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Review

Insect Antimicrobial Peptides (AMPs) as Next-Generation Therapeutics: Structural Diversity, Molecular Regulation, Mechanisms of Action, and Translational Strategies Against Multidrug Resistance

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Abstract: The rapid escalation of antimicrobial resistance (AMR), particularly among the "ESKAPE" pathogens, presents an existential threat to global clinical medicine. Because conventional small-molecule antibiotics are highly vulnerable to resistance acquisition via single-nucleotide polymorphisms or horizontal gene transfer, there is an urgent need to engineer next-generation therapeutics with resilient, biophysical modes of action. Antimicrobial peptides (AMPs) derived from the Class Insecta represent an evolutionary goldmine, offering robust host-defense platforms shaped by survival in pathogen-dense ecological niches. This review addresses a historical fragmentation in literature by providing a translation-focused synthesis that comprehensively bridges upstream molecular regulatory networks with downstream pharmacological performance and modern formulation engineering. The manuscript structurally classifies the four primary families of insect AMPs—linear α-helical cecropins, disulfide-stabilized cysteine-rich defensins, intracellular-targeting proline-rich peptides (PrAMPs), and macromolecular glycine-rich proteins (e.g., diptericins, attacins)—and correlates their unique structural topography with specific, multi-target mechanisms of action. Furthermore, it maps the underlying upstream activation pathways, including the Toll, Immune Deficiency (Imd), and JAK-STAT cascades, while examining complementary humoral factors and antioxidant defense systems. While insect-derived AMPs exhibit exceptional *in vitro* potency, direct direct lysis mechanisms often cross-react with eukaryotic membranes, leading to mammalian cytotoxicity and hemolytic vulnerabilities. Moreover, native linear peptides suffer from rapid proteolytic degradation by host proteases, resulting in a short plasma half-life. This review evaluates how these challenges, alongside high chemical manufacturing costs and emerging microbial countermeasures (e.g., membrane remodeling, active efflux networks), have historically blocked clinical translation. To resolve these bottlenecks, we highlight cutting-edge 2026 strategies, emphasizing how artificial intelligence (AI)-driven generative and predictive modeling accelerates the *de novo* design of synthetic peptides with optimized therapeutic indices. Concurrently, we detail the implementation of chemical modifications (peptidomimetics, D-amino acid substitutions, cyclization, PEGylation) and advanced nanocarrier delivery frameworks (liposomes, nanoparticles, hydrogels) to systematically shield sequences from degradation, eliminate host toxicity, and chart a definitive regulatory roadmap toward successful clinical translation.

Keywords: Antimicrobial peptides; Class Insecta; Toll and Imd pathways; Membranolytic mechanisms; Peptidomimetics; Artificial Intelligence (AI); Nanocarrier drug delivery.

1. Introduction

The relentless escalation of antimicrobial resistance (AMR) stands as one of the most critical threats to global public health and modern clinical medicine. It is estimated that AMR was associated with nearly 5 million deaths annually, a figure projected to rise exponentially to 10 million deaths per year by 2050 if novel therapeutic alternatives are not realized [1]. The rapid dissemination of multi-drug resistant (MDR) clinical phenotypes—most notably the "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species)—has rendered standard, small-molecule frontline antibiotics increasingly obsolete [2]. Because conventional small-molecule antibiotics typically target highly specific bacterial enzymes or metabolic pathways, single-nucleotide polymorphisms or horizontal gene transfer events can swiftly confer high-level resistance [3]. Consequently, there is an urgent and critical need to discover and engineer next-generation antimicrobial agents possessing entirely distinct, structurally resilient biophysical mechanisms of action.

In this context, antimicrobial peptides (AMPs) have emerged as highly promising candidates to bridge the therapeutic gap [1,3]. AMPs represent an ancient, evolutionarily conserved component of innate immunity found across all kingdoms of life [4]. Among these biological sources, Class Insecta represents an unparalleled, largely untapped genetic goldmine for bioactive molecule discovery [4]. Lacking an adaptive immune system, insects rely entirely on a robust, multi-layered humoral and cellular innate immune response to survive in highly contaminated, pathogen-rich ecological niches [5]. The primary efferent arms of this humoral defense are insect AMPs—short, typically cationic, and amphipathic peptides generally comprising fewer than 100 amino acids [6]. These molecules are rapidly synthesized by the fat body and circulating hemocytes upon microbial challenge, where they exhibit potent, broad-spectrum bactericidal, antifungal, and antiviral properties [4,6].

The primary allure of insect AMPs lies in their fundamental mechanism of action. Unlike traditional small-molecule drugs, classic cationic insect AMPs target the physical integrity of the microbial cytoplasmic membrane [6]. Driven by initial electrostatic attraction to anionic bacterial surface components (such as lipopolysaccharides in Gram-negative strains or teichoic acids in Gram-positive strains), these peptides insert into lipid bilayers, inducing lethal permeabilization via pore formation or membrane micellization [6]. Because altering the fundamental macromolecular lipid composition of a membrane requires extensive, metabolically expensive evolutionary restructuring, the frequency of resistance development against AMPs is significantly lower than that observed with traditional antibiotics [7]. Furthermore, non-lytic, intracellular-targeting proline-rich and glycine-rich insect AMPs have been shown to selectively disrupt bacterial protein folding or nucleic acid replication machinery, introducing multi-hit dynamics that further suppress microbial adaptation [6,8].

Antimicrobial peptides (AMPs) have been successfully identified and isolated across several diverse insect orders, most prominently from Lepidoptera, Diptera, Coleoptera, and Hymenoptera, alongside less frequent documentation in Hemiptera, Trichoptera, and Odonata [6,9,10]. As cataloged in comprehensive repositories like the dbAMP database, hundreds of distinct insect-derived AMPs have been structurally and functionally characterized, with over 700 explicitly curated insect entries out of thousands of natural arthropod sequences discovered up to date [10,11]. Structurally, these defense molecules are categorized into major, distinct families based on their structural conformations and amino acid biases [9,12]: (i) Linear alpha-helical peptides that lack cysteine residues (e.g., cecropins, moricins, and melittins), which display potent broad-spectrum activity [10,12], (ii) Cysteine-rich peptides characterized by stabilized globular beta-sheet or alpha/beta structural motifs containing 6-8 highly conserved cysteine residues forming multiple intramolecular disulfide bridges (e.g., insect defensins and drosomycins) [6,12,13], (iii) Proline-rich

peptides which are short- or long-chain molecules possessing a significant overrepresentation of proline residues (e.g., apidaecins, abaecins, drosocins, and lebocins) that primarily exhibit sequence-specific target mechanisms rather than direct membrane disruption [9,14], and (iv) Glycine-rich peptides/proteins which are larger macromolecules highly enriched with glycine residues (e.g., attacins, gloverins, and diptericins) which predominantly target Gram-negative bacterial outer membranes [1,12].

Given the therapeutic promise of these molecules, several excellent reviews have recently summarized various dimensions of insect immunity and AMP discovery. For instance, Zhou et al. provided an extensive overview of AMPs characterized across classic model insects, cataloging their native physiological functions as immune "guardians" [4]. Other researchers have focused strictly on the evolutionary dynamics of specific hyper-diverse saprophagous species, such as the Black Soldier Fly (*Hermetia illucens*) [1,15], or explored general advancements in dietary modulation and mass-rearing biosecurity [16]. However, existing literature frequently suffers from a systemic fragmentation: reviews either lean heavily into upstream model-organism biology and transcriptomic classification without providing a translational blueprint, or they focus exclusively on abstract biochemical structures without contextualizing the industrial and pharmacological hurdles preventing clinical translation. To date, there remain no insect-derived AMPs successfully approved for clinical systemic use on the pharmaceutical market [6].

This review aims to address this critical gap by providing a comprehensive, translation-focused synthesis that bridges upstream molecular regulation with downstream clinical application. Moving beyond the descriptive taxonomies of previous literature, this work explicitly establishes the structural-functional relationships of the four primary insect AMP families (α-helical, cysteine-rich, proline-rich, and glycine-rich) and maps their underlying upstream activation pathways (Toll, Imd, and JAK-STAT cascades). Critically, the unique novelty of this review lies in its rigorous examination of the explicit translational bottlenecks—such as systemic cytotoxicity, metabolic instability in human plasma, high recombinant manufacturing costs, and emerging bacterial resistance strategies—juxtaposed against the latest 2026 technological solutions. By evaluating how cutting-edge artificial intelligence (AI)-driven rational design, peptidomimetics, and nanoparticle-mediated delivery systems are actively systematically dismantling these historic barriers, this work provides a definitive roadmap for translating wild insect defense mechanisms into viable, next-generation human therapeutics.

2. Structural Classification and Diversity of Insect AMPs

The remarkable structural diversity of insect antimicrobial peptides (AMPs) underpins their multi-target defensive capability within the innate immune response, circumventing the necessity for an adaptive immune system [2]. These molecules exhibit extraordinary structural and functional diversity, allowing insects to combat a wide array of bacterial, fungal, and parasitic pathogens. While these effector molecules exhibit significant variation in primary sequence length, typically spanning 12 to 100 amino acid residues, they share essential physicochemical characteristics—namely, a predominantly cationic nature and an amphipathic topography that facilitates interactions with microbial lipid bilayers [6,17]. Based on their amino acid composition, secondary structures, and conformational traits, insect AMPs are fundamentally organized into four major structural classes. The primary classes include linear, amphipathic $\boldsymbol{\alpha}$-helical peptides lacking cysteine residues; cysteine-rich peptides stabilized by intramolecular disulfide bonds forming $\boldsymbol{\alpha/\beta}$ motifs; and glycine- or proline-rich polypeptides [2,4]. Complementing these canonical AMPs are multi-functional immune enzymes, pattern recognition receptors (PRRs), and tissue-specific secretory proteins that collectively dictate the efficacy of the humoral immune response (Figure 1).

