Moléculas bioativas de *tenebrio molitor*: Uma perspectiva interdisciplinar em biologia estrutural, farmacologia antiviral e saúde única

Bioactive molecules from tenebrio molitor: An interdisciplinary perspective on structural biology, antiviral pharmacology, and one health

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Abstract

Yellow mealworm (*Tenebrio molitor*, Coleoptera: Tenebrionidae) larvae are a promising and underexplored platform for the discovery of bioactive molecules. Experimental data specific to this species concern mainly its immune system and the antibacterial and antifungal activity of antimicrobial peptides (AMPs) such as the tenecins. For lipopeptides, enzymes, and volatile metabolites, links to antiviral or human pharmacological activity are largely indirect or hypothetical. This narrative review, which has a prospective component, brings together (i) the immunological biology of *T. molitor*; (ii) structural biology approaches, including solution nuclear magnetic resonance (NMR), cryo-electron microscopy (cryo-EM), and small-angle X-ray scattering (SAXS), that could be used to characterize these compounds; (iii) the antiviral potential of insect AMPs and lipopeptides against chikungunya virus, Zika virus, and SARS-CoV-2; and (iv) the One Health perspective. Throughout the text we separate experimental evidence obtained in *T. molitor*, indirect evidence from other insects or systems, and hypotheses. The limitations of the review and of the available literature are also discussed. We conclude that *T. molitor* may be a useful platform within a One Health framework, but that clinical translation will depend on structural, pharmacological, toxicological, pharmacokinetic, and *in vivo* validation that has not yet been carried out for molecules from this species.

Keywords: Antimicrobial Peptides; Emerging Viral Diseases; One Health; Structural Biology; *Tenebrio Molitor*.

Resumo

As larvas de *Tenebrio molitor* (Coleoptera: Tenebrionidae) são uma plataforma promissora e ainda pouco explorada para a descoberta de moléculas bioativas. Os dados experimentais disponíveis para a espécie referem-se sobretudo ao sistema imune do inseto e à atividade antibacteriana e antifúngica de peptídeos antimicrobianos (PAMs), como as tenecinas. Para lipopeptídeos, enzimas e metabólitos voláteis, a relação com atividade antiviral ou farmacológica em humanos é, em grande parte, indireta ou hipotética. Este artigo é uma revisão narrativa, com componente prospectivo, que reúne (i) a biologia imunológica de *T. molitor*; (ii) abordagens de biologia estrutural, como ressonância magnética nuclear (RMN) em solução, crio-microscopia eletrônica (crio-EM) e espalhamento de raios X a baixo ângulo (SAXS), que podem ser aplicadas à caracterização desses compostos; (iii) o potencial antiviral de PAMs e lipopeptídeos frente ao vírus Chikungunya, ao vírus Zika e ao SARS-CoV-2; e (iv) a perspectiva de Saúde Única (*One Health*). Ao longo do texto, separam-se a evidência experimental obtida em *T. molitor*, a evidência indireta, proveniente de outros insetos ou sistemas, e as hipóteses. As limitações da revisão e da literatura disponível também são discutidas. Conclui-se que *T. molitor* pode ser uma plataforma útil no contexto de Saúde Única, mas que a tradução clínica dependerá de validação estrutural, farmacológica, toxicológica, farmacocinética e *in vivo* que ainda não foi realizada para moléculas específicas da espécie.

Palavras-Chave: Biologia Estrutural; Doenças Virais Emergentes; Peptídeos Antimicrobianos; Saúde Única; *Tenebrio Molitor*.

1. Introduction

Insects are the most species-rich group of animals, and their innate immune systems have been shaped by hundreds of millions of years of selection. They produce antimicrobial peptides (AMPs), lipopeptides, enzymes, and secondary metabolites with activity against bacteria, fungi, and parasites and, in some cases, against viruses (Lemaitre & Hoffmann, 2007; Zasloff, 2002). Among the insects studied so far, the yellow mealworm beetle *Tenebrio molitor* has become a widely used model in insect immunology and a species of growing biotechnological interest.

Several practical features explain this interest. *T. molitor* is easy to rear under controlled conditions, gives a high biomass yield per unit area, and its larvae can feed on agricultural residues, food waste, and even some synthetic polymers (Yang et al., 2015; Brandon et al., 2018). Larvae also mount a strong immune response that induces several AMPs (Johnston et al., 2014). In 2021 the European Union authorized dried *T. molitor* larvae as a novel food, the first insect to receive this status (European Commission, 2021). So far, however, the interest generated by this authorization concerns mainly nutrition and feed, and not pharmacology.

In parallel, RNA viruses able to spread rapidly across continents have caused repeated public health emergencies. Chikungunya virus (CHIKV), an arthritogenic alphavirus transmitted by *Aedes* mosquitoes, has caused outbreaks in Africa, Asia, the Americas, and Europe (Berneck et al., 2019). As of 2026, no antiviral drug is approved for chikungunya, and two vaccines have been licensed since 2023, one of them with restrictions on use (European Centre for Disease Prevention and Control [ECDC], 2026). SARS-CoV-2 caused the COVID-19 pandemic, and the structure of its spike glycoprotein and of the complex between the receptor-binding domain and angiotensin-converting enzyme 2 (ACE2) was determined at near-atomic resolution soon after the outbreak began (Wrapp et al., 2020; Yan et al., 2020). Zika virus (ZIKV), a flavivirus also transmitted by *Aedes* mosquitoes, was associated with congenital microcephaly and Guillain-Barré syndrome during the 2015–2016 epidemic in the Americas and, to our knowledge, still has no approved specific antiviral therapy (Lazear & Diamond, 2016). Insects and other unconventional biological sources are therefore being examined as possible sources of antiviral leads, alongside conventional drug discovery.

This review addresses three questions. What is known experimentally about the immune system of *T. molitor* and the classes of bioactive molecules it produces? Which structural biology techniques could be used to characterize these molecules and their interactions with viral targets? And what is the evidence, direct or indirect, that molecules from *T. molitor* or from related insects have antiviral activity? We discuss the answers within the One Health framework, which treats human, animal, and environmental health as interdependent. A recurring point is that the evidence for *T. molitor* is uneven: it is solid for immunity and for antibacterial peptides, thin for antiviral activity, and largely hypothetical for structure-guided drug design.

1.1. Review Design and Literature Search

This article is a narrative (thematic) review with a prospective component. It is not a systematic review and was not conducted under a registered protocol. Because the selection of studies is not exhaustive, selection bias cannot be excluded (Section 7).

Literature was identified through targeted searches of PubMed, Scopus, and Web of Science, covering January 2000 to September 2026, using combinations of the terms "*Tenebrio molitor*", "antimicrobial peptide", "tenecin", "lipopeptide", "surfactin", "chikungunya", "Zika virus", "SARS-CoV-2", "structural biology", "cryo-EM", and "One Health". Approximately 240 records were screened by title and abstract, and 52 were retained after removing duplicates and studies that did not address *T. molitor* biology, AMP structure or function, or the specific viral targets discussed here. Foundational sources were kept when they defined a technique, a structure, or a concept, and recent studies (2022–2026) were prioritized for antiviral targets, epidemiology, and regulatory status. Primary experimental studies were preferred over reviews. Publications from the author's group are cited only where they provide directly relevant data (Sections 4.2, 4.3, and 6.2).

