***Minireview Article***

**Insect-Derived Antimicrobial Peptides and Their Microbial Targets: Biochemical Mechanisms and Synthetic Biology Approaches**

**Abstract**

Insects, which make up the largest portion of animal biodiversity on Earth, thrive in environments abundant with pathogenic microorganisms. Their survival is largely due to a highly effective innate immune system that compensates for the lack of adaptive immunity. A central element of this defense system is antimicrobial peptides (AMPs), which are small, usually positively charged, and amphipathic molecules capable of neutralizing a wide range of microbial pathogens. These AMPs exhibit significant variability in their sequences, structures, and mechanisms of action, targeting microbial membranes as well as intracellular components. Given the growing concern of antibiotic-resistant pathogens, insect AMPs have attracted attention as promising templates for new antimicrobial agents. Recent progress in synthetic biology offers tools to engineer AMPs with improved features such as enhanced stability, specificity, and delivery. This review discusses the diversity of insect AMPs, their microbial targets, biochemical and molecular mechanisms, synthetic biology strategies for their enhancement, and their applications in medicine, agriculture, and industry.

**Key Words**: Insect antimicrobial peptides, Innate immunity, Synthetic biology, Antibiotic resistance, Therapeutic applications

**Introduction**

Insects are the most diverse group of animals on Earth, with millions of species inhabiting nearly every terrestrial and aquatic habitat. However, the exact number of insect species remains a mystery, with estimates ranging from 5.5 million to 7 million. Insects also serve as efficient decomposers. Wood-boring beetles, dung beetles, and termites are just a few examples of insects that break down organic matter, recycle nutrients, and maintain soil fertility. Insects play a crucial role in the Earth’s natural decomposition process, ensuring the efficient breakdown of organic matter and preventing the accumulation of waste, a vital function that would be severely hindered without their presence (Chivian, 2002).

**Microbial Targets of Insect AMPs**

Insect AMPs demonstrate broad-spectrum activity against a variety of pathogens, including Gram-positive and Gram-negative bacteria, fungi, and potentially protozoa and enveloped viruses. In Gram-negative bacteria, AMPs such as cecropins and attacins bind to lipopolysaccharides (LPS) in the outer membrane, destabilizing it and forming pores that result in cell lysis (Yi et al., 2014). Diptericins complement this action by interfering with LPS biosynthesis, thereby further weakening bacterial defenses (Hetru et al., 1998). Recently, novel insights have highlighted how attacins also inhibit outer membrane protein assembly, further enhancing bactericidal activity (Wu et al., 2018). Against Gram-positive bacteria, defensins interact with lipoteichoic acid and peptidoglycan, creating channels that disrupt ionic gradients and cause cell death (Bulet et al., 1999). Studies on coleopteran-derived defensins have revealed additional mechanisms involving the inhibition of cell wall biosynthetic enzymes (García-Bayona & Comstock, 2018).

In terms of antifungal activity, drosomycin and termicin inhibit fungi by binding to β-glucans or chitin in fungal cell walls, thereby interfering with hyphal elongation and cell wall synthesis (Fehlbaum et al., 1994; Lamberty et al., 2001). Newer studies suggest that insect AMPs can also induce reactive oxygen species (ROS) accumulation in fungal cells, contributing to oxidative stress-mediated killing (Wang et al., 2021). Insect AMPs have demonstrated activity not only against common fungi but also emerging fungal pathogens such as *Candida auris* (Mahlapuu et al., 2020).

Recent studies have focused on the efficacy of insect AMPs against multidrug-resistant (MDR) bacteria. For example, cecropins have demonstrated potent activity against MDR *Escherichia coli* and *Pseudomonas aeruginosa* (Giacometti et al., 2000; Silva et al., 2020). Furthermore, novel AMPs like ponericins and mastoparans show promising activity against carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* (Chung et al., 2021; Samuelsen et al., 2022). Insect AMPs are also being evaluated for their anti-biofilm properties and their use in combination therapies with conventional antibiotics, which has been shown to reduce the minimum inhibitory concentrations of standard drugs against biofilm-embedded bacteria (Batoni et al., 2016; Dosler & Karaaslan, 2021). Advances in synthetic biology and peptide engineering have also enabled the design of insect AMP derivatives with enhanced stability and selectivity, opening avenues for therapeutic development (Mookherjee et al., 2020).

**Molecular Mechanisms of Action**

The molecular mechanisms by which insect AMPs act can be broadly divided into membrane-disruptive models and intracellular targeting strategies. The barrel-stave model, typified by cecropins, involves peptides inserting perpendicularly into membranes, forming transmembrane pores that allow uncontrolled ion leakage, depolarization, and ultimately cell death (Steiner et al., 1981). The toroidal pore model, observed in some cecropin hybrids and moricin analogs, forms transient pores where lipid monolayers bend continuously through the pore, blending peptide and lipid components (Yeaman & Yount, 2003; Zhang et al., 2019). The carpet model, associated with attacins, diptericins, and certain glycine-rich AMPs, involves peptides covering the membrane surface like a carpet, leading to micellization and membrane disintegration (Hetru et al., 1998).

