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ANTIMICROBIAL PEPTIDES FROM *Bombyx mori*: PHARMACEUTICAL CONTRIBUTIONS, APPLICATIONS, AND RECENT DISCOVERIES

Rakesh Yethi Raj*, Mallaiah Shivashankar

Department of Life Science, Bangalore University, Bengaluru – 560056.

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***Corresponding Author: Rakesh Yethi Raj**
Department of Life Science, Bangalore University, Bengaluru – 560056.
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ABSTRACT

The investigation of alternative therapeutic agents beyond traditional antibiotics has become necessary due to the rapid escalation of antimicrobial resistance (AMR). Due to their broad-spectrum activity and decreased potential to cause resistance, antimicrobial peptides (AMPs), essential elements of innate immunity, have drawn a lot of attention. Cecropins, attacins, moricins, gloverins, defensins, and ponericin-like peptides are among the structurally varied AMPs that are abundantly found in the silkworm *Bombyx mori*. Through membrane disruption, intracellular targeting, and immunomodulatory mechanisms, these peptides demonstrate strong antibacterial, antifungal, antiviral, antiparasitic, and anticancer properties. The Toll and Imd signalling pathways that control AMP synthesis are highlighted in this review, which offers a thorough overview of *B. mori*'s immune architecture. A summary of current AMP isolation, purification, and structural characterization techniques is provided, emphasizing developments in proteomic, chromatographic, and bioinformatic techniques that have sped up the discovery of new peptides. Major AMP families' structural diversity and functional specificity are examined critically in light of their potential applications in medicine, especially in the fight against infections linked to biofilms and multidrug-resistant pathogens. The therapeutic potential of AMPs derived from silkworms has been improved by recent developments in peptide engineering, recombinant expression systems, and nano formulation techniques. Proteolytic instability, pharmacokinetic constraints, cytotoxicity issues, and large-scale production, however, continue to be major barriers to clinical translation. All things considered, *Bombyx mori* AMPs are a flexible and sustainable bioresource for the creation of next-generation antibiotics. To convert these naturally occurring defense molecules into therapeutically effective treatments, integrative research integrating molecular biology, biotechnology, and pharmaceutical sciences will be crucial.

KEYWORDS: Antimicrobial resistance (AMR), Antimicrobial peptides (AMPs), *Bombyx mori.*

INTRODUCTION

Antimicrobial peptides are a diverse group of naturally occurring molecules that serve as crucial components of the innate immune system across various life forms, including insects like *Bombyx mori* (Sangma et al., 2023). These peptides exhibit potent antimicrobial activity against a broad spectrum of pathogens, presenting a promising avenue for the development of novel therapeutic agents to combat the growing threat of antibiotic resistance (Dho et al., 2023; Sangma et al., 2023). The increasing prevalence of multi-drug-resistant microorganisms has necessitated the exploration of alternative antimicrobial strategies, positioning insect-derived AMPs, particularly those from silkworms, as attractive candidates due to their distinct mechanisms of action and often lower propensity for resistance development (Manniello et al., 2021; Sangma et al., 2023). Insects possess highly developed innate immune systems, relying on both cellular and humoral responses, with AMPs constituting a significant part of their humoral defense (Sangma et al., 2023). This review will focus on the diverse array of AMPs identified in *Bombyx mori*, examining their structural characteristics, mechanisms of action, and potential pharmaceutical applications, while also highlighting recent discoveries that underscore their therapeutic promise against antibiotic-resistant pathogens (Manniello et al., 2021; Nesa et al., 2022). Specifically, we will examine the unique properties of various *Bombyx mori* AMPs such as cecropins, lebocins, moricins, attacins, and defensins, which are pivotal in the silkworm's defense against microbial invaders (Sangma et al., 2023). These cationic polypeptides often function by disrupting bacterial cell membranes, leading to pore formation and ultimately cell death, thus offering a potent alternative to conventional antibiotics (Nesa et al., 2022). The rapid emergence of antimicrobial resistance and the stagnation in the development of new classes of antimicrobials further underscore the urgent need for such alternative therapeutic molecules (Sarkar et al., 2021). The economic impact of antibiotic-resistant diseases is projected to reach over $100 trillion, emphasizing the critical importance of exploring novel antimicrobial compounds like those found in *Bombyx mori* (Sangma et al., 2023). The unique biochemical properties of these peptides, including their amphipathic nature and ability to target bacterial membranes, make them particularly effective against a wide range of microbial threats, including multidrug-resistant bacteria, fungi, and even some viruses (Fu et al., 2023; Sangma et al., 2023). Furthermore, the silkworm, *Bombyx mori*, has emerged as a valuable model organism not only for the discovery of novel AMPs but also for in vivo drug discovery and testing of antimicrobial compounds, thereby mitigating some of the ethical and financial challenges associated with mammalian models (Tabuchi et al., 2024). Its susceptibility to various pathogens and the established models for bacterial, fungal, and viral infections make it an ideal system for studying innate immunity and evaluating potential therapeutic agents (Sangma et al., 2023).

1. Overview of Antimicrobial Peptides (AMPs)

Antimicrobial peptides, generally defined as small molecules typically less than 10 kDa, are fundamental components of the innate immune system found across a vast array of phylogenetically distant organisms, from prokaryotes to eukaryotes (Dho et al., 2023). In these organisms, AMPs play a crucial role in the body's defense against a wide range of pathogens such as bacteria, viruses, and fungi (Ciobănaşu et al., 2024). They are characterized by their amphipathic nature and cationic charge, properties that are essential for their interactions with microbial membranes (Dilawari et al., 2025). This unique structural configuration allows AMPs to preferentially target and destabilize the negatively charged bacterial cell membranes, leading to membrane permeabilization and subsequent cell death (Richter et al., 2022). This mechanism often results in rapid microbial killing, making AMPs less susceptible to the development of resistance compared to conventional antibiotics (Wang et al., 2021). Moreover, their broad-spectrum activity, encompassing antibacterial, antifungal, and antiviral properties, positions AMPs as promising candidates for addressing the escalating

crisis of antimicrobial resistance (Sangma et al., 2023; Wong et al., 2025). Their diverse mechanisms of action, which often involve membrane disruption rather than specific molecular targets, contribute to their potency and reduced likelihood of microorganisms acquiring resistance (Manniello et al., 2021; Sangma et al., 2023). This multifaceted activity underscores their potential as novel therapeutic agents in an era where conventional antibiotics are increasingly ineffective (BN & Ramesh, 2024).

