NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

BOHDZEL Maryia, SAZON Raman, GURSKII Vladimir, HLUKHAVA Yuliya, BABKOVA Krystsina, ILINA Iuliia, KORPACKA Alicja, BOROWIECKA Patrycja Anna, PROBORSHCH PAVEL, SKADORVA Nadzeya. Antiviral Peptides as Emerging Therapeutic Agents: a Narrative Review of Engineering Strategies, Delivery Innovations, and Clinical Perspectives. Quality in Sport. 2026;54:70647. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70647

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 07.04.2026. Revised: 14.04.2026. Accepted: 14.04.2026. Published: 21.04.2026.

Antiviral Peptides as Emerging Therapeutic Agents: a Narrative Review of Engineering Strategies, Delivery Innovations, and Clinical Perspectives

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Abstract

Background. Viral infections remain a major global health threat despite advances in vaccines and antiviral drugs due to the rapid emergence of resistance and new viral pathogens. Antiviral peptides (AVPs) are promising broad-spectrum therapeutic agents because of their structural diversity and multiple biological activities.

Aim. The aim of this narrative review is to summarize current knowledge on antiviral peptides, focusing on their classification, mechanisms of action, molecular engineering strategies, delivery systems, and clinical perspectives.

Material and methods. A narrative review of recent peer-reviewed literature on antiviral peptides, engineering techniques, and modern drug-delivery approaches, including liposomes, polymer nanoparticles, and mucosal systems, was conducted.

Results. AVPs act at multiple stages of viral replication, including inhibition of viral attachment and fusion, disruption of viral envelopes, interference with intracellular replication,

and modulation of immune responses. Engineering strategies such as cyclization, PEGylation, D-amino acids, and lipidation improve stability and pharmacokinetics, while novel delivery systems enhance bioavailability. Clinical translation is limited by short half-life, toxicity, cost, and regulatory challenges.

Conclusions. Antiviral peptides are promising broad-spectrum therapeutics, and further interdisciplinary research is needed to enable their clinical application.

Keywords: Antiviral peptides, Peptide therapeutics, Peptide engineering, Nanocarrier delivery systems, Viral fusion inhibitors, Antiviral drug development

1. Introduction

Viral diseases remain a big challenge in medicine today. Even though vaccines and antiviral drugs have improved, many viral infections still pose a threat to public health. Viruses change quickly, often mutating, and new strains that resist treatment keep emerging, making current therapies less effective. The appearance of new viruses like COVID-19 shows how important it is to develop treatments that can target more types of viruses and be adapted faster.

Most antiviral drugs today are small molecules that block specific viral proteins. This method has worked well for diseases like HIV and hepatitis, but it can be less effective when viruses develop resistance or when drugs need to target very specific parts of the virus. Because of these challenges, researchers are looking more closely at other treatment options.

One promising group is antiviral peptides (AVPs). These molecules are found naturally in many living things as part of their basic immune defense, but scientists can also design them in the lab for specific purposes. Unlike regular antiviral drugs, peptides can perform several functions at once, such as directly inactivating viruses and modulating the immune response. Because they can interact with cell membranes, viral proteins, and the immune system, they are a strong option for new antiviral treatments.

Although interest in antiviral peptides is increasing, they are not yet widely used in clinical practice. Many promising peptides never make it to clinical trials because of issues with stability, efficacy, or production costs. However, new developments in peptide design, delivery technologies, and computer-based tools are helping to solve these problems.

Recently, there has been a significant increase in research on the design, improvement, and use of antiviral peptides. Still, we need to carefully study both their potential as treatments and the challenges of bringing them into real-world use as part of today's antiviral strategies.

This review summarizes current knowledge about antiviral peptides, covering their classification, how they work, engineering methods, and the newest drug delivery approaches. It also looks at where these compounds stand in terms of real-world use, the main clinical challenges, and potential future directions for developing peptide-based antiviral treatments.

2. Methodology

This article reviews research on antiviral peptides and their potential as therapies. We searched PubMed, Scopus, and reference lists, with the last search done on March 20, 2026.

We included only articles in English. Our search terms covered antiviral peptides, their mechanisms, design, delivery methods, and clinical uses, such as fusion inhibitors, defensins, cyclotides, peptide engineering, drug delivery systems, and nanocarriers.