Beyond membrane disruption, several insect AMPs penetrate the plasma membrane to exert intracellular effects. Defensins and cecropins have been shown to translocate across membranes, where they can bind to nucleic acids, interfering with transcription and translation (Yi et al., 2014). Some AMPs inhibit key intracellular enzymes, such as DNA gyrase or RNA polymerase, or interact with ribosomes, impairing protein synthesis (Mahlapuu et al., 2020). Drosomycin binds β-glucans, hindering fungal cell wall assembly, while termicins and related AMPs may inhibit chitin synthase and trigger reactive oxygen species accumulation in fungal pathogens (Lamberty et al., 2001; Wang et al., 2021).

Recent research employing NMR spectroscopy, cryo-electron microscopy (cryo-EM), and molecular dynamics (MD) simulations has provided atomic-level resolution of AMP-lipid and AMP-protein interactions, offering deeper insights into their dynamics and selectivity (Mandal et al., 2020; Jenssen et al., 2006; Schmitt et al., 2022). For example, MD simulations have revealed how specific residues in insect AMPs stabilize pore structures or preferentially target bacterial versus mammalian membranes (Schmitt et al., 2022). Moreover, machine-learning-aided structure–function studies have begun to predict AMP activity based on sequence motifs and biophysical properties, accelerating the design of synthetic AMP analogues (Pirtskhalava et al., 2021).

Emerging evidence also suggests that some insect AMPs modulate host immune signaling pathways, acting as immunomodulators in addition to their direct antimicrobial effects, which could enhance their therapeutic potential (Mookherjee et al., 2020).

**Synthetic Biology Approaches for Enhancing Insect AMPs**

Synthetic biology offers powerful tools to engineer and produce antimicrobial peptides (AMPs) at scale with tailored properties for diverse applications in medicine, agriculture, and industry. Recombinant expression systems such as *Escherichia coli*, *Pichia pastoris*, *Bacillus subtilis*, and insect cell lines (e.g., Sf9 cells) have facilitated the production of insect-derived AMPs, allowing for cost-effective scaling (Li et al., 2021; Lee et al., 2023). Despite their utility, these systems can suffer from low yields, peptide toxicity to host cells, and post-translational modification issues. Strategies such as fusion protein tags (e.g., thioredoxin or SUMO) and secretion signals have improved peptide solubility, folding, and recovery (Zhang et al., 2021).

Rational design approaches have enhanced AMP potency and stability. Amino acid substitutions, particularly the incorporation of arginine and tryptophan residues, improve membrane affinity and facilitate deeper insertion into bacterial lipid bilayers (Porto et al., 2018). Likewise, cyclization and backbone modification using D-amino acids or peptidomimetics significantly increase resistance to proteolytic degradation, improving pharmacokinetics and serum stability (Mandal et al., 2020; Cherkasov et al., 2021).

Hybrid AMPs, such as cecropin–defensin and melittin–magainin chimeras, offer the combined benefits of broader antimicrobial spectra, enhanced potency, and reduced immunogenicity (Silva et al., 2020). These chimeras also lower the risk of resistance development by targeting multiple microbial components simultaneously. Additionally, PEGylation, lipidation, and glycosylation are being explored to increase systemic circulation and reduce toxicity in vivo (Lei et al., 2022).

Translational applications of insect AMPs have expanded through transgenic expression systems. For instance, transgenic plants expressing insect AMPs such as cecropins or defensins have shown resistance to bacterial and fungal phytopathogens, offering eco-friendly alternatives to chemical pesticides (Gao et al., 2017; Wang et al., 2023). Engineered probiotics and microbiome modulators that express AMPs locally in the gut are also being developed to combat enteric pathogens and reduce antibiotic dependence (Charbonneau et al., 2020).

A transformative development is the integration of machine learning (ML) and AI-guided design. These tools accelerate the identification and optimization of novel AMP sequences with desired biophysical properties, using large-scale databases and predictive algorithms (Gabere & Noble, 2017; Torres et al., 2022). AI platforms now support de novo AMP generation, guided by quantitative structure–activity relationships (QSAR), enabling the fine-tuning of selectivity, cytotoxicity, and pharmacodynamics. Additionally, CRISPR-based genome editing has enabled the direct integration of AMP genes into microbial or plant genomes for stable expression and controlled AMP release.

Together, these synthetic biology innovations are advancing the therapeutic potential of insect AMPs, supporting their use in combating multidrug-resistant pathogens, promoting sustainable agriculture, and modulating microbiomes in health and disease.

**Applications of Insect AMPs**

Insect AMPs, due to their broad-spectrum antimicrobial activity, structural diversity, and relatively low propensity for inducing resistance, are increasingly explored for practical applications across medicine, agriculture, food preservation, environmental management, and industrial biotechnology.

In medicine, insect AMPs such as cecropins, defensins, attacins, and hybrid peptides (e.g., cecropin–defensin chimeras) are being actively developed as alternatives or adjuncts to traditional antibiotics, particularly for combating multidrug-resistant (MDR) pathogens (Silva et al., 2020; Mahlapuu et al., 2016; Chung et al., 2021). Their efficacy against biofilm-associated infections, where conventional antibiotics often fail, has been highlighted (Batoni et al., 2016; Dosler & Karaaslan, 2021). For instance, defensins and cecropins have been incorporated into hydrogels, nanofibers, and lipid-based nanocarriers, enabling controlled, localized delivery in wound dressings, tissue engineering scaffolds, and implant coatings, where they prevent infections and promote tissue regeneration (Charbonneau et al., 2020; Felício et al., 2017; Lei et al., 2022). Engineered AMPs are also used in medical device coatings for catheters, stents, prosthetics, and orthopedic implants to prevent biofilm formation by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Costa et al., 2019; Ramasamy & Lee, 2016). In oncology, insect AMPs are being investigated for their selective cytotoxicity towards cancer cells, mediated by interactions with negatively charged tumor cell membranes (Hale & Hancock, 2007).

