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Insect Immune System-Inspired Antiviral Strategies: A Conceptual Perspective with Special Emphasis on HIV/AIDS

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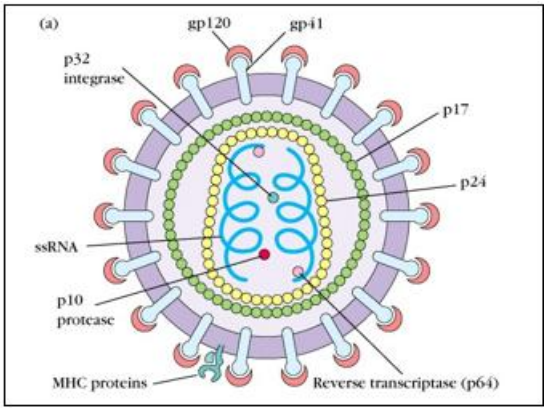
Abstract: ***This study investigates insect immune system–inspired antiviral mechanisms as potential templates for innovative therapies against viral diseases, with emphasis on HIV/AIDS. Key mechanisms reviewed include antimicrobial peptides, lectins, the prophenoloxidase cascade, and autophagy-related antiviral defenses. Their possible antiviral relevance, delivery methods, and translational challenges, including toxicity, specificity, and engineering optimization are discussed. Emerging technologies such as CRISPR gene editing, nanoparticle encapsulation, and peptide engineering may facilitate adaptation of these mechanisms into realistic biomedical applications. Although largely conceptual and requiring comprehensive experimental validation, insect-inspired immunotherapeutic strategies represent a promising direction for future antiviral research and developments.***

Keywords: HIV-1; insect immunity; antimicrobial peptides; lectins; prophenoloxidase cascade; autophagy; biomimetic antivirals; innate immunity; translational therapeutics

1. Introduction

This study aims to introduce a new field of study in medicine, integrating insects' immune system inspired therapies to cure viral diseases (with special emphasis on HIV AIDS) in humans. Insects have one of the best immune systems present on our planet. Even with the absence of an adaptive immune system. Whether due to the presence of hemocytes, exclusive AMPs or proteins like Dscam. This study suggests how some of the components of the insect immune system possess promising properties to contribute towards the cure or prevention of many viral diseases. Some insect derived proteins, polypeptides, and antibodies have already been researched for their potential to combat viral diseases such as dengue, hepatitis, RSV, influenza, etc. HIV (Human Immunodeficiency Virus) causes AIDS by targeting CD4+ immune cells. The viral envelope glycoprotein gp120 binds to host CD4 receptors, inducing a conformational change. This allows gp41 to mediate membrane fusion, releasing the viral capsid into the host cytoplasm. Once inside the cell, the RNA is converted into double stranded DNA by the enzyme reverse transcriptase. The viral DNA then enters the cell and is integrated via the enzyme integrase. This DNA is integrated into mRNA, which is then translated to viral protein. Hence, reproducing rapidly, damaging the functioning of our immune system and making us prone to several other lethal diseases.

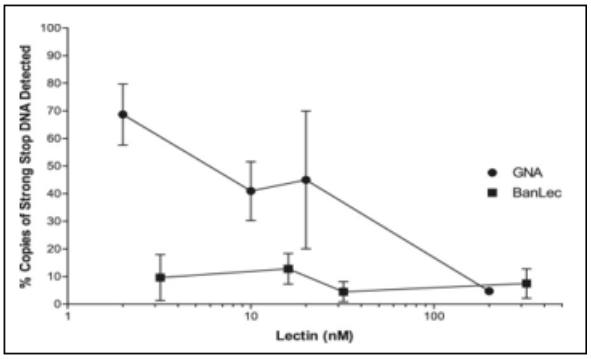


Source: https://share.google/jST9mPUsOOAfIJ7f8
Cross-sectional schematic diagram of HIV virion.

