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Antiviral peptides: Natural defenses reimagined for clinical use.

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Introduction

In the ongoing battle against viral diseases, nature has long provided a blueprint for defense. Among its most potent tools are antiviral peptides (AVPs)—short chains of amino acids produced by organisms across all domains of life to combat viral infections. These peptides, part of the innate immune arsenal, exhibit broad-spectrum antiviral activity, low toxicity, and a reduced risk of resistance development. As synthetic biology and peptide engineering advance, AVPs are being reimagined for clinical use, offering a promising frontier in antiviral drug development [1].

Antiviral peptides are found in a wide range of organisms, including humans, animals, plants, fungi, and bacteria. In nature, they function as first-line defenses, disrupting viral replication and preventing infection. Human defensins and cathelicidins, for example, are expressed in epithelial tissues and immune cells, where they neutralize viruses like HIV, influenza, and herpes simplex virus (HSV). Plants produce AVPs such as thionins and cyclotides, which inhibit viral entry and replication. Microorganisms, including bacteria and archaea, also synthesize AVPs to protect against viral predators like bacteriophages. These naturally occurring peptides have inspired researchers to explore their therapeutic potential [2].

AVPs combat viruses through diverse mechanisms, often targeting multiple stages of the viral life cycle: Many AVPs bind to viral envelope proteins or host cell receptors, blocking attachment and fusion. For instance, peptides targeting HIV gp41 or influenza hemagglutinin prevent membrane fusion and viral entry. Amphipathic AVPs interact with viral lipid membranes, causing pore formation, leakage, and viral inactivation. Defensins and cationic peptides are known for this mechanism. Some AVPs penetrate infected cells and inhibit viral replication by binding to viral RNA or proteins involved in transcription and translation. AVPs can enhance host immune responses by recruiting immune cells, promoting cytokine production, or modulating inflammation [3].

These multifaceted actions make AVPs attractive candidates for broad-spectrum antiviral therapy. Compared to traditional small-molecule antivirals, AVPs offer several advantages: Many AVPs are effective against multiple viruses, including RNA and DNA viruses. AVPs target conserved viral structures and mechanisms, reducing the likelihood of resistance mutations. Naturally derived peptides tend to have low cytotoxicity and good tolerability. AVPs often act quickly by disrupting viral membranes or blocking entry. These properties are particularly valuable in treating emerging or re-emerging viral infections where rapid response is critical. A synthetic peptide that inhibits HIV fusion by targeting gp41. It was the first AVP approved by the FDA for clinical use [4].

Derived from red algae, this lectin-like peptide binds to glycosylated viral envelopes and shows potent activity against HIV, SARS-CoV, and Ebola. A human cathelicidin with broad antiviral activity, currently under investigation for respiratory viruses including influenza and SARS-CoV-2. Engineered for enhanced stability and specificity, cyclic AVPs are being explored for their resistance to enzymatic degradation and improved pharmacokinetics. These candidates demonstrate the therapeutic versatility of AVPs across different viral targets. Converting linear peptides into cyclic forms improves stability and

resistance to proteolysis. Incorporating D-amino acids increases half-life and reduces immunogenicity. Addressing these challenges through formulation technologies, delivery platforms, and regulatory frameworks is essential for successful clinical adoption. Topical or inhalable AVPs could serve as preventive agents in high-risk populations or outbreak settings. As research advances, AVPs are poised to become integral components of the antiviral arsenal [5].

Conclusion

Antiviral peptides represent a compelling fusion of nature's ingenuity and modern biotechnology. With their broad-spectrum activity, low resistance potential, and diverse mechanisms of action, AVPs offer a powerful alternative to conventional antivirals. Through strategic design and clinical innovation, these natural defenders are being reimagined as next-generation therapeutics—ready to meet the challenges of current and future viral threats.

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