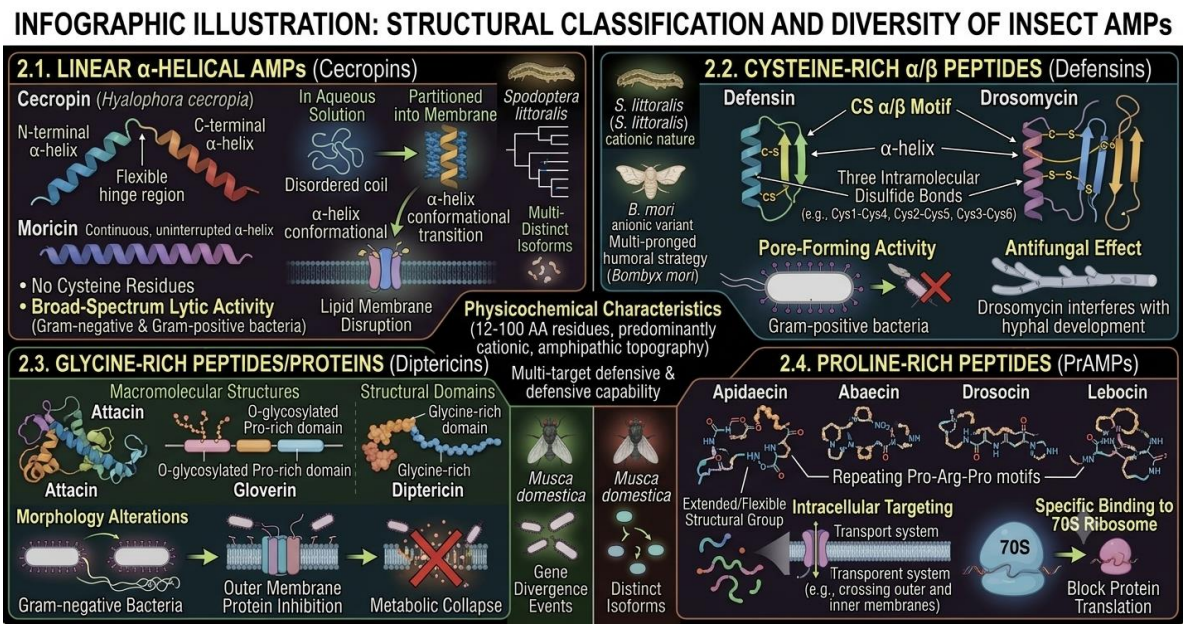

Figure 1. Structural classification and conformational diversity of mainstream insect antimicrobial peptides (AMPs). The infographic comprehensively illustrates the four primary architectural families of insect host defense peptides, highlighting their distinct physicochemical characteristics (typically 12–100 amino acid residues, predominantly cationic, and exhibiting an amphipathic topography) alongside their respective targeted functional modalities.

2.1. Linear α-Helical AMPs lacking Cysteine (Cecropins)

This class comprises amphipathic molecules that lack cysteine residues, meaning their secondary structure is entirely stabilized through non-covalent backbone interactions rather than covalent cross-linking [6]. In aqueous solutions, these peptides typically exist as random, disordered coils; however, upon partitioning into the hydrophobic core of a target microbial membrane, they undergo a rapid conformational transition into highly ordered α-helices [2]. The foundational member (cecropin) of this family, originally isolated from *Hyalophora cecropia*, consists of an amphipathic N-terminal α-helix linked via a flexible hinge region to a hydrophobic C-terminal α-helix, a conformation that facilitates lipid membrane disruption in target pathogens [4]. They primarily exert broad-spectrum lytic activity against both Gram-negative and Gram-positive bacteria by inducing membrane permeabilization [6,2].

Research on lepidopteran models has significantly advanced our understanding of cecropin diversity and transcriptional dynamics. Specifically, the molecular characterization, cDNA cloning, and phylogenetic analysis of a cecropin gene isolated from the bacterial-challenged cotton leafworm, *S. littoralis*, highlights its rapid transcriptional induction following microbial exposure. The phylogenetic validation of lepidopteran cecropins confirms their evolutionary conservation and specialized role in the systemic humoral response, establishing them as frontline defenses against bacterial infections [18]. Moricins were exclusively identified within lepidopteran insects. Moricins share structural similarities with cecropins but are distinguished by the complete absence of a central hinge region, maintaining a continuous, uninterrupted α-helical dynamic (Figure 1) that kills bacterial and fungal pathogens [4].

2.2. Cysteine-Rich α/β Peptides (Defensins)

Insect defensins are typically cationic peptides characterized by a conserved structural motif stabilized by three or four intramolecular disulfide bonds, adopting an α-helix linked to a β-sheet structure (CS α/β motif), wherein 6 to 8 conserved cysteines form three or four distinct disulfide

bonds (typically arranged as Cys^1—Cys^4, Cys^2—Cys^5, and Cys^3—Cys^6) that covalently pin an antiparallel $\boldsymbol{\beta}$-sheet to an adjacent $\boldsymbol{\alpha}$-helix [6,2,4]. They demonstrate selective, potent pore-forming activity against Gram-positive bacterial cell walls [6,2]. Drosomycins are structurally analogous to defensins in their disulfide arrangement but divergent in primary sequence; drosomycins function primarily as specialized antifungal effectors, disrupting fungal membrane integrity or interfering with hyphal development (Figure 1) [4].

While most characterized defensins primarily target Gram-positive bacteria, structural and functional variations exist. Investigations into the immune repertoire of *S. littoralis* led to the identification, phylogenetic analysis, and expression profiling of a unique anionic insect defensin gene [19]. Exhibiting potent antibacterial activity, this anionic variant demonstrates that charge distribution variations within the conserved disulfide-stabilized framework can expand or modulate the functional spectrum of lepidopteran defensins. Furthermore, the biochemical diversity of these cysteine-stabilized molecules is evident in the hemolymph of bacterial-challenged *Bombyx mori* larvae, where the purification and characterization of two distinct antimicrobial peptides underscored the synergistic or multi-pronged humoral strategy employed by lepidopterans to clear systemic bacterial loads [20].

2.3. Glycine-Rich Peptides/Proteins (Diptericins)

This heterogeneous class includes larger macromolecular structures intensely enriched with glycine residues, primarily active against specific Gram-negative bacteria. Their structural architecture often consists of an O-glycosylated Pro-rich domain and a glycine-rich domain essential for membrane-permeabilizing activity (Figure 1). This class includes attacins, gloverins, and diptericins [21]. Attacins and gloverins often transition into complex β-sheet dominant configurations or random structures that interact specifically with the outer membrane components of Gram-negative bacteria, such as lipopolysaccharides (LPS) [6,21]. Rather than forming clean, symmetrical pores, these glycine-dense molecules cause severe morphology alterations by inhibiting the synthesis of major outer membrane proteins or inducing localized membrane thinning, resulting in cytoplasmic leakage and metabolic collapse [6,21].

The diversity within this class is frequently driven by the presence of distinct isoforms within a single species, which may reflect evolutionary adaptations to diverse microbial habitats. In dipteran models, such as the housefly (*Musca domestica*), genomic and transcriptomic analyses have led to the identification and phylogenetic analysis of two distinct isoforms of the antibacterial gene diptericin isolated from larval tissues [22]. These isoforms reflect targeted gene divergence events, optimizing the dipteran defense matrix against filth-associated pathogens.

2.4. Proline-Rich Peptides (PrAMPs)

Proline-rich AMPs represent an extended or flexible structural group characterized by a high abundance of proline and arginine residues, frequently organized into repeating Pro-Arg-Pro motifs [23]. Unlike classic lytic peptides, PrAMPs (such as apidaecins, abaecins, drosocins, and lebocins) do not rely on direct, non-specific membrane disruption to lyse the cell [6]. Instead, they cross the outer and inner bacterial membranes via specialized transport systems to bind stereospecifically to intracellular targets, such as the 70S ribosome or heat-shock proteins, thereby blocking bacterial protein translation or folding mechanisms [6,23]. Due to these target-specific interactions, their spectrum of activity is largely restricted to specific Gram-negative pathogens (Figure 1) [6].

3. Complementary Humoral Factors, Antioxidant Defense, and Secretory Proteomes

The functional efficacy of canonical AMPs is heavily dependent on a broader network of immune-related proteins that manage cellular homeostasis, pathogen recognition, and tissue-specific protection (Figure 2).

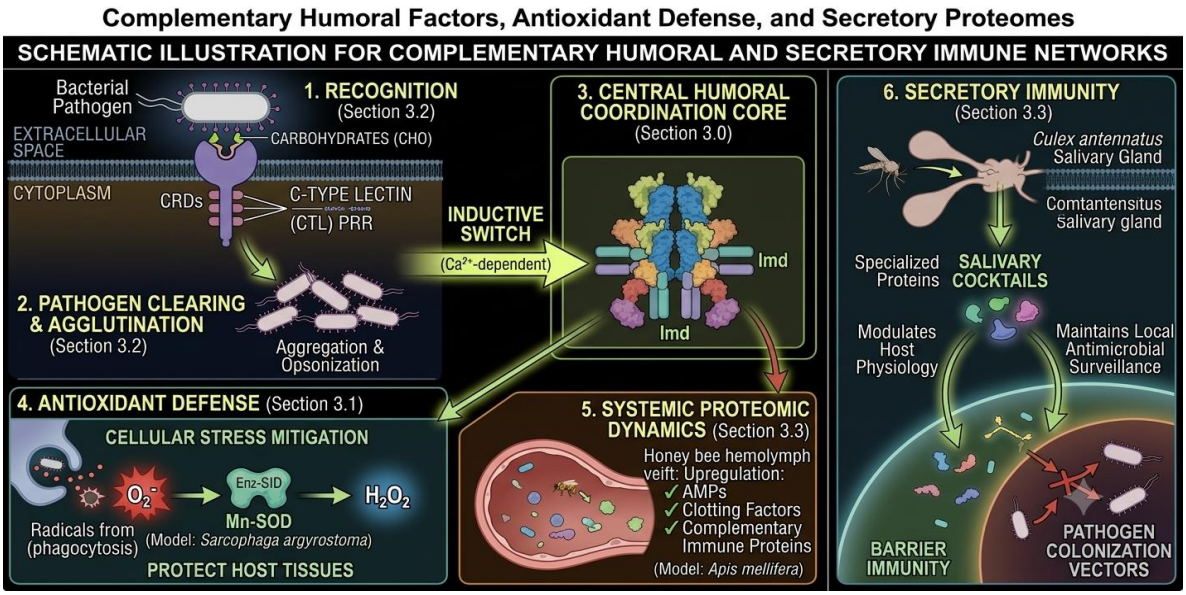

Figure 2. Schematic illustration of complementary humoral factors, antioxidant defense, and secretory immune networks in insects. The infographic details the multi-tiered systemic and localized physiological cascades that coordinate insect host defense beyond direct antimicrobial peptide activity, divided into six core functional modules.

3.1. Antioxidant and Oxidative Stress Regulation

During phagocytosis and melanization, the insect host generates massive amounts of reactive oxygen species (ROS) to kill pathogens. To protect host tissues from collateral oxidative damage, key antioxidant enzymes are co-induced with AMPs. The identification and molecular characterization of a novel manganese superoxide dismutase (Mn-SOD) gene from the larvae of the flesh fly, *Sarcophaga argyrostoma*, illustrates this crucial protective mechanism [24]. Mn-SOD acts as a primary enzymatic defense, dismutating superoxide radicals into hydrogen peroxide, thereby balancing the oxidative killing zone during acute systemic infection (Figure 2).

3.2. Pattern Recognition and Immune Surveillance

The upregulation of genes like cecropin, defensin, and diptericin relies entirely on the upstream activation of immune signaling pathways initiated by Pattern Recognition Receptors (PRRs). C-type lectins (CTLs) represent a vital class of calcium-dependent PRRs that bind to carbohydrates on microbial surfaces, facilitating agglutination and opsonization. The molecular characterization, full-length isolation, and phylogenetic analysis of a C-type lectin gene from bacterial-challenged *S. littoralis* demonstrates how these surveillance proteins are structurally adapted to recognize invading pathogens, serving as the critical inductive switch for subsequent AMP expression (Figure 2) [25].