Because the literature on *T. molitor* is uneven, statements in this review are classified into three levels of evidence, and the wording is chosen accordingly. Level 1 is experimental evidence obtained with *T. molitor* or with molecules isolated from it, described with verbs such as "was shown" or "has been demonstrated". Level 2 is indirect evidence from other insect species, from bacterial or synthetic analogues, or from unrelated systems, described as "reported for" the system concerned. Level 3 comprises hypotheses, computational predictions, and proposed applications, introduced with "we hypothesize", "could", or "remains to be tested". Table 1 summarizes this classification for the main molecule classes, and Figures 1, 2, and 4 use the same scheme.

2. Insect Immunity and Bioactive Molecule Production: The Immunological Framework

2.1. The Insect Immune System: Innate Defense Without Adaptive Immunity

Insects lack the adaptive immune system of vertebrates: they have no B or T lymphocytes and no somatic recombination machinery that generates antibody diversity. Host defense therefore rests on innate responses, both cellular and humoral (Lemaitre & Hoffmann, 2007; Hultmark, 2003). The cellular arm includes hemocytes, circulating cells that phagocytose microbes, encapsulate parasites, and form nodules around aggregated bacteria. The humoral arm, which is the main source of the molecules of pharmacological interest discussed here, includes AMPs, lectins, reactive oxygen species, and the prophenoloxidase (proPO) cascade. The proPO cascade generates cytotoxic quinones and melanin, and it is sometimes compared, in functional terms only, with the vertebrate complement system.

In *Drosophila melanogaster*, the main genetic model of insect immunity, two signaling pathways control AMP gene induction. The Toll pathway responds mainly to Gram-positive bacteria and fungi, and the Immune Deficiency (IMD) pathway responds mainly to Gram-negative bacteria and is related to the mammalian TNF receptor and NF-κB axis (Lemaitre & Hoffmann, 2007). *T. molitor* belongs to the order Coleoptera, not Diptera, but orthologs of the components of both pathways have been identified in its transcriptome, and bacterial challenge induces a sustained AMP response (Johnston et al., 2014; Chae et al., 2012). AMPs are produced mainly by the fat body, an organ often compared with the vertebrate liver for its combined metabolic and immune roles, and also by hemocytes and the gut epithelium (Yi et al., 2014). The conservation of these pathways across insect lineages supports the use of *T. molitor* as a model of insect immunity. It does not by itself show that its molecules are suited to therapeutic use, which is a separate question addressed in later sections.

2.2. Antimicrobial Peptides of *Tenebrio Molitor*: Classes, Activities, and Level of Evidence

The AMPs of *T. molitor* have been characterized mainly by biochemical purification, cDNA cloning, and gene-expression studies (Table 1). The best studied are the tenecins. Tenecin 1 is an inducible defensin with a cysteine-stabilized α/β fold that is active mainly against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Lee et al., 1998; Chae et al., 2012). Tenecin 2 is a coleoptericin-like peptide with activity toward Gram-negative bacteria, and tenecin 4 is a glycine-rich, attacin-like peptide that is bactericidal for *Escherichia coli* but not for *Bacillus subtilis* or *Candida albicans* (Chae et al., 2012). Tenecin 3 is a constitutively expressed glycine-rich peptide active against fungi (Chae et al., 2012). Infection also induces further defensin-like, attacin, and coleoptericin transcripts (Johnston et al., 2014). These findings are the main Level 1 evidence available for *T. molitor* AMPs, and all of them concern antibacterial or antifungal activity.

Defensins from other insects have been developed further as anti-infective candidates. Lucifensin, from larvae of the blowfly *Lucilia sericata* used in maggot therapy, is one example (Cerovsky & Bem, 2014). Such work shows a translational path for insect defensins, but it is indirect (Level 2) with respect to *T. molitor*.

Antiviral activity is a different matter. We did not find, in the sources reviewed, an experimental demonstration that a purified *T. molitor* peptide inhibits CHIKV, ZIKV, or SARS-CoV-2 (Level 1). The available data are indirect (Level 2), namely antiviral effects of AMPs from other organisms in cell culture (Jenssen et al., 2006), or computational (Level 3), such as an *in silico* analysis of the *T. molitor* peptidome that predicted antiviral activity for some peptide sequences and stressed the need for experimental confirmation (Gonzalez-de la Rosa et al., 2025).

Lipopeptides related to surfactin are a separate case. Surfactin is a cyclic lipopeptide produced by *Bacillus* species through non-ribosomal synthesis. In the sources reviewed, we found no evidence that *T. molitor* itself synthesizes surfactin-like lipopeptides, or that microorganisms associated with it do (Level 3). What has been shown in *T. molitor* is that bacterial lipopeptides such as fengycin and iturin A, and the glycolipid rhamnolipid, act as immune elicitors: they induce AMP expression through Spätzle-dependent Toll signaling and increase larval survival after *E. coli* challenge (Edosa et al., 2020). The lipopeptides discussed in this review are therefore of bacterial origin (surfactin and related compounds) or synthetic (surfactin-derived analogues, Section 4.3), and they are not established products of the insect. Whether gut bacteria or other microbes associated with *T. molitor*, including *Bacillus* species, produce such compounds in the larva is an open question.

Figure 1: Sources of bioactive molecules and products associated with the *Tenebrio molitor* larva, and their relation to One Health domains, with the level of evidence for each. Numbered circles indicate Level 1 (experimental evidence in *T. molitor*), Level 2 (indirect evidence), or Level 3 (hypothesis or prospective use); dashed outlines mark hypotheses. Host AMPs have Level 1 support for antibacterial and antifungal activity, whereas antiviral use is a hypothesis. Surfactin-type lipopeptides are shown outside the larva: they are produced by *Bacillus* species or obtained synthetically, and their production by *T. molitor* or its associated microbiota has not been shown. Frass as a fertilizer and degradation of polystyrene and polyethylene have Level 1 support, whereas production of volatile fatty acids by the larval gut microbiota is a hypothesis. AMPs, antimicrobial peptides.

