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Insect-derived antimicrobial peptides (AMPs): A promising tool against multidrug-resistant pathogens

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Abstract

The growing threat of multidrug-resistant (MDR) pathogens poses a serious obstacle to current medical treatments, driving the need for novel antimicrobial agents. Insects, which primarily depend on innate immunity, naturally produce a wide array of antimicrobial peptides (AMPs) as part of their defence against microbial invasion. These peptides are typically small, cationic molecules that either disrupt microbial membranes or interfere with vital cellular activities, resulting in the swift destruction of pathogens. Insect-derived AMPs exhibit broad-spectrum antimicrobial properties, acting against a variety of bacteria, fungi, and some viruses. Notably, they have shown potent activity against drug-resistant strains such as MRSA, VRE, and ESBL-producing *Escherichia coli*. Their distinctive mechanisms-particularly those involving direct membrane targeting-make it more difficult for pathogens to acquire resistance. Furthermore, certain AMPs can modulate the host immune response, adding another layer to their therapeutic potential.

Despite these promising features, clinical application remains limited due to issues like low stability, possible toxicity, and high production costs. However, current research is exploring synthetic modifications, nanocarriers, and recombinant production to improve their usability. This review explores the origin, mechanism, and therapeutic potential of insect AMPs in combating drug-resistant infections.

Keywords: Insect AMPs, drug resistance, host defence peptides, antibacterial agents, therapeutic potential, multidrug resistance

Introduction

The increasing spread of antimicrobial resistance (AMR) has emerged as a critical threat to global health systems. It is estimated that by 2050, resistant infections may result in 10 million deaths per year if alternative antimicrobial therapies are not implemented (O'Neill 2016) [1]. As conventional antibiotics lose effectiveness, researchers are exploring new strategies to manage drug-resistant pathogens. Among the most promising are antimicrobial peptides (AMPs), naturally occurring molecules with broad-spectrum activity and unique modes of action (Mylonakis *et al.* 2016) [2].

Insects, comprising the largest class of animals, have evolved robust innate immune systems in the absence of adaptive immunity. A major component of their immune defence includes the production of AMPs, which are short, positively charged peptides capable of targeting bacteria, fungi, and viruses (Bulet, Stocklin, and Menin 2004) [3]. These peptides exert antimicrobial activity primarily through membrane disruption, but some also interfere with intracellular processes, making them especially effective against multidrug-resistant (MDR) organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) (Sayeed, Rahman, and Haque 2022) [4].

Despite their promise, clinical translation of insect-derived AMPs faces several obstacles, including proteolytic degradation, cytotoxicity, and production challenges. Nonetheless, innovations in peptide engineering, recombinant expression systems, and nanocarrier-based delivery are helping to address these limitations (Wang, Li, and Wang 2016 [5]; Yi, Lee, and Kim 2020) [6]. This review aims to explore the classification, mechanisms of action, and potential applications of insect-derived AMPs in the fight against MDR pathogens.

Classification of Insect-Derived Antimicrobial Peptides (AMPs)

Insect antimicrobial peptides (AMPs) are small, functionally diverse molecules that serve as essential components of the insect's innate immune system. These peptides generally consist of 10 to 50 amino acids and are typically positively charged and amphipathic in nature, enabling them to interact with and disrupt microbial cell membranes (Bulet, Stocklin, and Menin 2004) [3]. Based on their structure and amino acid makeup, insect AMPs are primarily grouped into four categories: α-helical, β-sheet, proline-rich, and glycine-rich peptides (Mylonakis *et al.* 2016) [2].

- **α-Helical peptides** (e.g., cecropins and moricins) are often disordered in water but form amphipathic α-helices when in contact with microbial membranes, showing strong antimicrobial activity, particularly against Gram-negative bacteria (Yi, Lee, and Kim 2020) [6].
- **β-Sheet peptides**, such as defensins, possess a structure reinforced by several disulfide bonds, making them

especially effective against Gram-positive bacterial strains (Bulet, Stocklin, and Menin 2004) [3].

- **Proline-rich peptides**, including apidaecins, function mainly inside bacterial cells by attaching to ribosomes and halting protein production. These are particularly effective against pathogens like *Escherichia coli* and *Pseudomonas aeruginosa* (Sayeed *et al.* 2022) [4].
- **Glycine-rich peptides**, such as *attacins*, interfere with outer membrane synthesis and function, primarily targeting Gram-negative bacteria (Wang, Li, and Wang 2016) [5].