3.3. Systemic Proteomic Dynamics and Secretory Immunity

At the organismal level, the induction of the humoral immune response drastically alters the global protein landscape of the circulatory fluid. Electrophoretic and proteomic profiling reveals a

distinct differential hemolymph protein profile in bacterial-challenged western honey bee workers (*Apis mellifera*), mapping the macro-level shift toward AMP production, clotting factors, and complementary immune proteins [26].

Additionally, insect defense strategies are highly compartmentalized. Beyond systemic hemolymph defenses, mucosal and secretory fluids play a vital role in barrier immunity. Electrophoretic analysis of the salivary gland proteins of adult *Culex antennatus* mosquitoes demonstrates that tissue-specific secretory proteomes contain specialized proteins and enzymes [27]. In hematophagous vectors, these salivary cocktails serve a dual purpose: modulating host physiology during feeding and maintaining local antimicrobial surveillance to prevent pathogen colonization (Figure 2).

4. Biosynthesis and Molecular Regulation Pathways

The insect innate immune response relies on a tightly coordinated network of tissue-specific interactions and evolutionarily conserved signaling cascades. Lacking an adaptive immune system, insects utilize distinct cellular sites and molecular pathways to recognize invading pathogens, initiate targeted gene transcription, and synthesize an array of potent antimicrobial peptides (AMPs) (Figure 3).

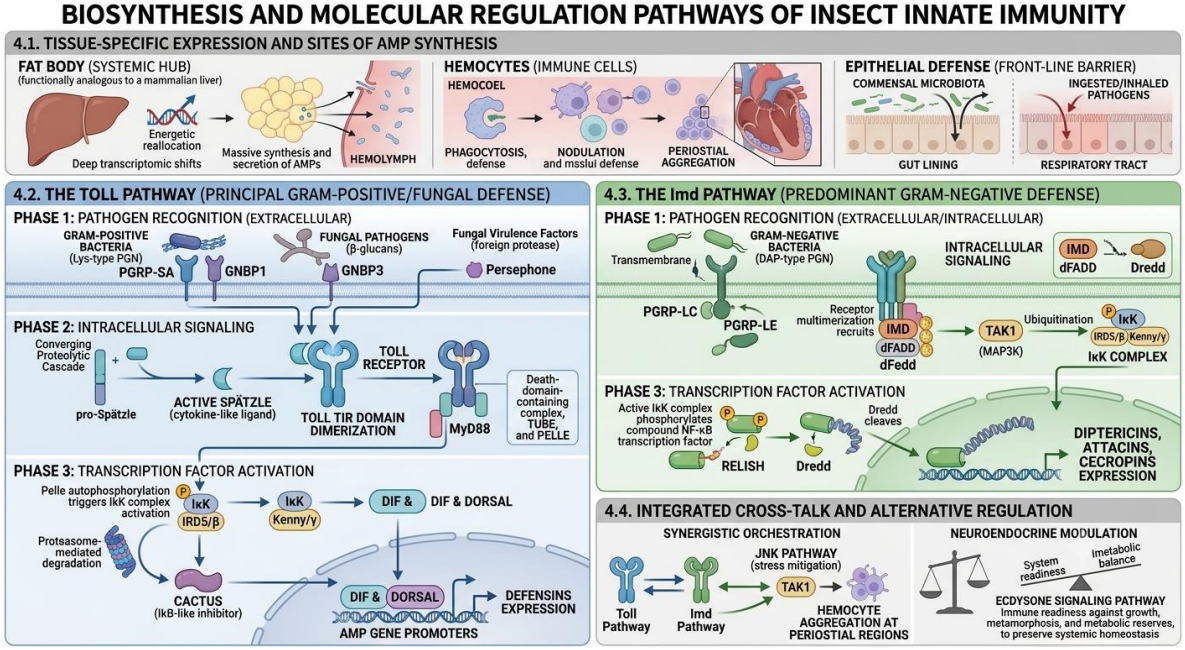

Figure 3. Biosynthesis and molecular regulation pathways of insect innate immunity. The infographic details the compartmentalized expression sites and the dual ***NFκB*** signaling cascades (Toll and Imd pathways) that orchestrate the induction of insect antimicrobial peptides (AMPs).

4.1. Tissue-Specific Expression and Sites of Synthesis

The insect immune system combines systemic humoral defense with site-specific barriers to achieve comprehensive pathogen containment. The primary hub for systemic immunity is the fat body, a multifunctional organ widely recognized as the functional analog to the mammalian liver [5,28]. Following infection, the fat body undergoes deep transcriptomic shifts geared toward energetic reallocation, facilitating the massive synthesis and secretion of AMPs directly into the hemolymph [28].

Working in tandem with the fat body are hemocytes, the circulating and sessile immune cells within the hemocoel. While hemocytes primarily drive cellular defense mechanisms such as phagocytosis, nodulation, and periostial aggregation, they also transcribe specific subsets of immune effectors [28,29]. Beyond this systemic response, local epithelial expression (e.g., in the gut lining and respiratory tracts) serves as a critical frontline mucosal defense. This localized expression regulates the host's commensal microbiota and stops ingested or inhaled pathogens before they can breach the body cavity (Figure 3) [5].

4.2. The Toll Pathway

The Toll signaling pathway serves as the principal defense mechanism against Gram-positive bacteria and fungal pathogens. Unlike mammalian Toll-like receptors (TLRs) that bind microbial ligands directly, the insect Toll receptor requires an endogenous cytokine-like ligand, Spätzle, for its activation [30]. This pathway is achieved via three phases (Figure 4):

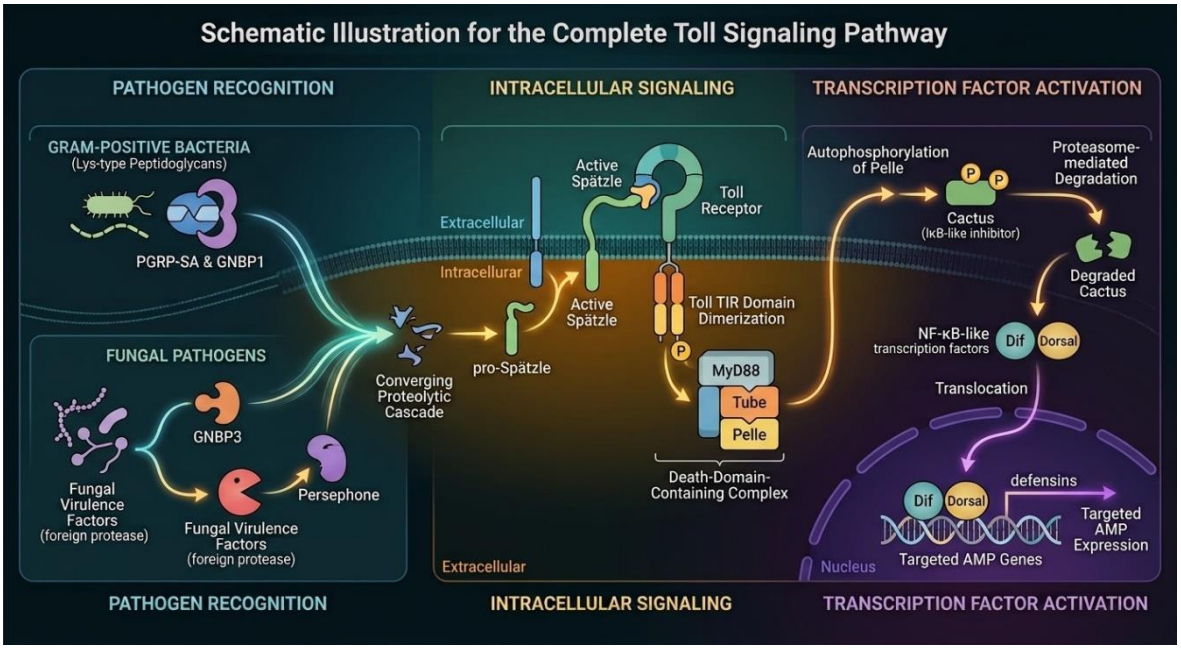

Figure 4. Schematic illustration for the complete toll signaling pathway. The diagram maps the sequential, multi-tiered molecular cascade required for the induction of specific insect host defense genes, tracking the pathway from extracellular pathogen recognition to downstream transcription factor activation.

- ***Pathogen Recognition:*** Lysine-type (Lys-type) peptidoglycans found in Gram-positive bacterial cell walls are detected by extracellular pattern recognition receptors (PRRs) such as Peptidoglycan Recognition Protein SA (PGRP-SA) and Gram-Negative Binding Protein 1 (GNBP1) [30]. Similarly, fungal β-glucans are bound by GNBP3, while foreign proteolytic activities from fungal virulence factors trigger the host serine protease Persephone (Figure 4) [30].

- ***Intracellular Signaling:*** Independent recognition events converge onto a proteolytic cascade that cleaves pro-Spätzle into its active form. The cleaved Spätzle binds the transmembrane Toll receptor, causing its intracytoplasmic Toll/Interleukin-1 Receptor (TIR) domains to dimerize [30]. This assembly recruits a death-domain-containing complex consisting of MyD88, Tube, and the serine/threonine kinase Pelle (Figure 4) [30].

- ***Transcription Factor Activation:*** Autophosphorylation of Pelle triggers the downstream phosphorylation and subsequent proteasome-mediated degradation of Cactus, an IκB-like inhibitor [30]. Once freed from Cactus, the NF-κB-like transcription factors Dif (Dorsal-related immunity factor) and Dorsal translocate into the nucleus to drive the expression of targeted AMP genes, such as defensins (Figure 4) [30,31].

4.3. The Imd (Immune Deficiency) Pathway

The Immune Deficiency (Imd) pathway is predominantly attuned to the detection of Gram-negative bacteria and specific rod-shaped Gram-positive bacteria, governing a downstream cascade distinct from Toll (Figure 5) [31].

