2018). Antimicrobial peptides: diversity, mechanism of action and strategies to improve the activity and biocompatibility in vivo. Biomolecules 8(1): 4. https://doi.org/10.3390/biom8010004

Lei J, Sun L, Huang S, Zhu C, Li P, He J, He Q. (2019). The antimicrobial peptides and their potential clinical applications. American Journal of Translational Research 11(7): 3919-3931.

Li J, Hu S, Jian W, Xie C, Yang X. (2021). Plant antimicrobial peptides: structures, functions, and applications. Botanical Studies 62(1): 5. https://doi.org/10.1186/s40529-021-00312-x

Li S, Wang Y, Xue Z, Jia Y, Li R, He C, Chen H. (2021). The structure-mechanism relationship and mode of actions of antimicrobial peptides: A review. Trends in Food Science and Technology 109: 103-115. https://doi.org/10.1016/j.tifs.2021.01.005

Lima AM, Azevedo MI, Sousa LM, Oliveira NS, Andrade CR, Freitas CD, Souza PF. (2022). Plant antimicrobial peptides: An overview about classification, toxicity and clinical applications. International Journal of Biological Macromolecules 214: 10-21. https://doi.org/10.1016/j.ijbiomac.2022.06.043

Linz MS, Mattappallil A, Finkel D, & Parker D. (2023). Clinical impact of Staphylococcus aureus skin and soft tissue infections. Antibiotics 12(3): 557. https://doi.org/10.3390/antibiotics12030557

Lipkin RB, Lazaridis T. (2015). Implicit membrane investigation of the stability of antimicrobial peptide β-barrels and arcs. The Journal of Membrane Biology 248: 469-486. https://doi.org/10.1007/s00232-014-9759-4

Lopez-Cano A, Ferrer-Miralles N, Sanchez J, Carratala JV, Rodriguez XR, Ratera I, Guasch J, Pich OQ, Bierge P, Garcia-de-la-Maria C, Miro JM, Gracia-Fruitos E, Aris A, Investigators F. (2023). A novel generation of tailored antimicrobial drugs based on recombinant multidomain proteins. Pharmaceutics 15(4): 1068. https://doi.org/10.3390/pharmaceutics15041068

Luo Y, Song Y. (2021). Mechanism of antimicrobial peptides: antimicrobial, anti-inflammatory and antibiofilm activities. International Journal of Molecular Sciences 22(21): 11401. https://doi.org/10.3390/ijms222111401

Matkawala F, Nighojkar A, Kumar A. (2019). Antimicrobial Peptides in Plants: Classes, Databases, and Importance. Canadian Journal of Biotechnology 3(2): 158. https://doi.org/10.24870/cjb.2019-000130

Mattar C, Edwards S, Baraldi E, Hood J. (2020). An overview of the global antimicrobial resistance research and development hub and the current landscape. Current Opinion in Microbiology 57: 56-61. https://doi.org/10.1016/j.mib.2020.06.009

Maximiano MR, Franco OL. (2021). Biotechnological applications of versatile plant lipid transfer proteins (LTPs). Peptides 140: 170531. https://doi.org/10.1016/j.peptides.2021.170531

Mhlongo JT, Waddad AY, Albericio F, de la Torre BG. (2023). Antimicrobial peptide synergies for fighting infectious diseases. Advanced Science 10(26): e2300472. https://doi.org/10.1002/advs.202300472

Mikucki A, McCluskey NR, Kahler CM. (2022). The host-pathogen interactions and epicellular lifestyle of *Neisseria meningitidis*. Frontiers in Cellular and Infection Microbiology 12: 862935. https://doi.org/10.3389/fcimb.2022.862935

Moo CL, Yang SK, Yusoff K, Ajat M, Thomas W, Abushelaibi A, Lai KS. (2020). Mechanisms of antimicrobial resistance (AMR) and alternative approaches to overcome AMR. Current Drug Discovery Technologies 17(4): 430-447. https://doi.org/10.2174/1570163816666190304122219

Odintsova T, Shcherbakova L, Slezina M, Pasechnik T, Kartabaeva B, Istomina E, Dzhavakhiya V. (2020). Hevein-like antimicrobial peptides WAMPs: Structure–function relationship in antifungal activity and sensitization of plant pathogenic fungi to tebuconazole by WAMP-2-derived peptides. International Journal of Molecular Sciences 21(21): 7912. https://doi.org/10.3390/ijms21217912

