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DIVERSITY, IMMUNE REGULATION AND BIOLOGICAL SIGNIFICANCE OF ANTIMICROBIAL PEPTIDES IN LEPIDOPTERAN INSECTS

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ABSTRACT

Lepidopteran insects, including moths and butterflies, represent the second largest insect order and are widely distributed across diverse ecological niches. Their remarkable evolutionary success is largely attributed to sophisticated immune defenses, particularly antimicrobial peptides (AMPs). AMPs are small, gene-encoded peptides produced in response to microbial infection and play a crucial role in innate immunity. Lepidopteran AMPs are classified into several families, including cecropins, moricins, defensins, attacins, lebocins, gloverins, and defensin-like peptides, among others. These peptides exhibit broad spectrum antimicrobial activities against bacteria, fungi, viruses, and parasites. This review highlights the diversity, molecular characteristics, mechanisms of action, and immune regulation of AMPs in lepidopteran insects. It also explores their potential applications in medicine, agriculture, and biotechnology, emphasizing the prospects of AMP engineering and recombinant production. Overall, lepidopteran AMPs offer promising alternatives to conventional antibiotics and represent a valuable resource for developing next-generation antimicrobial agents.

KEYWORDS: Antimicrobial peptides; Lepidoptera; Insects; Insect immunity.

1. INTRODUCTION

The insect order Lepidoptera (butterflies and moths) is the second largest order after the order Coleoptera.[1] Approximately 180,000 species of lepidopteran insects have been described all over the world, some of which act as forestry and agricultural pests, such as butterflies, moths, and skippers.[2] The evolutionary dominance of insects is driven by three key factors: their capacity to colonize diverse niches through varied diets, their sophisticated immune responses to shifting pathogens, and their inherent biological versatility. These traits not only ensure their survival in the wild but also provide a strategic advantage in biotechnology, where insect cells serve as an economical medium for the production of heterologous proteins[3,4] **(Table 1)**

Table 1: Diversity of antimicrobial peptides (AMPs) reported from lepidopteran species.

Sl. No.	Species	Common Name	AMPs	References
1.	*Hyalophora cecropia*	Giant Silk Moth	Cecropins (A, B, C, D)	[5]
2.	*Bombyx mori*	Silkworm	Moricin	[6]
3.	*Bombyx mori*	Silkworm	Lebocin	[7]
4.	*Samia cynthia ricini*	Eri Silkworm	Gallerimycin	[8]
5.	*Manduca sexta*	Tobacco Hornworm	Gloverin	[9]
6.	*Manduca sexta*	Tobacco Hornworm	Attacin	[10]
7.	*Heliothis virescens*	Tobacco Budworm	Heliomicin	[11]
8.	*Galleria mellonella*	Greater Wax Moth	Gallerimycin	[12]
9.	*Papilio xuthus*	Swallowtail Butterfly	Papiliocin	[13]
10.	*Spodoptera litura*	Tobacco Cutworm	Spodopsin	[14]
11.	*Trichoplusia ni*	Cabbage Looper	Trichoplusin	[15]
12.	*Antheraea mylitta*	Tasar Silkworm	Cecropins-like	[16]

In insect immune system it employs both cellular & humoral immune system to fight against the infections or wound healings, although they possess adaptive immunity as present in higher vertebrates. Cellular immunity is mainly mediated in hemocytes by executing processes such as phagocytosis, encapsulation, and nodulation.[17] Humoral reactions include synthesis of AMPs which are secreted into the hemolymph and trigger proteolytic cascades leading to coagulation [18]. Activation of a phenoloxidase cascade to produce the melanin and toxic intermediates against invading pathogens, and production of reactive oxygen species **(Figure 1).**