These structural classifications not only reflect their diversity but also correlate with their antimicrobial mechanisms and spectrum of activity, making them excellent candidates for drug development against resistant pathogens.

Table 1: Classification of Common Insect-Derived AMPs

Structural Class	Example AMP	Insect Source	Target Pathogens	Mechanism of Action
α-Helical	Cecropin	Hyalophora cecropia	Gram-negative bacteria	Membrane disruption
β-Sheet (Defensins)	Defensin-1	Apis mellifera	Gram-positive bacteria	Pore formation in membranes
Proline-rich	Apidaecins	Apis mellifera	MDR *E. coli*, *P. aeruginosa*	Inhibits protein synthesis
Glycine-rich	Attacins	Manduca sexta	Gram-negative bacteria	Inhibits outer membrane synthesis

Source: Organisms of Insect Antimicrobial Peptides (AMPs)

Insects, due to their evolutionary exposure to diverse microbial environments, have developed a strong innate immune system in which antimicrobial peptides (AMPs) play a central role. These antimicrobial peptides are synthesized in tissues like the fat body, haemocytes, and epithelial cells, and are released into the haemolymph in response to microbial invasion (Bulet, Stocklin, and Menin 2004) [3]. Different insect orders contribute unique types of AMPs. For example, Lepidopteran species like *Hyalophora cecropia* and *Manduca sexta* produce cecropins, attacins, and moricins, which are primarily effective against Gram-negative bacteria (Mylonakis *et al.* 2016) [2]. Dipteran insects such as *Drosophila melanogaster* produce peptides like drosomycin, which exhibits antifungal activity, while Hymenopteran insects like *Apis mellifera* (honeybee) produce defensins and apidaecins with broad-spectrum antibacterial action (Sayeed, Rahman, and Haque 2022) [4]. Coleopteran insects, such as *Tenebrio molitor*, produce tenecins, which are active against Gram-positive pathogens (Mylonakis *et al.* 2016) [2]. These AMPs are structurally diverse and have evolved to efficiently combat specific microbial threats. The diversity of insect species offers a vast natural library of AMPs that can be explored for new antimicrobial therapies.

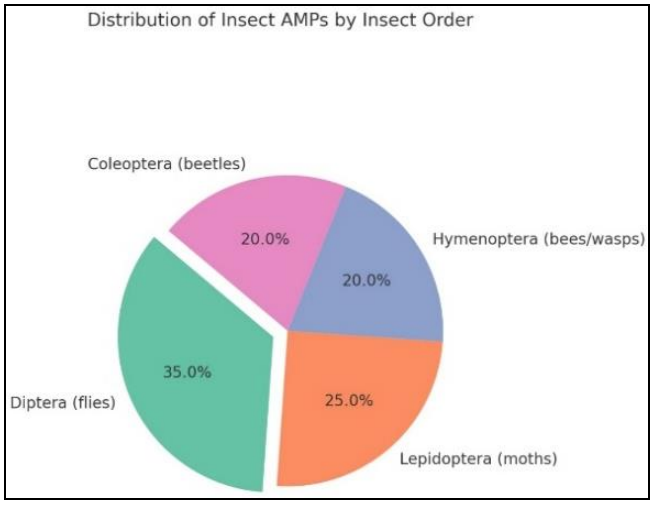

Fig 1: Common insect orders producing AMPs [6]

Mechanism of Action of Insect-Derived AMPs

Antimicrobial peptides (AMPs) derived from insects act mainly by targeting and compromising the integrity of microbial membranes. Due to their amphipathic and positively charged nature, these peptides are strongly attracted to the negatively charged membranes of microbes, especially bacterial cells (Bulet, Stocklin, and Menin 2004) [3]. The primary mode of action involves disruption of the microbial cell membrane. After attaching to the membrane surface, AMPs penetrate into the lipid bilayer, forming pores or channels. This pore formation results in the leakage of essential intracellular contents, dissipation of membrane potential, and eventually leads to cell lysis and death (Mylonakis *et al.* 2016) [2]. Notably, peptides such as cecropins and defensins operate via this mechanism, rapidly disturbing the membrane structure and function (Yi, Lee, and Kim 2020) [6].

Another important mechanism involves intracellular targeting. Some AMPs, especially proline-rich peptides like *apidaecins*, can enter microbial cells without destroying the membrane. Once inside, they bind to specific molecules like ribosomes and inhibit essential processes such as protein synthesis or DNA replication (Sayeed, Rahman, and Haque 2022) [4]. In addition to direct antimicrobial activity, certain insect AMPs also have immunomodulatory effects, where they stimulate the host immune system to fight infections more effectively (Wang, Li, and Wang 2016) [5]. The diversity in structure and function of AMPs allows them to act quickly and with less risk of resistance development, making them powerful candidates for future antimicrobial therapies.