Several polypeptides derived from various insects like Gloverin , Melittin, Cecropin A , Moricin ,etc. have shown potential against HIV, by disrupting the membrane of viral cells, viral inactivation, inhibiting the replication of virus, etc. They can not only provide a mechanism for destroying the virus inside but also for building resistance against other disease during the malfunctioning of our adaptive immunity. For example, chitosan, a polysaccharide has shown exceptionally well antiviral properties, in addition to it, it is not toxic to humans and is comparatively biocompatible. It has shown enhancement in phagocytosis, stimulating pattern recognition receptors, and modulation of cytokine production. Chitin has also shown delivery of tenofovir and saquinavir. Saquinavir is an antiretroviral medication used to treat HIV infection, it belongs to a class of protease inhibitors, which work by blocking the protease enzyme that is needed by HIV in order to replicate. Tenofovir belongs to the class of nucleotide reverse transcriptase inhibitor and is also used in the medication of hepatitis B. Some of the components or mechanisms that will be discussed in this paper show some degree of toxicity towards human body, however in some cases our immune system degrades its toxicity on its own, the toxicity can also be inhibited via altering structure of these polypeptides, Proteins, anti-bodies by using technologies

such as CRISPR , peptide engineering, amino acid substation, etc. Besides antimicrobial peptides, lectins also hold a huge potential in combating viral diseases. For HIV many lectins are studied for the cure , but the primary motivation of the research was focused on lectins derived from plants. The table below showcases some of the lectins known to inhibit HIV and their sources.

Lectins	Source
Griffithsin	Red algae
BanLec	Banana
Urtica dioica agglutinin	Stinging nettles.
Galanthus nivalis agglutinin	Snow drop bulbs
Cyanovirin-N	Cyanobacteria



BanLec inhibits production of early HIV-1 reverse transcription products in peripheral blood lymphocytes. Peripheral blood lymphocytes were treated with different lectin concentrations 30 min before infection with HIV-1 Bru. Three hours post-infection, cellular DNA of the infected cells was harvested, and strong-stop DNA was quantified by real-time PCR. The number of copies was normalized to a PBS-treated control (100%). The known anti-HIV lectin GNA (circles) was used as a positive control and to assess the relative molar potency of BanLec (squares).
Source : Swanson, M. D., Winter, H. C., Goldstein, I. J., & Markovitz, D. M. (2010). A lectin isolated from bananas is a potent inhibitor of HIV replication. Journal of Biological Chemistry, 285(12), 8646–8655.

Hence, we have focused on only one insect derived lectins, that is the mermaid lectins derived from marine symbiotic nematodes. Furthermore, we have a mechanism known as prophenoloxidase system (proPO). This pathway is absent in humans and is predominantly found in arthropods and several other invertebrate groups. Plants also possess a similar pathway that functions in a similar way, that is the Polyphenol Oxidase system. It is interesting to note that according to research conducted by Cong Wang and others at Xiamen University, Polyphenol extracts from grape seeds, apple, pomegranate, and bilberry can act as latency-reversing agents (LRAs). They stimulate Tat-independent HIV-1 transcription by promoting the release of P-TEFb from 7SK snRNP in Jurkat T cells, offering a potential inhibition strategy. The proPO system in insects triggers an enzymatic cascade that activates phenoloxidase. This produces quinones and melanin, which neutralize viruses by cross-linking proteins, releasing toxic radicals, and physically entombing pathogens to prevent infection. Lastly, we will discuss the potential of insect autophagy. Autophagy serves as a cellular garbage disposal that targets viruses, bacteria, and parasites for lysosomal degradation. This specialized process, known as xenophagy, restricts the replication of intracellular pathogens. While autophagy normally acts as an antiviral mechanism by removing pathogens, in human body, HIV-1 manipulates it to enhance survival and cause CD4+ T cell death. Early in infection, HIV releases Nef protein which binds to BECLIN-1, preventing autophagosomes from fusing with lysosomes. Other proteins such as Tat and Vpr , which are regulatory and accessory proteins encoded by HIV genome also interfere with human autophagy. This stops the degradation process and allows the virus to evade destruction. Already experiments conducted on humanized mice shows that autophagy boosting drugs such as rapamycin have shown to reduce the infections. Autophagy is highly conserved between humans and insects, with many Atg (autophagy-related genes) and regulatory pathways (such as mTOR) functioning similarly. However, significant differences exist, which can be used to immunize human autophagy from HIV.