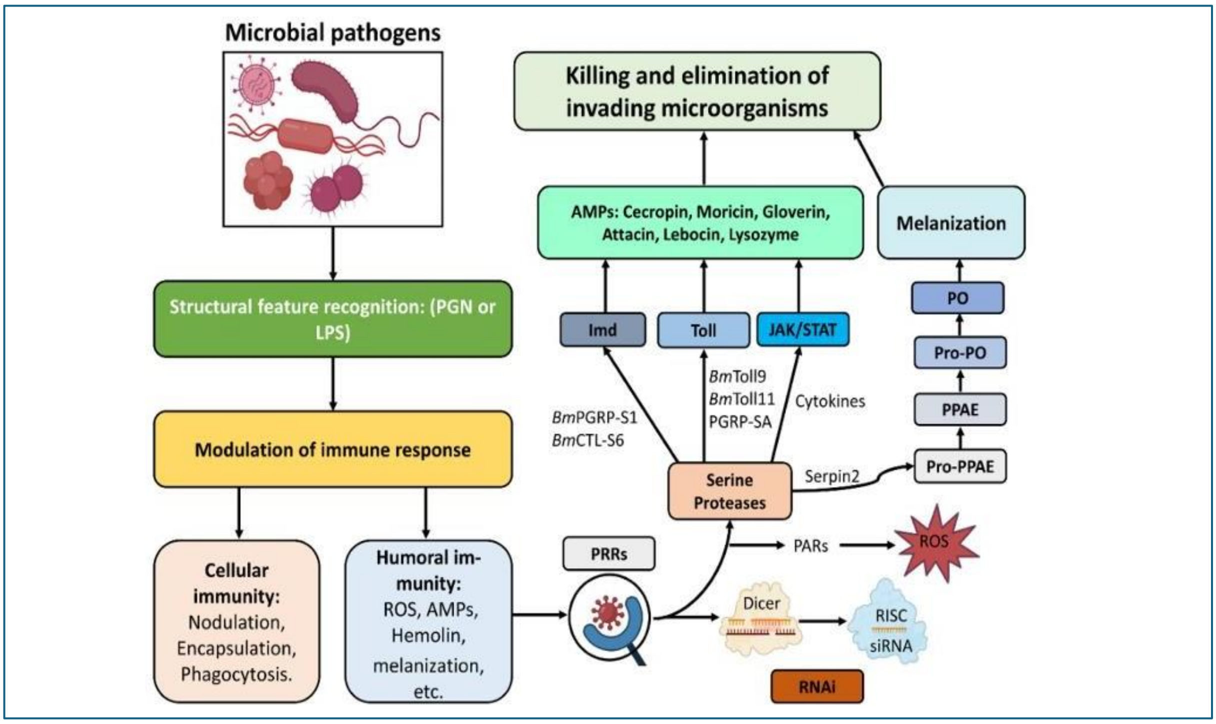

Figure 1: Schematic representation of the silkworm immune system.[19]

Synthesis of AMPs in insects occurs in special tissues such as fat bodies (similar to mammalian liver) as well as hemocytes upon microbial infection or septic injury. To date, the global catalog of antimicrobial peptides (AMPs) has reached a significant milestone, with the Data Repository of Antimicrobial Peptides (DRAMP 4.0) reporting a total of 30,260 entries from various kingdoms of life, synthetic sequences[20] although many are derived from vertebrates and plants, most are derived from invertebrate species. The majority of these AMPs have antibacterial properties, followed by a few which are antifungal, anticancer, antiviral, or antiparasitic in nature.[21,22,23,24,25,26]. AMPs are broadly classified based on (1) source, (2) activity, (3) structural characteristics, and (4) amino acid-rich species **(Figure 2)**.