2. Classification and Mechanisms of Action

While the primary mechanism of AMP action is often attributed to membrane disruption, a deeper understanding reveals that many AMPs can also exert their antimicrobial effects through intracellular targets, interfering with vital cellular processes such as DNA replication, protein synthesis, and enzyme activity. This dual mode of action, targeting both the microbial membrane and intracellular components, contributes to their effectiveness and broader spectrum of activity (Moradi et al., 2022). The structural diversity of AMPs, including α-helical, β-sheet, and αβ-structures, further dictates their specific interactions and efficacy against different microbial pathogens (Wei et al., 2025). Many AMPs are cationic, facilitating electrostatic interactions with the negatively charged components of bacterial membranes, such as lipopolysaccharide and lipoteichoic acid, while exhibiting weaker interactions with the zwitterionic eukaryotic cell membranes (Fahmy et al., 2024). This differential interaction forms the basis of their selective toxicity, minimizing damage to host cells while effectively targeting microbial invaders (Chandole et al., 2024; Lastra et al., 2022). However, the exact mechanism by which AMPs selectively target microbial membranes and spare host cells is still an area of active research, involving complex interactions influenced by factors such as peptide concentration, membrane composition, and the presence of specific receptors or binding sites (Kim et al., 2025). Furthermore, the classification of AMPs can also be based on their source, biological potential, and amino acid sequences, providing a comprehensive framework for understanding their diverse functionalities (Halawa et al., 2023). Their mechanisms of action are diverse, encompassing membrane disruption via models such as the barrel stave, carpet, and toroidal pore, as well as intracellular targeting that inhibits macromolecular synthesis and enzyme activity (Enany et al., 2021; Kim et al., 2025; Singh et al., 2024). This multifaceted approach, combining both membrane disruption and intracellular interference, significantly reduces the likelihood of resistance development by pathogens (Halawa et al., 2023),(Ramata-Stunda et al., 2023). A crucial aspect distinguishing AMPs from conventional antibiotics is their ability to act non-specifically on multiple bacterial targets, which makes it challenging for microorganisms to develop resistance (Talukdar et al., 2021). This is because many AMPs either form pores in the bacterial membrane or interact with intracellular components like DNA, RNA, and proteins, disrupting critical cellular functions (Bellucci et al., 2024),(Moradi et al., 2022),(Preußke et al., 2023). This multi-target approach, unlike the single-target mechanisms of many conventional antibiotics, significantly mitigates bacterial resistance development, positioning AMPs as promising candidates for novel antimicrobial therapies (Kim et al., 2025).

3. Significance of Natural Sources for AMP Discovery

The discovery of novel AMPs from natural sources is paramount, as these peptides often possess unique structural and functional characteristics that can lead to improved therapeutic efficacy and reduced toxicity. For example, AMPs derived from insects like *Bombyx mori* often exhibit potent activity against multidrug-resistant pathogens due to their distinct evolutionary pressures and innate immune strategies, offering a rich source for novel drug leads (Mekhalfi & Berteina-Raboin, 2025). These natural AMPs often employ sophisticated mechanisms of action that can bypass established resistance mechanisms, providing a strategic advantage over existing antimicrobial agents (Zhang et al.,

2021). The study of insect AMPs, therefore, provides valuable insights into diverse defense strategies and offers a promising avenue for the development of new antimicrobial therapies (Fahmy et al., 2023). Specifically, *Bombyx mori* has emerged as a significant source of novel AMPs, showcasing a diverse repertoire of these molecules with considerable pharmaceutical potential (Zhou et al., 2024). The unique composition of AMPs from *Bombyx mori* includes a variety of peptides, each with distinct structural motifs and antimicrobial specificities that warrant individual examination. This review will therefore detail the pharmaceutical contributions, applications, and recent discoveries concerning the antimicrobial peptides exclusively from *Bombyx mori* (Bhat & Altınok, 2023; Manniello et al., 2021). Specifically, we will delve into the molecular characteristics, proposed mechanisms of action, and therapeutic potential of each identified *Bombyx mori* AMP, providing a comprehensive overview of its individual contributions to antimicrobial research.

4. *Bombyx mori* as a Source of Antimicrobial Peptides

Insects represent a rich and largely unexplored reservoir of antimicrobial peptides, offering promising alternatives to conventional antibiotics in the face of growing resistance (Sahoo et al., 2021). This is particularly relevant given the global health crisis posed by multidrug-resistant pathogens, often referred to as "superbugs," which cause millions of deaths annually and render many conventional treatments ineffective (Niod et al., 2024; Richter et al., 2022). The innate immune systems of insects, honed over millions of years of evolution, produce a diverse array of AMPs that exhibit broad-spectrum activity against bacteria, fungi, and even viruses, making them compelling candidates for drug discovery (Manniello et al., 2021; Sahoo et al., 2021). Unlike traditional antibiotics, which often target specific bacterial pathways, insect-derived AMPs typically employ mechanisms such as membrane disruption, making the development of resistance less probable (Dho et al., 2023; Sahoo et al., 2021). Their robust activity and novel mechanisms of action position insect AMPs as valuable templates for developing next-generation antimicrobial agents, particularly in combating biofilms and other persistent infections (Sahoo et al., 2021). Specifically, the silkworm *Bombyx mori* has garnered significant attention as a prolific producer of various AMPs, offering a unique opportunity to explore novel therapeutic agents (Sangma et al., 2023). This lepidopteran insect, vital to sericulture, produces a diverse array of antimicrobial peptides with distinct structural and functional characteristics, including cecropins, moricins, and defensins (Sadeeq et al., 2025; Sangma et al., 2023). These peptides, each characterized by unique structural motifs and modes of action, play crucial roles in the insect's immune response and hold significant promise for pharmaceutical applications (Mahanta et al., 2023). A deeper understanding of these *Bombyx mori*-derived AMPs, encompassing their specific structures, mechanisms of action, and potential for modification, is crucial for harnessing their full therapeutic potential against a wide range of microbial threats (Villanueva et al., 2023). This section will therefore comprehensively analyze the specific antimicrobial peptides identified in B. mori, elucidating their individual characteristics and contributions to the insect's immune defense (Sangma et al., 2023). Among the prominent AMPs found in B. mori are cecropins, moricins, and ponericins, each contributing uniquely to the host's defense mechanisms (Nesa et al., 2022; Sangma et al., 2023). These peptides represent distinct families with varied structures and antimicrobial spectra, underscoring the complexity and efficacy of the *Bombyx mori* immune system (Sahoo et al., 2021; Wang et al., 2021). A detailed examination of each of these AMP classes—cecropins, moricins, and ponericins—is essential to appreciate their individual contributions to pharmaceutical development.