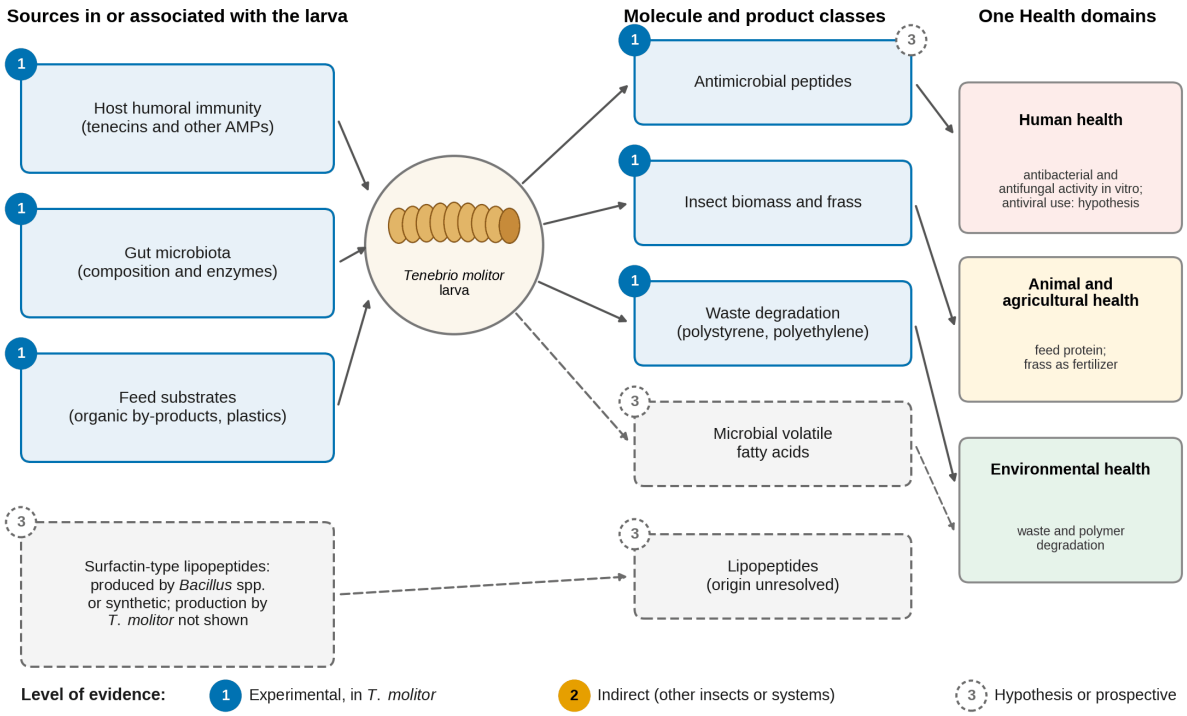


Table 1: Status of the evidence for the main molecule classes and topics discussed in this review.

Molecule class or topic	Level 1: experimental evidence in *T. molitor*	Level 2: indirect evidence	Level 3: hypotheses and proposed uses
Tenecin 1 (defensin-like peptide)	Purified from larvae; active mainly against Gram-positive bacteria, including MRSA; structure–function studies (Lee et al., 1998; Chae et al., 2012)	Insect defensins from other species studied as anti-infectives, e.g., lucifensin (Cerovsky & Bem, 2014)	Antiviral use; engineered variants to block viral glycoproteins (Section 4.2)
Tenecins 2, 3, and 4 (coleoptericin-like, glycine-rich antifungal, attacin-like)	Tenecin 4 purified and bactericidal for *E. coli*; tenecin 3 antifungal; induction by infection (Chae et al., 2012; Johnston et al., 2014)	Related peptide families in other insects	Effects on viral proteases or other intracellular targets (Section 4.2)
Antiviral activity of *T. molitor* peptides	Not demonstrated in the sources reviewed	Antiviral effects of AMPs from other organisms in cell culture (Jenssen et al., 2006)	*In silico* predictions for peptides from the *T. molitor* peptidome (Gonzalez-de la Rosa et al., 2025); activity against CHIKV, ZIKV, and SARS-CoV-2 untested
Surfactin-type lipopeptides	Bacterial lipopeptides (fengycin, iturin A) and rhamnolipid induce AMPs and increase larval survival (Edosa et al., 2020); production of surfactin-like lipopeptides by *T. molitor* not shown	Surfactin from *Bacillus* inactivates enveloped viruses *in vitro* (Vollenbroich et al., 1997; Kracht et al., 1999; Yuan et al., 2018); synthetic surfactin-derived analogues (Vazquez et al., 2018)	Production by the insect or its microbiota; antiviral use of analogues against arboviruses
Gut microbiota and volatile fatty acids	Gut microbiota composition and enzymatic profile characterized in larvae on different diets (Przemieniecki et al., 2020)	VFAs are products of microbial fermentation in other animals	VFA production by the larval gut microbiota and use as preservatives; contribution to resistance to colonization
Waste degradation and frass	Degradation of polystyrene and polyethylene (Yang et al., 2015; Brandon et al., 2018); frass as fertilizer (Houben et al., 2020)	None needed for the claims made	Integrated production of biomass, fertilizer, and bioactive molecules
Structural characterization	Structure–function studies of tenecin 1 (Lee et al., 1998); no NMR, cryo-EM, or SAXS structure of a *T. molitor* peptide identified	NMR, cryo-EM, and SAXS studies of other AMPs and of viral targets (Bonmatin et al., 1994; Song et al., 2019)	Structural pipeline of Figure 2 applied to *T. molitor* molecules

3. Structural Biology Approaches Applied to Insect Bioactive Molecules

This section describes techniques and what they have shown for AMPs in general (Level 2). For *T. molitor* molecules, structural data are limited to structure–function work on tenecin 1 (Level 1), and the use of NMR, cryo-EM, and SAXS is prospective (Level 3).

3.1. Solution NMR: Atomic-Resolution Characterization of AMPs in Membrane-Mimetic Environments

Solution NMR can describe the structure and dynamics of AMPs in environments that approximate a membrane, which is the setting where they act (Wüthrich, 1986). X-ray crystallography needs crystals and represents the fluid bilayer poorly, whereas solution NMR can be performed with detergent micelles (SDS, DPC, DHPC), bicelles, or lipid nanodiscs. Multidimensional heteronuclear experiments (^{1}H-^{15}N HSQC, ^{1}H-^{13}C HSQC, NOESY, TOCSY, and relaxation measurements) allow assignment of backbone and side-chain resonances, structure calculation, and analysis of motions from picoseconds to milliseconds (Wüthrich, 1986).

For amphipathic helical peptides such as the cecropins of other insects, NMR in membrane-mimetic media has been used to define the orientation of the helix, the depth of insertion, and the conformational change on lipid binding (Level 2), all parameters that matter for peptide design. For cysteine-rich defensins, NMR restraints help define the disulfide connectivity and the rigidity of the cystine-stabilized α/β scaffold, a feature associated with greater protease resistance and thermal stability than linear peptides (Bulet et al., 2004). Tenecin 1 belongs to this fold family, and synthetic tenecin 1 and peptides derived from its β-sheet domain have been studied for structure–function relationships (Lee et al., 1998). We did not identify, however, an NMR structure of a *T. molitor* defensin or of any other *T. molitor* peptide (Level 3). Such structures would be a starting point for peptidomimetic or stapled-peptide design, and they remain to be determined.

3.2. Cryo-Electron Microscopy: Visualizing Peptide–Virus Interactions

Cryo-electron microscopy (cryo-EM) has undergone a resolution revolution since about 2013, and single-particle analysis now routinely reaches near-atomic resolution (2–4 Å) for macromolecular complexes. For enveloped viruses such as CHIKV and SARS-CoV-2, it has revealed the architecture of surface glycoproteins, the geometry of receptor-binding sites, and conformational changes linked to fusion (Song et al., 2019; Wrapp et al., 2020). The 2019 study of the CHIKV receptor MXRA8 combined X-ray crystallography of the MXRA8–E protein complex with cryo-EM of MXRA8 bound to virus-like particles (Song et al., 2019). This kind of structure defines the surfaces that an inhibitor would have to engage and provides a basis for structure-guided design. Insect peptides or lectins that bind the same surfaces could in principle be visualized on viral particles by cryo-EM (Level 3), but no such complex has been reported for *T. molitor* molecules.

Cryo-EM is also useful for assemblies that are difficult to study by other methods, such as AMP–membrane complexes in lipid nanodiscs. Their size limits solution NMR, and their lipid-embedded, heterogeneous nature limits crystallography. Membrane scaffold proteins and polymer-bounded nanodiscs are being used for membrane protein assemblies, but high-resolution structures of AMP pores remain rare. Whether AMPs form defined pores, carpet-like assemblies, or heterogeneous structures depends on the peptide and on the lipid composition (Epand & Vogel, 1999).