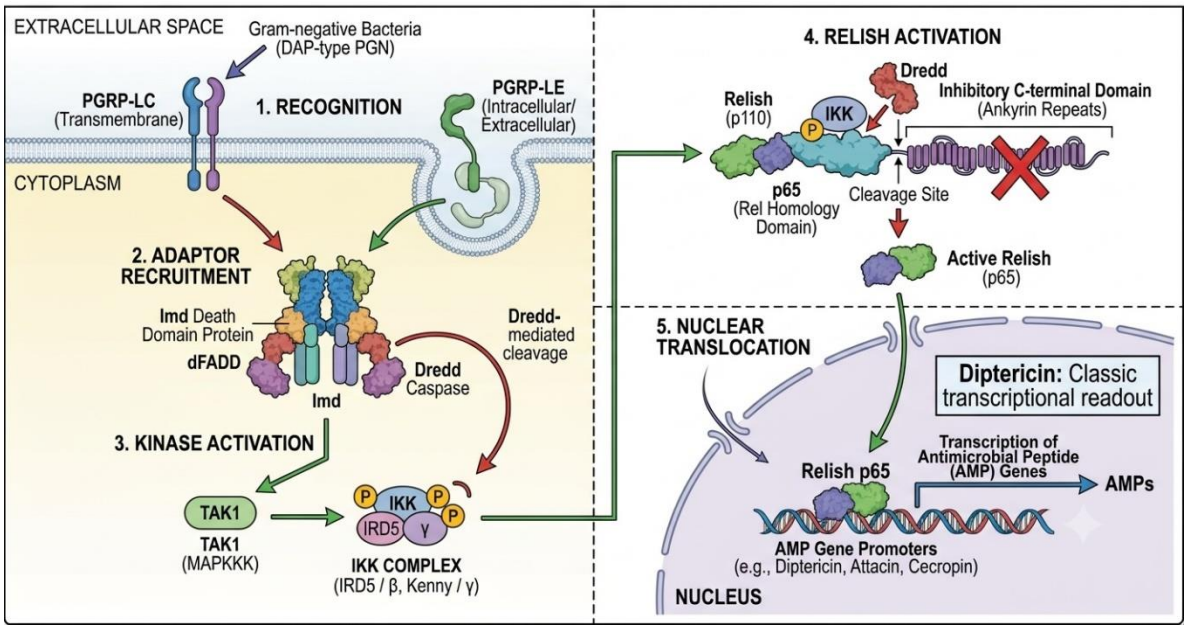

Figure 5. Schematic illustration for the complete immune deficiency (imd) signaling pathway. The diagram maps the structural architecture and sequential molecular checkpoints of the IMD pathway, which serves as the principal defense cascade against Gram-negative bacterial infections in insects.

- ***Pathogen Recognition:*** The pathway is triggered by the binding of diaminopimelic acid-type (DAP-type) peptidoglycans to the transmembrane receptor PGRP-LC or the intracellular receptor PGRP-LE (Figure 5) [31].

- ***Intracellular Signaling:*** Initiated via receptor multimerization and recruitment of the intracellular adaptor molecule IMD, which acts as a scaffold to recruit the Fas-associated death domain ortholog (dFADD) and the caspase-8 homolog Dredd [31]. Ubiquitination events mediated by these adaptors activate the MAP3K protein TAK1, which subsequently recruits and phosphorylates the IκB kinase (IκK) complex (comprising IκKβ and IκKγ) (Figure 5) [31].

- ***Transcription Factor Activation:*** The active IκK complex phosphorylates the compound NF-κB transcription factor Relish [31]. Dredd then endoproteolytically cleaves Relish, removing its inhibitory C-terminal ankyrin repeat domain. The active N-terminal DNA-binding domain of Relish translocates to the nucleus to induce the transcription of basic and glycine-rich AMPs, such as diptericins, attacins, and cecropins (Figure 5) [31].

4.4. Cross-Talk and Alternative Regulation

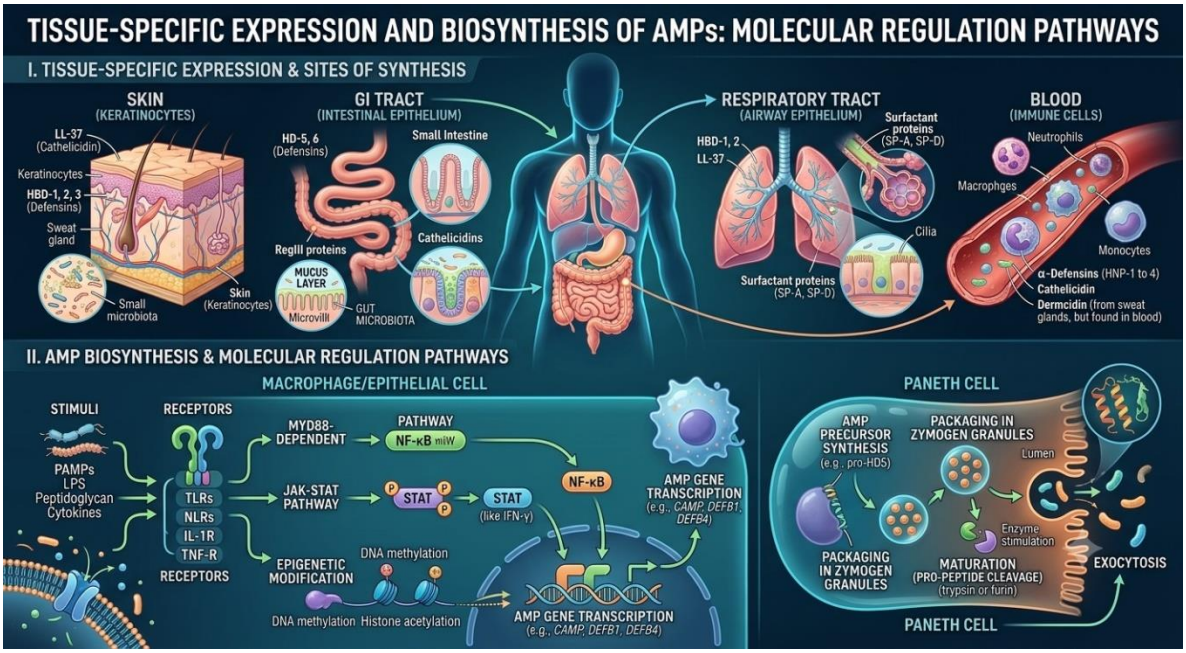

Figure 6. Tissue-specific expression and biosynthesis of antimicrobial peptides (amps): molecular regulation pathways. The infographic maps the mammalian anatomical distribution, cellular sources, and intracellular regulatory networks that control the constitutive and inducible production of host defense peptides.

Insect immunity is not a collection of isolated pathways, but rather a highly integrated molecular network. Synergistic orchestration between the Toll and Imd pathways ensures a calibrated response to polymicrobial infections, optimizing effector output based on the pathogen composition. This coordination expands to the JNK (c-Jun N-terminal kinase) pathway, which shares upstream signaling elements (such as TAK1) with the Imd pathway. The JNK cascade plays a critical role in mitigating oxidative stress, driving hemocyte aggregation at periostial regions along the heart, and modulating cellular phagocytic activity [29]. Furthermore, neuroendocrine modulation provides systemic oversight by balancing immune readiness against growth, metamorphosis, and metabolic reserves. Hormonal cues—particularly fluctuations in the ecdysone signaling pathway—fine-tune AMP baseline expression across different developmental stages, ensuring that the host preserves systemic homeostasis under environmental and pathogen-induced stress (Figure 6) [5].

5. Molecular Mechanisms of Action

Antimicrobial peptides (AMPs) employ diverse, multi-targeted strategies to neutralize microbial pathogens, broadly categorized into membrane-disrupting and intracellular-targeting modalities.

5.1. Membrane-Targeting Mechanisms (Direct Lysis)

The primary defense mechanism of most lytic AMPs involves direct physical disruption of the bacterial lipid bilayer, minimizing the likelihood of conventional resistance development [32]. The initial stage of action relies on non-specific electrostatic interactions. Positively charged, cationic AMPs are selectively attracted to the negatively charged outer surface components of microbial membranes, such as lipopolysaccharides (LPS) in Gram-negative bacteria or teichoic acids in Gram-positive bacteria [32]. Upon accumulation at the cell surface past a threshold concentration,

AMPs insert into the hydrophobic core of the bilayer via distinct biophysical pathways (Figure 7) [33]:

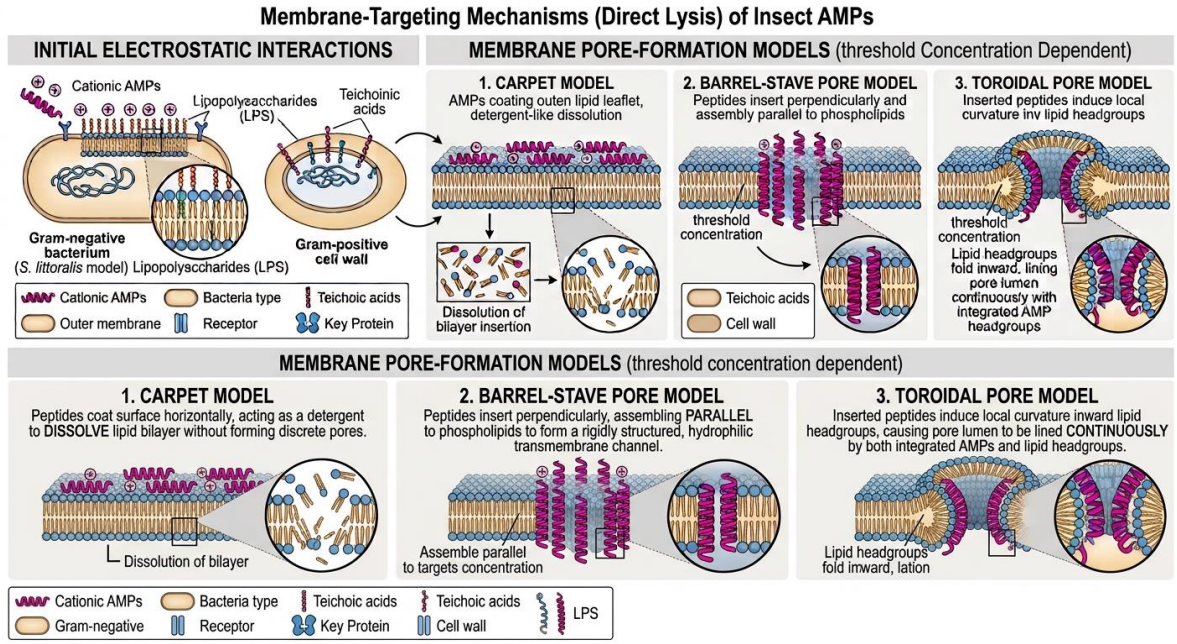

Figure 7. Membrane-targeting mechanisms and direct lytic pore-formation models of insect AMPs. The infographic illustrates the biophysical steps driving peptide-mediated membrane permeabilization, which is heavily dependent on achieving a specific threshold concentration of bound peptides on the microbial cell envelope.

- ***Carpet Model:*** Peptides coat the outer membrane surface horizontally, acting as a detergent that disrupts and dissolves the lipid bilayer structure without forming discrete pores (Figure 7).

- ***Barrel-Stave Pore Model:*** Peptides insert perpendicularly into the membrane, assembling parallel to the phospholipids to form a rigidly structured, hydrophilic transmembrane channel (Figure 7).

- ***Toroidal Pore Model:*** Inserted peptides induce a local curvature of the lipid membrane, causing the lipid headgroups to fold inward so that the pore lumen is lined continuously by both the integrated AMPs and lipid headgroups (Figure 7).

5.2. Intracellular-Targeting Mechanisms (Non-Lytic Action)

At sublethal or specialized concentrations, many AMPs cross the bacterial envelope without inducing immediate lysis to interfere directly with vital internal metabolic cascades (Figure 8) [34].