5. Immune System of *Bombyx mori*

The immune system of *Bombyx mori*, like other insects, relies predominantly on an innate immune response to combat invading pathogens, characterized by both cellular and humoral components. The humoral response, in particular, is mediated by the rapid synthesis and secretion of a diverse array of antimicrobial peptides into the hemolymph, serving as a primary defense against bacterial and fungal infections (Nesa et al., 2022). The midgut, for instance, plays a critical role in this immune function by producing AMPs and reactive oxygen species, essential for neutralizing threats and maintaining microbial balance (Awais et al., 2024). This intricate immune machinery is crucial for *Bombyx mori*'s survival and provides a rich blueprint for isolating and characterizing novel AMPs with therapeutic potential. Among these humoral factors, several key families of AMPs, including cecropins, moricins, and ponericins, have been extensively studied for their potent antimicrobial activities and distinct mechanisms of action (Zhou et al., 2024). These peptides are integral to the insect's ability to resist a wide spectrum of pathogens, reflecting an evolutionary adaptation that has led to the expansion and modification of existing immune genes to counter diverse microbial challenges (Geng et al., 2021). Further investigations into the induction and regulation of these AMPs reveal a highly sophisticated gene expression network, providing insights into potential strategies for enhancing their production or designing synthetic analogs (Mahanta et al., 2023). For example, the observation of heightened antibacterial activity in hemolymph isolated from *Bombyx mori* larvae after bacterial infection underscores the induced nature of these immune responses and highlights their potential as sources for AMP purification and characterization (Nesa et al., 2022). This robust inducible defense system, characterized by the swift production of AMPs, positions B. mori as a prime candidate for the discovery of new antimicrobial agents to address escalating antibiotic resistance (Nesa et al., 2022). This innate immunity effectively recognizes pathogen-associated molecular patterns on microbial surfaces, triggering a cascade of downstream signals that culminate in the production of immune effectors like AMPs (Heng et al., 2022). The cellular response involves hemocytes, which are crucial for phagocytosis, encapsulation, and nodule formation, while the humoral response primarily orchestrates the synthesis of AMPs, lysozymes, and prophenoloxidase system components (Sangma et al., 2023),(Krejčová & Bajgar, 2025). Hemolin, a member of the immunoglobulin superfamily, further exemplifies the complexity of this immune system, participating in both cellular immunity by promoting hemocyte melanization and aggregation, and humoral immunity through the regulation of AMP expression (He et al., 2022),(He et al., 2025). Moreover, the Toll and immune deficiency pathways are crucial signaling cascades that regulate the synthesis of AMPs in response to specific pathogen recognition, with β-1,3-glucans and lysine-type peptidoglycans activating the Toll pathway, and diaminopimelic acid-peptidoglycans activating the Imd pathway (He et al., 2022; Nesa et al., 2022). These pathways ultimately converge on NF-κB transcription factors, which upregulate the expression of various AMP genes, thereby mounting a rapid and effective antimicrobial response (Zhou et al., 2022). The Imd and Toll pathways are canonical NF-κB-dependent pathways involved in the innate immunity of insects, wherein they activate the downstream antimicrobial peptide genes transcription mediated by two distinct orthologs of the NF-κB transcription factor (Jiang, 2021). The Toll pathway is primarily implicated in antifungal and Gram-positive bacterial responses, while the Imd pathway predominantly mediates responses against Gram-negative bacteria, although there can be cross-talk and overlapping functions depending on the pathogen and insect species (Jang et al., 2022). For instance, the Imd signaling cascade is activated when peptidoglycan recognition proteins recognize pathogen-associated molecular patterns, such as the diaminopimelic acid-type peptidoglycan in the cell walls of Gram-negative bacteria, leading to the nuclear translocation of the NF-κB transcription factor Relish and subsequent production of AMPs (Meraj et al., 2024). Conversely, the Toll pathway, triggered by β-glucans and lysine-type peptidoglycans from

fungi and Gram-positive bacteria, respectively, culminates in the activation of NF-κB-like transcription factors such as Dorsal and Dif, which then induce the expression of a distinct set of AMP genes (Li et al., 2023; Mahanta et al., 2023; Manniello et al., 2021). This intricate regulatory network ensures a targeted and efficient immune response, tailoring the specific AMP arsenal to the detected microbial threat (Keith, 2023; Ren et al., 2024; Zaković et al., 2025). In the Imd pathway, the binding of meso-diaminopimelic acid-type peptidoglycan by peptidoglycan recognition protein-LC initiates a signaling cascade involving the adaptor protein Imd, the Fas-associated protein with death domain, and the caspase DREDD, leading to the K63-ubiquitination and subsequent activation of Imd (Alvarado-Delgado et al., 2022; Manniello et al., 2021). This ultimately results in the phosphorylation and nuclear translocation of the transcription factor Relish, which then upregulates the expression of numerous AMP genes, including attacin, cecropin, defensin, diptericin, drosocin, and drosomycin, showcasing broad-spectrum antibacterial effects (Weber et al., 2024). Meanwhile, the Toll pathway, triggered by molecules like proteolytically cleaved Spätzle, activates a signaling complex involving MyD88, Tube, and Pelle, which subsequently phosphorylates and degrades Cactus, liberating NF-κB transcription factors like Dorsal or Dif to initiate AMP gene transcription (Arch et al., 2022; Lilia et al., 2024; Mahanta et al., 2023). This complex interplay between the Imd and Toll pathways, often involving synergistic actions and cross-regulation, ensures a robust and adaptable immune response in insects like *Bombyx mori* (Alvarado-Delgado et al., 2022; Jang et al., 2022; Mahanta et al., 2023; Salcedo-Porras et al., 2022).

6. Methods for AMP Isolation and Characterization from *Bombyx mori*

Given the critical role of AMPs in insect immunity, a comprehensive understanding of their isolation, purification, and characterization methodologies is indispensable for their potential pharmaceutical development. These methodologies often begin with the extraction of hemolymph from infected or unchallenged larvae, followed by various chromatographic techniques to isolate and purify individual peptides (Nesa et al., 2022). Subsequent characterization often involves mass spectrometry for sequence determination and circular dichroism for secondary structure analysis, providing crucial data for understanding their mechanisms of action and potential for synthetic replication. Furthermore, functional assays are conducted to assess their antimicrobial spectrum against a range of pathogens, determining their minimum inhibitory concentrations and evaluating their hemolytic and cytotoxic profiles to ascertain their therapeutic potential and safety (Chen et al., 2022). For instance, the precise methods for AMP purification from *Bombyx mori* typically involve an initial immune challenge to induce AMP production, followed by the collection of hemolymph (Sangma et al., 2023). Subsequently, various chromatographic techniques, such as cation exchange, reverse-phase high-performance liquid chromatography, and size-exclusion chromatography, are employed to isolate and purify individual AMPs based on their physicochemical properties (Wu et al., 2021). This is often followed by structural characterization using techniques like nuclear magnetic resonance spectroscopy or X-ray crystallography to elucidate their three-dimensional conformation, which is vital for understanding their mechanism of action at a molecular level. Beyond structural elucidation, functional characterization typically involves antimicrobial assays to determine spectrum and potency against bacterial, fungal, and viral pathogens, along with cytotoxicity evaluations on mammalian cells to assess therapeutic indices. For example, researchers have successfully isolated ponericin-like peptides from *Bombyx mori* hemolymph using reverse-phase high-performance liquid chromatography, followed by mass spectrometry for identity confirmation and antibacterial assays for functional validation (Nesa et al., 2022). These purified AMPs are subjected to further in vitro antimicrobial sensitivity assays, such as zone of inhibition tests, to quantify their effectiveness against target pathogens (Morejón & Michel, 2023; Nesa et al., 2022). These extensive characterization efforts are crucial for understanding the interactions of AMPs with target pathogens and optimizing

their efficacy and safety for future therapeutic applications (Sadeeq et al., 2025). High-performance liquid chromatography is universally recognized as the most effective method for analyzing and purifying a wide range of compounds and has become a crucial method in the characterization of peptides and proteins (Islam et al., 2023). This technique, often coupled with mass spectrometry, enables precise molecular weight determination and sequence analysis, which are critical for identifying novel AMPs and confirming known ones (Islam et al., 2023),(Wang et al., 2021). Other common extraction methods involve chemical processes using buffer solutions like water acetonitrile-trifluoroacetic acid or nonpolar organic solvents such as methanol, ethanol, or chloroform (Islam et al., 2023). Following extraction, techniques like Edman degradation are employed for N-terminal sequencing, while circular dichroism provides insights into secondary and tertiary structural elements, aiding in the comprehensive biophysical analysis of these peptides (Islam et al., 2023). Moreover, advanced methods such as ultrafiltration can further concentrate AMPs, particularly when dealing with large volumes or low concentrations of peptides, thereby facilitating subsequent analytical procedures (Islam et al., 2023). In addition to these traditional techniques, the advent of high-throughput methods, including next-generation sequencing and transcriptome analysis, has significantly accelerated the discovery of new AMPs by allowing for the de novo assembly of transcriptomes and subsequent in silico prediction of peptide sequences based on physicochemical properties and nucleotide similarity (Sahoo et al., 2021). Further, the integration of computational mining of AMP databases and virtual screening methods has emerged as a powerful approach for identifying novel AMPs with desired characteristics, complementing experimental purification techniques (Yang et al., 2024). These in silico methods, often utilizing advanced machine learning algorithms, can rapidly screen vast datasets to pinpoint potential AMP candidates with specific structural motifs and predicted biological activities, significantly streamlining the discovery process (Richter et al., 2022). Specifically, mass spectrometry, often coupled with de novo sequencing, plays a pivotal role in detecting and characterizing AMPs, even those present in low concentrations, by enabling the determination of amino acid sequences from dissociated peptide ions (Enany et al., 2021; Ngashangva et al., 2021). Furthermore, techniques like proteomics and peptidomics, alongside advanced bioinformatics tools and genomic analytical tools, are increasingly employed to analyze extensive peptide data, predict potential AMP motifs, and understand their synthesis pathways (Singh et al., 2024; Turatbekova et al., 2024).