2. Literature Review

Though, the concept of using insect immune system inspired therapies to combat diseases in general is comparatively a new field of study and we do not have much research conducted in this field. But we do have enough research to form the basics of the idea. We already have immense knowledge on both insect immune system and HIV AIDS separately; we must relate them to accelerate the research. Scientists have already figured out the importance of antimicrobial peptides derived from insects to block various viruses, their main focus lies in integrating these peptides with nanoparticle technology, leading to reduced toxicity and increased life span of peptides. Another aspect of the insect immune system that scientists have been vigorously studying is the RNAi and Gene Silencing system. RNA interference (RNAi) serves as the primary defense mechanism in the insects, functioning as a sequence-specific immune memory that identifies and destroys viral genetic material. (Galiana-Arnoux, D., et al., 2006). In insects, this process is triggered when the cell detects double-stranded RNA, leading to the activation of the Dicer enzyme which breaks the invader into small interfering RNAs (siRNAs). Researchers are now adapting this "molecular scissor" approach to treat HIV by designing synthetic siRNAs that mimic insect responses (Novina, C. D., et al., 2002). These molecules are programmed to target the HIV-1 pre-genomic RNA, effectively silencing the genes required for the virus to package itself and exit the host cell. Research has also been made on insect derived Pattern Recognition Receptors (PRRs). Unlike human antibodies that look for surface proteins, insect PRRs like Dicer-2 detect the physical structure of dsRNA(Sinha, N. K., et al., 2015). This is critical for HIV research because while HIV is a ssRNA virus, it forms dsRNA-like structures during its replication cycle that these insect-inspired sensors can theoretically target. Lastly, research has been carried out on the JAK/STAT Pathway. In insects, this pathway is a primary engine for the innate immune response, where the activation of Janus kinases (JAK) and STAT transcription factors trigger the rapid expression of specific viral restriction factors that limit RNA virus replication. In Drosophila, the pathway is triggered by ligands like Unpaired (Upd), which bind to the Domeless (Dome) receptor, activating the JAK kinase Hopscotch (Hop) and the STAT protein Stat92E (Zeidler, M. P., et al., 2014). HIV-1 frequently survives in human hosts by selectively inhibiting STAT1 phosphorylation, effectively silencing the interferon-mediated signals that would otherwise clear the infection. By studying the insect-specific mechanisms of Stat92E activation and the ligands that trigger it, researchers

are investigating how to bypass viral blocks and restore functional JAK/STAT signaling in human cells.

3. Methodology

This study employs a qualitative, conceptual framework approach to explore the potential application of insect innate immune mechanisms to human HIV therapeutics. Unlike traditional experimental designs, this qualitative approach is best suited for synthesizing cross-disciplinary data from entomology and virology to generate a novel theoretical model for biomimetic HIV suppression. The following research has been conducted through deep analysis of previously existing data, research , case studies, and theoretical knowledge. Data were collected through a systematic and multi-disciplinary search of authoritative peer-reviewed literature. Primary biomedical data were retrieved from PubMed, ScienceDirect, and Embase, while specialized entomological and cross-species immunological research was sourced from CABI Digital Library and the BIOSIS Citation Index. Keywords for the search included "Antimicrobial Peptides (AMPs)," "Insect Autophagy," "C-type Lectins," and "Prophenoloxidase (PPO) System" in conjunction with "HIV-1 pathogenesis" and "antiviral therapy". Structure of molecules, especially AMPs, were studied, and comprehensive analysis and studies were made on their theoretical interaction with HIV AIDS. Key databases for structural analysis of molecules included the RCSB, Avogadro, PubChem ,ChemSpider and MolView. Using tools like UniProt and the Protein Data Bank (PDB), the primary and tertiary structures of C-type lectins (CTLs) from marine nematodes (Laxus oneistus) were compared against human DC-SIGN. This established structural mimicry, suggesting mermaid lectins could act as a competitive antagonist for HIV-1. Previous research papers, existing theories, data and structural analysis of molecules led to the establishment of hypothesis for the potential of autophagy and prophenoloxidase systems.