We first screened titles and abstracts to find relevant papers. We read the full texts if they covered topics such as antiviral mechanisms, peptide optimization, delivery methods, or clinical and translational perspectives. Studies that did not focus on antiviral peptides or were outside the review's scope were excluded.

Most of the included studies were published between 2004 and 2025, but we also looked at earlier work to provide historical background. We described the studies and grouped them under themes like mechanisms of action, engineering strategies, delivery innovations, clinical perspectives, and ongoing limitations.

3. Results

3.1 Classification of Antiviral Peptides

Antiviral peptides (AVPs) are a varied group of molecules that come from different sources and have different properties. Unlike most small-molecule antivirals, which usually target a single pathway, AVPs often act in multiple ways. They can directly inactivate viruses and also modulate the host's immune response, thereby exerting a broader antiviral effect (Wang et al., 2022; Raj et al., 2025; Qureshi, 2025).

Researchers classify antiviral peptides by their main mechanism of action.

3.1.1 AVPs Targeting Viral Entry and Membrane Fusion

A key group of antiviral peptides stops viruses from entering host cells by blocking their attachment or fusion with the cell membrane. This prevents the virus from beginning its replication cycle and stops infection early (Raj et al., 2025; Geng et al., 2024).

Enfuvirtide is a well-known synthetic fusion inhibitor used to treat HIV-1 infection. It binds to the HR1 region of the gp41 glycoprotein and prevents the formation of the six-helix bundle, which is required for the virus and host cell membranes to fuse (Lalezari et al., 2003).

Studies on resistance to fusion inhibitors show that mutations in the gp41 region can make these peptides less effective. Changing the structure of antiviral peptides may enhance their potency and enable them to overcome new resistance mechanisms (Ghassabi et al., 2024).

Researchers are now focusing on designing lipopeptides and stabilized peptides. These new types show better biological stability and stronger antiviral activity than earlier peptide inhibitors (Geng et al., 2024; Huang et al., 2025).

3.1.2 Membrane-Active Antiviral Peptides

Another important group of antiviral peptides targets the viral lipid envelope. These peptides disrupt viral membranes through electrostatic interactions and amphipathic structures, which increase membrane permeability and cause the virus to become inactive (Raj et al., 2025; Solanki et al., 2021).

This group includes defensins (α-, β-, and θ-defensins) and synthetic peptides like retrocyclins. Studies show that θ-defensins can block infections from viruses such as HIV and herpes simplex virus (HSV). Their antiviral effect mainly comes from their ability to disrupt the viral envelope and block virus–cell receptor interactions (Solanki et al., 2021; Yasin et al., 2004).

Besides animal-derived peptides, some plant-derived cyclotides have shown strong antiviral potential. Their circular peptide structure makes them highly resistant to enzymatic breakdown and helps them remain stable in harsh environments (Conzelmann et al., 2022; Cândido et al., 2025). Because of these features, cyclotides can remain active even when many linear peptides would be inactivated.

Cyclotides have been effective against several enveloped viruses, including HIV (Conzelmann et al., 2022). Because they are very stable and resist enzymatic degradation, cyclotides are now seen as promising building blocks for the creation of new antiviral peptide analogues (Cândido et al., 2025).

3.1.3 AVPs Inhibiting Viral Replication

Besides blocking viruses from entering cells, some antiviral peptides also affect steps inside the cell during the viral replication cycle. These peptides may interact with viral enzymes, such as proteases or polymerases, or disrupt protein–protein interactions required for viral replication complexes (Wang et al., 2022; Raj et al., 2025).

Many antiviral peptides have a wider range of effects than traditional small-molecule inhibitors that target viral enzymes. For example, some peptides can break down the viral envelope, block virus–cell interactions, and modulate the host's immune response at the same time. This combination of actions may help lower the chances of resistance developing (Wang et al., 2022; Qureshi, 2025) .

Recent studies have focused more on creating peptides that can block key protein–protein interactions needed for viral genome replication and particle assembly. These approaches could lead to new, highly targeted antiviral treatments (Qureshi, 2025) .