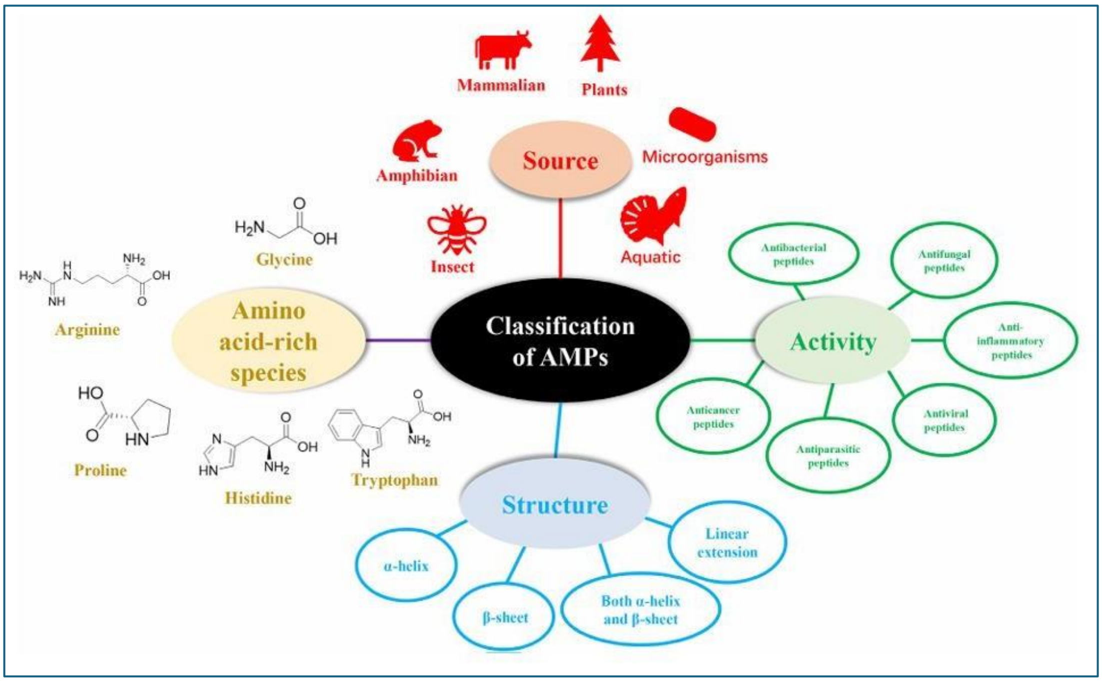

Figure 2: Schematic classification of antimicrobial peptides.[27]

2. ANTIMICROBIAL PEPTIDES IN LEPIDOPTERAN INSECTS

Antimicrobial peptides in Lepidoptera are grouped into different families, namely, cecropins, attacins, moricins, lebocins, gloverins, defensins, and defensin-like (spodoptericin, heliomicin, gallerimycin, galiomicin) and anionic peptides, lyozymes, cobatoxin, and X-tox. Apart from these, rarely found species-specific AMPs like hinnavins I and II dipausin hyphancins 3D, 3E, 3F, and 3G and papiliocin[28] Several different types of antimicrobial peptides in lepidopteran insects were reported by various researchers around the world (**Table 2)**.

2.1. Cecropins

Cecropins represent the pioneering class of α-helical, cationic, immune-inducible AMPs, first identified in the hemolymph of the wild silkmoth *Hyalophora cecropia*.[51] These peptides are evolutionarily widespread, appearing in insects, tunicates, and *Ascaris* nematodes. Structurally, mature cecropins (35–39 amino acids) lack cysteine and feature two linear α- helices joined by a hinge. This structure allows them to disintegrate bacterial membranes and hit intracellular targets. Genetically, there are 13 types categorized into five subtypes: Cecropin A (2 genes), B (6 genes), C (1 gene), D (1 gene), E (1 gene), and enbocin (2 genes).[52,53,54] They function by binding to lipid membranes via their hydrophobic C-terminus, inducing pore formation and disrupting electrolyte balance.[55,56,8]

2.2. Moricins

Moricins are a specialized AMP class exclusive to the Lepidoptera order, first found in *Bombyx mori*. These 42-residue peptides possess a unique, elongated α-helical structure.[6] The *B. mori* genome contains 13 moricin-related genes: one encoding moricin, four for subtype A, and eight for subtype B.[30] Recent NGS data also identified 6 moricin-like contigs in *Galleria mellonella*.[34] Their primary mechanism involves targeting Lipopolysaccharides (LPS) to inhibit the formation of bacterial outer membranes.