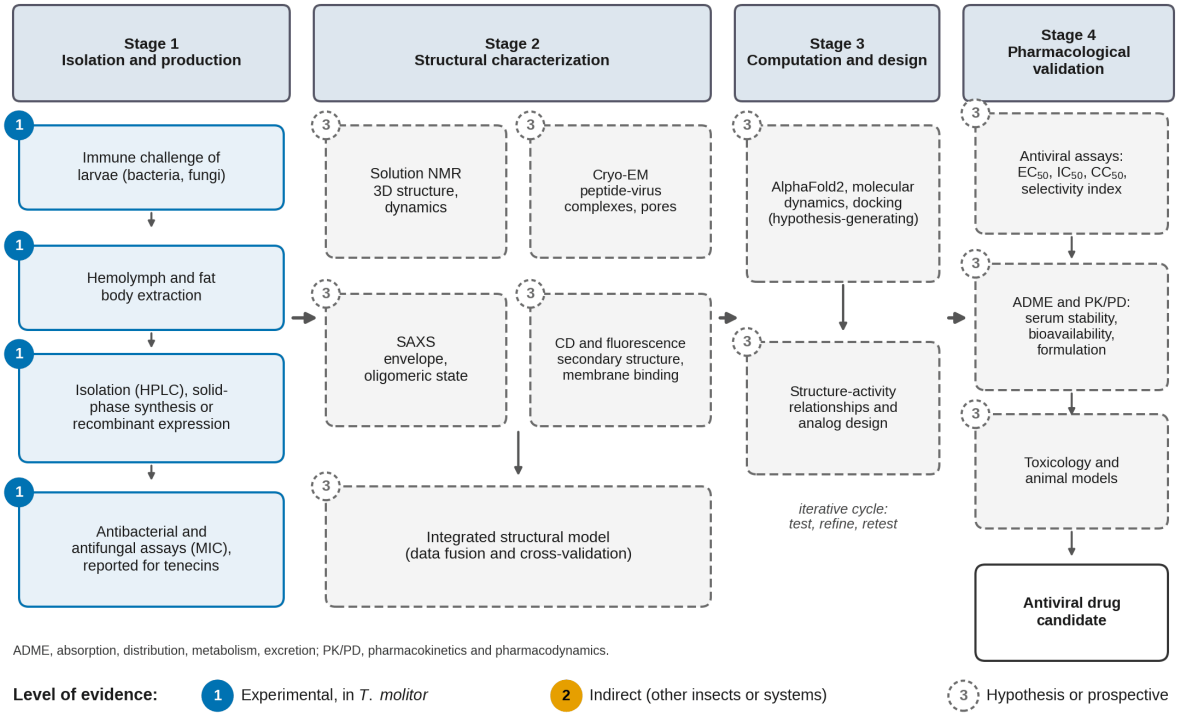
3.3. Small-Angle X-Ray Scattering and Complementary Biophysical Techniques

Small-angle X-ray scattering (SAXS) provides low-resolution (about 10–50 Å) information on biomolecules in solution under near-physiological conditions, and it suits the study of conformational states of AMPs, lipopeptides, and their complexes. Analysis through the pair-distance distribution function P(r), the Kratky plot (for flexibility), and *ab initio* envelope calculations can separate monomeric from oligomeric states and follow concentration-dependent self-assembly, which is relevant to multimeric pore-forming assemblies (Epand & Vogel, 1999). Circular dichroism (CD) gives a rapid estimate of secondary structure and of its change on lipid binding, for example the transition of many linear AMPs from a random coil in water to an α-helix in the presence

of membranes. Fluorescence spectroscopy, using tryptophan residues as intrinsic probes or fluorophores in lipid vesicles, measures peptide–membrane binding and the kinetics of membrane disruption (Epand & Vogel, 1999).

Together, solution NMR, SAXS, CD, and fluorescence spectroscopy form a biophysical pipeline that can take a peptide from sequence to a structural model of its membrane interaction (Figure 2). For *T. molitor* molecules this pipeline is a proposal and not a completed body of work: isolation, synthesis, and antibacterial testing have been carried out for the tenecins (Level 1), whereas the structural, computational, and antiviral stages are prospective (Level 3). For surfactin-derived lipopeptides, solid-phase synthesis of designed analogues and their functional testing (cytotoxicity, hemolysis, emulsifying properties, and synergy with vancomycin) have been reported (Vazquez et al., 2018). This is Level 2 evidence for the approach, because those molecules do not come from *T. molitor*.

Figure 2: Proposed structural biology pipeline for the characterization and pharmacological development of *Tenebrio molitor*-derived bioactive molecules. Numbered circles indicate the level of evidence for *T. molitor* (Level 1, experimental; Level 3, prospective). Stage 1 (isolation and production) comprises immune challenge of larvae, hemolymph and fat body extraction, and isolation, solid-phase peptide synthesis, or recombinant expression; antibacterial and antifungal assays (minimum inhibitory concentration, MIC) have been reported for tenecins. Stage 2 (structural characterization) integrates solution NMR, cryo-EM, SAXS, and circular dichroism and fluorescence spectroscopy into an integrated structural model. Stage 3 (computation and design) applies AlphaFold2 predictions, molecular dynamics, and docking, which generate hypotheses, together with structure–activity relationship analysis. Stage 4 (pharmacological validation) comprises antiviral assays reporting the 50% effective concentration (EC_{50}), the 50% inhibitory concentration (IC_{50}), the 50% cytotoxic concentration (CC_{50}), and the selectivity index (SI); absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic/pharmacodynamic (PK/PD) studies, including serum stability, bioavailability, and formulation; and toxicology and animal models.



4. Antiviral Potential of *Tenebrio molitor*-Derived Bioactive Molecules

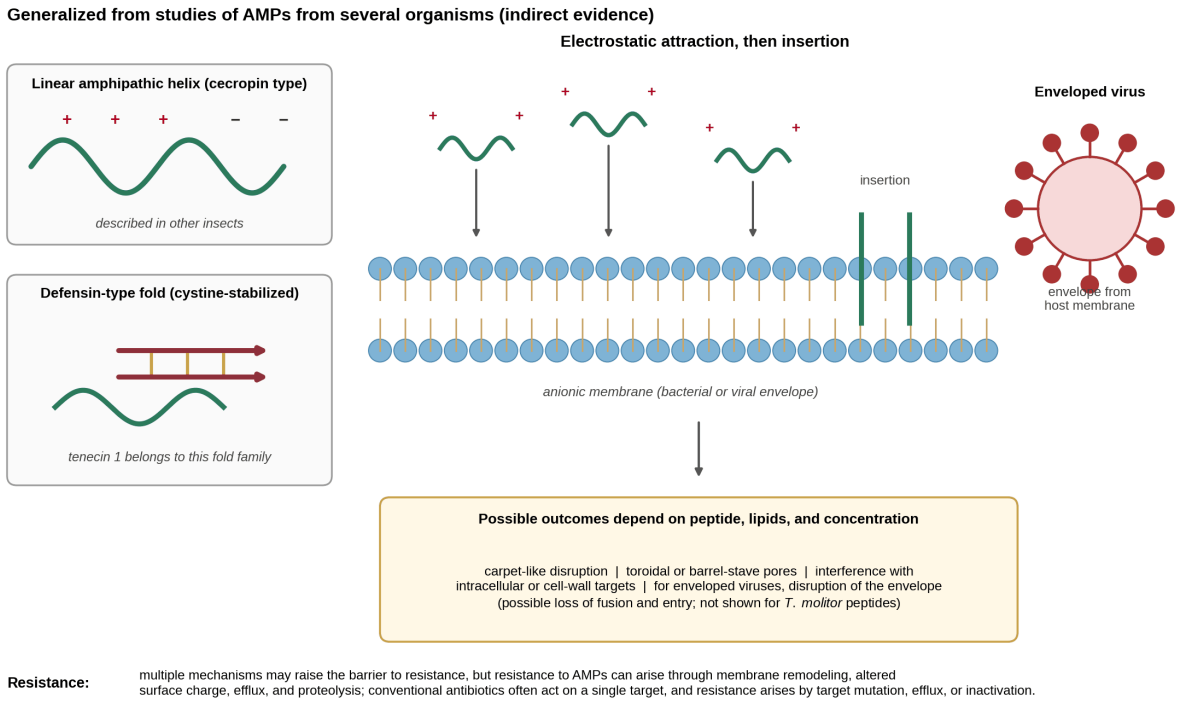
4.1. Mechanistic Basis of AMP Antiviral Activity