4. Discussion

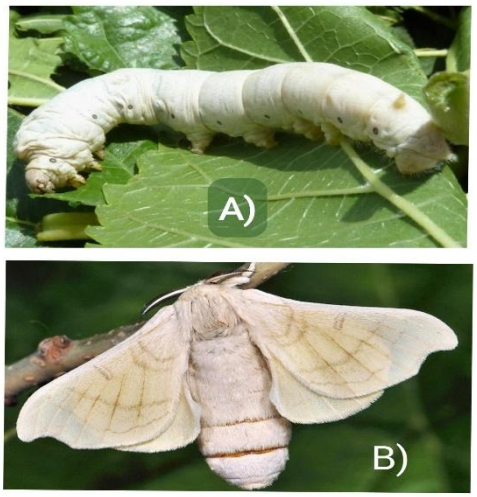
4.1 How do antimicrobial peptides Interfere with HIV?

One of the mechanisms involves rupture of the viral membrane. These peptides are mostly cationic while viral membrane is negatively charged, hence these peptides form a coating over the membrane and force the viral membrane to curve inward, creating toroidal pores. These pores allow the internal contents of the virus to leak out, damaging the virus. Another method involves suppression of viral gene expression by entering the host cell nucleus and then directly blocking the activity of the Long Terminal Repeat (LTR) promoter, which prevents the recruitment of essential transcription factors and viral Tat protein required for viral RNA synthesis (Wachinger, M., et al. (1998)) . These peptides have also shown to inhibit crucial HIV enzymes, acting as pseudosubstrates. Some bind directly into the protease's active site—which typically contains the conserved Asp-Thr-Gly Triad (Mager, 2001; Wlodawer et al., 1989), blocking the enzyme from accessing actual viral proteins. For example, Melittin activates phospholipase A2 (Saini et al., 1993) and decreases the activity of calmodulin (Comte et al., 1983) and protein kinase C (O'Brian et al., 1988), which are necessary for the cellular transcription factors that Reverse transcriptase depends on (Park et al., 2007; Wachinger et al., 1998).

Let us now look at some of the antimicrobial peptides in detail and their interactions with HIV.

1) Gloverin

It is derived from silkworm Bombyx mori and specifically exhibits broad-spectrum activity against gram-negative bacteria and certain fungal pathogens. Gloverin mainly accumulates on the surface of viral particles, causing membrane tension or pore formation that destroys the envelope (Moreno-Habel, D. A., et al., 2012). Gloverin has already shown antiviral activity against certain viruses, including AcMNPV (Autographa californica multiple nucleopolyhedrovirus) and BmNPV (Bombyx mori nucleopolyhedrovirus). Studies conducted on Bombyx mori gloverin A2 (BMGlvA2) have demonstrated that the protein has no negative influence on the viability of mammalian cells even at high concentrations (Lin, Q., et al., 2019). The key reason is that human cell membranes are packed with cholesterol, which makes them sturdy and resistant to being "popped." The HIV envelope is much more fragile and can be easily damaged (Campbell, T. D., et al., 2001).