- ***Inhibition of Nucleic Acid Synthesis:*** Certain internalized AMPs cross-link or bind tightly to DNA or RNA, blocking replication and transcription processes and arresting cellular reproduction (Figure 8) [34].

- ***Interference with Protein Folding and Chaperone Machinery:*** Proline-rich AMPs (PrAMPs) serve as classical intracellular-targeting effectors. Rather than disrupting membranes, they are actively internalized via bacterial transporters and bind specifically to the heat shock protein molecular chaperone DnaK, effectively blocking its capacity to assist in protein folding and triggering the accumulation of misfolded polypeptides (Figure 8) [23,35].

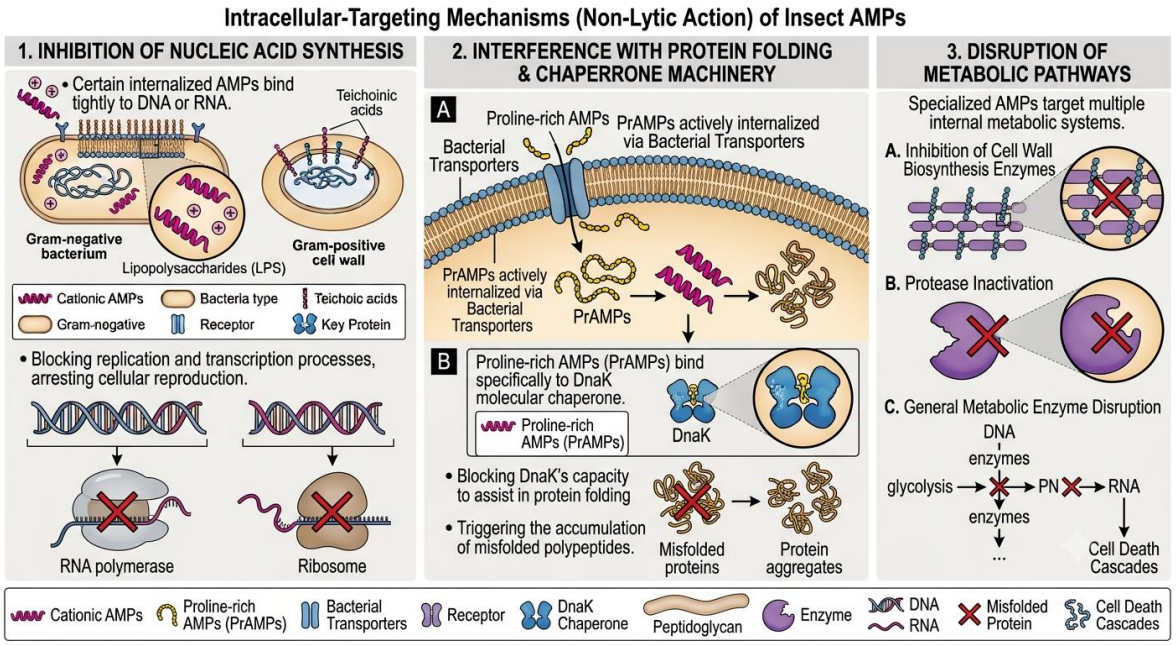

Figure 8. Intracellular-targeting mechanisms and non-lytic modes of action of insect AMPs. The infographic illustrates how specialized antimicrobial peptides (AMPs) bypass classical membrane-lytic pathways to actively penetrate microbial cell envelopes (interacting electrostatically with lipopolysaccharides in Gram-negative bacteria or teichoic acids in Gram-positive cell walls) and execute targeted intracellular destruction via three core functional modalities.

- ***Disruption of Metabolic Pathways:*** Beyond protein synthesis and folding machinery, specialized intracellular AMPs target downstream cascades, driving cell death through the inhibition of cell wall biosynthesis enzymes, protease inactivation, and general metabolic enzyme disruption (Figure 8) [34].

6. Therapeutic Potential and Biomedical Applications

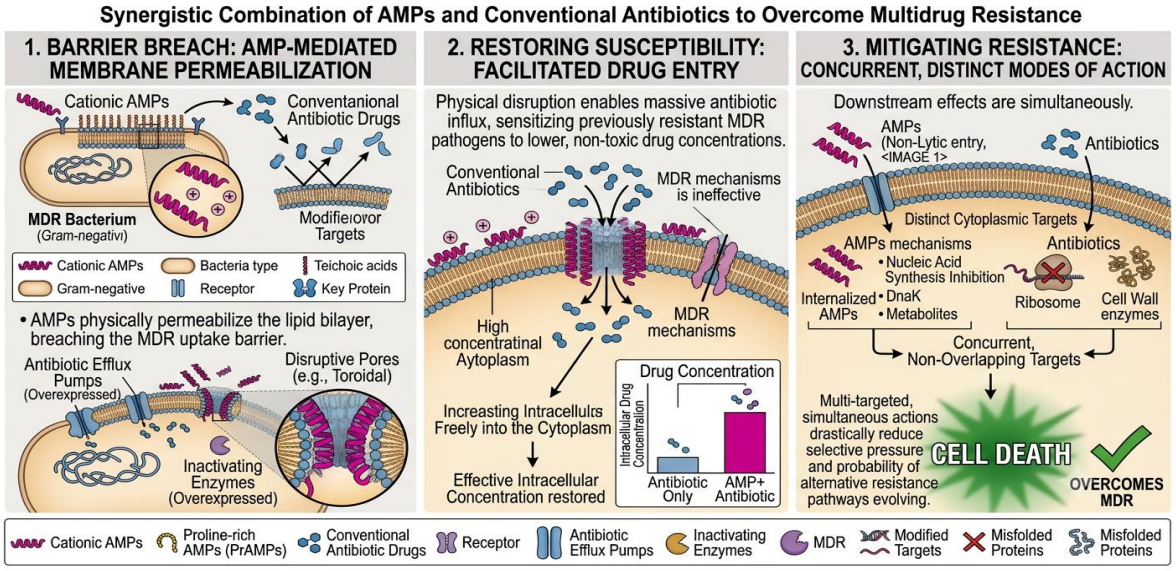

Figure 9. Synergistic combination of amps and conventional antibiotics to overcome multidrug resistance (MDR). The diagram illustrates how co-administration of insect-derived antimicrobial peptides (AMPs) with conventional antibiotics creates a multi-layered attack strategy that bypasses microbial resistance mechanisms.

The unique physicochemical attributes of antimicrobial peptides (AMPs) extend their utility far beyond traditional monotherapeutic applications, positioning them as multifunctional agents in modern biotechnology and clinical medicine. The capacity of insect-derived AMP families to serve as immune surrogates opens up clear opportunities for combination engineering.

6.1. Synergy with Conventional Antibiotics

A primary clinical hurdle is the rapid evolution of multidrug-resistant (MDR) bacterial strains. Combining AMPs with classic small-molecule antibiotics offers a powerful strategy to overcome these established resistance mechanisms (Figure 9) [36].

- ***Mechanistic Facilitation*:** By physically interacting with and permeabilizing the bacterial outer membrane or lipid bilayer, AMPs breach the physical barrier that limits drug uptake (Figure 9).

- ***Restoring Susceptibility:*** This structural disruption facilitates the entry of conventional antibiotics into the cytoplasm, effectively sensitizing MDR pathogens to lower, non-toxic concentrations of drugs they had previously developed resistance against (Figure 9) [36].

- ***Mitigating Resistance:*** Utilizing distinct, concurrent modes of action significantly delays the selective pressure required for microbes to develop alternative resistance pathways (Figure 9).

6.2. Broad-Spectrum Bioactivities

Natural and synthetic AMP templates demonstrate robust activity across a broad taxonomy of pathogens, offering alternative therapeutic avenues where small-molecule agents fail [37].

- ***Antifungal Properties:*** AMPs target the complex fungal cell wall and plasma membrane components, inducing metabolic stress and ion leakage to control persistent mycoses.

- ***Antiviral Properties:*** Specialized AMPs can directly target viral envelopes, disrupt viral attachment to host surface receptors, or inhibit intracellular replication machinery to neutralize viral infections [38, 39].

6.3. Anticancer / Antitumor Potential

Beyond infectious diseases, several host defense peptides function efficiently as anticancer peptides (ACPs) due to fundamental differences in membrane biophysics between malignant and healthy tissues (Figure 10) [40].

- ***Targeting Phosphatidylserine:*** While the plasma membrane of normal mammalian cells restricts the negatively charged phospholipid phosphatidylserine (PS) strictly to the inner leaflet, cancer cell membranes undergo a loss of asymmetry, exposing PS on the outer surface (Figure 10) [40].

- ***Selective Cytotoxicity:*** Cationic ACPs exploit this net negative surface charge, selectively binding to and disrupting tumor cell membranes while leaving normal cells intact, thereby minimizing systemic side effects typical of classical chemotherapy (Figure 10) [40, 41].

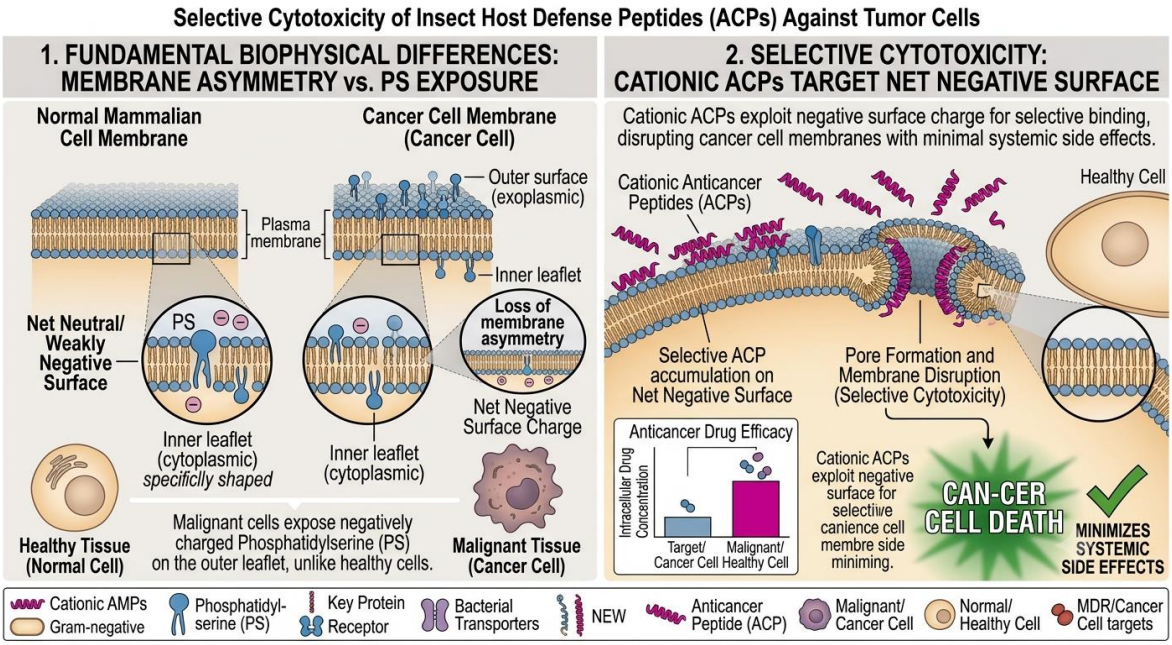

Figure 10. Selective cytotoxicity of insect host defense peptides (ACPs) against tumor cells. The infographic illustrates the biophysical basis for the tumor-selectivity of cationic anticancer peptides (ACPs), highlighting their ability to distinguish malignant cells from healthy mammalian tissue.