The antiviral activity of AMPs has been described most clearly for enveloped viruses such as herpes simplex virus (HSV), HIV, and influenza virus, where peptides disrupt the lipid envelope and inactivate the virion (Jenssen et al., 2006). The envelope derives from host membranes and, unlike a bacterial cell wall, offers no additional barrier

to amphipathic peptides, so that virions can in some cases be inactivated at concentrations below those that damage host cells (Jenssen et al., 2006). This selectivity is not guaranteed. It depends on the peptide, the virus, and the medium, and serum components can lower the effective concentration of membrane-active compounds (Vollenbroich et al., 1997). All of this evidence comes from peptides of other origins, including other insects (Level 2), and none of it has been demonstrated for *T. molitor* molecules (Level 1).

Other mechanisms have been proposed for AMPs in general: (i) binding to viral surface glycoproteins, which would block attachment or fusion; (ii) interference with viral proteases; (iii) immunomodulation that strengthens innate antiviral responses in the host; and (iv) inhibition of the viral RNA-dependent RNA polymerase (RdRp), for instance through interaction with the RNA or with the polymerase active site (Jenssen et al., 2006). The strength of the evidence differs among these mechanisms. Membrane disruption and blockade of entry are the best supported, whereas effects on proteases and polymerases have been shown for few peptides and should be treated as potential mechanisms until they are supported by enzyme kinetics or structural data. NMR, cryo-EM, and docking could be used to study such interactions, but so far these methods have not been applied to *T. molitor* peptides and viral targets.

Figure 3: Proposed mechanisms of action of insect AMPs, generalized from studies of AMPs from several organisms (Level 2). None of the antiviral mechanisms shown has been demonstrated for *T. molitor* peptides. Left, linear amphipathic α-helical peptides (cecropin type, described in other insects) and cystine-stabilized defensin-type peptides (tenecin 1 belongs to this fold family). Center, electrostatic attraction of cationic peptides to negatively charged membranes, followed by insertion; the outcome may be carpet-like disruption, pore formation, or interference with intracellular or cell-wall targets, depending on the peptide, the lipid composition, and the concentration. For enveloped viruses, disruption of the envelope could prevent fusion and entry. Bottom, multiple mechanisms may raise the barrier to resistance, but resistance to AMPs can arise through membrane remodeling, altered surface charge, efflux, and proteolysis. AMPs, antimicrobial peptides.



4.2. Chikungunya, Zika, and SARS-CoV-2: Structural Targets and Candidate Inhibitors

For each virus below we distinguish two things: a validated viral target, meaning a protein or interface whose structure and role in the viral cycle are established, and a validated *T. molitor*-derived inhibitor, meaning a

molecule whose binding and inhibition of that target have been demonstrated experimentally. The first exists for all three viruses. The second does not exist, in the sources we reviewed, for any of them.

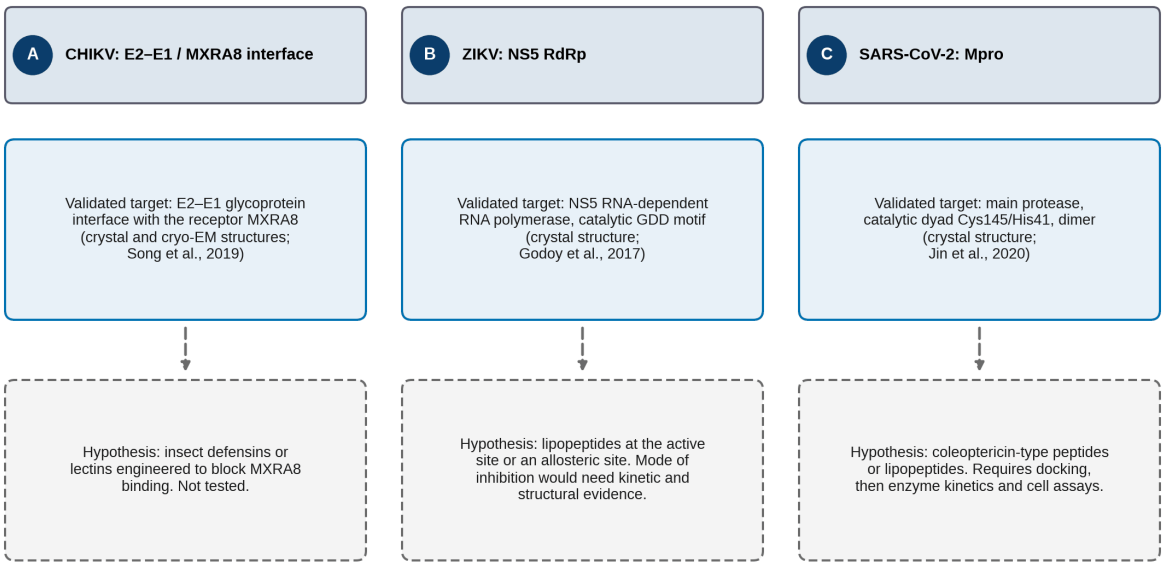
CHIKV causes acute fever and severe polyarthralgia that can persist for months or years in a substantial share of patients. No specific antiviral is approved, and two vaccines have been licensed since 2023 (ECDC, 2026). Entry depends on binding of the E2–E1 glycoprotein heterodimers on the virion to the cell-surface receptor MXRA8. Crystal structures of MXRA8 bound to the CHIKV E protein, together with a cryo-EM reconstruction of MXRA8 bound to virus-like particles, define the receptor-binding interface (Song et al., 2019). This interface is a structurally defined target, and blocking it with peptide inhibitors is a rational strategy. Whether defensins, lectins, or other insect molecules can be engineered to bind the E2–E1 surface and compete with MXRA8 is a hypothesis that has not been tested (Level 3).