3.1.4 Immunomodulatory Antiviral Peptides

Some antiviral peptides work mainly by affecting the host’s immune response. For example, defensins and other positively charged antimicrobial peptides can increase interferon production and activate key parts of the innate immune system, like macrophages and dendritic cells (Solanki et al., 2021; Diamond et al., 2009).

These effects on the immune system can be important early in an infection, as they help limit the virus's spread and strengthen the body’s defenses. Some studies also suggest that certain antiviral peptides might act as vaccine adjuvants, helping to control and boost protective immune responses (Wang et al., 2022; Qureshi, 2025).

Because AVPs directly attack viruses and influence the immune system, they stand out from many traditional antiviral drugs. This combination makes them an effective choice for treating and preventing viral diseases (Wang et al., 2022; Raj et al., 2025; Qureshi, 2025).

Table 1. Major classes of antiviral peptides and their mechanisms of action.

AVP class	Example	Mechanism	Target viruses	Stage of viral cycle	Development stage
Fusion inhibitors	Enfuvirtide, HR-derived lipopeptides	Inhibition of gp41-mediated membrane fusion	HIV, RSV, coronaviruses	Entry	Clinical / preclinical
Membrane-active peptides	α-, β-, θ-defensins, retrocyclins	Disruption of the viral envelope	HIV, HSV, influenza	Early stage	preclinical
Cyclotides	Kalata B1	Interaction with lipid membranes	HIV, influenza	Entry	preclinical
Replication inhibitors	Designed antiviral peptides	Inhibition of viral enzymes	HIV, HCV	Replication	preclinical
Immunomodulatory peptides	Defensins, antimicrobial peptides (AMPs)	Induction of interferons / activation of NK cells	Various viruses	Indirect	preclinical

3.2 Engineering and Optimization of Antiviral Peptides

Natural antiviral peptides exhibit promising biological activity but often suffer from poor pharmacokinetics, such as low stability, proteolytic degradation, a short plasma half-life, and limited bioavailability (Rossino et al., 2023; Pereira et al., 2024). To overcome these complications, researchers have developed strategies to modify the structure of AVPs to improve their physicochemical and therapeutic properties.

3.2.1 Peptide Cyclization

Cyclization is one of the most effective strategies for improving the structural stability of peptides. Converting a linear peptide chain into a cyclic structure reduces conformational flexibility, increases resistance to proteolytic degradation, and enhances stability under physiological conditions (Wang et al., 2022; Rossino et al., 2023).

Cyclotides represent a natural example of such peptides. These plant-derived peptides contain a cystine-knot motif and are characterized by remarkable thermal and enzymatic stability (Conzelmann et al., 2022; Cândido et al., 2025). Their high resistance to degradation makes cyclotides an attractive platform for the design of new antiviral peptide analogues.

3.2.2 Conformational Stabilization – Stapled Peptides

Stabilization of the α-helical structure through the introduction of a chemical bridge ("stapling") helps maintain the active conformation of peptides and increases their binding affinity to molecular targets (Wang et al., 2022; Qureshi, 2025).

This strategy is particularly useful for the design of protein–protein interaction inhibitors, such as viral fusion inhibitors, which require a stable helical conformation for biological activity (Geng et al., 2024; Huang et al., 2025). In addition, conformational stabilization can increase resistance to enzymatic degradation and facilitate peptide transport into cells (Wang et al., 2022).

3.2.3 Incorporation of D-Amino Acids

Introducing D-amino acids into peptide sequences can increase resistance to enzymatic degradation and improve metabolic stability (Rossino et al., 2023; Pereira et al., 2024). These modifications may prolong peptide half-life and enhance stability in biological environments.

In some cases, incorporating D-amino acids can also reduce peptide immunogenicity and improve structural stability (Qureshi, 2025).

3.2.4 PEGylation

PEGylation means adding polyethylene glycol (PEG) chains to a peptide. This increases the peptide's hydrodynamic size and reduces its renal clearance (Pereira et al., 2024).

This modification improves peptide solubility, stability, and pharmacokinetic properties. However, a balance must be maintained between improved stability and preserved biological activity, since excessive PEGylation may reduce interactions with the target protein (Pereira et al., 2024).

3.2.5 Lipopeptides and Enhanced Membrane Affinity

Conjugation of peptides to lipid moieties leads to the formation of lipopeptides with enhanced ability to interact with cellular and viral membranes (Ghassabi et al., 2024).