7. Major Antimicrobial Peptides Identified from *Bombyx mori*

Bombyx mori is a rich source of diverse antimicrobial peptides, which have garnered significant attention due to their broad-spectrum activity against various pathogens and low propensity for inducing resistance (Sahoo et al., 2021). These naturally occurring peptides play a crucial role in the silkworm's innate immune system, offering a robust defense against microbial infections (Sangma et al., 2023). The extensive research on B. mori AMPs highlights their potential as promising antibiotic candidates, with applications extending to pharmaceuticals, biomaterials, and food biopreservation, offering a viable alternative to traditional antibiotics in combating multi-drug resistant infections (Sangma et al., 2023). The availability of extensive high-throughput sequencing data from butterflies and other insects has facilitated the design of integrated bioinformatics approaches for the efficient discovery of novel, naturally occurring AMPs, moving beyond traditional laboratory isolation methods (Wang et al., 2021). This computational methodology has allowed for the identification of a substantial number of previously uncharacterized AMPs from genomic data, providing a foundation for understanding their structural and functional diversity (Wang et al., 2021). Moreover, the integration of advanced bioinformatics and artificial intelligence tools, such as machine learning and deep learning algorithms, further enhances this discovery pipeline, enabling the prediction of AMP activity, toxicity,

and optimal structures from genome sequences, thereby accelerating the identification of high-potential candidates for further experimental validation (Richter et al., 2022; Sahoo et al., 2021; Wei et al., 2025; Yang et al., 2023).

7.1. Cecropins

As one of the most extensively studied classes of insect-derived antimicrobial peptides, cecropins were first discovered in the giant silk moth, *Hyalophora cecropia* L., and are characterized by their potent broad-spectrum antibacterial activity (Sangma et al., 2023). These peptides typically consist of 30-40 amino acid residues, possessing a high content of cationic and hydrophobic amino acids, which contribute to their amphipathic α-helical structure crucial for membrane interaction and disruption (Wang et al., 2021). This structural characteristic enables cecropins to exert their antimicrobial effects by forming pores in bacterial membranes, leading to cell lysis and death, which contributes to their effectiveness against both Gram-positive and Gram-negative bacteria (Fu et al., 2023; Sangma et al., 2023). Cecropins from various species, including B. mori, have been shown to exhibit rapid bactericidal activity, often within minutes, making them highly effective agents against bacterial infections (Dilawari et al., 2025). Their mechanism of action primarily involves electrostatic interaction with the negatively charged bacterial membrane, followed by insertion and formation of transmembrane pores, which ultimately disrupts membrane integrity and cellular homeostasis (Fu et al., 2023; Sarkar et al., 2021). Additionally, some cecropins have demonstrated antifungal properties and low toxicity to mammalian cells, making them attractive candidates for therapeutic development (Manniello et al., 2021). Specifically, B. mori cecropins, such as Cecropin B, have been isolated and characterized, revealing distinct sequences and modifications that contribute to their unique antimicrobial profiles against clinically relevant pathogens (Manniello et al., 2021). This includes activity against a wide range of bacteria, encompassing both Gram-positive and Gram-negative strains, thereby highlighting their versatility as potential antibacterial agents (Manniello et al., 2021; Punginelli et al., 2021). Cecropins are typically linear peptides that adopt an α-helical conformation upon interaction with microbial membranes, distinguishing them from other AMPs like insect defensins, which often possess disulfide bridges (Manniello et al., 2021; Moretta et al., 2021). Genomic sequencing of the silkworm has revealed a total of 11 cecropin genes, categorized into five subtypes (A, B, C, D, and E), with Cecropin A, B, and D being the most extensively studied forms (Sangma et al., 2023). Cecropin B, in particular, has been a focus of genetic engineering efforts, leading to its overexpression in transgenic silkworms to produce antibacterial silk, showcasing its therapeutic potential (Sangma et al., 2023). The α-helical structure of cecropins, particularly their strongly basic N-terminal region and hydrophobic C-terminal region, is crucial for their antimicrobial properties, enabling interaction with and subsequent permeabilization of bacterial membranes (Guevara-Lora et al., 2023). Studies have further elucidated that this amphipathic nature facilitates the insertion of cecropins into the lipid bilayer, leading to the formation of voltage-dependent channels that ultimately disrupt cellular integrity and function (Mandel et al., 2021).

7.2. Attacins

Attacins are another significant class of Gly-rich AMPs, initially purified from the hemolymph of immunized *Hyalophora cecropia* pupae, and are recognized for their distinct mechanism of action involving interactions with bacterial outer membranes (Manniello et al., 2021). These large, glycine-rich peptides are particularly effective against Gram-negative bacteria by inhibiting their outer membrane protein synthesis and interfering with cell division (Manniello et al., 2021; Sangma et al., 2023). Attacins are typically classified into acidic and basic forms, each with unique amino acid compositions that contribute to their specific antimicrobial spectra and potencies (Sahoo et al., 2021; Sangma et al., 2023). The presence of a high quantity of glycine residues often leads to a random coil structure, though

some attacins, like persulcatusin, can adopt α-helical and β-sheet configurations stabilized by disulfide bonds (Sarkar et al., 2021). Attacins from *Spodoptera exigua*, for instance, have demonstrated efficacy against a broad spectrum of microorganisms, including *Escherichia coli*, *Pseudomonas cichorii*, *Bacillus subtilis*, and *Candida albicans*, underscoring their versatile antibacterial and antifungal capabilities (Mandal et al., 2021). This inhibitory action against Gram-negative bacteria is primarily achieved by increasing outer membrane permeability and blocking the synthesis of essential outer membrane proteins at the transcriptional level, which subsequently hinders bacterial growth (Mahanta et al., 2023; Szczepanik & Świątkiewicz, 2023). This specific activity against Gram-negative bacteria positions attacins as promising candidates for treating infections caused by these increasingly antibiotic-resistant pathogens (Fahmy et al., 2023; Meraj et al., 2024). Furthermore, attacins have a mass of approximately 23 kDa and have been shown to increase the permeability of bacterial outer membranes, and to inhibit the synthesis of bacterial outer membrane proteins by binding their lipopolysaccharides (Ramírez et al., 2023). This disruption in outer membrane integrity leads to compromised cell wall synthesis, often resulting in the formation of elongated, non-dividing bacterial cells (Sahoo et al., 2021; Sangma et al., 2023). Moreover, attacins have been found in various insect orders beyond Lepidoptera, including Diptera and Coleoptera, indicating their evolutionary conservation and broad distribution within the insect kingdom (Keshavarz et al., 2023). The activity of attacins is predominantly directed toward Gram-negative bacteria, and their mechanism likely involves specific sequence sections with chemo-physical features like positive charge or numerous hydrophobic residues that influence membrane interactions and subsequent antimicrobial activity (Niod et al., 2024).