For SARS-CoV-2, the main protease (Mpro, also 3CLpro) is a well-validated antiviral target. It processes the viral polyproteins into the non-structural proteins of the replication complex, and its catalytic dyad (Cys145 and His41) and dimeric structure are established (Jin et al., 2020). Studies of small molecules illustrate how a target is validated. Agathisflavone was reported to inhibit SARS-CoV-2 replication by targeting its proteases (Chaves et al., 2022a), and apixaban to inhibit replication and Mpro in a non-competitive way (Chaves et al., 2022b). Atazanavir, tested in enzymatic, docking, cell-based, and mouse assays, was shown to be a competitive inhibitor of Mpro, increasing its Michaelis constant more than sixfold, to impair replication of viral variants, and to partially protect infected mice (Chaves et al., 2022c). In that work the mode of inhibition came from enzyme kinetics, and docking alone was not taken as proof. None of these compounds derives from *T. molitor*. Coleoptericin-like peptides have not been examined against viral proteases, and their antibacterial mechanism is not fully defined, so any effect on Mpro or on the papain-like protease (PLpro) is a hypothesis. It could be explored by docking against the available crystal structures, as a way of generating candidates, followed by enzymatic assays, kinetics, and cell-based tests (Level 3).

ZIKV encodes the NS5 protein, whose RdRp domain is essential for genome replication and is a validated antiviral target (Lazear & Diamond, 2016; Godoy et al., 2017). The active site of the RdRp contains the conserved GDD motif. A compound proposed to act at this site would have to be shown to inhibit competitively by enzyme kinetics, and assigning a binding site as allosteric requires structural evidence, for example a co-crystal structure or mutational analysis, or functional evidence such as non-competitive kinetics combined with site-directed mutagenesis. SAXS studies of ZIKV proteins in the presence of candidate inhibitors could contribute to screening (Level 3). No lipopeptide or other insect-derived compound has been reported to inhibit ZIKV NS5.

In general, molecular docking should be read as a hypothesis-generating tool. It ranks possible binding poses and can prioritize candidates, but its scores do not measure affinity reliably and do not show that a compound binds or inhibits its target. Binding should be measured directly (for example by surface plasmon resonance, isothermal titration calorimetry, or NMR titration), and inhibition should be quantified by enzyme kinetics and by cell-based assays that report EC_{50}, CC_{50}, and the selectivity index.

Figure 4: Validated structural viral targets and hypothesized insect-derived inhibitors. Solid blue boxes show viral targets whose structures have been determined experimentally; dashed boxes show hypotheses that have not been tested. (A) CHIKV: the E2–E1 glycoprotein interface with the receptor MXRA8 (Song et al., 2019); blockade by insect defensins or lectins is a hypothesis. (B) ZIKV: the NS5 RdRp and its catalytic GDD motif (Godoy et al., 2017); inhibition by lipopeptides has not been reported, and a competitive or allosteric mode would require kinetic and structural evidence. (C) SARS-CoV-2: the main protease Mpro, with catalytic dyad Cys145/His41 (Jin et al., 2020); an effect of coleoptericin-type peptides or lipopeptides is a hypothesis that requires docking followed by enzyme kinetics and cell-based assays. The summary table separates validated viral targets from validated *T. molitor*-derived inhibitors, for which none has been reported. RdRp, RNA-dependent RNA polymerase; SI, selectivity index.



Virus	Validated viral target	Validated *T. molitor*-derived inhibitor	Evidence needed
CHIKV	E2–E1 / MXRA8 interface	None reported	binding assays; EC_{50}, CC_{50}, SI
ZIKV	NS5 RdRp (GDD motif)	None reported	kinetics; structure for allosteric site
SARS-CoV-2	Mpro (Cys145/His41)	None reported	docking, then kinetics and cell assays

4.3. Lipopeptides as Antiviral Candidates: Surfactin and Its Analogues

Surfactin is a cyclic lipopeptide produced by the bacterium *Bacillus subtilis*. It consists of a heptapeptide ring closed by a lactone bond to a β-hydroxy fatty acid with 13 to 15 carbon atoms (Peypoux et al., 1999). *In vitro*, surfactin inactivates several enveloped viruses, including herpesviruses, retroviruses, and vesicular stomatitis virus, at micromolar concentrations, and enveloped viruses are inactivated much more efficiently than non-enveloped ones (Vollenbroich et al., 1997; Kracht et al., 1999). The main mechanism proposed is a physicochemical interaction of the amphiphilic molecule with the viral lipid membrane, and a cell-based study reported that surfactin inhibits membrane fusion during the entry of enveloped viruses (Yuan et al., 2018). These data come from a bacterial product and are Level 2 evidence with respect to *T. molitor*.

The solution structure of [Leu7]surfactin was determined by ^{1}H NMR in dimethyl sulfoxide combined with molecular modeling (Bonmatin et al., 1994), and surfactin is described as adopting a characteristic “horse-saddle” conformation in solution (Peypoux et al., 1999). How this conformation behaves in lipid bilayers is less well defined. The expectation that analogues with longer or branched acyl chains, or with modified charged residues, will show altered membrane affinity and specificity is a prediction that could be tested with the biophysical pipeline of Section 3.

Solid-phase synthesis allows the systematic production of surfactin-derived peptides and lipopeptides with designed changes in the amino acid sequence and the fatty acid moiety. Eight such molecules were synthesized by Fmoc chemistry and showed low toxicity in Vero cell, hemolysis, and cytotoxicity assays, emulsifying properties, and synergy with vancomycin against *S. aureus* (Vazquez et al., 2018). Activity of these analogues against CHIKV, ZIKV, or SARS-CoV-2 has not been reported, to our knowledge, and would have to be tested (Level 3).

The relationship between these lipopeptides and *T. molitor* needs to be stated with care. Surfactin is bacterial, and the synthetic analogues are laboratory products. Insect-derived lipopeptides comparable to surfactin have not been described in *T. molitor*, and whether the insect or its associated microbiota produce them is unknown (Level 3). The link demonstrated so far runs in the opposite direction: bacterial lipopeptides stimulate the immune system of *T. molitor* and induce AMP expression (Edosa et al., 2020). Surfactin-type lipopeptides are therefore treated here as a model class of antiviral candidates and as immune elicitors in *T. molitor*, and not as products of the insect.

5. One Health Perspective: Insects at the Interface of Ecosystems, Agriculture, and Human Health

5.1. One Health as a Conceptual Framework

One Health is an integrated approach that aims to balance and optimize the health of people, animals, and ecosystems. It was defined by the One Health High-Level Expert Panel, which advises the Quadripartite formed by the Food and Agriculture Organization (FAO), the United Nations Environment Programme (UNEP), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH) (Adisasmito et al., 2022). The emergence of zoonotic viruses is a typical One Health problem. It includes SARS-CoV-2, a virus of probable animal origin, Nipah virus, which passes from bats to humans directly or through pigs, and arboviruses such as CHIKV and ZIKV, which circulate between vertebrate hosts and arthropod vectors. Changes in land use, biodiversity loss, and climate change are among the drivers of such events.

Insects occupy several roles in this framework. They are vectors of human and animal pathogens (mosquitoes, ticks, sandflies), biocontrol agents of agricultural pests, decomposers in nutrient cycles, and sources of food and feed protein with a lower environmental footprint than many conventional livestock systems (van Huis et al., 2013). This review adds a further role that is still prospective, that of producers of molecules that might be developed into drugs. The composition of the gut microbiome of *T. molitor* changes with diet (Przemieniecki et al., 2020), which links insect biotechnology to microbial ecology.