2.3. Defensins

Lepidopteran defensins are cysteine-rich peptides (34–51 residues) primarily targeting Gram- positive bacteria.[57,58]. They are found across diverse taxa, including fungi, plants, and mammals. They are grouped into five categories (plant, invertebrate, α-, β and Ɵ-defensins) based on cysteine spacing. A hallmark is the "cysteine- stabilized helix α and β sheet motif," held by three disulfide bridges.[36] While typically cationic, some species like *Plutella xylostella* produce anionic versions (PxDef) in response to *Bacillus thuringiensis.*[59] They act by oligomerizing and forming pores, leading to cytoplasmic leakage.[60]

2.4. Attacins

First purified from *H. cecropia*, attacins (20–23 kDa) are divided into basic (A–D) and acidic (E–F) groups.[61] For example, Attacin F is a proteolytic derivative of Attacin E.[62] Though encoded by separate genes, basic and acidic forms share high sequence similarity.[63,64] They are produced as pre-pro-proteins containing a P domain and two glycine-rich (G) domains.[65] Found in various Lepidoptera and Diptera, they primarily target Gram-negative bacteria like *E. coli* by binding LPS and inhibiting the synthesis of outer membrane proteins like OmpC and OmpF.[66,67]

2.5. Lebocins

Lebocins are proline-rich, O-glycosylated 32-residue peptides first found in *B. mori*.[68] They share 41% identity with the honeybee peptide abaecin.[69] While lebocin precursors are found in many Lepidoptera (e.g., *Manduca sexta*, *Trichoplusia ni*), the specific 32-residue C-terminal peptide is unique to *B. mori.*[70,71] They target both bacteria and fungi; notably, O-glycosylation is essential for the full potency of *B. mori* lebocins.[68]

2.6 Gloverins

Gloverins are ~14-kDa glycine-rich, heat-stable proteins exclusive to Lepidoptera.[72] They have been identified in species ranging from *G. mellonella* to *B. mori.*[16,73] Synthesized as pre-pro-proteins, they feature a conserved RXXR motif.[73] While most are active against *E. coli* with rough LPS mutants,[72] some variants show activity against viruses, Gram-positive bacteria, and fungi.[74,73]

2.7 Defensin-like peptides

Lepidopteran defensin-like peptides (DLPs) have evolved specifically to combat fungal threats. Peptides like heliomicin and gallerimycin utilize a stable "knot-like" αβ motif to survive protease-heavy environments.[58] Galiomicin and gallerimycin serve different roles: the former responds to early stress, while the latter peaks during systemic infection.[75] Heliomicin targets fungal sphingolipids rather than just disrupting membranes,[76] while spodoptericin represents an evolutionary adaptation against entomopathogenic fungi.[8]

Table 2: Antimicrobial peptides identified in lepidopterans.

Species	Antimicrobial peptides	Key characteristics	Activity against	References
Bombyx mori	Cecropins (A–E); Moricins (A, B); Gloverins (A, B); Attacins; Ebocins; Lebocin; Defensin	Linear, amphipathic, α-helical; glycine-rich; proline-rich; cysteine-rich	Bacteria; fungi; yeast	[29,6,30]
Danaus plexippus	Cecropins; Moricin-like; Gloverin; Attacin- like; Defensin; Gallerimycin; Proline-rich peptides; Hyphancin	Mostly α-helical or glycine- /proline-rich; defensin-like	Not tested (predicted antibacterial/antifunga l)	[31,32]