In agriculture, insect AMPs have been successfully expressed in transgenic crops, including rice, tomato, potato, and tobacco, to enhance resistance against a wide range of bacterial, fungal, and oomycete pathogens (Gao et al., 2017; Montesinos & Bardají, 2008; Wang et al., 2023). This strategy reduces reliance on chemical pesticides, supporting more sustainable agricultural practices. Beyond transgenic plants, insect AMPs are being delivered via engineered endophytes, symbiotic bacteria, and plant growth-promoting rhizobacteria, offering biological control solutions that can adapt to diverse crop systems (Charbonneau et al., 2020; Yang et al., 2022). Insect AMP sprays or coatings are also being explored as biopesticides that target pest-associated microbiomes, reducing vector competence without harming beneficial insects.

In food preservation, insect AMPs are gaining attention as natural preservatives capable of inhibiting spoilage organisms and foodborne pathogens such as *Listeria monocytogenes*, *Salmonella spp.*, and *Escherichia coli* O157:H7 (Chikindas et al., 2018; Ramaswamy et al., 2021). AMPs can be incorporated into edible coatings, bio-based packaging films, and smart packaging systems to extend shelf life while avoiding synthetic chemicals (da Costa et al., 2019; Ben Said et al., 2020). AMP-functionalized surfaces with antimicrobial and antifouling properties are under development for use in food processing equipment and contact materials.

In industrial biotechnology, insect AMPs are studied for biofilm prevention and control in settings such as water treatment plants, cooling towers, paper manufacturing, and pipelines, where microbial fouling leads to equipment degradation, reduced efficiency, and increased maintenance costs (Zasloff, 2019; Bahar & Ren, 2013). AMP-based solutions offer environmentally friendly alternatives to conventional chemical biocides, helping industries move toward greener practices (Schmitt et al., 2022).

Emerging applications include veterinary medicine, where insect AMPs are incorporated into animal feeds, topical formulations, or aquaculture systems to control infections in livestock and aquatic species, reducing the need for conventional antibiotics and mitigating the spread of antimicrobial resistance (Falco et al., 2016; Sahoo et al., 2021). Insect AMPs are also being explored for use in personal care products, including oral hygiene (e.g., antimicrobial mouthwashes, toothpastes) and dermatological formulations for managing acne, atopic dermatitis, and wound healing (Mahlapuu et al., 2016; Lei et al., 2022).

Importantly, the integration of synthetic biology, machine learning, and AI-guided design is revolutionizing AMP-based product development. These approaches enable the custom design of AMPs with optimized spectra of activity, pharmacokinetics, and selectivity while minimizing host cytotoxicity and immunogenicity (Gabere & Noble, 2017; Porto et al., 2018; Torres et al., 2022). Advances in peptide engineering, including cyclization, lipidation, glycosylation, and fusion constructs, are addressing challenges related to peptide stability, production cost, and delivery (Cherkasov et al., 2021).

**Challenges and Future Perspectives**

Despite their promise, insect AMPs face several challenges in clinical and industrial translation. A major hurdle is their susceptibility to proteolytic degradation by endogenous proteases in blood, tissues, or gastrointestinal environments, which can limit bioavailability and efficacy (Mahlapuu et al., 2016; Lei et al., 2022). This necessitates frequent dosing or high concentrations, raising concerns about cost and potential toxicity. Additionally, while insect AMPs are generally selective for microbial membranes, some peptides exhibit off-target cytotoxicity towards host cells, particularly at higher doses or with prolonged exposure (Mookherjee et al., 2020). Addressing these issues requires careful optimization of peptide sequences, charge distribution, hydrophobicity, and secondary structure.

High production costs and scalability remain significant barriers to commercial deployment. Chemical synthesis of AMPs is expensive, especially for long sequences or modified peptides. Although recombinant expression in microbial or plant systems offers cost advantages, challenges such as low yields, formation of inclusion bodies, and downstream purification complexity persist (Ghosh et al., 2022). Furthermore, large-scale production systems must meet Good Manufacturing Practice (GMP) standards and ensure batch consistency, adding regulatory and economic complexity.

On the regulatory front, AMP-based therapies must undergo comprehensive evaluations of pharmacokinetics, pharmacodynamics, immunogenicity, and long-term safety to gain approval. The lack of standardized guidelines for peptide-based antimicrobial agents has also slowed regulatory pathways (Mahlapuu et al., 2016; Mookherjee et al., 2020).

Future research should prioritize strategies to enhance peptide stability, such as incorporation of D-amino acids, cyclization, backbone modifications (e.g., peptidomimetics), and conjugation with polymers like PEG (Haney et al., 2019; Cherkasov et al., 2021). Advances in engineered microbial factories — including CRISPR-edited strains of *E. coli*, *Bacillus subtilis*, and *Pichia pastoris* — promise to reduce production costs and improve yields of AMPs and their analogs (Gupta et al., 2023; Ghosh et al., 2022).

In parallel, computational and AI-guided design tools are revolutionizing AMP discovery and optimization, enabling the creation of peptides with improved selectivity, reduced toxicity, and enhanced pharmacokinetic properties (Rao et al., 2021; Torres et al., 2022). Structural biology, including cryo-electron microscopy and NMR, continues to elucidate the mechanisms of action at atomic resolution, guiding rational engineering efforts (Schmitt et al., 2022).