5.2. *Tenebrio Molitor* in Waste Valorization, Circular Bioeconomy, and Microbial Metabolites

Beyond their pharmacological interest, *T. molitor* larvae are studied in the circular bioeconomy. They grow on organic by-products, including food-processing residues, agricultural residues, and lignocellulosic materials, and they yield insect biomass (protein and lipid for food or feed) and frass, which can be used as an organic fertilizer (van Huis et al., 2013; Houben et al., 2020). Larvae can also degrade polystyrene and polyethylene, with the involvement of gut microbes (Yang et al., 2015; Brandon et al., 2018), and the composition and enzymatic profile of their gut microbiota change with the substrate they consume (Przemieniecki et al., 2020). These are Level 1 findings for *T. molitor*, but they concern waste degradation and fertilizer use, and not the production of antimicrobial compounds.

It has been proposed that fermentation by gut bacteria yields short-chain volatile fatty acids (VFAs), such as acetic, propionic, and butyric acids, and that VFAs and related alcohols might contribute to resistance to pathogen colonization in the larval gut or be harvested as natural preservatives. We did not find primary studies that measure VFA production by the gut microbiota of *T. molitor* larvae or that test the antimicrobial activity of such compounds in this system. The idea therefore remains a hypothesis (Level 3). VFAs are common products of microbial fermentation in other animals, which makes the hypothesis plausible, but it needs direct measurements of VFAs in larval gut contents and frass, together with tests of their antimicrobial effect at the concentrations found.

The metabolic versatility of *T. molitor*, which includes polymer biodegradation, protein and lipid production, and possibly the production of microbial metabolites, makes the species a potentially valuable platform within a One Health framework. Cultivation on organic by-products could reduce food waste (environmental health), the biomass provides protein for food and feed (food security and agricultural health), and the immune molecules could be studied as drug candidates (human health). Each of these claims has a different level of support: the first two are supported by the studies cited above, and the third is the hypothesis explored in this review. Integrated study of these dimensions, with metagenomics of the gut microbiome, metabolomics of frass and hemolymph, and transcriptomics of immune genes, is a reasonable research strategy.

5.3. Antimicrobial Resistance and the Potential of Insect Molecules

Antimicrobial resistance (AMR) is a major global health problem. A systematic analysis estimated 1.27 million deaths directly attributable to bacterial AMR in 2019 and 4.95 million deaths associated with it (Murray et al., 2022). The WHO Global Action Plan on AMR, adopted in 2015, calls for a One Health response (World Health Organization, 2015). Insect AMPs are of interest as sources of new anti-infectives (Hancock & Sahl, 2006) for three reasons. They evolved in host defense against microbes that have long co-existed with insects. Their structural diversity, from α-helical cecropins and cystine-stabilized defensins to glycine-rich attacin- and coleoptericin-like peptides, covers chemical space that is not well represented in synthetic libraries (Boman, 1995; Bulet et al., 2004). And many of them act through mechanisms different from those of conventional antibiotics.

The idea that AMPs inherently limit the development of resistance because they act through several mechanisms should be treated with caution. Multiple modes of action, such as membrane disruption combined with intracellular targeting, can raise the barrier to resistance in some settings. Even so, bacteria resist AMPs through changes in membrane lipid composition and surface charge, efflux pumps, proteases that degrade peptides, and other mechanisms (Andersson et al., 2016), and resistance to host-defense peptides has been documented experimentally. Widespread therapeutic use of AMPs could also select for resistance to the host-defense peptides of the patient, with possible consequences for host immunity (Lazzaro et al., 2020).

Peptide stability in biological fluids is a further obstacle because of rapid proteolysis and clearance. Cyclization, D-amino acid substitution, lipidation, and PEGylation are used to prolong half-life, and their effects on activity must be tested peptide by peptide (Di, 2015; Fosgerau & Hoffmann, 2015). Insect peptides engineered for protease resistance have protected mice and rats against bacterial infection in experimental models (Otvos, 2000). This shows that improved stability is achievable, although those peptides are not from *T. molitor*. Structural characterization (Section 3) can guide such modifications.

6. Pharmacological Outlook: From Larva to Lead Compound

6.1. The Drug Discovery Pipeline for Insect-Derived Bioactive Molecules

The development of an insect-derived molecule from biological source to clinical candidate can be organized in six stages. (i) Discovery and primary characterization: hemolymph and fat body proteomics, transcriptomics of immune-challenged larvae, bioinformatic prediction of AMP sequences, and solid-phase peptide synthesis. (ii) Structural characterization: NMR, cryo-EM, SAXS, CD, and fluorescence spectroscopy, to define three-dimensional structure and membrane interaction. (iii) Pharmacological profiling: MIC assays against standardized bacterial and fungal panels; for antiviral candidates, cell-based infection assays that report the 50% effective concentration (EC_{50}), the 50% cytotoxic concentration (CC_{50}), and the selectivity index ($SI = CC_{50}/EC_{50}$), together with inhibition kinetics for proteases or polymerases (IC_{50} and Ki) and measurement of hemolytic activity. (iv) Optimization: structure–activity relationship (SAR) studies to improve potency, selectivity, protease resistance, and solubility. (v) Absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic/pharmacodynamic (PK/PD) evaluation, including serum stability, plasma protein binding, bioavailability, and delivery or formulation. (vi) Preclinical validation of efficacy and toxicity in animal models (Bulet et al., 2004; Di, 2015; Fosgerau & Hoffmann, 2015).

MIC is the standard measure of antibacterial and antifungal potency, but it is not suited to antiviral work, where EC_{50}, IC_{50}, CC_{50}, and the selectivity index are the usual parameters. Activity should also be re-measured in the presence of serum, since serum components can lower the effective concentration of membrane-active compounds, as shown for surfactin (Vollenbroich et al., 1997). Structural biology contributes most at stages (ii) and (iv), where it turns empirical SAR exploration into rational design.

Resistance should be considered throughout the pipeline. For antibacterial peptides, resistance mechanisms include changes in membrane composition, efflux, and proteolytic degradation (Andersson et al., 2016), as discussed in Section 5.3. For antiviral candidates, the high mutation rate of RNA viruses can produce escape mutations in the target glycoprotein or protease, which argues for combination approaches or for targeting conserved viral elements as well as host processes.

6.2. HIV-1 Reverse Transcriptase as a Model of Antiviral Resistance

HIV-1 reverse transcriptase (RT) is included here as a comparator, and a relationship with *T. molitor* has not been shown. There is no evidence that *T. molitor* molecules target RT. The reason for its inclusion is that RT is one of the best studied viral polymerases with respect to resistance, and it illustrates what any inhibitor of a viral polymerase, such as the RdRp of ZIKV or CHIKV, will have to face. RT is the target of the largest class of approved antiretrovirals (nucleoside and non-nucleoside inhibitors), and the accumulation of resistance mutations alters substrate usage and reduces drug susceptibility. A recombinant RT variant carrying twelve resistance-associated substitutions was produced and characterized functionally as a platform for antiretroviral screening (Dos Santos-Filho et al., 2026). A platform of this kind is relevant to the pipeline above because candidate inhibitors can be tested early against heavily mutated enzyme variants. Whether insect-derived molecules could target conserved, structurally constrained regions of viral polymerases, where mutation is limited by catalytic requirements, remains a hypothesis.

6.3. Computational Tools and Artificial Intelligence

Computational methods can speed up the analysis of insect AMP sequences, the prediction of their structures, and the design of variants, but they generate hypotheses and do not replace experimental validation. AlphaFold2 predicts protein structures from sequence with high accuracy for many proteins (Jumper et al., 2021). It can provide structural models of newly identified *T. molitor* immune proteins for testing by NMR, SAXS, or cryo-EM, although its reliability may be lower for short, flexible peptides whose conformation depends on the membrane environment. Molecular dynamics simulations of peptide–membrane systems can explore conformational space at time and length scales that are hard to reach experimentally, and they should be checked against experimental data such as NMR and SAXS.