Insect-derived antimicrobial peptides (AMPs) neutralize microbial threats through multiple sophisticated strategies that primarily involve targeting the microbial cell membrane and internal components. Their amphipathic and cationic structures enable selective interaction with negatively charged bacterial membranes, making them ideal tools for combating drug-resistant infections. One well-recognized explanation for how AMPs function is the barrel-stave model, where peptides insert themselves into the lipid bilayer and align to form a barrel-like pore. These channels facilitate the uncontrolled movement of ions and small molecules, leading to membrane depolarization and ultimately microbial cell death (Brogden 2005) [7]. Insect-derived peptides such as cecropins and defensins are frequently associated with this mechanism.

Another mechanism is the carpet model, wherein peptides accumulate extensively on the membrane surface, forming a layer resembling a carpet. Once a critical concentration is achieved, they disrupt the membrane in a detergent-like fashion, leading to total membrane disintegration without forming defined pores (Hoskin and Ramamoorthy 2008) [8]. Some AMPs bypass the membrane entirely and operate through intracellular targeting. These peptides cross the membrane barrier and interfere with key cellular functions like protein folding, DNA replication, or enzymatic activity. A notable example is apidaecins, which interact with bacterial chaperones (such as DNA-binding proteins), effectively inhibiting protein synthesis without damaging the cell membrane (Krizsan, Knappe, and Hoffmann 2015) [9].

A fourth mode of action involves modulating the host immune response, where AMPs stimulate immune signalling pathways and enhance production of cytokines and other immune molecules. This dual action-direct killing and immune support-adds further therapeutic potential to insect AMPs (Brown and Hancock 2006) [10]. These varied mechanisms not only contribute to AMP effectiveness but also help reduce the risk of resistance development, making them strong candidates for next-generation antimicrobial therapies.

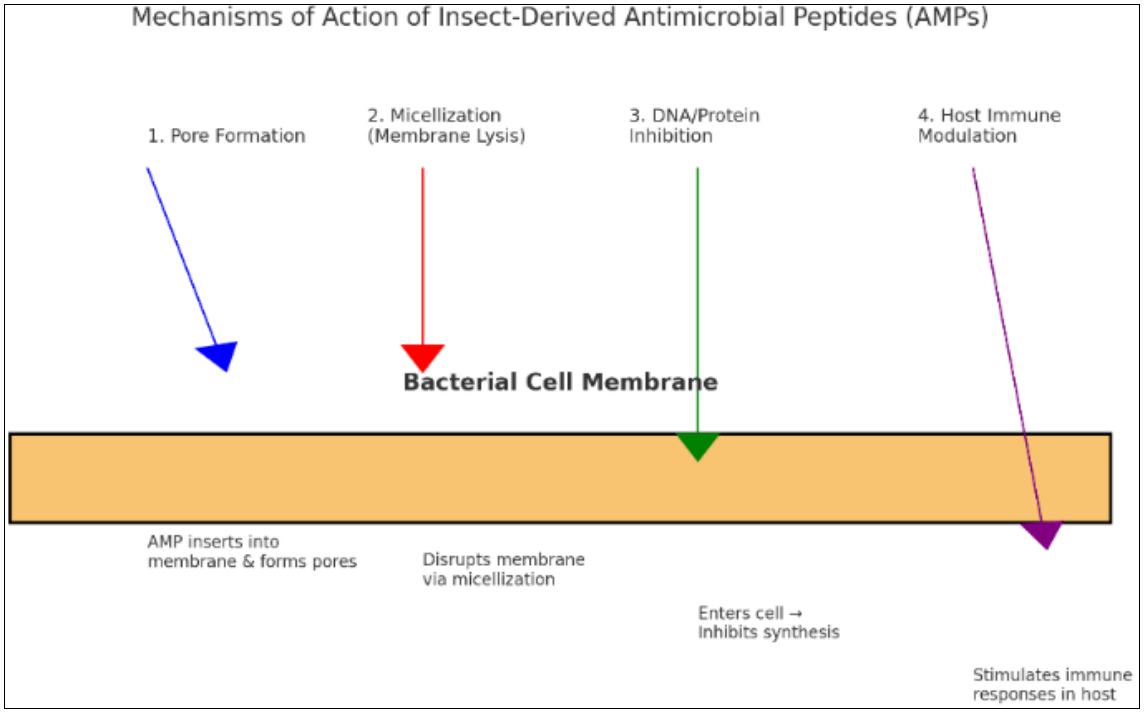

Fig 2: Mechanisms of action of insect-derived antimicrobial peptides (AMPs) [7]