7.3. Moricin

Moricins, a family of proline-rich antimicrobial peptides, were first identified in the silkworm *Bombyx mori* and are characterized by their α-helical structure and potent antibacterial properties (Niod et al., 2024). These peptides demonstrate a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, with some studies indicating a slight preference for Gram-negative organisms due to their amphipathic nature and net positive charge (Wang et al., 2021). Their mechanism of action primarily involves disrupting bacterial membrane integrity, leading to increased permeability and eventual cell lysis. Moreover, moricins have been shown to induce membrane depolarization, interfering with crucial cellular processes such as ATP synthesis and nutrient uptake (Fahmy et al., 2023). This membrane disruption is often attributed to their ability to form pores or carpet-like structures on the bacterial surface, leading to the leakage of intracellular components and ultimately cell death. Beyond their direct antimicrobial effects, some moricins exhibit immunomodulatory functions, influencing the host immune response to infection. Their high proline content also contributes to a relatively flexible structure, allowing for adaptive interactions with diverse bacterial membrane compositions (Mahanta et al., 2023). This structural flexibility allows them to traverse the bacterial cell wall and cytoplasmic membrane effectively, leading to diverse mechanisms of action, such as the inhibition of nucleic acid and protein synthesis (Manniello et al., 2021). Moricins from *Bombyx mori* share structural similarities with cecropins, although moricins specifically lack the hinge region present in the latter that links their N- and C-terminal α-helices (Zhou et al., 2024). This structural difference, combined with their highly basic nature (isoelectric point ~12.0), allows moricins to strongly interact with negatively charged bacterial surfaces, facilitating their antimicrobial action (Sangma et al., 2023). One notable feature of moricins is their amphipathic α-helical N-terminus, which is critical for increasing membrane permeability and thereby destroying pathogens, while the C-terminus is positively charged (Sangma et al., 2023). This positive charge significantly enhances the interaction of moricins with negatively charged bacterial cell membranes, potentially leading to pore formation and subsequent

leakage of intracellular components, as has been observed with other cationic AMPs (Nesa et al., 2022; Wang et al., 2021). Nine moricin genes have been identified in the B. mori genome, and twelve moricin-coding genes have been observed and can be further categorized into three subtypes: Bmmor, moricin-like A, and moricin-like B (Mahanta et al., 2023; Sangma et al., 2023). Moricins, which are characterized by a molecular weight of approximately 4.4 kDa, have been exclusively identified within the order Lepidoptera, demonstrating significant sequence similarity and a monophyletic origin across various species within this order (Kordaczuk et al., 2022; Wang et al., 2021). The amphipathic segment of the α-helix at the N-terminus of moricins is crucial for their antibacterial activities, yet the precise function of the positively charged C-terminal segment remains to be fully elucidated (Wang et al., 2021). Moricins, along with gloverins, are unique to Lepidopteran insects, distinguishing them from other ubiquitous antimicrobial peptides like defensins and cecropins (Sangma et al., 2023).

7.4. Gloverin

Gloverin, a prominent glycine-rich antibacterial protein, was initially isolated from the pupal hemolymph of the giant silk moth, *Hyalophora gloveri*, and is characterized by a molecular weight of approximately 14 kDa and a notable absence of cysteine residues (Sangma et al., 2023). This peptide is characterized by an unusual amino acid composition, featuring a high proportion of glycine residues and a repeated nine-amino acid motif (Manniello et al., 2021). Gloverins are broad-spectrum AMPs, exhibiting potent antibacterial activity against both Gram-positive and Gram-negative bacteria, and their mechanism of action is primarily attributed to their ability to disrupt bacterial membrane integrity (Kordaczuk et al., 2022). Specifically, gloverins are known to bind to the bacterial cell surface, subsequently permeabilizing the outer membrane and potentially interfering with the synthesis of macromolecules crucial for bacterial survival (Buonocore et al., 2021). This interaction can lead to the formation of pores or channels, resulting in the leakage of intracellular components and ultimately cell death (Dho et al., 2023). Furthermore, gloverins, like CpGlv from *Chilo suppressalis*, have demonstrated an ability to inhibit biofilm formation and directly compromise bacterial cell walls and membranes, as evidenced by studies observing leakage of intracellular nucleic acids, proteins, alkaline phosphatase, and β-galactosidase (Lian et al., 2025). This multifaceted action highlights gloverins as promising candidates for therapeutic applications, particularly in combating antibiotic-resistant bacterial strains. Their induction has been observed in various lepidopteran species, including *Spodoptera exigua*, where Gloverin expression was significantly upregulated following a septic challenge with *Serratia marcescens* and has been implicated in resistance against *Bacillus thuringiensis* (Feistler et al., 2022). Research has also indicated that gloverins can exhibit synergistic effects when combined with other antimicrobial agents, enhancing their overall efficacy against challenging bacterial infections. Notably, the transcription of gloverin is upregulated in response to bacterial infection, signifying its critical role in the innate immune response of Lepidoptera, which also includes the agglutination of bacteria and inhibition of hemocyte aggregation (Admella & Torrents, 2022). Gloverins generally demonstrate potent antibacterial effects against Gram-negative bacteria, particularly rough LPS-type mutant *E. coli*, though some reports also indicate activity against Gram-positive strains (Lian et al., 2025). For instance, BmGlvA2 has been shown to effectively inhibit Gram-negative bacteria like *E. coli* and *Salmonella typhimurium*, while also inhibiting Gram-positive bacteria such as *S. aureus* and *Bacillus subtilis* (Lian et al., 2025). In *Bombyx mori*, four distinct gloverin genes (BmGlv1, BmGlv2, BmGlv3, and BmGlv4) have been identified, each contributing to the host's robust defense mechanisms against a spectrum of pathogens (Sangma et al., 2023). The expression of gloverins in B. mori against E. coli is mediated by NF-κB immune responses; downstream signaling of Toll receptors is also implicated in their transfer from the cytoplasm in response to Gram-positive bacteria (Zhou et al., 2022). Intriguingly, *Spodoptera frugiperda* expresses gloverina and attacina genes

when challenged by both bacteria and entomopathogenic fungi such as *Beauveria bassiana*, indicating their multifaceted role in the insect's immune arsenal (Feistler et al., 2022). The structural conservation of the FGTLG region across different Gloverins, despite variations in their antimicrobial activities, underscores the evolutionary pressure for maintaining core functional motifs while allowing for adaptability against diverse microbial threats (Lian et al., 2025). Gloverin 1, considered the ancestral gene in B. mori, is expressed in the gonads of larval pupae, while gloverins 2-4 are expressed exclusively in the adult gonads, suggesting a developmental and tissue-specific regulation of these antimicrobial peptides (Sangma et al., 2023).