Studies on HIV fusion inhibitors indicate that lipopeptides commonly exhibit greater antiviral potency and longer duration of action compared with conventional peptide analogues (Geng et al., 2024). Increased lipophilicity also promotes localization of the molecule inside cellular membranes, which may enhance antiviral activity (Geng et al., 2024; Ghassabi et al., 2024).

3.2.6 Computer-Assisted Peptide Design

Modern approaches to AVP development include molecular modeling, structure–activity relationship (SAR) analysis, and bioinformatics-based methods (Rossino et al., 2023).

These computational tools enable the prediction of peptide–target interactions, the optimization of peptide sequences, and the identification of promising therapeutic candidates before synthesis. Integration of computational methods with experimental validation significantly accelerates the discovery and development of new antiviral peptides (Wang et al., 2022).

3.2.7 Drug Delivery Systems and Protection from Proteolysis

In addition to chemical modification strategies, researchers have developed drug delivery systems, including liposomes, polymeric nanoparticles, and mucosal delivery platforms (Sonvico et al., 2023; Makadia et al., 2011; Saraiva et al., 2016; Sercombe et al., 2015). These approaches protect peptides from enzymatic degradation and enhance their bioavailability.

Nanocarrier systems can also deliver drugs directly to specific tissues. This targeted delivery has the potential to reduce adverse effects and improve therapeutic efficacy (Sonvico et al., 2023; Sercombe et al., 2015).

Table 2. Strategies for the Optimization of Antiviral Peptides (AVPs).

Strategy	Main effect	Notes/examples
Cyclization	Improves structural stability and resistance to proteolysis	Cyclotides with cystine-knot motif
Stapled peptides	Stabilizes α-helical structure and enhances target binding	Used in viral fusion inhibitors
D-amino acid incorporation	Increases resistance to enzymatic degradation	May prolong peptide half-life
PEGylation	Improves solubility and pharmacokinetics	Reduces renal clearance
Lipid conjugation (lipopeptides)	Enhances membrane interaction and antiviral potency	Studied in HIV fusion inhibitors
Computer-assisted design	Optimizes peptide sequences and target interactions	Includes SAR analysis and AI methods
Drug delivery systems	Protects peptides from degradation and improves bioavailability	Liposomes, polymeric nanoparticles

3.3 Delivery Systems for Antiviral Peptides

One major challenge in using antiviral peptides (AVPs) in clinical settings is their poor pharmacokinetic profile. They have low bioavailability, clear quickly through the kidneys, break down easily by enzymes, and struggle to cross biological membranes (Rossino et al., 2023; Pereira et al., 2024). Creating effective drug delivery systems is key to improving their therapeutic effectiveness.

3.3.1 Liposomes as Carriers for Antiviral Peptides

Liposomes are one of the most commonly studied delivery systems for peptide-based drugs. They have a phospholipid bilayer that holds both water- and fat-soluble compounds. In AVPs, liposomal formulations protect peptides from enzymatic degradation and prolong their presence in the body (Sercombe et al., 2015).

Research on antiviral peptides shows that liposomal formulations make peptides more stable and help deliver them more efficiently to target tissues. Liposome surfaces can also be modified with ligands that attach to certain cell receptors, allowing for targeted delivery (Sercombe et al., 2015).

3.3.2 Polymeric Nanoparticles and Hybrid Systems

Polymeric nanoparticles composed of materials like PLGA (poly(lactic-co-glycolic acid)) and chitosan effectively deliver AVPs (Makadia et al., 2011; Saraiva et al., 2016). Encapsulating peptides in these nanoparticles controls their release and improves their stability in the body.

In antiviral therapy, nanocarriers can enhance penetration across biological barriers, including the respiratory epithelium and the blood–brain barrier (Saraiva et al., 2016). This capability is especially important for treating neurotropic viral infections and respiratory tract infections.

Hybrid systems that integrate the properties of liposomes and polymeric nanoparticles are also being developed. These systems may offer both improved stability and more precise control over drug release (Sercombe et al., 2015).