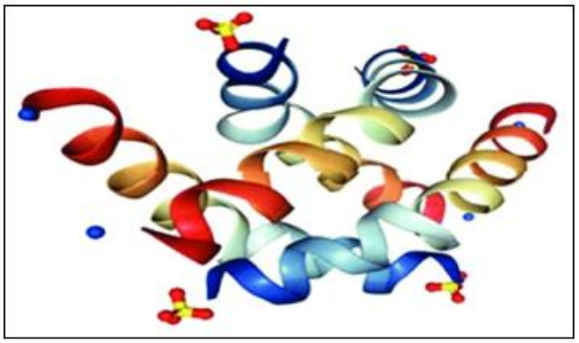


A):The larva (or caterpillar) stage of Bombyx mori. Source: Research Gate
B):Adult moth stage (also called the imago) of the Bombyx mori. Source: Moths and Butterflies of Europe and North Africa

2) Melittin

Melittin is the main compound found in bee venom, it binds to the lipid bilayer of viral particles, disrupting their structure and integrity, forming pores in the viral membranes (Hood, J. L., et al., 2013). Melittin can inhibit viral transcription by binding to viral RNA or DNA, preventing the synthesis of viral proteins. It reduces the activity of the HIV Long Terminal Repeat (LTR) and decreases the overall levels of HIV-1 mRNAs. Melittin significantly reduces intracellular levels of the Gag antigen (Wachinger, M. et al., 1998). Melittin can also interfere with the translation of viral mRNA into proteins, reducing the production of viral proteins essential for replication (Uddin, M. B. et al. (2020)). It has also shown to complement existing inhibitors like Azidovudine (AZT) in blocking reverse transcription. Mellitin also stimulates the production of antiviral proteins, such as interferons, which can inhibit viral replication.

Production of antiviral cytokines like IFN-γ (interferon-gamma) (Mansouri, M., et al. (2012)) and chemokines like CXCL8 (C-X-C motif chemokine ligand 8)(Alqarni, A. M., et al. (2018)) is also enhanced by melitin. It is of utmost importance to note that Melittin itself is highly toxic to human cells, especially RBCs. This problem can be overcome by research and development of nano technology, for example Scientists at Washington University developed perfluorocarbon nanoparticles, causing the particles to simply bounce off human cells while allowing the much smaller HIV virus to fit through the gaps and reach the Melittin.



Structure of mellitin
Source : Research Gate

3) Cecropin A

Cecropin A is primarily found in The Giant Silk Moth (*Hyalophora cecropia*), The Greater Wax Moth (*Galleria mellonella*) and fruit flies (*Drosophila melanogaster)* It suppresses HIV-1 replication at sub-toxic concentrations by directly interfering with the host cell-directed gene expression of the virus. It decreases the activity of the HIV Long Terminal Repeat (LTR) promoter, meaning the virus cannot effectively read its own genes to reproduce (*Wachinger et al., 1998*) .

4) Moricin

Moricin is mainly found in Lepidoptera (moths and butterflies) and Holotrichia diomphalia (a species of beetle). Moricin's amphipathic α-helical structure allows it to interact with and disrupt microbial membranes, potentially inhibiting viral replication. Moricin can also form voltage-dependent pores in cell membranes, altering membrane permeability and potentially preventing viral entry or replication. Research also suggests that Moricin-like peptides may as well suppress the synthesis of virus-specific genes without altering viral adsorption and entry into host cells.

4.2 Investigating the potential of lectins

Lectins are proteins (or glycoproteins) with specific carbohydrate-binding domains (CBDs) that allow them to recognize and bind to certain sugar molecules on the surfaces of cells, pathogens, or viruses. Lectins derived from insects provide promising effects toward viruses and bacteria. For example, HIV's surface protein, gp120, is heavily glycosylated, lectins with high mannose-binding affinity can attach to gp120 and block the virus from entering the cell. Comprehensive research has already been conducted on effects of some lectins on certain viral diseases. A few types of lectins and the virus targeted by them are as follows