7.5. Defensins

Defensins are small, cysteine-rich cationic peptides ranging from 34 to 51 amino acid residues, characterized by the presence of six conserved cysteine residues forming three intramolecular disulfide bridges, which are critical for their structural stability and biological activity (Manniello et al., 2021). These disulfide bonds contribute to a conserved three-dimensional fold that is essential for their broad-spectrum antimicrobial activity against Gram-positive bacteria, fungi, and even some viruses and parasites by disrupting microbial membranes and inhibiting cell wall synthesis (Ren et al., 2024; Sangma et al., 2023). Insect defensins, specifically, are predominantly effective against Gram-positive bacteria, such as *Staphylococcus aureus* and *Bacillus subtilis*, but some variants also exhibit activity against Gram-negative bacteria like *Escherichia coli* (Manniello et al., 2021). Their mechanism of action typically involves electrostatic interactions with negatively charged microbial membranes, leading to pore formation and subsequent disruption of cellular homeostasis (Zhang et al., 2021). This membrane disruption allows for the leakage of vital intracellular components, leading to microbial cell death (Ren et al., 2024). Moreover, insect defensins are critical components of the innate immune response, often upregulated following microbial challenge and regulated by immune signaling pathways such as Toll and IMD pathways (Tang et al., 2025; Zhou et al., 2022). For instance, BmDefensinB, identified in the fat body of B. mori, is regulated by these pathways and shows activity against both bacteria and fungi (Sangma et al., 2023). These peptides are widely distributed across diverse insect orders, encompassing both ancient apterygotes and more evolved holometabolous insects like Lepidoptera, Coleoptera, and Diptera, signifying their evolutionary importance in host defense (Rashid, 2024). Their ubiquitous presence across various insect species, including those in the orders Diptera, Hymenoptera, Hemiptera, Coleoptera, Lepidoptera, and Phthiraptera, underscores their critical role as key effectors of the innate immune response, primarily mediating resistance against Gram-positive bacterial infections (Gao & Zhu, 2024). The classification of these peptides typically distinguishes classical defensins, β-defensins, and insect defensins, each possessing distinct structural characteristics and antimicrobial spectra (Sahoo et al., 2021). Specifically, insect defensins are structurally defined by an N-terminal loop followed by an antiparallel β-sheet core, stabilized by three to four intramolecular disulfide bonds, classifying them primarily as β-defensins based on the spatial distribution of these cysteines (Fahmy et al., 2024). For example, louse defensins, while demonstrating high antibacterial activity, exhibit no apparent hemolytic activity, a characteristic shared with other defensin peptides (Yoon et al., 2023). Insect defensins typically consist of an α-helix connected by a loop to an antiparallel β-sheet, ranging from 38 to 45 amino acids in length (Szczepanik & Świątkiewicz, 2023; Yoon et al., 2023). This conserved structural motif, characterized by a cysteine-stabilized α-helix and β-sheet superfamily, includes three disulfide bridges that are crucial for maintaining their compact and stable fold (Gao & Zhu, 2024). These structures often include a short amphipathic α-helix followed by a C-terminal antiparallel β-sheet, with disulfide bond patterns typically arranged as 1-4, 2-5, and 3-6 when numbering cysteine residues from the N-terminus (Rashid, 2024). This intricate arrangement of disulfide bridges is pivotal for the potent antimicrobial activity of insect defensins, enabling them to effectively target

bacterial membranes (Yoon et al., 2023). The first insect defensins were discovered in two dipteran insects in the 1980s, and since then, they have been identified in nearly all insect species examined across various orders (Gao & Zhu, 2024).

8. Pharmaceutical Contributions of *Bombyx mori* AMPs

The diverse array of antimicrobial peptides isolated from *Bombyx mori* offers significant promise for the development of novel therapeutic agents against antibiotic-resistant pathogens, given their potent and broad-spectrum antimicrobial activities (Stączek et al., 2023). Specifically, the unique structural features and mechanisms of action of B. mori AMPs, such as cecropins and defensins, provide a foundation for designing peptide-based drugs with reduced susceptibility to conventional resistance mechanisms (Halawa et al., 2023). For example, the direct membrane-disrupting properties of many insect AMPs circumvent efflux pumps and target modifications that render traditional antibiotics ineffective (Makwana et al., 2023). Furthermore, their immunomodulatory capabilities, including anti-inflammatory effects and promotion of wound healing, suggest additional therapeutic avenues beyond direct antimicrobial action, particularly in the context of chronic infections or conditions where inflammation is a significant complicating factor (Sangma et al., 2023). Moreover, the relatively low cytotoxicity of many B. mori AMPs towards mammalian cells makes them attractive candidates for systemic or topical applications, minimizing adverse effects often associated with conventional antibiotics. Given the increasing global threat of multidrug-resistant bacteria, B. mori AMPs represent a critical resource for pharmaceutical innovation, potentially offering new strategies to combat recalcitrant infections and improve patient outcomes (Sahoo et al., 2021). This focus on natural defense mechanisms from insects aligns with the growing interest in bioprospecting for novel antimicrobial agents to address the current antibiotic resistance crisis (Manniello et al., 2021).

8.1. Antibacterial Activities

The antibacterial efficacy of *Bombyx mori* AMPs stems from their diverse mechanisms, primarily membrane disruption, which often bypasses traditional resistance mechanisms, making them particularly effective against multidrug-resistant strains (Mandal et al., 2021; Nesa et al., 2022). For instance, Bm-ponericin-L1, isolated from B. mori hemolymph, has demonstrated potent antibacterial and antibiofilm activity against various human pathogenic bacteria without exhibiting toxicity to human cells, highlighting its potential as an alternative therapeutic against antibiotic-resistant infections (Nesa et al., 2022). Moreover, the silkworm itself has emerged as a valuable in vivo model for drug discovery, facilitating the evaluation of novel antimicrobial agents and their efficacy against resistant bacterial infections (Tabuchi et al., 2024). The inherent capacity of insect AMPs, such as those from B. mori, to target bacterial membranes and inhibit biofilm formation further positions them as promising agents for combating difficult-to-treat infections, including those caused by ESKAPE pathogens (Ciobănaşu et al., 2024; Sahoo et al., 2021). This characteristic is particularly significant given the rising global health crisis of antimicrobial resistance, which necessitates the discovery of novel compounds with unique modes of action to circumvent established resistance mechanisms (Sangma et al., 2023). The broad-spectrum activity and low propensity for resistance development of these peptides offer a compelling alternative to conventional antibiotics, which are increasingly losing efficacy (Dho et al., 2023; Sahoo et al., 2021). Therefore, exploring the antibacterial potential of B. mori AMPs provides a critical avenue for developing novel therapeutics that can address the urgent need for new antimicrobial strategies (Sahoo et al., 2021; Sangma et al., 2023).

8.2. Antifungal Activities

Beyond their robust antibacterial properties, several *Bombyx mori* AMPs also exhibit potent antifungal activities, providing a broader spectrum of action against various microbial threats (Makwana et al., 2023). For example, certain AMPs derived from B. mori have been shown to effectively inhibit the growth of numerous fungal strains, including species of *Aspergillus*, *Botrytis*, and *Cryptococcus*, which are significant human and agricultural pathogens (Sangma et al., 2023). This broad-spectrum efficacy underscores their potential as versatile antimicrobial agents, capable of addressing both bacterial and fungal infections, thereby offering a multifaceted approach to combating microbial pathogenesis (Manniello et al., 2021). The mechanisms underlying these antifungal effects often involve the disruption of fungal cell membranes and inhibition of essential cellular processes, similar to their antibacterial actions, yet with specific structural adaptations that enable targeting of fungal-specific components. Such peptides present a compelling avenue for the development of new antifungal drugs, especially in light of the growing resistance to conventional antifungal agents and the limited therapeutic options available.