Galleria mellonella	Cecropins; Galiomicin; Gallerimycin; Gloverins; Lebocins; Moricins; Anionic peptides; Proline-rich peptides; podopptericin	α-helical; glycine-rich; proline-rich; defensin-like	Bacteria; fungi; yeast	[33,34,35,36]
Helicoverpa armigera	Cecropins; Moricin-like; Gloverin-like; Gallerimycin-like; Attacin; Galiomicin-like; Cobatoxin-like	α-helical; glycine-rich; defensin-like; cysteine-rich	Bacteria; fungi; virus	[37,38]
Heliothis virescens	Cecropins; Gallerimycin; Gloverin-like; Attacin-A; Heliocin; Atypical defensins (toxins)	α-helical; glycine-rich; defensin-like	Bacteria; fungi	[39]
Spodoptera exigua	Cecropin; Attacin; Gloverin; Diapausin; Lebocin; Moricin; Cobatoxin	α-helical; glycine-/proline- rich; defensin-like	Bacteria; yeast; SeMNPV	[40]
Plutella xylostella	Moricin-like; Gloverin; Proline-rich peptide; Cecropins	α-helical; glycine-/proline-rich	*Diadegma semiclausum* ichnovirus	[41]
Manduca sexta	Cecropin; Moricin; Gloverin; Lebocin; Attacin; X-tox	α-helical; glycine-/proline- rich; defensin-like	Bacteria; fungi	[9,42,43]
Spodoptera frugiperda	Cecropin-B1; Spodoptericin; Gallerimycin; Cobatoxin	α-helical; defensin-like	Bacteria; fungi	[44,45,46]
Antheraea mylitta	Cecropin-like; Attacin-like; Gloverin-like; Lebocin-like	α-helical; glycine-/proline-rich	Bacteria	[16,47]
Hyalophora cecropia	Cecropins (A, B, D); Attacins (B, E); Gloverin	α-helical; glycine-rich	Bacteria	[48,49,50]

3. MECHANISM OF ACTION

AMPs work against bacteria in two different ways: membrane-targeted AMPs damage the integrity of cell membranes, whereas non-membrane targeting AMPs primarily prevent the production of enzymes, functional proteins, and nucleic acids.[77]

3.1. Membrane Targeting Mechanism

The membrane-targeting mechanisms of AMPs can be described through models, including the pole and carpet models and the pole model can be further divided into the toroidal pore and barrel-stave models (**Figure 3**).

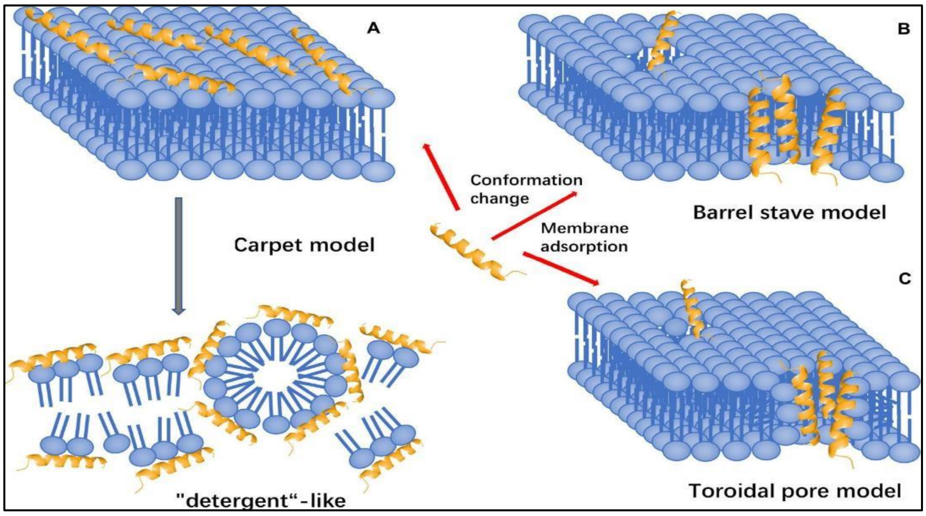

Figure 3: Schematic representation of extracellular antimicrobial peptide (AMP) mechanisms of action: (A) carpet model, (B) barrel-stave model, and (C) toroidal pore model.[27]

3.2. The Toroidal Pore Model

The toroidal pore model is also known as the wormhole model. In this model, AMPs vertically embedded in the cell membrane accumulate and then bend to form a ring hole with a diameter of 1- 2 nm The typical examples of this model are magainin 2, lacticin Q, and arenicin. Furthermore, cationic peptides, including TC19, TC84, and BP2, compromise the membrane barrier by creating fluid domains.[78,79].