The future of insect AMPs lies in integrated approaches that combine structural biology, synthetic biology, systems biology, and machine learning. Such multi-disciplinary efforts will help realize the full therapeutic and industrial potential of insect AMPs, facilitating their transition from laboratory research to real-world applications. The development of smart delivery systems (e.g., responsive hydrogels, nanocarriers, and microneedles) will further support clinical translation by improving bioavailability, targeted delivery, and patient compliance (Felício et al., 2017; Lei et al., 2022).

**Conclusion**

Based on the comprehensive review presented in the document “Insect-Derived Antimicrobial Peptides and Their Microbial Targets: Biochemical Mechanisms and Synthetic Biology Approaches,” it is evident that insect antimicrobial peptides (AMPs) represent a highly promising and versatile class of biomolecules with far-reaching implications across medicine, agriculture, and industry. The analytical synthesis of this review reveals several key themes and insights, which collectively underscore both the remarkable potential and the ongoing challenges associated with the translation of insect AMPs from basic research to real-world applications.

First and foremost, insect AMPs are highlighted as a cornerstone of innate immunity in insects, enabling these organisms to thrive in microbe-rich environments despite lacking adaptive immune responses. Their broad-spectrum activity against Gram-positive and Gram-negative bacteria, fungi, and, in some cases, viruses, is rooted in their structural diversity and adaptability. The review details how different classes of insect AMPs—such as cecropins, defensins, attacins, and drosomycins—exert their effects through a variety of molecular mechanisms. These include direct disruption of microbial membranes via pore formation (barrel-stave, toroidal pore, and carpet models) and interference with intracellular targets such as nucleic acids, ribosomes, and biosynthetic enzymes. The ability of some insect AMPs to induce oxidative stress in fungal pathogens or modulate host immune signaling further expands their functional repertoire and therapeutic promise.

A particularly salient aspect of the review is the discussion of insect AMPs as templates for next-generation antimicrobials in the face of escalating antibiotic resistance. The emergence of multidrug-resistant (MDR) pathogens has catalyzed interest in AMPs, given their unique mechanisms of action that differ from those of conventional antibiotics. The review presents compelling evidence of insect AMPs’ efficacy against MDR bacteria, biofilm-associated infections, and even emerging fungal threats such as Candida auris. Moreover, the synergistic use of insect AMPs with traditional antibiotics is shown to enhance antimicrobial efficacy while potentially mitigating resistance development.

The integration of synthetic biology and advanced bioengineering is another major theme, positioning insect AMPs at the frontier of molecular innovation. Recombinant expression systems, rational peptide design, and chemical modifications (e.g., cyclization, PEGylation, lipidation) have collectively addressed many of the production, stability, and delivery challenges historically associated with peptide therapeutics. The creation of hybrid and chimeric AMPs, as well as the application of machine learning and AI-guided design, has accelerated the discovery and optimization of novel peptides with enhanced potency, selectivity, and pharmacokinetic profiles. These advances are not only propelling the clinical development of AMP-based drugs but are also enabling their deployment in agriculture as transgenic crop protectants and in industry as environmentally friendly biofilm inhibitors.

The review also provides a nuanced examination of the practical applications of insect AMPs. In medicine, their use extends from topical wound care and implant coatings to potential roles in oncology and immunomodulation. In agriculture, transgenic plants expressing insect AMPs offer sustainable alternatives to chemical pesticides, while engineered probiotics and microbiome modulators promise to reduce antibiotic dependence in livestock and aquaculture. In food preservation and industrial biotechnology, AMPs are being developed as natural preservatives and antifouling agents, supporting greener and safer production processes.

Despite these advances, the review does not shy away from the significant challenges that remain. Chief among these is the susceptibility of AMPs to proteolytic degradation in biological environments, which can limit their bioavailability and necessitate frequent or high-dose administration. While chemical modifications and delivery systems are mitigating some of these issues, concerns about off-target cytotoxicity, immunogenicity, and production costs persist. Furthermore, the regulatory landscape for peptide-based therapeutics and genetically modified organisms remains complex, potentially slowing the translation of laboratory successes into commercial products.

Looking forward, the review suggests that the future of insect AMP research and application will likely hinge on continued interdisciplinary collaboration. Advances in structural biology, computational modeling, and systems biology will be critical for elucidating the precise determinants of AMP specificity, potency, and safety. Synthetic biology platforms, combined with AI-driven sequence optimization, will further expand the chemical space accessible for AMP engineering, enabling the rapid prototyping of peptides tailored to specific pathogens or application contexts. Importantly, the integration of AMPs into holistic antimicrobial stewardship strategies—spanning human health, animal husbandry, agriculture, and environmental management—will be essential for maximizing their societal impact while minimizing the risk of resistance development.

In conclusion, insect-derived antimicrobial peptides stand at the intersection of evolutionary biology, molecular medicine, and biotechnology. Their intrinsic diversity, multifaceted mechanisms of action, and amenability to synthetic enhancement make them uniquely positioned to address some of the most pressing challenges of the 21st century, including antibiotic resistance, sustainable agriculture, and safe food production. While significant hurdles remain, the convergence of advances in peptide engineering, synthetic biology, and computational design is rapidly transforming the landscape, bringing the promise of insect AMPs closer to widespread practical realization. The review thus calls for sustained investment in research, innovation, and regulatory harmonization to fully unlock the potential of these remarkable molecules for the benefit of human health and global sustainability.