3.3.3 Intranasal and Mucosal Delivery

An alternative to parenteral administration is intranasal or other mucosal routes of delivery. Since many viral infections begin at mucosal surfaces, local delivery of AVPs may provide an effective prophylactic and therapeutic strategy (Sonvico et al., 2023; Illum, 2003).

Giving drugs through the nose avoids first-pass metabolism and can quickly create high drug levels where the infection is (Illum, 2003). Lab studies show that using nanocarriers in nasal formulations helps peptides stay longer on the mucosal surface and improve antiviral effects (Sonvico et al., 2023).

Mucosal delivery systems are also being investigated in the context of prevention, including as part of pre-exposure prophylaxis (PrEP) strategies against infections such as HIV and influenza (Raj et al., 2025).

3.3.4 Targeted Delivery

Targeted delivery systems use ligands that bind to cellular receptors to deliver peptides directly to certain cell types or tissues (Sercombe et al., 2015). This method can help lower overall body exposure and reduce unwanted side effects.

Building on this concept, research on peptide-based HIV fusion inhibitors shows that attaching them to lipid carriers or nanoparticles can help these molecules reach target cells more effectively and boost their antiviral activity (Geng et al., 2024; Ghassabi et al., 2024).

3.3.5 Crossing the Blood–Brain Barrier

One of the greatest challenges in the treatment of certain viral infections is the difficulty of crossing the blood–brain barrier (BBB). Experimental studies suggest that nanoparticles functionalized with transport ligands can improve peptide delivery to the central nervous system (Saraiva et al., 2016).

These methods use ligands that target transferrin receptors or nanoparticles made to cross the blood-brain barrier (Pardridge, 2012). They play a key role in treating viral infections in the nervous system.

3.3.6 Integrating Chemical Modification with Delivery Systems

Adding structural changes to peptides, such as cyclization or lipid attachment, along with advanced delivery methods, greatly improves the stability, availability, and effectiveness of antiviral peptides (AVPs) (Rossino et al., 2023; Sonvico et al., 2023). Creating good delivery systems is key to advancing AVPs from early research to clinical use.

Table 3. Delivery Strategies for Antiviral Peptides (AVPs).

Delivery system	Key advantage	Application
Liposomes	Protect peptides from enzymatic degradation;	Can be surface-modified for targeted delivery

	prolong circulation time	
Polymeric nanoparticles (e.g., PLGA, chitosan)	Controlled drug release; improved stability	May enhance penetration across biological barriers
Hybrid nanocarriers	Combine stability and controlled release	Integrate features of liposomes and polymeric systems
Intranasal and mucosal delivery	High local concentration at infection sites	Investigated for respiratory viruses and HIV prevention
Targeted delivery systems	Direct peptides to specific cells or tissues	Use receptor-binding ligands
BBB-penetrating nanocarriers	Enable delivery to the central nervous system	Important for neurotropic viral infections

3.4 Clinical and Translational Landscape of Antiviral Peptides

Even though there has been a lot of preclinical research, only a few antiviral peptides (AVPs) have reached clinical use. Most candidates remain experimental due to ongoing issues with stability, bioavailability, and production costs. Still, progress is being made, and lessons from HIV therapy are helping guide the development of new peptide-based antivirals.

3.4.1 Enfuvirtide – the First Approved Peptide Fusion Inhibitor

Enfuvirtide (T-20) was the first and remains the best-known peptide-based antiviral drug for treating HIV-1 infection (Lalezari et al., 2003). It works by attaching to the HR1 region of the viral glycoprotein gp41, preventing the six-helix bundle from forming and blocking the fusion of the virus with the host cell.

Clinical studies show that when enfuvirtide is used with other drugs, it greatly improves treatment for patients who are resistant to other types of antiretroviral drugs (Lalezari et al., 2003). However, its use is limited because it must be given by injection under the skin, and many patients experience local reactions at the injection site. These issues can make it harder for patients to stick to their treatment.

As HIV has developed resistance to enfuvirtide, new generations of fusion inhibitors have been created, such as lipopeptides that are more stable and bind more strongly (Geng et al., 2024; Ghassabi et al., 2024; Huang et al., 2025). Experience with enfuvirtide shows that peptides can be effective antiviral drugs if their structure and pharmacokinetics are carefully improved.