Deep-learning classifiers trained on curated AMP datasets can distinguish AMPs from non-AMPs. Their performance is normally reported as accuracy, sensitivity, specificity, area under the receiver operating characteristic curve, and Matthews correlation coefficient on held-out test sets (Veltri et al., 2018). These metrics depend on how negative examples were chosen and on redundancy between training and test sequences, and a good classification score does not indicate potency, selectivity, or antiviral activity, which must be measured (EC_{50}, CC_{50}). The design of analogues inspired by *T. molitor* peptides with such tools is therefore a cycle in which predictions are tested in the laboratory and the results are used to refine the models.

7. Discussion

This review examined *T. molitor* at the meeting point of AMR, emerging viral diseases, the circular bioeconomy, and One Health. The species is a useful model of insect immunity and a plausible source of bioactive molecules. The main conclusion of the evidence review, however, is that the support differs greatly by topic. It is direct for AMP biology and for the antibacterial and antifungal activity of the tenecins, limited for structural characterization, and largely indirect or hypothetical for antiviral activity, lipopeptide production, and microbial volatile metabolites (Table 1). The AMP repertoire of the insect was selected during evolution for host defense

against the pathogens that infect it (Lazzaro et al., 2020), and this does not mean that the molecules are suited to human therapy. Selectivity for host cells, stability in human fluids, and safety have to be shown case by case.

Structural biology is the strongest reason to study these molecules systematically. The main limitation has been the difficulty of obtaining enough correctly folded insect AMPs for biophysical work, which solid-phase peptide synthesis, recombinant expression in bacterial and insect cells, and cell-free translation now make manageable. Cryoprobe-equipped NMR spectrometers, improved cryo-EM detectors and image-processing software, and synchrotron SAXS beamlines make the pipeline of Section 3 feasible for *T. molitor* peptides, but to date it has been applied to them only in part (Table 1). Work on surfactin-derived analogues (Vazquez et al., 2018) shows that solid-phase synthesis of designed lipopeptides and their functional testing are tractable, although those molecules are not insect products.

From an antiviral perspective, the structural data for CHIKV E2–E1 (Song et al., 2019), SARS-CoV-2 Mpro (Jin et al., 2020), and ZIKV NS5 (Godoy et al., 2017) provide well-defined targets for structure-guided design. The small-molecule studies cited in Section 4.2 show that structurally diverse natural or repurposed compounds can inhibit Mpro through distinct modes (Chaves et al., 2022a, 2022b, 2022c). This supports the general feasibility of targeting the protease but is not evidence about insect molecules. Whether coleoptericins, defensins, or lipopeptides interact with these targets is unknown, and it should be tested systematically, starting with binding and enzyme assays and continuing with cell-based assays and selectivity indices.

The One Health framing has practical implications for research design, regulation, and communication. Programs that study the larval gut microbiome (environmental health), the safety of frass as fertilizer (agricultural health), and larval-derived AMPs (human health) together may produce more integrated knowledge than isolated projects. In the European Union, dried *T. molitor* larvae were the first insect authorized as a novel food (European Commission, 2021), and insect products are now handled within an established framework in which allergenicity, including cross-reactivity in people allergic to crustaceans or house dust mites, is addressed through labeling (EFSA Panel on Nutrition, Novel Foods and Food Allergens, 2021). Pharmaceutical ingredients would fall under different regulation, which novel-food law does not cover, so any extension would need separate assessment.

Several gaps stand out. Antiviral activity of *T. molitor*-derived molecules has been examined mostly *in silico* or inferred from other insect species, and systematic *in vitro* and *in vivo* testing against CHIKV, ZIKV, and SARS-CoV-2 variants with *T. molitor*-specific compounds is still missing. The pharmacokinetics of insect AMPs in mammalian models, including half-life, tissue distribution, metabolic stability, and toxicology, are incompletely characterized. The biological origin of the lipopeptides and volatile metabolites associated with the larva needs to be clarified experimentally, for example with axenic or antibiotic-treated larvae, metabolite profiling of hemolymph and gut contents, and genomic searches for biosynthetic gene clusters. Immunomodulatory effects of insect peptides and lipopeptides on human immune cells, such as dendritic cell activation, interferon induction, and NF-κB signaling, have received little attention.

The literature also contains findings that temper an optimistic reading. The *in vitro* potency of AMPs often falls in the presence of physiological salts, divalent cations, and serum, and activity measured in simple media may not carry over to biological fluids, as illustrated by the serum dependence of the antiviral effect of surfactin (Vollenbroich et al., 1997). Many peptide candidates have shown limited efficacy, toxicity, or poor stability during clinical development, and few AMPs have reached approval (Magana et al., 2020). The selectivity of membrane-active compounds for viral over host membranes is not guaranteed, and hemolysis and cytotoxicity must be measured alongside antiviral activity. Within *T. molitor* itself, activity is not uniform across peptides: tenecin 1 is active mainly against Gram-positive bacteria, tenecin 4 against Gram-negative bacteria, and tenecin 3 against fungi (Chae et al., 2012), which argues against treating the peptide repertoire as a single broad-spectrum resource. The mechanism of action of many insect AMPs has been established for few molecules. Risks associated with consumption, such as allergy, should also be considered if insect materials are proposed for pharmaceutical use.

This review has limitations. First, it is a narrative review, and the literature was not identified by a systematic search or with predefined screening criteria applied by independent reviewers. Relevant studies may have been missed, and the selection may reflect the author's familiarity with structural biology and with the viral targets discussed. Second, the published literature on AMPs and on insects as sources of drugs is probably affected by publication bias, since positive results are more likely to be reported than negative ones, so the apparent promise of these molecules may be overstated. Third, the risk of bias of individual studies was not assessed. Fourth, part of the content is prospective and reflects the author's proposals, which we have labeled as hypotheses.

8. Final Considerations

Tenebrio molitor is an established source of food and feed and a well-studied model of insect immunity. It is also a promising and underexplored platform for bioactive molecules. Its AMP repertoire was evolutionarily selected for host defense and includes peptides with documented antibacterial and antifungal activity. Whether these or other molecules of the species have antiviral activity, and whether they can be developed into drug candidates, remains unproven.

Within a One Health framework, *T. molitor* represents a potentially valuable platform: research on it can produce knowledge relevant to waste management, agricultural sustainability, antimicrobial resistance, and antiviral discovery, while regulatory and safety questions are addressed in parallel. The structural biology, computational design, and synthesis tools described here offer a feasible route to test the hypotheses raised in this review, provided that each step is accompanied by the pharmacological assays the field requires (EC_{50}, CC_{50}, selectivity indices, kinetics, ADME, and PK/PD).

The biological origin of the lipopeptides and volatile metabolites associated with the larva remains to be established. Future clinical translation, if it occurs, will depend on systematic structural, pharmacological, toxicological, pharmacokinetic, and *in vivo* validation of specific molecules. Until then, what can be claimed for the pharmacology of *T. molitor* is what Table 1 lists as Level 1, and the rest is a research agenda.

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Declaração Ética

Conflito de Interesse: Nada a declarar. **Financiamento:** Nada a declarar. **Revisão por Pares:** Dupla-cega.

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