**References**

Bahar, A. A., & Ren, D. (2013). Antimicrobial peptides. *Pharmaceuticals*, 6(12), 1543–1575. https://doi.org/10.3390/ph6121543

Batoni, G., Maisetta, G., Brancatisano, F. L., Esin, S., & Campa, M. (2016). Use of antimicrobial peptides against microbial biofilms: advantages and limits. *Current Medicinal Chemistry*, 23(36), 4100–4124. https://doi.org/10.2174/0929867323666160727142405

Batoni, G., Maisetta, G., Brancatisano, F. L., Esin, S., & Campa, M. (2016). Use of antimicrobial peptides against microbial biofilms: advantages and limits. *Current Medicinal Chemistry*, 23(36), 4100–4124. https://doi.org/10.2174/0929867323666160727142405

Ben Said, L., Gaudreau, H., Dallaire, L., & Fliss, I. (2020). Bioprotective cultures and antimicrobial peptides: promising alternatives to chemical preservatives for food safety. *Trends in Food Science & Technology*, 98, 257–270. https://doi.org/10.1016/j.tifs.2020.02.019

Bulet, P., Hetru, C., Dimarcq, J. L., & Hoffmann, D. (1999). Antimicrobial peptides in insects; structure and function. *Developmental & Comparative Immunology*, 23(4-5), 329–344. https://doi.org/10.1016/S0145-305X(99)00015-4

Charbonneau, M. R., Isabella, V. M., Li, N., & Kurtz, C. B. (2020). Developing a new class of engineered live bacterial therapeutics to treat human diseases. Nature Communications, 11(1), 1738. https://doi.org/10.1038/s41467-020-15474-0

Charbonneau, M. R., Isabella, V. M., Li, N., & Kurtz, C. B. (2020). Developing a new class of engineered live bacterial therapeutics to treat human diseases. *Nature Communications*, 11, 1738. https://doi.org/10.1038/s41467-020-15474-0

Cherkasov, A., Hilpert, K., Jenssen, H., Fjell, C. D., Waldbrook, M., Mullaly, S. C., ... & Hancock, R. E. (2021). Use of artificial intelligence in the design of small peptide antibiotics effective against a broad spectrum of highly antibiotic-resistant superbugs. ACS Chemical Biology, 6(9), 1887–1896. https://doi.org/10.1021/cb200342m

Cherkasov, A., Hilpert, K., Jenssen, H., Fjell, C. D., Waldbrook, M., Mullaly, S. C., ... & Hancock, R. E. W. (2021). Use of artificial intelligence in the design of small peptide antibiotics effective against a broad spectrum of highly antibiotic-resistant superbugs. *ACS Chemical Biology*, 6(9), 1887–1896. https://doi.org/10.1021/cb200342m

Cherkasov, A., Hilpert, K., Jenssen, H., Fjell, C. D., Waldbrook, M., Mullaly, S. C., ... & Hancock, R. E. W. (2021). Use of artificial intelligence in the design of small peptide antibiotics effective against a broad spectrum of highly antibiotic-resistant superbugs. ACS Chemical Biology, 6(9), 1887–1896. https://doi.org/10.1021/cb200342m

Chikindas, M. L., Weeks, R., Drider, D., Chistyakov, V. A., & Dicks, L. M. T. (2018). Functions and emerging applications of bacteriocins. *Current Opinion in Biotechnology*, 49, 23–28. https://doi.org/10.1016/j.copbio.2017.07.011

Chung, P. Y., Khanum, R., & Chowdhury, N. (2021). Insect-derived antimicrobial peptides as potential therapeutics against multidrug-resistant Gram-negative pathogens. *Frontiers in Microbiology*, 12, 710356. https://doi.org/10.3389/fmicb.2021.710356

Chung, P. Y., Khanum, R., & Chowdhury, N. (2021). Insect-derived antimicrobial peptides as potential therapeutics against multidrug-resistant Gram-negative pathogens. *Frontiers in Microbiology*, 12, 710356. https://doi.org/10.3389/fmicb.2021.710356

Costa, F., Carvalho, I. F., Montelaro, R. C., Gomes, P., & Martins, M. C. L. (2019). Covalent immobilization of antimicrobial peptides (AMPs) onto biomaterial surfaces. *Acta Biomaterialia*, 10(9), 3515–3526. https://doi.org/10.1016/j.actbio.2014.04.003

da Costa, J. P., Cova, M., Ferreira, R., Vitorino, R. (2019). Antimicrobial peptides: an alternative for innovative medicines? *Applied Microbiology and Biotechnology*, 103(7), 2541–2557. https://doi.org/10.1007/s00253-019-09674-1

Dosler, S., & Karaaslan, E. (2021). Antimicrobial and antibiofilm activities of antimicrobial peptides. *Future Microbiology*, 16, 711–729. https://doi.org/10.2217/fmb-2020-0250

Dosler, S., & Karaaslan, E. (2021). Antimicrobial and antibiofilm activities of antimicrobial peptides. *Future Microbiology*, 16, 711–729. https://doi.org/10.2217/fmb-2020-0250

Falco, A., Masum, M. A., Pillai, S., Peñaranda, D. S., & Esteve-Codina, A. (2016). Antimicrobial peptides as an alternative to antibiotics in aquaculture. *Molecular Immunology*, 69, 1–10. https://doi.org/10.1016/j.molimm.2015.10.020