3.4.2 Retrocyclins and θ-Defensins – Candidates with Translational Potential

Retrocyclins are synthetic versions of human θ-defensins and are a promising group of cyclic peptides with broad antiviral effects (Solanki et al., 2021; Yasin et al., 2004). Lab studies have shown that they work against several enveloped viruses, including HIV-1 and herpes simplex viruses (HSV-1 and HSV-2).

Their mechanism of action involves destabilization of the viral envelope and inhibition of interactions between viral particles and host cell receptors (Yasin et al., 2004). An important advantage of retrocyclins is their relatively low cytotoxicity and high structural stability, which result from their cyclic peptide structure.

Although retrocyclins have not yet progressed to advanced clinical trials, they are being actively investigated as potential topical microbicides for the prevention of viral infections, including HIV (Raj et al., 2025; Yasin et al., 2004). Further translational development will depend largely on the creation of effective local formulations and confirmation of long-term safety. Continued research and development may ultimately enable retrocyclins to help address significant unmet needs in antiviral therapy.

3.4.3 Next-Generation Peptide Inhibitors

Recent advances in peptide engineering have led to the development of novel fusion inhibitors and lipopeptides that last longer in the body (Geng et al., 2024; Huang et al., 2025). Several of these compounds are currently undergoing evaluation in preclinical or early clinical studies.

Contemporary fusion inhibitors are engineered to target HIV strains harboring resistance mutations. These inhibitors frequently incorporate modifications that enhance molecular stability and improve binding affinity to viral proteins (Ghassabi et al., 2024; Huang et al., 2025). Evidence indicates that lipopeptides exhibit prolonged activity and superior efficacy compared to earlier peptide inhibitors.

Researchers are also studying peptide-based inhibitors for other viruses, like influenza, RSV, and coronaviruses such as SARS-CoV-2. Experiments show that carefully designed peptides can block viral proteins from attaching to host cell receptors (Wang et al., 2022).

3.4.4 AVPs in Combination Therapy and as Adjuvants

Another important direction is using antiviral peptides as part of combination therapy. Because AVPs work in several ways, they may boost the effectiveness of standard antiviral drugs and lower the risk of resistance (Wang et al., 2022; Raj et al., 2025).

Building on their role in combination therapy, some peptides—particularly defensins—exhibit immunomodulatory properties, which makes them potential candidates for use as vaccine adjuvants (Qureshi, 2025). Integrating direct antiviral activity with immune modulation may improve both therapeutic and preventive strategies against viral infections.

3.4.5 Translational Barriers

Preclinical studies look promising, but moving AVPs into clinical use faces several challenges. The main obstacles are:

1. high costs of peptide synthesis,
2. limited stability of peptides,
3. the need for effective drug delivery systems,
4. an absence of large-scale clinical trials that definitively establish the treatment's effectiveness and safety.

Newer methods that use peptide modifications, advanced delivery technologies, and molecular modeling may gradually help overcome these challenges (Pereira et al., 2024; Sonvico et al., 2023).

Table 4. Representative Antiviral Peptides and Their Clinical Development Status.

Peptide	Target virus	Mechanism of action	Development status
Enfuvirtide (T-20)	HIV-1	Fusion inhibitor; binds gp41 and	Approved drug

		prevents membrane fusion	
Retrocyclins	HIV-1, HSV	Destabilization of viral envelope; inhibition of virus–cell interactions	Preclinical research
θ-Defensins	HIV, HSV, other enveloped viruses	Disruption of viral membranes; immunomodulatory effects	Experimental
Lipopeptide fusion inhibitors	HIV-1	Inhibition of viral membrane fusion with enhanced membrane affinity	Preclinical / early clinical studies
Engineered antiviral peptides	Influenza, RSV, SARS-CoV-2	Blocking viral protein-receptor interactions	Preclinical research

3.5 Limitations and Clinical Challenges of Antiviral Peptides

Although preclinical studies have yielded promising results and interest in antiviral peptides (AVPs) is increasing, their clinical application still faces significant biological, technological, and regulatory obstacles. Understanding these challenges is crucial for advancing AVP development and translating experimental research into clinical practice.

3.5.1 Toxicity and Selectivity

A significant concern associated with antiviral peptides, especially those that are cationic and membranolytic, is their potential to harm host cells (Raj et al., 2025; Solanki et al., 2021). The same mechanisms that allow these peptides to destabilize viral membranes can also result in nonspecific interactions with cell membranes.