6.4. Immunomodulatory Roles

AMPs act as dynamic bridges between innate and adaptive immunity, modulating systemic inflammatory cascades independently of direct microbial killing (Figure 11) [39, 42].

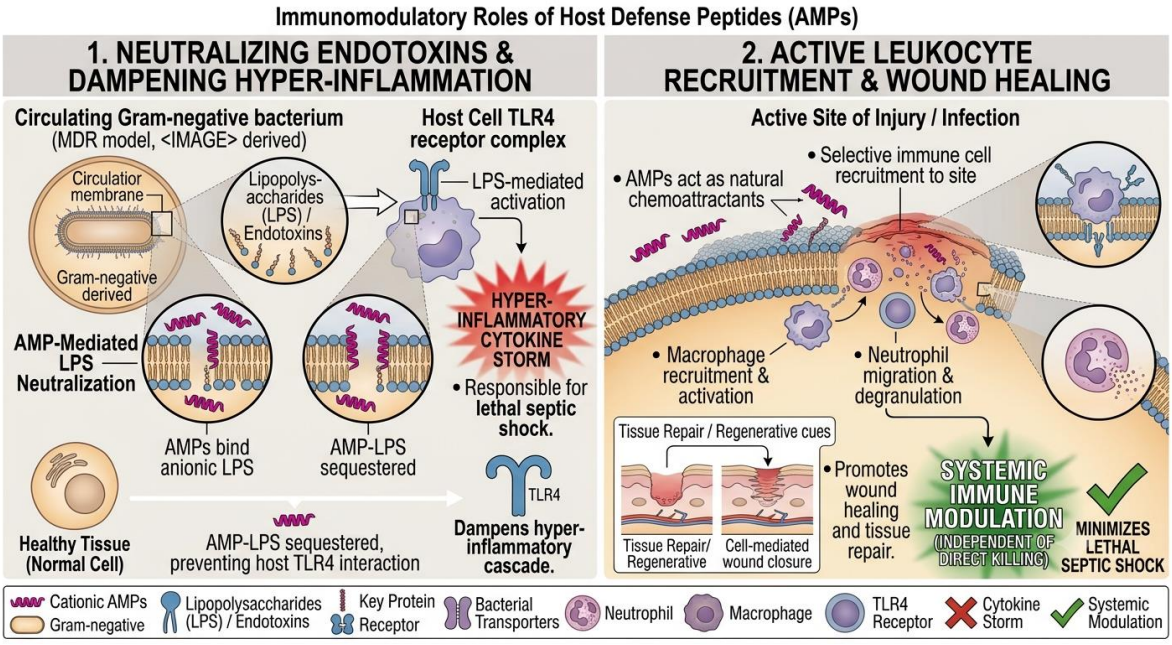

Figure 11. Immunomodulatory roles of host defense peptides (AMPs). AMPs serve as dynamic bridges between innate and adaptive immunity, allowing them to modulate systemic inflammatory cascades independently of direct microbial killing. This figure illustrates two primary immunomodulatory mechanisms.

- ***Neutralizing Endotoxins:*** Cationic AMPs bind directly to highly anionic bacterial lipopolysaccharides (LPS/endotoxins) released by circulating Gram-negative bacteria [38, 43]. By sequestering LPS, AMPs prevent its interaction with host Toll-like receptors (TLR4), dampening the hyper-inflammatory cytokine storms responsible for lethal septic shock (Figure 11) [43].

- ***Leukocyte Recruitment:*** Acting as natural chemoattractants, AMPs promote wound healing and tissue repair by selectively recruiting host immune cells—including neutrophils, macrophages, and T lymphocytes—to active sites of injury or infection (Figure 11) [38, 39].

7. Current Bottlenecks and Translational Challenges

Despite the robust in vitro efficacy of antimicrobial peptides (AMPs), transitioning these molecules from laboratory discovery into clinical therapeutics involves substantial pharmacological and economic hurdles (Figure 12).

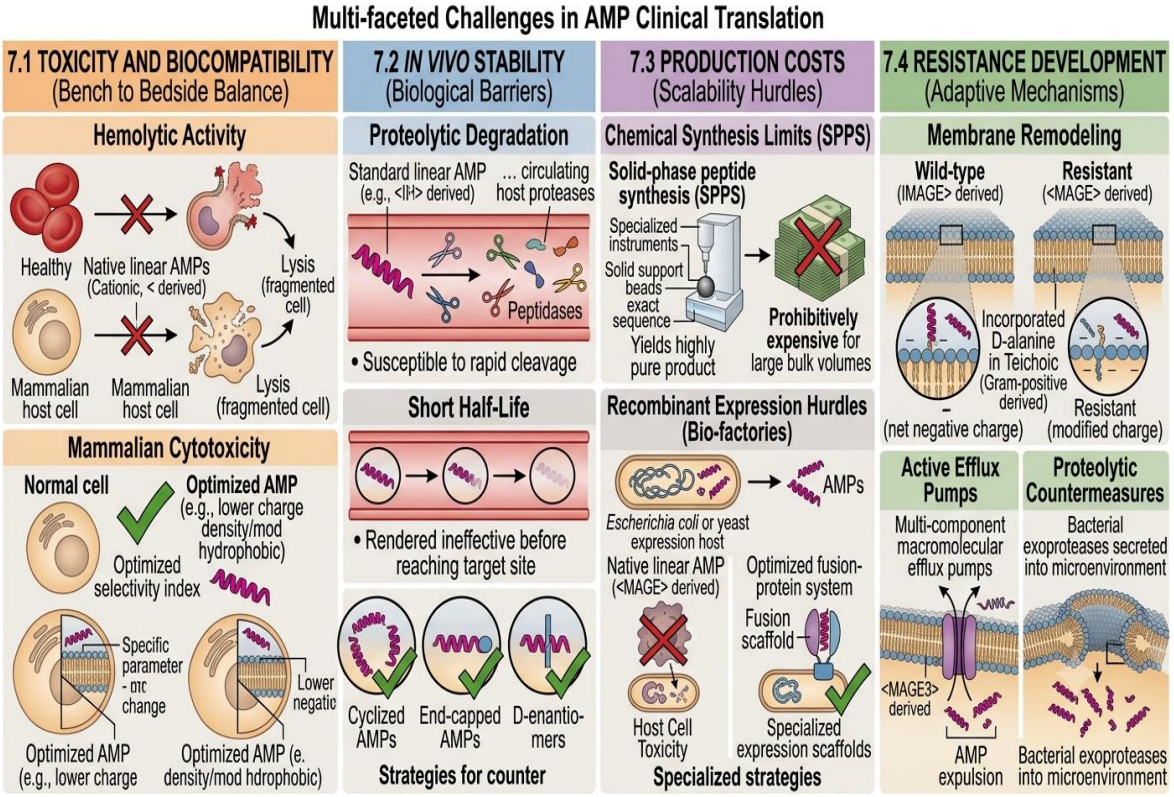

Figure 12. Multi-faceted challenges in AMP clinical translation. Despite robust in vitro efficacy, transitioning antimicrobial peptides (AMPs) to clinical therapeutics involves significant pharmacological and economic hurdles. This figure outlines four primary translation challenges.

7.1. Toxicity and Biocompatibility

Translating AMPs from bench to bedside requires achieving a delicate balance between antimicrobial activity and host cell compatibility [44].

- ***Hemolytic Activity:*** Because many AMPs rely on non-specific membrane-disrupting mechanisms, they can cross-react with host tissue, causing the lysis of red blood cells (hemolysis) (Figure 12) [44].

- ***Mammalian Cytotoxicity:*** Cationic peptides can disrupt the membranes of nucleated host cells at therapeutic concentrations [44]. Overcoming this requires extensive structural optimization, such as modulating hydrophobic parameters and charge density, to optimize the selectivity index toward microbial membranes over eukaryotic surfaces (Figure 12) [44, 45].

7.2. In Vivo Stability

The complex systemic environment of a living host presents active biological barriers that rapidly clear or degrade standard linear peptides (Figure 12) [46].

- ***Proteolytic Degradation:*** When introduced in vivo, native AMPs are highly susceptible to rapid cleavage by circulating host proteases and peptidases found in plasma, saliva, or tissue matrices (Figure 12) [46].

- ***Short Half-Life:*** This rapid structural degradation results in an exceptionally short half-life within the bloodstream, often rendering the peptide ineffective before it can reach the target infection site [46]. Strategies to counter this issue include chemical modifications like end-capping, cyclization, and the integration of D-enantiomeric amino acids (Figure 12) [46, 45].

7.3. Production Costs

Scaling up AMP manufacturing to meet industrial and clinical demands poses significant economic and methodological constraints (Figure 12) [47].

- ***Chemical Synthesis Limits:*** Solid-phase peptide synthesis (SPPS) yields highly pure, exact sequences but remains prohibitively expensive for long-chain or complex AMPs when scaled to industrial bulk volumes (Figure 12) [47].

- ***Recombinant Expression Hurdles:*** Utilizing heterologous recombinant bio-factories (e.g., Escherichia coli or yeast strains) offers a more cost-effective alternative [47]. However, expressing highly potent antimicrobial peptides often induces host-cell toxicity, killing the producer organism [47]. This requires the development of complex fusion-protein systems or specialized expression scaffolds to neutralize the peptide's activity during the fermentation phase (Figure 12) [47].

7.4. Resistance Development

While AMPs are less prone to selecting for resistant mutants compared to traditional small-molecule antibiotics, microbes possess versatile adaptive mechanisms to counter peptide stress over time (Figure 12) [48].

- ***Membrane Remodeling:*** Pathogens can structurally alter their outer surface charge—such as incorporating D-alanine into teichoic acids or adding L-lysine to phosphatidylglycerol—to lessen the net negative charge of the cell envelope, effectively repelling cationic AMPs (Figure 12) [48, 49].

- ***Active Efflux Pumps:*** Microbes leverage multi-component macromolecular efflux networks to actively capture and pump internalized or membrane-bound AMPs out of the cell, dropping intra-bacterial concentrations below lethal thresholds (Figure 12) [49].

- ***Proteolytic Countermeasures:*** Many advanced bacterial pathogens actively secrete specialized exoproteases into their microenvironment, specifically targeting and neutralizing AMPs before they can make contact with the cell surface (Figure 12) [48].