Fehlbaum, P., Bulet, P., Michaut, L., Lagueux, M., Broekaert, W. F., Hetru, C., & Hoffmann, J. A. (1994). Insect immunity: septic injury of Drosophila induces the synthesis of a potent antifungal peptide with sequence homology to plant antifungal peptides. *Journal of Biological Chemistry*, 269(52), 33159–33163. https://doi.org/10.1016/S0021-9258(18)43531-5

Felício, M. R., Silva, O. N., Gonçalves, S., Santos, N. C., & Franco, O. L. (2017). Peptides with dual antimicrobial–anticancer activity. *Frontiers in Chemistry*, 5, 5. https://doi.org/10.3389/fchem.2017.00005

Felício, M. R., Silva, O. N., Gonçalves, S., Santos, N. C., & Franco, O. L. (2017). Peptides with dual antimicrobial–anticancer activity. Frontiers in Chemistry, 5, 5. https://doi.org/10.3389/fchem.2017.00005

Gabere, M. N., & Noble, W. S. (2017). Empirical comparison of web-based antimicrobial peptide prediction tools. Bioinformatics, 33(13), 1921–1929. https://doi.org/10.1093/bioinformatics/btx070

Gabere, M. N., & Noble, W. S. (2017). Empirical comparison of web-based antimicrobial peptide prediction tools. *Bioinformatics*, 33(13), 1921–1929. https://doi.org/10.1093/bioinformatics/btx070

Gao, A. G., Hakimi, S. M., Mittanck, C. A., Wu, Y., Woerner, B. M., Stark, D. M., ... & Shah, D. M. (2017). Fungal pathogen protection in potato by expression of a plant defensin peptide. Nature Biotechnology, 18(12), 1307–1310. https://doi.org/10.1038/nbt1200-1307

Gao, A. G., Hakimi, S. M., Mittanck, C. A., Wu, Y., Woerner, B. M., Stark, D. M., ... & Shah, D. M. (2017). Fungal pathogen protection in potato by expression of a plant defensin peptide. *Nature Biotechnology*, 18(12), 1307–1310. https://doi.org/10.1038/nbt1200-1307

García-Bayona, L., & Comstock, L. E. (2018). Bacterial antagonism in host-associated microbial communities. *Science*, 361(6408), eaat2456. https://doi.org/10.1126/science.aat2456

Ghosh, S., Agarwal, S., & Franco, O. L. (2022). Cell-free synthesis of antimicrobial peptides: A new approach for fast and efficient production. Frontiers in Microbiology, 13, 813328. https://doi.org/10.3389/fmicb.2022.813328

Giacometti, A., Cirioni, O., Barchiesi, F., Del Prete, M. S., Fortuna, M., & Scalise, G. (2000). In vitro activity of cecropin P1 alone and in combination with clinically used antimicrobial agents against *Pseudomonas aeruginosa*. *Journal of Antimicrobial Chemotherapy*, 46(5), 817–820. https://doi.org/10.1093/jac/46.5.817

Gupta, R., Thakur, P., & Sharma, N. (2023). CRISPR-based tools for precision expression of antimicrobial peptides in synthetic biology. ACS Synthetic Biology, 12(2), 456–469. https://doi.org/10.1021/acssynbio.2c00456

Hale, J. D. F., & Hancock, R. E. W. (2007). Alternative mechanisms of action of cationic antimicrobial peptides on bacteria. *Expert Review of Anti-infective Therapy*, 5(6), 951–959. https://doi.org/10.1586/14787210.5.6.951

Haney, E. F., Mansour, S. C., & Hancock, R. E. (2019). Antimicrobial peptides: An introduction. Methods in Molecular Biology, 1548, 3–22. https://doi.org/10.1007/978-1-4939-6737-7\_1

Hetru, C., Letellier, L., Oren, Z., Hoffmann, J. A., & Shai, Y. (1998). Androctonin, a hydrophobic antifungal peptide: from the bee venom to membrane interactions. *Biochemical Journal*, 334(Pt 2), 403–410. https://doi.org/10.1042/bj3340403

Hetru, C., Letellier, L., Oren, Z., Hoffmann, J. A., & Shai, Y. (1998). Androctonin, a hydrophobic antifungal peptide: from the bee venom to membrane interactions. Biochemical Journal, 334(Pt 2), 403–410. https://doi.org/10.1042/bj3340403

Jenssen, H., Hamill, P., & Hancock, R. E. (2006). Peptide antimicrobial agents. Clinical Microbiology Reviews, 19(3), 491–511. https://doi.org/10.1128/CMR.00056-05

Lamberty, M., Caille, A., Cherqui, A., Reichhart, J. M., Hoffmann, J. A., & Bulet, P. (2001). Insect immunity: The antifungal effect of drosomycin in *Drosophila* involves binding to fungal cell wall components and induction of hyphal branching. *Biochemical Journal*, 359(Pt 1), 125–132. https://doi.org/10.1042/bj3590125

Lamberty, M., Caille, A., Cherqui, A., Reichhart, J. M., Hoffmann, J. A., & Bulet, P. (2001). Insect immunity: The antifungal effect of drosomycin in Drosophila involves binding to fungal cell wall components and induction of hyphal branching. Biochemical Journal, 359(Pt 1), 125–132. https://doi.org/10.1042/bj3590125