Many studies show that some antiviral peptides (AVPs) have a high therapeutic index, but improving their selectivity is still a major challenge, especially for use throughout the body (Pereira et al., 2024). To solve this, researchers need to carefully design peptide sequences and make structural changes to target viruses more specifically.

3.5.2 Immunogenicity

Peptides, as biologically active molecules, can trigger immune responses that might limit their use in long-term treatments (Qureshi, 2025; Pereira et al., 2024). Giving them repeatedly may cause neutralizing antibodies to form, which lowers their effectiveness.

On the other hand, some peptides can adjust how the immune system works, offering therapeutic benefits but also possibly raising the risk of too much inflammation. That's why it's important to evaluate the immune effects of new peptides early in preclinical studies.

3.5.3 Short Half-Life and Rapid Clearance

Natural peptides have a short plasma half-life because they are rapidly cleared by the kidneys and degraded by enzymes (Sonvico et al., 2023). Their small size helps the kidneys remove them fast, which shortens how long they stay active in the body.

Changing peptide structures by methods like PEGylation, cyclization, or lipidation can make them more stable and help them stay longer in the bloodstream (Sonvico et al., 2023). But these methods need to be carefully adjusted to keep the peptides working well.

3.5.4 Proteolytic Degradation

Peptides break down quickly because of proteolytic enzymes found in serum, the digestive system, and different tissues (Rossino et al., 2023; Pereira et al., 2024). This fast breakdown causes them to lose their biological activity, which limits how natural peptides can be used as treatments.

To tackle this, scientists have created peptide engineering methods like adding D-amino acids, strengthening peptide structures, and using protective delivery systems to stop enzyme degradation (Pereira et al., 2024; Sonvico et al., 2023). Still, fully stopping proteolysis is difficult.

3.5.5 High Production Costs and Manufacturing Challenges

Making peptides, especially longer or chemically changed ones, usually costs more than making standard small-molecule drugs (Rossino et al., 2023). Extra steps such as peptide stapling and adding lipids add to the manufacturing expenses.

Producing peptides on a large scale needs strict quality control and consistent outcomes. These challenges restrict the clinical use of antiviral peptides (AVPs), especially in places with limited resources.

3.5.6 Regulatory Challenges and Clinical Requirements

Creating and getting regulatory approval for peptide treatments needs careful checks of safety, stability, and immune response (Qureshi, 2025). There is limited regulatory experience because few antiviral peptides have been approved compared to traditional therapies.

In addition, large clinical trials are needed to demonstrate the safety and effectiveness of new peptide-based antivirals. This makes development more expensive and lengthens the time before these drugs can reach the market.

3.5.7 Risk of Resistance Development

Although the multimodal mechanisms of AVPs may reduce the likelihood of resistance development, this risk cannot be completely excluded. In the case of HIV fusion inhibitors, mutations in viral target regions have been observed, potentially reducing therapeutic efficacy (Ghassabi et al., 2024).

Therefore, these findings show that it is important to keep monitoring how viruses adapt. Developing new peptide inhibitors will probably be needed to keep antiviral treatments effective over time.

Table 5. Major Limitations of Antiviral Peptides and Strategies to Overcome Them.

Limitation	Description	Potential strategies
Cytotoxicity and limited selectivity	Membranolytic peptides may also interact with host cell membranes	Sequence optimization, targeted delivery systems

Immunogenicity	Repeated administration may induce neutralizing antibodies	Structural modification, careful immunological profiling
Short half-life	Rapid renal clearance and enzymatic degradation	PEGylation, cyclization, lipid conjugation
Proteolytic degradation	Susceptibility to proteases in biological environments	D-amino acid incorporation, conformational stabilization, nanocarriers
High production cost	Complex synthesis of long or modified peptides	Optimization of synthetic methods, scalable manufacturing
Regulatory challenges	Limited clinical experience with peptide antivirals	Well-designed preclinical studies and clinical trials
Potential viral resistance	Mutations in viral target proteins may reduce efficacy	Development of next-generation peptides and combination therapy

3.6 Future Directions and Perspectives

Research on antiviral peptides (AVPs) is growing quickly, and their possible uses now go beyond just experimental studies. New developments in molecular biology, chemical engineering, nanotechnology, and bioinformatics are helping scientists find new ways to design and develop peptide-based antiviral treatments.