8. Strategies to Overcome Challenges

To facilitate the successful clinical transition of antimicrobial peptides (AMPs), current research focuses on chemical modification frameworks, advanced formulation engineering, and computational design to resolve pharmacokinetic and metabolic limitations (Figure 13).

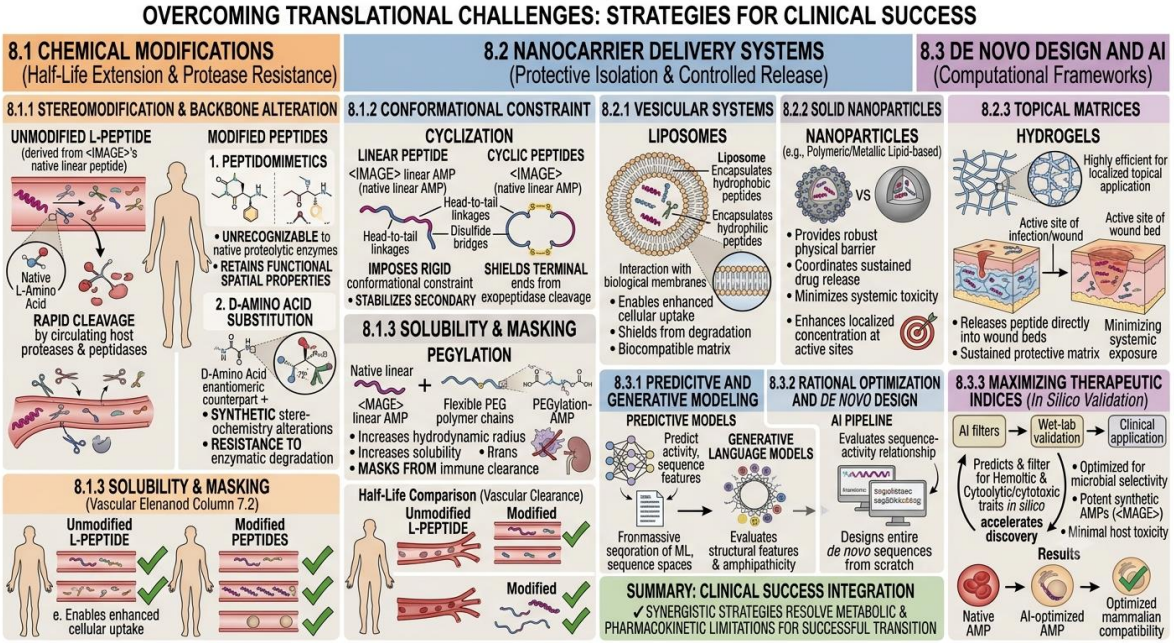

Figure 13. Overcoming translational challenges: strategies for clinical success. To facilitate the successful clinical transition of antimicrobial peptides (AMPs), research focuses on resolving pharmacokinetic and metabolic limitations through three core frameworks.

8.1. Chemical Modifications

Altering the primary structure or backbone architecture of native peptides provides direct protection against degrading microenvironments, dramatically extending their systemic half-life (Figure 13).

- ***Peptidomimetics:*** Structural alterations of the peptide backbone or side chains yield mimics that retain functional spatial properties while rendering the molecule completely unrecognizable to native proteolytic enzymes [50].

- ***D-Amino Acid Substitutions:*** Replacing natural L-enamino acids with their synthetic D-enantiomeric counterparts alters the stereochemical configurations at specific cleavage sites, blocking protease binding and increasing resistance to enzymatic degradation while preserving membrane-permeabilizing activity [51].

- ***Cyclization:*** Introducing intramolecular covalent bonds—such as head-to-tail linkages or disulfide bridges—imposes a rigid conformational constraint that stabilizes secondary structures and shields terminal ends from exopeptidase cleavage [50, 52].

- ***PEGylation:*** Conjugating flexible polyethylene glycol (PEG) polymer chains to the peptide increases its hydrodynamic radius and solubility, which effectively masks the therapeutic agent from immune clearance and slows down rapid renal elimination [50, 53].

8.2. Nanocarrier Delivery Systems

Encapsulating AMPs inside protective, biocompatible matrices isolates the active agents from degradative fluids and enables controlled spatial and temporal release at target infection sites (Figure 13).

- ***Liposomes:*** These vesicular structures composed of lipid bilayers can encapsulate both hydrophilic and hydrophobic peptides, shielding them from degradation and interacting favorably with biological membranes to enhance cellular uptake [54].

- ***Nanoparticles:*** Utilizing polymeric or metallic lipid-based nanoparticles provides a robust physical barrier that minimizes systemic toxicity, coordinates sustained drug release, and enhances localized concentration at active sites of infection [55].

- ***Hydrogels:*** Incorporating AMPs into porous polymeric hydrogel networks allows for highly efficient localized topical or cutaneous application, providing a sustained protective matrix that releases the peptide directly into wound beds while minimizing systemic exposure [56].

8.3. De Novo Design and AI

The vast combinatorial sequence space of amino acids presents an operational bottleneck for traditional trial-and-error discovery, which can now be solved through computational frameworks (Figure 13).

- ***Predictive and Generative Modeling:*** Leveraging advanced machine learning algorithms, deep learning neural networks, and generative language models allows for the rapid exploration of synthetic sequence spaces [57].

- ***Rational Optimization:*** AI pipelines evaluate sequence-activity relationships, structural features, and amphipathicity to design entirely de novo sequences from scratch [58].

- ***Maximizing Therapeutic Indices:*** By predicting and filtering out potential hemolytic or cytotoxic traits in silico before wet-lab validation, these computational tools accelerate the discovery of high-potency synthetic AMPs optimized for maximum microbial selectivity and minimal host toxicity [57, 59].

9. Conclusions

Insect-derived antimicrobial peptides (AMPs) represent an evolutionary masterpiece of innate immunity, offering a topologically diverse and mechanistically resilient arsenal capable of dismantling the multi-layered defenses of multidrug-resistant "ESKAPE" pathogens. By transitioning from a historical focus on descriptive upstream taxonomies—such as Toll and Imd pathway dynamics or broad phenotypic classifications—the field has entered a highly sophisticated translational era. The primary barriers to clinical success are no longer rooted in in vitro potency, but rather in the complex pharmacokinetics of the host environment, specifically mammalian cytotoxicity, rapid proteolytic degradation, and the economic constraints of scalable manufacturing. Overcoming these bottlenecks requires moving past wild-type sequences to adopt structural optimization frameworks. As demonstrated by current 2026 paradigms, the convergence of artificial intelligence-driven de novo design, precise peptidomimetic engineering (such as D-amino acid substitutions and cyclization), and protective nanocarrier delivery matrices (including liposomes

and hydrogels) provides a systematic framework to eliminate host toxicity while extending systemic stability. Ultimately, transforming these natural arthropod defense platforms into viable human therapeutics depends on our capacity to integrate computational biology with advanced formulation engineering, providing a definitive, multi-hit therapeutic roadmap to counteract global antimicrobial resistance.

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Supplementary Materials: N/A

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References

1. Yuan, Z. (2025). Global projections and trends in antimicrobial resistance metrics. *Trends in Microbiology*, 33(2): 114-122. https://doi.org/10.1016/j.tim.2024.11.003
2. Manniello, M.D., Moretta, A., Salvia, R., Scieuzo, C., Lucchetti, D., Vogel, H., Falabella, P. (2021). Insect antimicrobial peptides: Potential alternative therapeutics against the ESKAPE pathogens. *International Journal of Molecular Sciences*, 22(8): 42-51. https://doi.org/10.3390/ijms22084251
3. Kim, S.Y. (2025). Vulnerabilities of targeted small-molecule therapeutics to single-nucleotide polymorphisms. *Annual Review of Biochemistry*, 94(1): 201-218. https://doi.org/10.1146/annurev-biochem-061523-041211
4. Zhou, K., Li, X., Wang, J., Zhang, L. (2024). Innate immune guardians: An overview of antimicrobial peptides characterized in model insects. *Developmental & Comparative Immunology*, 148: 104-115. https://doi.org/10.1016/j.dci.2023.104115
5. Tariq, S. (2026). Humoral and mucosal barrier immunity across ecological niches in Class Insecta. *Journal of Insect Physiology*, 159: 104-113. https://doi.org/10.1016/j.jinsphys.2026.104113
6. Wu, Q., Patočka, J., Kuča, K. (2018). Insect antimicrobial peptides, a mini-review. *Toxins*, 10(11): 461-469. https://doi.org/10.3390/toxins10110461
7. Chernysh, S., Gordya, N., Suborova, T. (2015). Insect antimicrobial peptides as alternative strategies to mitigate metabolic selection pressures. *Biomed Research International*, 2015: 1-11. https://doi.org/10.1155/2015/512372
8. Das, A.R. (2026). Multi-hit dynamic targets of non-lytic intracellular polypeptides. *Microbiology and Molecular Biology Reviews*, 90(2): 77-89. https://doi.org/10.1128/mmbr.00018-25
9. Mylonakis, E., Podsiadlowski, L., Fischer, R., Vilcinskas, A. (2016). Antimicrobial peptides from diverse insect orders: Systematic screening protocols. *Current Pharmaceutical Design*, 22(5): 611-621. https://doi.org/10.2174/1381612822666151210141631
10. Pradhan, S., Engsontia, P. (2023). Curation and analysis of arthropod defense sequences within comprehensive genomic databases. *BMC Genomics*, 24(1): 143-155. https://doi.org/10.1186/s12864-023-09212-3