3.3. Barrel-Stave Model

Antimicrobial peptides aggregate with each other, penetrate the bilayer of the cell membrane in the form of multimers, and form channels that result in the cytoplasmic outflow. In severe cases, AMPs can induce cell membrane collapse and lead to cell death.[80] For instance, Alamethicin performs its pore-forming activity by using this model. Besides, hairpin AMP protegrin-1 can form stable octameric β-barrels and tetrameric arcs (half barrels) in implicit and explicit membranes by simulations.[81]

3.4. Carpet-Like Model

Antimicrobial peptides are arranged parallel to the cell membrane. Their hydrophilic end faces the solution, and their hydrophobic end faces the phospholipid bilayer. AMPs will cover the membrane surface that similar to a carpet and destroy the cell membrane in a 'detergent'-like manner.[82] However, this pore-forming mechanism requires a certain concentration threshold and the required concentration of AMPs.

3.5. Non-Membrane Targeting Mechanisms

Some AMPs function by translocating across the bacterial membrane without causing significant disruption and then interfering with essential intracellular processes, such as DNA replication and protein synthesis. Once translocated in the bacterial cytoplasm, these non- membrane targeting AMPs act on various intracellular molecules of bacteria (**Figure 4**). Non-membrane Targeting Mechanism is the way of AMPs entering cells, which is direct penetration or endocytosis. After entering the cytoplasm, AMPs will identify and act on the target. Depending on the target, AMPs can be divided into the following categories.

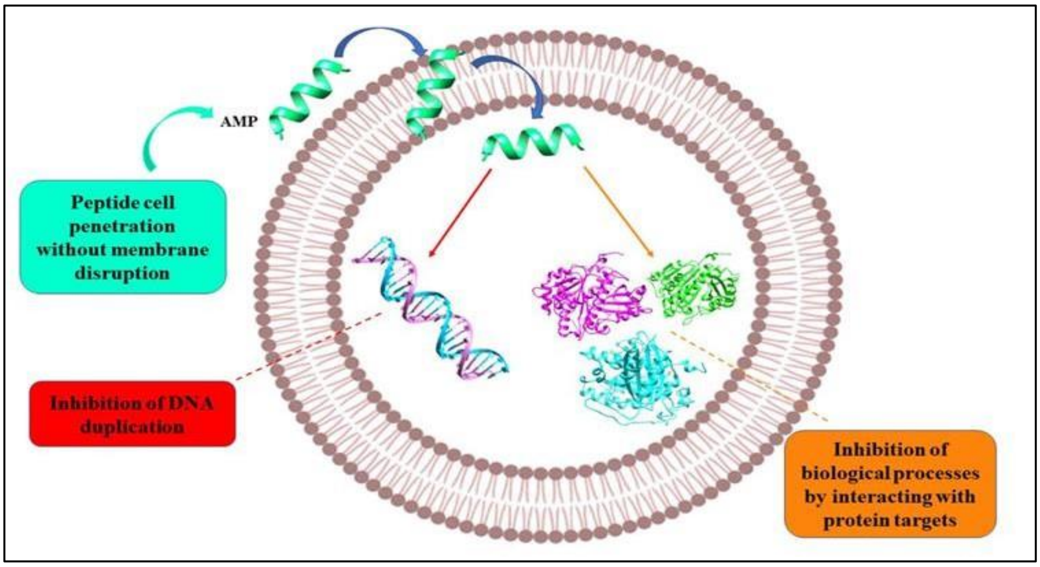

Figure 4: Schematic illustration of non-membrane-targeting mechanisms of antimicrobial peptides (AMPs).[83]

4. IMMUNE REGULATION OF LEPIDOPTERAN LARVAE

The immune regulation of lepidopteran larvae is governed by a highly coordinated network of interconnected innate immune signalling pathways that enable accurate recognition of diverse classes of pathogens and the induction of appropriate, proportionate immune responses. These pathways integrate signals derived from pattern recognition receptors that detect pathogen-associated molecular patterns, thereby allowing the host to discriminate among bacterial, fungal, viral, and parasitic infections [67],[84],[85]. Upon activation, downstream signalling cascades modulate the expression of antimicrobial peptides, myelinization responses, cellular immune reactions, and stress-related genes. The coordinated interplay among these pathways ensures immune efficiency while minimizing self-damage and unnecessary metabolic costs. Such regulatory complexity underscores the adaptive nature of lepidopteran innate immunity and highlights its importance in maintaining immune homeostasis during development and environmental stress (**Figure 5**).