8.3. Antiviral Activities

Beyond their well-established antibacterial and antifungal properties, an emerging body of research indicates that *Bombyx mori* AMPs also possess significant antiviral activities, expanding their therapeutic potential to combat viral infections (Ngashangva et al., 2026). These peptides can interfere with various stages of viral replication, including viral entry, replication, and assembly, through mechanisms such as direct viral inactivation or modulation of host immune responses (Egessa, 2022; Wong et al., 2025). This broad-spectrum antiviral activity suggests that B. mori AMPs could represent a novel class of antiviral agents, particularly given emerging viral threats and the limitations of current antiviral therapeutics. For instance, some B. mori AMPs have demonstrated efficacy against enveloped viruses, suggesting a membrane-targeting mechanism similar to their antibacterial and antifungal actions (Singh et al., 2024). Further investigation into the specific binding sites and structural modifications that enable antiviral activity will be crucial for designing optimized antiviral peptides.

8.4. Antiparasitic Activities

While primarily recognized for their antibacterial, antifungal, and antiviral properties, a subset of *Bombyx mori* AMPs also demonstrates promising antiparasitic activities, which broadens their potential therapeutic applications further (Sangma et al., 2023). These peptides have been observed to inhibit the growth and development of various parasitic organisms, including protozoa and helminths, by disrupting their cellular integrity or interfering with key metabolic pathways (Berghmans & Baggerman, 2021). This multifaceted action highlights the potential of B. mori AMPs as a novel source for developing antiparasitic agents, especially in regions where parasitic diseases remain a significant public health burden. The immunomodulatory effects of some AMPs also contribute to their antiparasitic potential by enhancing the host's immune response against parasitic invaders (Mazurkiewicz-Pisarek et al., 2023). Given the limited investment in new treatments for neglected tropical diseases caused by protozoans, which often involve toxic and partially effective drugs with emerging resistance, the discovery of novel antiparasitic peptides from B. mori could offer innovative solutions (Marciano et al., 2025).

8.5. Anticancer Potential

In addition to their antimicrobial and antiparasitic roles, accumulating evidence suggests that *Bombyx mori* AMPs also exhibit considerable anticancer potential, presenting a promising avenue for novel therapeutic development against

various malignancies. These peptides demonstrate selective cytotoxicity towards cancerous cells while sparing healthy ones, a characteristic that differentiates them from conventional chemotherapeutic agents and minimizes adverse side effects (Gallardo-Becerra et al., 2023). This selective action is often mediated through interactions with negatively charged phospholipids prevalent on cancer cell membranes, leading to membrane disruption and subsequent apoptotic or necrotic cell death (Enany et al., 2021). Furthermore, certain B. mori AMPs have been shown to modulate intracellular signaling pathways involved in cell proliferation, angiogenesis, and metastasis, offering a multi-pronged approach to tumor suppression (Sangma et al., 2023). Further research is needed to fully elucidate the precise mechanisms of action and to optimize these peptides for clinical application in oncology. The unique characteristics of these AMPs, such as their cationicity and high hydrophobicity, contribute to their dual antimicrobial and anticancer properties, positioning them as valuable candidates for further drug discovery efforts (Jafari et al., 2022). Specifically, Cecropin D from *Bombyx mori*, has demonstrated pro-apoptotic features and targets esophageal cancer by destabilizing mitochondrial membranes, indicating a direct mechanism of action against malignant cells (Sinha & Choudhury, 2024). Moreover, additional studies have shown that peptides like CecropinXJ can induce apoptosis in hepatocellular carcinoma cells through caspase activation and modulation of Bcl2 family proteins, further highlighting their potential in cancer therapy (Sinha & Choudhury, 2024). Beyond direct cytotoxic effects, some B. mori AMPs also exhibit immunomodulatory properties that can augment the host's anti-tumor response, further enhancing their therapeutic utility (Ratanabunyong et al., 2024).

8.6. Immunomodulatory Effects

The immunomodulatory capabilities of *Bombyx mori* AMPs extend beyond their direct antimicrobial and anticancer activities, playing a crucial role in shaping the host's immune response to various challenges, thereby contributing to overall host defense and tissue homeostasis. These peptides can influence both innate and adaptive immunity by modulating cytokine production, recruiting immune cells, and directly neutralizing pathogens or toxins, thereby offering a multifaceted approach to combating infections and inflammation. This complex interplay with the immune system suggests that B. mori AMPs could serve as valuable therapeutic agents for conditions characterized by dysregulated immune responses (Qu et al., 2024). Specifically, B. mori AMPs can activate immune signaling pathways, such as the Toll and Imd pathways, which are critical for initiating humoral immune responses and the production of various effector molecules within immunocompetent tissues like the fat body, hemocytes, and midgut epithelium (Sangma et al., 2023). This intricate regulatory network underscores their potential to not only directly combat pathogens but also to fine-tune the immune system for enhanced protection (Sinha & Choudhury, 2024). This ability to modulate immune responses can be particularly beneficial in enhancing vaccine efficacy or treating inflammatory disorders where a balanced immune response is crucial. For example, certain AMPs have been shown to promote dendritic cell maturation and activate plasmacytoid dendritic cells, key components of the innate immune system, through pathways like NF-κB and IRF1, thereby strengthening natural tumor defenses and potentially synergizing with immunotherapies (Bahar et al., 2025). These immunomodulatory properties, including the elevation of cytokine production and enhancement of phagocytic activity, are also observed in other insect-derived peptides, further supporting the broader immunotherapeutic potential of AMPs (Sinha & Choudhury, 2024; Wang et al., 2023). The capacity of AMPs to stimulate various immune system molecules, such as chemokines, in response to disease highlights their therapeutic potential in infectious or immunosuppressive conditions (Polinário et al., 2023). This is further supported by evidence indicating that certain insect peptides can enhance the maturation of dendritic cells and natural killer cells, subsequently activating CD8+ T cells to destroy cancer cells (Sinha & Choudhury, 2024). Moreover,

AMPs can regulate cell surface receptors and intracellular signaling pathways, such as NF-κB and MAPK, thereby fine-tuning immune cell activities (Zhang et al., 2021). These peptides achieve their immunomodulatory effects by not only directly targeting pathogens but also by activating immune cells like neutrophils, macrophages, mast cells, and NK cells, which subsequently induce the production of cytokines and chemokines, leading to the engulfment and elimination of invading microorganisms (Zhang et al., 2021). Furthermore, AMPs from *Bombyx mori* can influence gene expression within immune cells, leading to altered production of antimicrobial effectors and immune signaling molecules, thereby orchestrating a more targeted and efficient immune response. These immunomodulatory actions position *Bombyx mori* AMPs as promising candidates for therapeutic interventions aimed at enhancing host immunity and managing inflammatory conditions (Duarte-Mata & Salinas-Carmona, 2023; Hassan et al., 2022).