4. Insect AMPs Against Multidrug-Resistant Pathogens

The growing threat of multidrug-resistant (MDR) microorganisms has greatly diminished the effectiveness of conventional antibiotics, creating an urgent need for alternative therapeutic solutions. Insect-derived antimicrobial peptides (AMPs) have gained attention as promising candidates owing to their distinct mechanisms and broad-spectrum antimicrobial properties (Bulet, Stocklin, and Menin 2004) [3]. Several AMPs from insects have shown significant activity against major MDR pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (Yi, Lee, and Kim 2020) [6]. For example, defensins from the honeybee (*Apis mellifera*) exhibit strong antibacterial effects against Gram-positive bacteria by compromising their membrane structure (Casteels *et al.* 1994) [11]. Likewise, cecropins, originally isolated from the silk moth (*Hyalophora cecropia*), are effective against Gram-negative organisms by forming membrane pores that lead to bacterial lysis (Steiner *et al. 1981*) [12].

In addition, *apidaecins*, proline-rich AMPs from bees, inhibit protein synthesis by entering bacterial cells without damaging their membranes, making them particularly effective against resistant Gram-negative strains (Sayeed, Rahman, and Haque 2022) [4]. Beetle-derived AMPs like *tenecins* from *Tenebrio molitor* also show promise due to their stability and targeted activity against Gram-positive MDR strains (Pfalzgraff, Brandenburg, and Weindl 2018) [13].

Table 2: Insect Sources of AMPs Active Against MDR Pathogens

Insect	AMP Type	Target MDR Pathogen
Apis mellifera (Bee)	Defensin, Apidaecins	MRSA, VRE, MDR E. coli
Drosophila (Fly)	Drosomycin	MDR Gram-positive bacteria
Tenebrio molitor	Tenecins	MRSA, MDR Gram-positive
Hyalophora cecropia	Cecropin	ESBL-producing E. coli

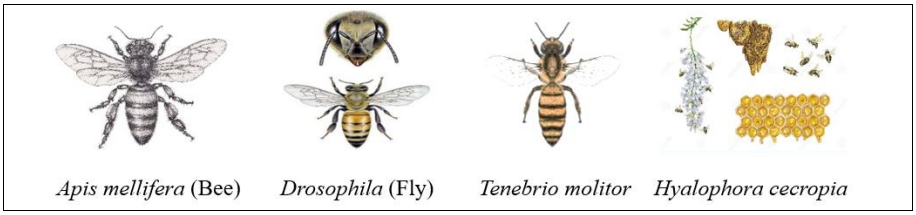

Fig 3: Representation of insect species that produce antimicrobial peptides (AMPs) with proven activity against multidrug-resistant (MDR) microorganisms (Gillespie, Kanost, & Trenczek 1997) [14].

Therapeutic Potential and Advantages of Insect-Derived AMPs

Antimicrobial peptides (AMPs) derived from insects show great potential as therapeutic agents, especially for treating infections caused by multidrug-resistant (MDR) organisms. Their rapid mode of action, broad-spectrum antimicrobial activity, and reduced likelihood of promoting resistance highlight their value in developing innovative anti-infective therapies (Yi, Lee, and Kim 2020) [6]. Unlike conventional antibiotics that usually have single molecular targets, insect AMPs exhibit multi-target mechanisms, including membrane disruption, inhibition of intracellular synthesis, and immune modulation. This multi-faceted activity not only enhances their effectiveness but also reduces the likelihood of resistance emergence (Hancock & Sahl 2006) [15].

Additionally, insect AMPs display selectivity for microbial cells over mammalian cells due to differences in membrane composition. This contributes to their low toxicity profiles in therapeutic settings (Fjell *et al.* 2012) [16]. Many AMPs, such as cecropins, defensins, and apidaecins, have demonstrated strong in *vivo* antimicrobial activity without inducing harmful side effects in the host organism (Bulet, Stocklin, and Menin 2004) [3]. Furthermore, some insect AMPs have been shown to synergize with traditional antibiotics, increasing the overall efficacy of treatment. For example, combining AMPs with β-lactams or aminoglycosides has enhanced antibacterial outcomes against resistant strains. This opens avenues for combination therapies where AMPs could restore the effectiveness of existing drugs.