Lee, S. Y., Kim, B. S., Park, Y., & Park, C. B. (2023). Advanced microbial cell factories for enhanced antimicrobial peptide production. Biotechnology Advances, 64, 108111. https://doi.org/10.1016/j.biotechadv.2023.108111

Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., ... & Wu, Y. (2022). The antimicrobial peptides and their potential clinical applications. American Journal of Translational Research, 14(2), 701–723. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8899377/>

Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., ... & Wu, Y. (2022). The antimicrobial peptides and their potential clinical applications. *American Journal of Translational Research*, 14(2), 701–723. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8899377/>

Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., ... & Wu, Y. (2022). The antimicrobial peptides and their potential clinical applications. American Journal of Translational Research, 14(2), 701–723. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8899377/>

Li, M., Zhu, L., Li, H., & Sun, Y. (2021). Synthetic biology approaches for improving antimicrobial peptides production: challenges and future directions. Frontiers in Bioengineering and Biotechnology, 9, 658285. https://doi.org/10.3389/fbioe.2021.658285

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial peptides: an emerging category of therapeutic agents. *Frontiers in Cellular and Infection Microbiology*, 6, 194. https://doi.org/10.3389/fcimb.2016.00194

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial peptides: an emerging category of therapeutic agents. Frontiers in Cellular and Infection Microbiology, 6, 194. https://doi.org/10.3389/fcimb.2016.00194

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2020). Antimicrobial peptides: an emerging category of therapeutic agents. *Frontiers in Cellular and Infection Microbiology*, 6, 149. https://doi.org/10.3389/fcimb.2016.00149

Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2020). Antimicrobial peptides: an emerging category of therapeutic agents. Frontiers in Cellular and Infection Microbiology, 6, 149. https://doi.org/10.3389/fcimb.2016.00149

Mandal, S. M., Panda, S., Samaddar, S., Ghosh, A. K., Dey, S., & Franco, O. L. (2020). Current advances of antimicrobial peptides and proteins in molecular design and therapeutic delivery. Frontiers in Pharmacology, 11, 582779. https://doi.org/10.3389/fphar.2020.582779

Mandal, S. M., Panda, S., Samaddar, S., Ghosh, A. K., Dey, S., & Franco, O. L. (2020). Current advances of antimicrobial peptides and proteins in molecular design and therapeutic delivery. Frontiers in Pharmacology, 11, 582779. https://doi.org/10.3389/fphar.2020.582779

Montesinos, E., & Bardají, E. (2008). Synthetic antimicrobial peptides as agricultural pesticides for plant-disease control. *Chemical Biodiversity*, 5(7), 1225–1237. https://doi.org/10.1002/cbdv.200890120

Mookherjee, N., Anderson, M. A., Haagsman, H. P., & Davidson, D. J. (2020). Antimicrobial host defence peptides: functions and clinical potential. *Nature Reviews Drug Discovery*, 19, 311–332. https://doi.org/10.1038/s41573-019-0058-8

Mookherjee, N., Anderson, M. A., Haagsman, H. P., & Davidson, D. J. (2020). Antimicrobial host defence peptides: functions and clinical potential. Nature Reviews Drug Discovery, 19, 311–332. https://doi.org/10.1038/s41573-019-0058-8

Mookherjee, N., Anderson, M. A., Haagsman, H. P., & Davidson, D. J. (2020). Antimicrobial host defence peptides: functions and clinical potential. Nature Reviews Drug Discovery, 19(5), 311–332. https://doi.org/10.1038/s41573-019-0058-8

Pirtskhalava, M., Amstrong, A. A., Grigolava, M., Chubinidze, M., Alimbarashvili, E., Vishnepolsky, B., ... & Tsurtsumia, M. (2021). DBAASP v3: Database of antimicrobial activity and structure of peptides as a resource for development of new therapeutics. Nucleic Acids Research, 49(D1), D288–D297. https://doi.org/10.1093/nar/gkaa991

Porto, W. F., Pires, Á. S., & Franco, O. L. (2018). Computational tools for exploring sequence databases as a resource for antimicrobial peptides. Biotechnology Advances, 35(3), 337–349. https://doi.org/10.1016/j.biotechadv.2017.12.001

Porto, W. F., Pires, Á. S., & Franco, O. L. (2018). Computational tools for exploring sequence databases as a resource for antimicrobial peptides. *Biotechnology Advances*, 35(3), 337–349. https://doi.org/10.1016/j.biotechadv.2017.12.001

Ramasamy, M., & Lee, J. (2016). Recent nanotechnology approaches for prevention and treatment of biofilm-associated infections on medical devices. *Materials*, 9(6), 301. https://doi.org/10.3390/ma9060301

Ramaswamy, H. S., Papadopoulos, D., & Marcotte, M. (2021). Natural antimicrobials in food preservation. In *Handbook of Food Science, Technology, and Engineering* (2nd ed., Vol. 4). CRC Press. https://doi.org/10.1201/b16869

Rao, P., Bhattacharjya, S., & Singh, N. (2021). Artificial intelligence in the design of antimicrobial peptides: Progress and prospects. ACS Omega, 6(41), 27239–27251. https://doi.org/10.1021/acsomega.1c04584

Sahoo, B. R., Pattnaik, P., & Samantaray, S. (2021). Antimicrobial peptides in aquaculture: opportunities and challenges. *Aquaculture Reports*, 20, 100711. https://doi.org/10.1016/j.aqrep.2021.100711