9. Recent Discoveries and Future Directions

Recent advancements in research have further broadened the understanding of *Bombyx mori* AMPs, revealing novel mechanisms of action and expanding their potential therapeutic spectrum beyond traditional antimicrobial roles. These discoveries include their efficacy against drug-resistant pathogens, their synergistic effects with conventional antibiotics, and their involvement in modulating complex immune responses within the host (Sangma et al., 2023). For instance, investigations into the silkworm midgut have unveiled a complex interplay of cell types, peritrophic membrane components, and digestive fluids that contribute to antiviral immunity, opening avenues for developing novel antiviral therapies (Awais et al., 2024). Moreover, the identification of specific hexapeptides from silkworm pupa hydrolysates that enhance splenocyte proliferation suggests novel immunomodulatory applications for food ingredients (Ghadiri et al., 2024). This deeper understanding not only promises to enhance our knowledge of immunity against pathogens but also opens new avenues for developing robust silkworm varieties, thereby benefiting sericulture practices and potentially yielding further bioactive compounds (Awais et al., 2024). Such ongoing research into novel AMPs and their multifaceted roles underscores the continued importance of B. mori as a biological model for discovering innovative therapeutic agents (Sangma et al., 2023). The identification of novel AMPs from B. mori, such as ponericin-like peptides isolated from hemolymph, further highlights the untapped potential of this insect as a source of diverse antimicrobial compounds (Nesa et al., 2022). These peptides exhibit potent activity against both Gram-positive and Gram-negative bacteria, further emphasizing their broad-spectrum efficacy (Villanueva et al., 2023). This continuous discovery of new AMPs reinforces the notion that B. mori serves as a rich bioresource for the development of next-generation antimicrobial agents, especially in the face of escalating antimicrobial resistance (Sangma et al., 2023). Furthermore, the broad utility of silkworm components extends beyond direct antimicrobial applications, with silk proteins and pupal derivatives finding roles in cosmetics and biodegradable materials due to their beneficial properties (Mahanta et al., 2023; Qadir & Islam, 2024). The ongoing exploration of B. mori's innate immune system, particularly its capacity to produce a wide array of AMPs, positions it as a critical model for understanding host-pathogen interactions and for the subsequent isolation of novel compounds with significant pharmaceutical potential (Miyashita & Sekimizu, 2021; Sangma et al., 2023). For instance, the sophisticated innate immune system of the silkworm, which includes both cellular and humoral defense mechanisms, allows it to effectively combat a wide array of pathogens despite lacking adaptive immunity (Sangma et al., 2023). This robust defense system, characterized by the rapid and diverse production of AMPs, provides a valuable platform for isolating novel therapeutic agents that could address the growing challenge of antimicrobial resistance in human medicine (Nesa et al., 2022). Beyond their direct antimicrobial capabilities, these peptides also offer significant promise for the development of alternative therapeutic strategies, particularly for targeting difficult-to-treat infections. The utilization of *Bombyx mori* as a model organism

has also facilitated the rapid screening of antimicrobial compounds against various pathogens, including multidrug-resistant bacteria, thereby accelerating the development of novel anti-infective agents (Hossain et al., 2023). This approach significantly reduces the ethical and financial burdens associated with mammalian models while providing a robust platform for preclinical drug discovery (Montali et al., 2022). The insights gained from studying B. mori's immune responses to various pathogens, such as *P. aeruginosa*, have also shed light on the intricate mechanisms of AMP induction and the subsequent modulation of host physiology, including feeding behavior and organ development (Nesa et al., 2022). The remarkable similarities between the innate immune systems of insects and mammals, including antimicrobial peptide gene expression and key signaling pathways, underscore the relevance of B. mori as a translational model for understanding and combating human infections (Hossain et al., 2023).

10. Addressing Challenges in Clinical Translation

Despite the promising preclinical data, translating *Bombyx mori* AMPs into clinical therapeutics necessitates overcoming challenges related to pharmacokinetics, bioavailability, and potential immunogenicity. Strategies to surmount these hurdles include chemical modifications to enhance stability and reduce degradation, as well as the development of advanced delivery systems such as nanoparticles or liposomes to improve targeted delivery and reduce systemic toxicity (Singh et al., 2024). Furthermore, ongoing research focuses on developing peptidomimetics and synthetic analogs of natural AMPs, which exhibit enhanced stability and specificity, thereby improving their therapeutic potential and addressing limitations associated with native peptides (Singh et al., 2024). These advanced strategies are crucial for optimizing the therapeutic index of B. mori-derived AMPs, ultimately facilitating their successful transition from laboratory discovery to effective clinical application (Wong et al., 2025). This comprehensive approach, combining structural optimization with innovative delivery methods, will be essential for realizing the full therapeutic potential of these powerful antimicrobial agents. The inherent advantages of insect models, such as their ease of breeding, low cost, and reduced ethical concerns compared to vertebrate models, further underscore their value in the initial stages of drug discovery and development (Manniello et al., 2021; Scheler & Binder, 2024). Consequently, silkworms have emerged as a viable and economical alternative to traditional mammalian models for evaluating drug toxicity and screening antiviral and anti-diabetic compounds, demonstrating metabolic pathways analogous to those in mammals (Liu et al., 2022).

CONCLUSION

The extensive research into *Bombyx mori* antimicrobial peptides has underscored their significant potential as novel therapeutic agents, offering promising avenues for addressing the global challenge of antimicrobial resistance and other health issues. This comprehensive review has highlighted the diverse pharmaceutical contributions, myriad applications, and recent groundbreaking discoveries pertaining to AMPs derived from the silkworm, solidifying its role as a pivotal bioresource for future drug development (Singh et al., 2024). Despite the substantial progress, continued interdisciplinary research and translational strategies are imperative to overcome existing hurdles in scaling up production and ensuring the clinical viability of these natural defense molecules (Singh et al., 2024; Wong et al., 2025). Further investigation into the pharmacokinetics, safety, and stability of B. mori AMPs in relevant in vivo models is essential for their successful transition from laboratory findings to clinical applications (Wong et al., 2025). This includes refining purification methods to enhance peptide yield and purity, exploring chemical modifications to improve stability and reduce immunogenicity, and developing advanced delivery systems to ensure targeted and sustained release of these potent compounds (Manniello et al., 2021; Wong et al., 2025). Moreover, understanding the

precise mechanisms of action of these AMPs against various pathogens is crucial for optimizing their therapeutic potential and for mitigating the development of resistance. The exploration of synthetic analogs and peptidomimetics based on B. mori AMPs also represents a promising avenue for developing agents with enhanced proteolytic stability and targeted activity against specific pathogens. Additionally, the integration of computational biology and artificial intelligence in peptide design can accelerate the discovery of new AMPs with optimized properties and reduced toxicity, thereby revolutionizing the drug discovery pipeline (Zhou et al., 2024). Despite the promising outlook, several challenges persist, including the vulnerability of natural AMPs to proteolytic degradation, potential hemolytic toxicity, and pharmacokinetic limitations that hinder effective delivery to target sites (Gallardo-Becerra et al., 2023; Zheng et al., 2025). Therefore, overcoming these limitations necessitates innovative approaches in peptide engineering, formulation, and delivery to fully harness their therapeutic potential (Sadeeq et al., 2025). Ultimately, addressing these challenges requires a concerted effort involving advanced biotechnological strategies for large-scale production and purification, sophisticated computational modeling for rational design, and the development of robust preclinical and clinical evaluation pipelines (Ma et al., 2024; Sadeeq et al., 2025). These efforts are crucial for translating the inherent potential of B. mori AMPs into clinically viable antimicrobial therapeutics, thereby expanding the arsenal against increasingly resistant microbial threats (Canesi et al., 2022; Pacheco et al., 2022). The current body of evidence remains fragmented, with inconsistencies in sample collection, isolation methodologies, and testing protocols, which collectively hinder direct cross-study comparisons and limit the reproducibility and reliability of reported findings (Wong et al., 2025). To address these inconsistencies, standardized protocols for AMP isolation, characterization, and functional assessment are urgently needed across the scientific community.

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