Lastly, the structural diversity and natural origin of insect AMPs make them attractive for bioengineering and synthetic modification, allowing the development of stable, potent, and cost-effective peptide drugs.

Challenges and Limitations of Insect-Derived AMPs

Although insect-derived antimicrobial peptides (AMPs) offer great potential in combating multidrug-resistant (MDR) pathogens, several limitations restrict their clinical utility. A primary concern is their instability due to proteolytic degradation in biological environments, which leads to a short half-life and reduced therapeutic activity. This degradation makes systemic administration challenging. Another significant limitation is cytotoxicity, as certain AMPs may harm human cells at higher doses. Additionally, these peptides suffer from low bioavailability, largely due to poor permeability across biological membranes and rapid renal clearance (Mahlapuu *et al.* 2016 [17]; Lei *et al.* 2019) [18].

Moreover, high production costs associated with peptide synthesis, purification, and formulation hinder large-scale manufacturing and commercial viability (Fjell *et al.* 2012) [16]. The challenge of targeted delivery further complicates their application; without efficient delivery systems, AMPs may lose effectiveness or cause off-target effects (Lei *et al.* 2019) [18].

Finally, the lack of standardized clinical protocols, limited in *vivo* studies, and regulatory challenges delay their translation from bench to bedside. Overcoming these barriers will require innovative drug delivery systems, peptide engineering, and more robust clinical trials.

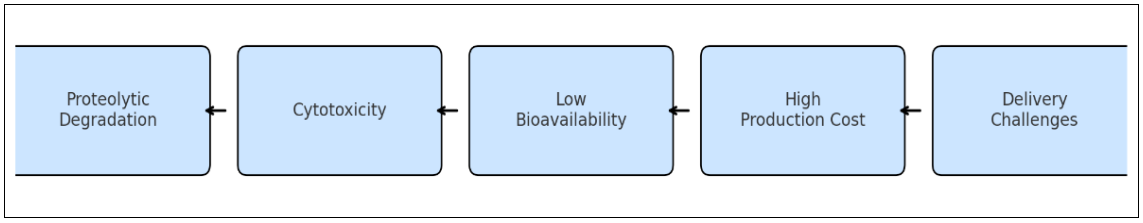

Fig 4: Key obstacles limiting the clinical development and therapeutic application of insect-derived antimicrobial peptides (AMPs)

Future Prospects of Insect-Derived AMPs

The future of insect-derived antimicrobial peptides (AMPs) lies in their strategic modification and integration into novel drug delivery systems to overcome existing limitations. One promising approach is the use of nanotechnology-based carriers, such as liposomes, solid lipid nanoparticles, and polymeric systems, to improve the stability, bioavailability, and targeted delivery of AMPs (Mahlapuu *et al.* 2016) [17]. Peptide engineering offers another pathway by designing analogs with enhanced specificity, lower toxicity, and resistance to proteolytic degradation. Advances in synthetic biology and recombinant expression systems now allow for cost-effective and scalable production of AMPs using bacterial, yeast, or plant-based platforms (Maróti *et al.* 2014 [19]; Li *et al.* 2012) [20]. Combining AMPs with conventional antibiotics has shown synergistic effects in multiple studies, helping to reduce required doses and delay resistance development (Pletzer, and Hancock 2016) [21]. This opens

the possibility of developing dual-therapy regimens against MDR pathogens. Additionally, the use of AMPs as immunomodulators or vaccine adjuvants is gaining attention, particularly in infectious disease and oncology research (Lei *et al.* 2019) [18].

Overall, insect AMPs represent a versatile and powerful tool in the fight against antimicrobial resistance. Their clinical potential will be realized by bridging research with formulation science, genetic engineering, and regulatory acceptance.

Conclusion

In light of the escalating global threat posed by antimicrobial resistance, insect-derived antimicrobial peptides (AMPs) emerge as promising alternatives to conventional antibiotics. Their rapid action, structural variety, and unique mechanisms-such as disrupting microbial membranes and influencing host immunity-make them valuable candidates for next-generation therapeutics. Unlike traditional drugs, AMPs are less likely to trigger resistance, which enhances their appeal in modern medicine. Despite these advantages, their clinical application is currently hindered by challenges like enzymatic degradation, potential toxicity, and limited bioavailability. Ongoing advancements in nanotechnology, molecular engineering, and drug delivery are actively addressing these limitations. Continued interdisciplinary research focusing on safety profiles, pharmacodynamics, and regulatory considerations will be critical in transforming insect AMPs from laboratory discoveries into viable clinical treatments.

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