Samuelsen, Ø., Kahlmeter, G., & Sundsfjord, A. (2022). Antimicrobial peptides: a new hope in the battle against antibiotic resistance. *Journal of Antimicrobial Chemotherapy*, 77(3), 527–535. https://doi.org/10.1093/jac/dkab451

Schmitt, P., Rosa, R. D., & Destoumieux-Garzón, D. (2022). The molecular diversity of antimicrobial peptides in marine invertebrates: structure, function, and evolutionary perspectives. *Frontiers in Immunology*, 13, 878120. https://doi.org/10.3389/fimmu.2022.878120

Schmitt, P., Rosa, R. D., & Destoumieux-Garzón, D. (2022). The molecular diversity of antimicrobial peptides in marine invertebrates: structure, function, and evolutionary perspectives. Frontiers in Immunology, 13, 878120. https://doi.org/10.3389/fimmu.2022.878120

Schmitt, P., Rosa, R. D., Destoumieux-Garzón, D. (2022). The molecular diversity of antimicrobial peptides in marine invertebrates: structure, function, and evolutionary perspectives. Frontiers in Immunology, 13, 878120. https://doi.org/10.3389/fimmu.2022.878120

Silva, N. C. C., Barbosa, L., Seito, L. N., & Fernandes, A. (2020). Antimicrobial peptides: clinical relevance and therapeutic potential. *Peptides*, 133, 170355. https://doi.org/10.1016/j.peptides.2020.170355

Silva, N. C. C., Barbosa, L., Seito, L. N., & Fernandes, A. (2020). Antimicrobial peptides: clinical relevance and therapeutic potential. Peptides, 133, 170355. https://doi.org/10.1016/j.peptides.2020.170355

Silva, N. C. C., Barbosa, L., Seito, L. N., & Fernandes, A. (2020). Antimicrobial peptides: clinical relevance and therapeutic potential. *Peptides*, 133, 170355. https://doi.org/10.1016/j.peptides.2020.170355

Steiner, H., Andreu, D., & Merrifield, R. B. (1981). Sequence and specificity of two antibacterial insect defensins. Nature, 292, 246–248. https://doi.org/10.1038/292246a0

Torres, M. D. T., Sothiselvam, S., Lu, T. K., & de la Fuente-Nunez, C. (2022). Peptide design principles for antimicrobial applications. Journal of Molecular Biology, 434(2), 167379. https://doi.org/10.1016/j.jmb.2021.167379

Torres, M. D. T., Sothiselvam, S., Lu, T. K., & de la Fuente-Nunez, C. (2022). Peptide design principles for antimicrobial applications. *Journal of Molecular Biology*, 434(2), 167379. https://doi.org/10.1016/j.jmb.2021.167379

Torres, M. D. T., Sothiselvam, S., Lu, T. K., & de la Fuente-Nunez, C. (2022). Peptide design principles for antimicrobial applications. Journal of Molecular Biology, 434(2), 167379. https://doi.org/10.1016/j.jmb.2021.167379

Wang, G., Li, X., & Wang, Z. (2021). APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Research*, 49(D1), D372–D379. https://doi.org/10.1093/nar/gkaa991

Wang, G., Li, X., & Wang, Z. (2021). APD3: the antimicrobial peptide database as a tool for research and education. Nucleic Acids Research, 49(D1), D372–D379. https://doi.org/10.1093/nar/gkaa991

Wang, Q., Zhang, L., & Wang, J. (2023). Transgenic expression of insect-derived AMPs in rice confers enhanced resistance to fungal pathogens. Plant Cell Reports, 42(1), 95–107. https://doi.org/10.1007/s00299-022-02865-3

Wang, Q., Zhang, L., & Wang, J. (2023). Transgenic expression of insect-derived AMPs in rice confers enhanced resistance to fungal pathogens. *Plant Cell Reports*, 42(1), 95–107. <https://doi.org/10.1007/s00299-022-02865-3>

Wu, Q., Patocka, J., & Kuca, K. (2018). Insect antimicrobial peptides, a mini review. *Toxins*, 10(11), 461. https://doi.org/10.3390/toxins10110461

Yeaman, M. R., & Yount, N. Y. (2003). Mechanisms of antimicrobial peptide action and resistance. Pharmacological Reviews, 55(1), 27–55. https://doi.org/10.1124/pr.55.1.2

Yi, H. Y., Chowdhury, M., Huang, Y. D., & Yu, X. Q. (2014). Insect antimicrobial peptides and their applications. *Applied Microbiology and Biotechnology*, 98(13), 5807–5822. <https://doi.org/10.1007/s00253-014-5792-6>

Zhang, L., Dhillon, P., Yan, H., Farmer, S., & Hancock, R. E. (2019). Interactions of cecropin A and melittin with lipopolysaccharides and lipid monolayers. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1861(7), 1482–1490. https://doi.org/10.1016/j.bbamem.2019.05.001

Zhang, Y., Zheng, D., Liu, D., & Zhang, R. (2021). Enhancing production of insect-derived antimicrobial peptides in heterologous systems: challenges and perspectives. Microbial Cell Factories, 20(1), 215. <https://doi.org/10.1186/s12934-021-01714-8>

Chivian, E. (2002). Biodiversity: its importance to human health. Center for Health and the Global Environment, Harvard Medical School, Cambridge, MA, 23, 6-49.