Olga K, Marina K, Alexey A, Anton S, Vladimir Z, Igor T. (2020). The role of plant antimicrobial peptides (AMPs) in response to biotic and abiotic environmental factors. Biological Communications 65(2): 187-199. https://doi.org/10.21638/spbu03.2020.205

Oliveira Junio, Reygaert WC. (2023). Gram Negative Bacteria. In: StatPearls. Treasure Island (FL), StatPearls Publishing, St. Petersburg, Florida, USA. PMID: 30855801

Palma E, Tilocca B, Roncada P. (2020). Antimicrobial resistance in veterinary medicine: An overview. International Journal of Molecular Sciences 21(6): 1914. https://doi.org/10.3390/ijms21061914

Pinto MEF, Najas JZ, Magalhaes LG, Bobey AF, Mendonça JN, Lopes NP, Leme FvM, Teixeira SP, Trovó M, Andricopulo AD. (2018). Inhibition of breast cancer cell migration by cyclotides isolated from

Pombalia calceolaria. Journal of Natural Products 81(5): 1203-1208. https://doi.org/10.1021/acs.jnatprod.7b00969

Salimi F, Zare EN. (2023). Current scenario on the microbial world and associated diseases. In Kumar a, Behera A, Bilal M, Gupta R, Nguyen TA, editors, Antiviral and antimicrobial smart coatings, Elsevier, pp. 71-86. https://doi.org/10.1016/b978-0-323-99291-6.00006-2

Santos-Silva CAD, Zupin L, Oliveira-Lima M, Vilela LMB, Bezerra-Neto JP, Ferreira-Neto JR, Ferreira JDC, de Oliveira-Silva RL, de Jesus Pires C, Aburjaile FF, de Oliveira MF, Kido EA, Crovella S, Benko-Iseppon AM. (2020). Plant antimicrobial peptides: state of the art, in silico prediction and perspectives in the omics era. Bioinformatics and Biology Insights 14: 1-22. https://doi.org/10.1177/1177932220952739

Sathoff AE, Velivelli S, Shah DM, Samac DA. (2019). Plant defensin peptides have antifungal and antibacterial activity against human and plant pathogens. Phytopathology 109(3): 402-408. https://doi.org/10.1094/PHYTO-09-18-0331-R

Seyfi R, Kahaki FA, Ebrahimi T, Montazersaheb S, Eyvazi S, Babaeipour V, Tarhriz V. (2020). Antimicrobial peptides (AMPs): roles, functions and mechanism of action. International Journal of Peptide Research and Therapeutics 26: 1451-1463. https://doi.org/10.1007/s10989-019-09946-9

Shah M, Meenakshi K, George IA. (2023). *Abrus precatorius* (Rosary Pea). In: Husen A, editor, Exploring poisonous plants: Medicinal values, toxicity responses, and therapeutic uses, CRC Press, Boca Raton. pp. 87-99.

Shahrour H, Ferrer-Espada R, Dandache I, Barcena-Varela S, Sanchez-Gomez S, Chokr A, Martinez-de-Tejada G. (2019). AMPs as anti-biofilm agents for human therapy and prophylaxis. Advances in Experimental Medicine and Biology 1117: 257-279. https://doi.org/10.1007/978-981-13-3588-4_14

Shanmugaraj B, Bulaon CJI, Malla A, Phoolcharoen W. (2021). Biotechnological insights on the expression and production of antimicrobial peptides in plants. Molecules 26(13): 4032. https://doi.org/10.3390/molecules26134032

Sharma R, Nimonkar Y, Sharma A, Rathore RS, Prakash O. (2018). Concept of microbial preservation: Past, present and future. In: Sharma SK, Varma A, editors, Microbial resource conservation: Conventional to modern approaches. Springer Cham, Switzerland. pp. 35-54. https://doi.org/10.1007/978-3-319-96971-8

Shi W, Hou T, Liu W, Guo D, He H. (2019). The hypolipidemic effects of peptides prepared from Cicer arietinum in ovariectomized rats and HepG2 cells. Journal of the Science of Food and Agriculture 99(2): 576-586. https://doi.org/10.1002/jsfa.9218