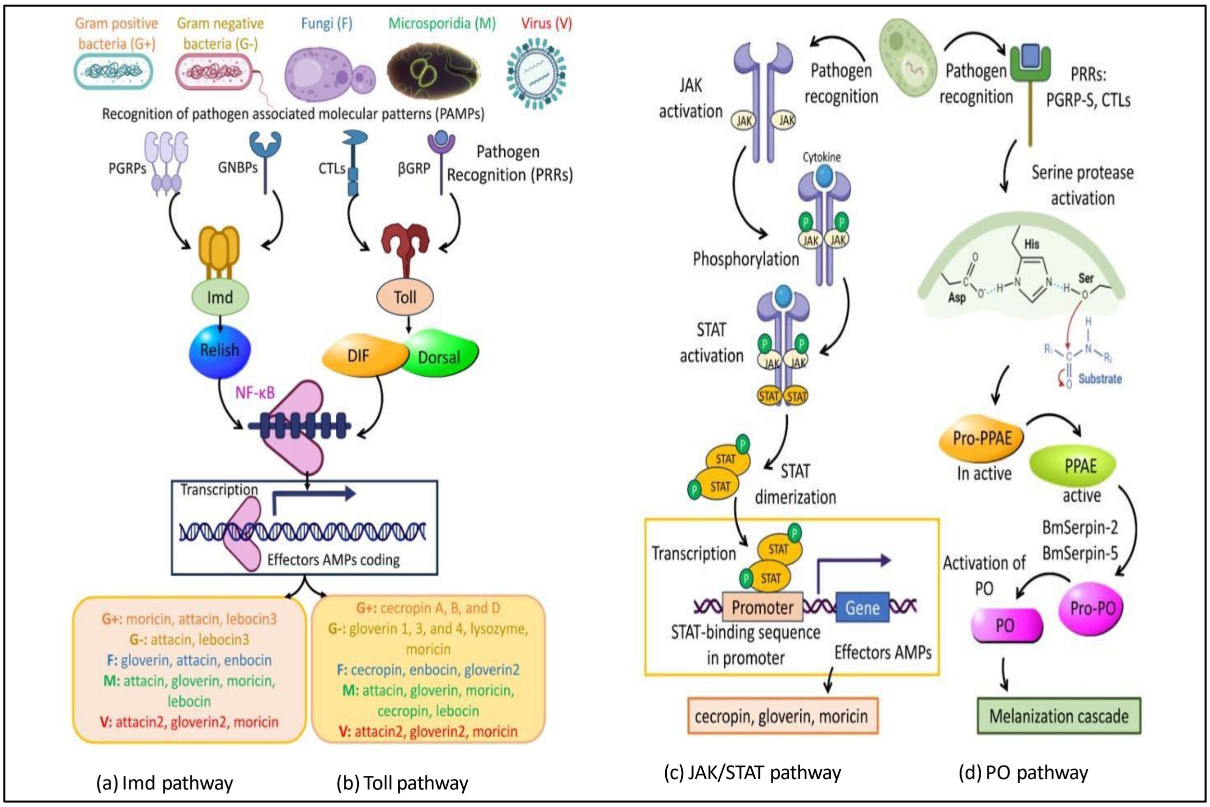

Figure 5: Innate immune regulation pathways regulating by antimicrobial peptide (AMP) in insects.[50]

4.1. Toll and Imd Pathways

The Toll pathway primarily responds to fungal and Gram-positive bacterial infections, while the Imd pathway is activated mainly by Gram-negative bacteria. Both pathways culminate in the activation of NF-κB transcription factors, leading to AMP gene expression and immune effector production.