Lectins	Targeted virus
C- type Lectins	West Nile, Zika, Dengue
Galectins	Baculovirus
Ficolin like lectins	Arbovirus
I-type Lectins	Hepatitis

lectins from plants, algae, and bacteria are famously known for their ability to block HIV, but there is limited focus on lectins derived from insects acting as anti-HIV agents till now. The Mermaid lectin is produced by marine nematode (*Laxus oneistus*). While it's primary role is to help the worm manage a protective layer of beneficial bacteria, it has also shown to block or combat HIV. HIV-1 normally hijacks the human DC-SIGN receptor on dendritic cells (DCs) to travel to the lymph nodes, where it infects T-cells. Because Mermaid and DC-SIGN share nearly the same structure and sugar-binding preferences, Mermaid can compete with DC-SIGN. It binds to the high-mannose sugars on the HIV envelope (gp120) before the virus can reach the human receptors.

4.3 Investigating the potential of the prophenoloxidase (proPO) system in insects to block or combat HIV

The prophenoloxidase (proPO) system is an enzymatic cascade that serves as the first responder of the insect immune system. Pathogen detection triggers a serine protease cascade that activates the zymogen prophenoloxidase (proPO) into phenoloxidase (PO) (Cerenius & Söderhäll, 2004). Active PO then oxidizes phenols like tyrosine or dopamine into reactive quinones and 5,6-dihydroxyindole (DHI) (Kan et al., 2008). Quinones exhibit high chemical reactivity, allowing them to form covalent bonds with viral surface proteins and cross-link envelope glycoproteins like gp120, thereby blocking host cell receptor binding (Vance et al., 2016). This oxidative process also generates Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which degrade viral membranes and genetic material (Nappi & Christensen, 2005). The cascade culminates in the production of melanin, which physically entombs pathogens to create a protective barrier against infection (Zhao et al., 2007).

4.4 Investigating the potential of insect autophagy in combating HIV

Human and insect autophagy systems diverge significantly. This can be exploited to block or inhibit HIV by using insect autophagy-inspired templates for treatment. For example, in humans, HIV activates the mTOR to suppress autophagy, whereas insects bypass this via the Vago/JAK-STAT pathway. (Deddouche et al., 2008; Wang et al., 2014). Furthermore, while the HIV Tat protein disables human PTEN to prevent cell death, structural mismatches in insect PTEN prevent this subversion (Chauhan et al., 2012). Similarly, viral proteins Nef**,** Vpu**,** and Gag fail to inhibit insect autophagy because they cannot bind to the insect orthologues Atg6 or Ref (2)P (Nakamura et al., 2014; Borel et al., 2015). Lastly, insects possess the **Toll-7** receptor to detect viral glycoproteins, an immune sensor that is entirely absent in humans (Nakamoto et al., 2012)

4.5 Potential application mechanisms

Along with studying the potential of these immune system mechanisms of insects in combating HIV , it is also of utmost importance to come up with ways to realistically implement them in human therapies and modify them so that they do not cause any harm to human cells . For example for application or delivery of AMPs in the human body ,we are exploring the integration of these AMPs with nanoparticles, Engineered Live Biotherapeutics (Probiotic bacteria or yeast are genetically modified to produce and secrete insect AMPs directly within the gut mucosa, a major site of HIV replication.) , Hydrogels, Peptide-Drug Conjugates and Viral Vector-Based Gene Therapy . Same goes for lectins. These may also be chemically or structurally modified for better drug delivery. CRISPR/Cas9 gene editing, exosome-mediated transport, Vector-induced gene silencing and Biomimetic Carriers can be explored to induce or deliver insect prophenoloxidase (proPO) system and autophagy in humans.

Conclusion

Insect immune system mechanisms offer intriguing biomimetic models for future antiviral strategy development, particularly for HIV/AIDS. Antimicrobial peptides, lectins, prophenoloxidase-related chemistry, and conserved autophagy pathways may provide conceptual foundations for therapeutic innovation, though substantial experimental validation, toxicity assessment, and translational engineering remain necessary. Future work should prioritize mechanistic validation, delivery platform development, and comparative in vitro and in vivo testing to assess feasibility of insect-inspired antiviral interventions.

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