Shoaib M, Xu J, Meng X, Wu Z, Hou X, He Z, Shang R, Zhang H, Pu W. (2023). Molecular epidemiology and characterization of antimicrobial-resistant *Staphylococcus haemolyticus* strains isolated from dairy cattle milk in Northwest, China. Frontiers in Cellular and Infection Microbiology 13: 1183390. https://doi.org/10.3389/fcimb.2023.1183390

Sinha R, Shukla P. (2019). Antimicrobial peptides: recent insights on biotechnological interventions and future perspectives. Protein and Peptide Letters 26(2): 79-87. https://doi.org/10.2174/0929866525666181026160852

Talapko J, Mestrovic T, Juzbasic M, Tomas M, Eric S, Horvat Aleksijevic L, Skrlec I. (2022). Antimicrobial peptides—Mechanisms of action, antimicrobial effects and clinical applications. Antibiotics 11(10): 1417. https://doi.org/10.3390/antibiotics11101417

Tam JP, Wang S, Wong KH, Tan WL. (2015). Antimicrobial peptides from plants. Pharmaceuticals 8(4): 711-757. https://doi.org/10.3390/ph8040711

Tang KWK, Millar BC, Moore JE. (2023). Antimicrobial resistance (AMR). British Journal of Biomedical Science 80: 11387. https://doi.org/10.3389/bjbs.2023.11387

Tang SS, Prodhan ZH, Biswas SK, Le CF, Sekaran SD. (2018). Antimicrobial peptides from different plant sources: Isolation, characterisation, and purification. Phytochemistry 154: 94-105. https://doi.org/10.1016/j.phytochem.2018.07.002

Tiwari P, Srivastava Y, Sharma A, Vinayagam R. (2023). Antimicrobial peptides: The production of novel peptide-based therapeutics in plant systems. Life 13(9): 1875. https://doi.org/10.3390/life13091875

Vikesland P, Garner E, Gupta S, Kang S, Maile-Moskowitz A, Zhu NI. (2019). Differential drivers of antimicrobial resistance across the world. Accounts of Chemical Research 52(4): 916-924. https://doi.org/10.1021/acs.accounts.8b00643

Wang X, van Beekveld RA, Xu Y, Parmar A, Das S, Singh I, Breukink E. (2023). Analyzing mechanisms of action of antimicrobial peptides on bacterial membranes requires multiple complimentary assays and different bacterial strains. Biochimica et Biophysica Acta (BBA)-Biomembranes 1865(6): 184160. https://doi.org/10.1016/j.bbamem.2023.184160

Weidmann J, Craik DJ. (2016). Discovery, structure, function, and applications of cyclotides: circular proteins from plants. Journal of Experimental Botany 67(16): 4801-4812. https://doi.org/10.1093/jxb/erw210

Wilson M, Wilson PJK. (2021). Microbes and infectious diseases. In: Wilson M, Wilson PJK, editors, Close encounters of the microbial kind. Springer Cham, Switzerland. pp. 3–48. https://doi.org/10.1007/978-3-030-56978-5_1

Xiao Z. (2023). Antimicrobial resistance mechanisms: using examples from gram-positive and gram-negative bacteria. In: Second International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Imperial College, London, 01 March 2023.

Yasir M, Willcox MDP, Dutta D. (2018). Action of antimicrobial peptides against bacterial biofilms. Materials 11(12): 2468. https://doi.org/10.3390/ma11122468

Yili A, Maksimov V, Ma QL, Gao YH, Veshkurova O, Salikhov S, Aisa HA. (2014). Antimicrobial peptides from the plants. Journal of Pharmacy and Pharmacology 2(1): 627-641. https://doi.org/10.17265/2328-2150/2014.11.00

Zhang QY, Yan ZB, Meng YM, Hong XY, Shao G, Ma JJ, Fu CY. (2021). Antimicrobial peptides: mechanism of action, activity and clinical potential. Military Medical Research 8(48): 1-25. https://doi.org/10.1186/s40779-021-00343-2

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Ali A, Ambrose S, Hussain D, Hafeez F, Asghar T, Shah SNA, Ahsan M, Shakir M, Ali A, Khan AMA, Javed MU. (2024). Antimicrobial resistance and antimicrobial activity of plant-based antimicrobial peptides against bacteria. Letters in Animal Biology 04(2): 19 – 27.