4.2. JAK/STAT Pathway and Viral Defense

The JAK/STAT pathway is crucial for antiviral immunity in insects. It regulates the expression of genes involved in antiviral responses, including certain AMPs and stress related proteins.

4.3. Prophenoloxidase (proPO) Cascade

The proPO cascade is responsible for melanization and wound healing. Activation of proPO generates melanin and reactive intermediates that encapsulate and kill pathogens, contributing to the humoral immune response.

5. APPLICATION AND FUTURE PROSPECTIVE

5.1. Current Applications

Lepidopteran larvae-derived antimicrobial peptides (AMPs) are a revolutionary area in biotechnology, providing a strong substitute for traditional antibiotics in the face of growing drug resistance worldwide. These peptides are currently being used in medical research as effective agents against a wide range of pathogens, such as fungi, viruses, and both Gram- positive and Gram-negative bacteria. Lepidopteran AMPs, such as cecropins and moricins, are used as anti-biofilm coatings for medical implants and as synergistic additions that improve the effectiveness of conventional medications in addition to their direct killing activity. The use in agriculture has changed to "molecular farming," in which transgenic crops are modified to express these insect peptides, giving them natural defense against destructive plant diseases including fungal blights and bacterial wilt. Additionally, these peptides are being used more often by the aquaculture and livestock sectors as sustainable feed additives to support gut health and lessen the need for growth-promoting antibiotics.

5.2. Future prospects

The field of lepidopteran antimicrobial peptides is transitioning from a primary focus on discovery toward engineering and commercialization. Future research is expected to emphasize the development of stable analogs, advanced delivery systems, and scalable production methods. Natural lepidopteran AMPs serve as templates for designing synthetic analogs (peptidomimetics) with improved stability and bioactivity. Native peptides are often rapidly degraded by host proteases, limiting their therapeutic potential. Structural modifications such as D-amino acid substitution, cyclization, and incorporation of non- natural residues can enhance resistance to enzymatic degradation, extend half-life, and improve pharmacokinetic properties. These optimized peptides could provide effective alternatives to conventional antibiotics. A major challenge for AMP therapeutics is maintaining stability and bioavailability in vivo. Nanotechnology offers promising solutions by encapsulating AMPs in liposomes, polymeric nanoparticles, or nano emulsions, protecting them from proteolytic degradation. Such delivery platforms enable targeted and controlled release, ensuring that AMPs reach infection sites or tumor microenvironments efficiently. This “smart delivery” approach may enhance efficacy while reducing off-target effects and toxicity.

High production costs remain a significant barrier to clinical translation of AMPs. Recombinant expression systems provide a scalable and cost-effective alternative to chemical synthesis. Future prospects include mass production of lepidopteran AMPs using bioreactors based on yeast, bacterial systems, insect cell lines, or transgenic organisms. This approach could lower production costs to levels comparable with conventional antibiotics, facilitating broader commercialization and clinical application.

CONCLUSION

Lepidopteran insects are a valuable source of antimicrobial peptides (AMPs) that play a central role in innate immunity. These peptides, including cecropins, moricins, defensins, attacins, lebocins, and gloverins, exhibit broad-spectrum activity against bacteria, fungi, and viruses. Their antimicrobial effects involve membrane disruption and intracellular targeting, which helps reduce resistance development. Immune signalling pathways such as Toll, Imd, JAK/STAT, and prophenoloxidase regulate AMP production and coordinate effective responses to infection. Beyond their biological significance, lepidopteran AMPs offer promising alternatives to conventional antibiotics amid rising antimicrobial resistance. Advances in peptide engineering, nanotechnology-based delivery, and recombinant production aim to address limitations such as rapid degradation, short half-life, and high production costs. However, clinical application requires further optimization of stability, selectivity, and safety, along with validation of in vivo efficacy. Continued research on lepidopteran AMPs is expected to support the development of novel antimicrobial agents and sustainable strategies for infection control and crop protection.

Ethical statement

Not applicable

Conflict of Interest

The authors declare that they have no known competing financial interests.

Consent for publication

Not applicable.

Availability of supporting data

The data is made available on request from the authors.

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