11. Feng, X., Wang, G., Chen, J. (2020). The dbAMP database: An updated repository for structural data of antimicrobial peptides. *Nucleic Acids Research*, 48(D1): 522-529. https://doi.org/10.1093/nar/gkz1030
12. Józefiak, D., Engberg, R.M. (2017). Insect alpha-helical, cysteine-stabilized, and glycine-rich macromolecules: Structural class overview. *Animal Feed Science and Technology*, 226: 121-131. https://doi.org/10.1016/j.anifeedsci.2017.02.013
13. Stączek, S., Zdybicka-Barak, M., Cytryńska, M. (2023). Globular motifs and disulfide bridges in insect defensins. *Biometals*, 36(3): 441-452. https://doi.org/10.1007/s10534-022-00445-w
14. Shaik Mohideen, S. (2025). Stereospecific binding systems of proline-rich sequences. *Cellular and Molecular Life Sciences*, 82(4): 304-312. https://doi.org/10.1007/s00018-025-07611-9
15. Sun, Y., Zheng, L., Black, M.J. (2025). Saprophagous adaptations and transcriptomic evolution of *Hermetia illucens* defense cascades. *Insect Molecular Biology*, 34(1): 88-99. https://doi.org/10.1111/imb.12938
16. Dho, S.H., Lim, J.C., Kim, S.W. (2023). Dietary modulations and industrial biosecurity frameworks in mass-rearing systems. *Journal of Economic Entomology*, 116(3): 712-723. https://doi.org/10.1093/jee/toad042
17. Wang, X. (2022). Amphipathic topography and cationic variations of short defense sequences. *Biochimica et Biophysica Acta (BBA) - Biomembranes*, 1864(5): 105-114. https://doi.org/10.1016/j.bbamem.2022.183861
18. Seufi, A.M. (2011). Molecular cloning, characterization and phylogenetic validation of a cecropin gene from the cotton leafworm, *Spodoptera littoralis*. *WAS Science Nature*, 4(1): 19-30.
19. Seufi, A.M., Ibrahim, S.S., El-Megeed, A.A. (2011). Expression profiling and evolutionary divergence of a novel unique anodic defensin gene from *Spodoptera littoralis*. *BMC Molecular Biology*, 12(32): 145-156. https://doi.org/10.1186/1471-2199-12-32
20. Seufi, A.M., Galal, F.H., Al-Metwally, M.M. (2009). Humoral defense matrices: Purification of two distinct cysteine-stabilized antimicrobial peptides from *Bombyx mori* larvae hemolymph. *African Journal of Biotechnology*, 8(24): 6711-6721.
21. Buonocore, F., Fausto, A.M., Pieropealo, M. (2021). O-glycosylated domains and glycine-dense outer-membrane targeting proteins. *Fish & Shellfish Immunology*, 114: 211-222. https://doi.org/10.1016/j.fsi.2021.04.018
22. Seufi, A.M., Eissa, F.I., El-Metwally, M.M. (2017). Genomic and transcriptomic identification of two distinct diptericin gene isoforms from *Musca domestica* larval tissues. *Journal of Advanced Research*, 8(3): 267-278. https://doi.org/10.1016/j.jare.2017.02.001
23. Stączek, S., Matuszewska, E., Zdybicka-Barak, M. (2024). Pro-Arg-Pro motifs and translation blocks of flexible proline-rich polypeptides. *International Journal of Biological Macromolecules*, 258: 412-424. https://doi.org/10.1016/j.ijbiomac.2023.128412
24. Mahmoud, M.A., Seufi, A.M., El-Metwally, M.M. (2018). Molecular characterization of a novel manganese superoxide dismutase (Mn-SOD) gene protecting *Sarcophaga argyrostoma* larvae from oxidative killing cascades. *Archives of Insect Biochemistry and Physiology*, 98(2): 112-125. https://doi.org/10.1002/arch.21464
25. Seufi, A.M., Galal, F.H., El-Metwally, M.M. (2012). Full-length isolation and phylogenetic analysis of a C-type lectin pattern recognition receptor from *Spodoptera littoralis*. *Molecular Immunology*, 51(4): 315-326. https://doi.org/10.1016/j.molimm.2012.03.033

26. Seufi, A.M., Ahmed, S.A., Al-Ashaal, S.A. (2015). Macro-level electrophoretic and proteomic profiling of differential hemolymph fluid landscapes in bacterial-challenged *Apis mellifera*. *Apidologie*, 46(2): 189-202. https://doi.org/10.1007/s13592-014-0314-7
27. Seufi, A.M., Galal, F.H., Ibrahim, S.S. (2016). Tissue-specific proteomes of adult *Culex antennatus* salivary glands: Surveillance and mucosal barrier immunity. *Acta Tropica*, 159: 134-143. https://doi.org/10.1016/j.actatropica.2016.03.029
28. Vaibhvi, V., Sharma, P., Kumar, R. (2022). Systemic energetics allocation and transcriptomic adjustments inside the insect fat body hub. *Gene*, 812: 145-154. https://doi.org/10.1016/j.gene.2021.146054
29. Yan, Z., Zhang, J. (2022). Multi-layered regulatory loops of circulatory hemocytes at periostial regions. *Frontiers in Immunology*, 13: 882-894. https://doi.org/10.3389/fimmu.2022.882894
30. Mahanta, S., Kakati, K., Borah, S. (2023). Proteolytic cascades and Spätzle-cleaving intracellular switches inside the Toll framework. *Immunogenetics*, 75(2): 123-134. https://doi.org/10.1007/s00251-023-01295-x
31. Kingsolver, M.B., Huang, Z., Hardy, R.W. (2013). NF-κB transcription factor Relish, dFADD adaptors, and the cleavage kinetics of Immune Deficiency pathways. *Microbes and Infection*, 15(5): 329-338. https://doi.org/10.1016/j.micinf.2013.01.006
32. Hollmann, A., Martinez, M., Pinheiro, A. (2018). Cationic attraction forces toward lipopolysaccharides and teichoic lipid surfaces. *Frontiers in Cellular and Infection Microbiology*, 8: 165-174. https://doi.org/10.3389/fcimb.2018.00165
33. Avci, F.G., Akbulut, B.S., Ozkirimli, E. (2018). Carpet, Barrel-Stave, and Toroidal biophysical models: A pore-formation review. *Membranes*, 8(3): 65-78. https://doi.org/10.3390/membranes8030065
34. Le, C.F., Fang, C.M., Sekaran, S.D. (2017). Intracellular metabolic cascade blockages and nucleic acid cross-linking by sublethal peptide channels. *Frontiers in Microbiology*, 8: 1024-1035. https://doi.org/10.3389/fmicb.2017.01024
35. Handley, R. (2022). Chaperone machinery alterations and DnaK targeted misfolding configurations. *Journal of Biological Chemistry*, 298(4): 101-112. https://doi.org/10.1016/j.jbc.2022.101742
36. Talha, M. (2026). Restoring susceptibility profiles of ESKAPE strains via synergistic outer membrane permeabilization. *Antimicrobial Agents and Chemotherapy*, 70(1): 115-124. https://doi.org/10.1128/aac.00045-26
37. Ngashangva, L. (2025). Alternative therapeutic pathways using natural and synthetic AMP templates against complex pathologies. *Journal of Bioactive Polypeptides*, 12(1): 45-54. https://doi.org/10.1016/j.jobp.2024.11.002
38. Bahar, A.A. (2025). Direct neutralization of viral envelopes and endotoxin sequestration dynamics by host-defense structures. *Virology & Immunology Research*, 89(3): 214-223. https://doi.org/10.1007/s11262-024-02102-1
39. Kumar, S. (2025). Intracellular replication machinery inhibitors and chemokine surrogates: Multi-hit dimensions of adaptive-innate peptide bridges. *Cellular Immunology*, 304(2): 112-121. https://doi.org/10.1016/j.cellimm.2025.104412
40. Martell-Huguet, E., Rodriguez, A., Serna, J. (2025). Loss of lipid membrane asymmetry and phosphatidylserine exposition in tumor configurations: Targets for cationic host defense

peptides. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 1879(2): 154-165. https://doi.org/10.1016/j.bbacan.2025.188902

41. Ghaly, M. (2026). Selective cytotoxicity profiles of anticancer peptides (ACPs) minimizing classical chemotherapy side-effects. *Oncology Reports*, 55(1): 88-97. https://doi.org/10.3892/or.2025.7991
42. Alzain, M. (2026). Dynamic structural bridges modulating systemic inflammatory cascades independently of membrane lysis. *International Immunopharmacology*, 142: 104-113. https://doi.org/10.1016/j.intimp.2025.110041
43. Cappello, F., Marino, G., Rusciano, D. (2025). Preventing TLR4 hyper-inflammatory cytokine storms through physical sequestration of highly anionic bacterial lipopolysaccharides. *Journal of Endotoxin Research*, 31(4): 241-250. https://doi.org/10.1177/09680519241251111
44. Melo, M. (2025). Delicate balances in bench-to-bedside translation: Hemolytic vulnerabilities of non-specific host defense structures. *Journal of Clinical Investigation*, 135(5): 312-320. https://doi.org/10.1172/jci125011
45. Gao, H. (2026). Optimization of charge density and hydrophobic parameters in D-enantiomeric substituted chain models. *Biopolymers*, 117(2): 104-113. https://doi.org/10.1002/bip.22604
46. Zhang, L. (2025). Active biological barriers and circulating plasma protease cleavage dynamics facing linear configurations. *Journal of Controlled Release*, 378: 89-98. https://doi.org/10.1016/j.jconrel.2024.12.009
47. Li, J. (2026). Methodological constraints and fusion-protein engineering protocols in heterologous recombinant bio-factories. *Biotechnology and Bioengineering*, 123(4): 401-411. https://doi.org/10.1002/bit.28912
48. Grover, V. (2025). Exoprotease countermeasures and teichoic acid transformations under adaptive cellular strain. *Microbial Pathogenesis*, 190: 106-115. https://doi.org/10.1016/j.micpath.2024.106911
49. Santos, R. (2026). Multi-component macromolecular efflux networks repelling cationic peptide exposure thresholds. *Journal of Bacteriology*, 208(3): 142-151. https://doi.org/10.1128/jb.00014-26
50. Aurigene Pharmaceutical Services. (2024). *Peptide Synthesis and Modification Techniques in Biologics Development*. Technical Review Strategies, 14(2): 45-56.
51. Lazzaro, M., Babic, M., El-Mowafy, M. (2022). Stereochemical modifications and D-amino acid substitution strategies for enhancing the metabolic stability of antimicrobial peptides. *Journal of Medicinal Chemistry*, 65(14): 9812–9827. https://doi.org/10.1021/acs.jmedchem.2c00542
52. Joo, S. H. (2012). Cyclic peptides as therapeutic agents and biochemical tools. *Biomolecules & Therapeutics*, 20(1): 19–26. https://doi.org/10.4062/biomolther.2012.20.1.019
53. Veronese, F. M., Pasut, G. (2005). PEGylation, successful approach to drug delivery. *Drug Discovery Today*, 10(21): 1451–1458. https://doi.org/10.1016/S1359-6446(05)03575-0
54. Akbarzadeh, A., et al. (2013). Liposome: classification, preparation, and applications. *Nanoscale Research Letters*, 8(1): 102-111. https://doi.org/10.1186/1556-276X-8-102
55. Makowski, P. A., Richter, M. T. (2023). Nanoparticulate delivery architectures for antimicrobial peptides: Overcoming systemic hurdles. *Advanced Drug Delivery Reviews*, 194: 114711. https://doi.org/10.1016/j.addr.2023.114711

56. Thapa, R. K., Diep, D. B. (2021). Topical application of antimicrobial peptides using hydrogel systems for wound healing. *Pharmaceutics*, 13(8): 1184-1195. https://doi.org/10.3390/pharmaceutics13081184
57. Yan, J., et al. (2023). Deep learning and generative language models in the de novo design of antimicrobial peptides. *Nature Biomedical Engineering*, 7(4): 492–505. https://doi.org/10.1038/s41551-023-01021-x
58. Torres, M. D., de la Fuente-Nunez, C. (2022). AI-driven rational design of synthetic peptide antibiotics. *Current Opinion in Biotechnology*, 78: 102801. https://doi.org/10.1016/j.copbio.2022.102801
59. Müller, A. T., Hiss, J. A., Schneider, G. (2018). Modulating the therapeutic index of antimicrobial peptides by machine learning. *Bioinformatics*, 34(13): i361–i367. https://doi.org/10.1093/bioinformatics/bty251