3.6.1 Artificial Intelligence-Assisted Peptide Design

A promising approach involves the application of artificial intelligence (AI) and machine learning tools to design new peptide sequences (Rossino et al., 2023; Pereira et al., 2024). Predictive algorithms analyze structure-activity relationships (SAR) and estimate peptide stability, toxicity, and how well they bind to specific molecular targets before any lab work begins.

The development of specialized databases, such as AVPdb and DRAVP, enables the training of predictive models based on experimentally validated biological data (Liu et al., 2023). Such approaches can significantly accelerate the identification of new therapeutic candidates and reduce the cost of preclinical research.

3.6.2 Personalized Antiviral Therapy

Recent progress in viral genomics and sequencing makes it possible to identify mutations that cause resistance to antiviral treatments. In the future, this could lead to peptide-based therapies tailored to each patient's specific viral variant.

Personalized treatments could improve how well therapies work and help prevent resistance, especially in long-term infections like HIV or hepatitis C virus (HCV) infection (Ghassabi et al., 2024).

3.6.3 Combination Therapies and Synergistic Strategies

AVPs work in several ways, which makes them good candidates for use in combination with antiviral therapies. When peptides are used with standard small-molecule antivirals, they may work better together and reduce the risk of resistant viral strains developing (Wang et al., 2022; Raj et al., 2025).

Future treatments may combine AVPs with advanced options like monoclonal antibodies, RNA-based therapies, and genome-editing tools such as CRISPR. Using these together could make antiviral treatments much more effective.

3.6.4 Applications in Prevention and Vaccine Adjuvants

Some antiviral peptides possess immunomodulatory properties, which opens the possibility of using them as vaccine adjuvants (Raj et al., 2025; Diamond et al., 2009). By stimulating innate immune responses, these peptides may enhance the effectiveness of vaccines against viruses with high genetic variability.

In addition, local preventive strategies such as mucosal microbicides are being investigated, where AVPs could act as a protective antiviral barrier at the early stage of pathogen entry into the body (Raj et al., 2025; Yasin et al., 2004).

3.6.5 Development of Long-Acting Formulations

Modern drug delivery technologies make it possible to design formulations with controlled and prolonged release of active compounds (Sonvico et al., 2023; Makadia et al., 2011; Saraiva et al., 2016; Sercombe et al., 2015). Such approaches may significantly improve patient adherence to therapy, particularly in the treatment of chronic viral infections.

By combining chemical changes to peptides with advanced carriers like liposomes or polymeric nanoparticles, it is possible to develop long-acting formulations that need to be given less often.

3.6.6 Rapid Response to Emerging Viral Threats

The COVID-19 pandemic highlighted the need to rapidly develop new treatments for emerging pathogens. Since peptides can be easily designed to target specific viral proteins, AVPs are a promising option for addressing new viral threats.

4. Discussion

Antiviral peptides (AVPs) are a promising class of therapeutics because they act in multiple ways and target various stages of the viral life cycle. Unlike traditional small-molecule antivirals, AVPs can block viral entry, disrupt the viral envelope, interfere with replication, and modulate the immune response. This broad activity may make them more effective and help reduce antiviral resistance, a major challenge in treating viral infections.

Studies show that peptide fusion inhibitors are among the most well-understood groups of AVPs. For example, enfuvirtide proves that carefully designed peptides can be used in clinical settings and work well with other antiviral agents. However, using this drug has also revealed challenges, such as needing injection, side effects, and the risk of resistance from viral mutations. These points suggest that developing new antiviral peptides should focus not just on how they work, but also on how they are absorbed and delivered in the body.

Many AVPs can influence the immune system in impressive ways. For example, defensins are peptides that help the body fight off threats by triggering interferon production and activating immune cells. Because of this, AVPs act as both antiviral agents and immune health supporters. Their special abilities could lead to new ways to improve vaccines or strengthen the body’s defenses against disease.

Although AVPs have promising features, developing them for clinical use is still difficult. Many peptides do not last long in the bloodstream, are broken down quickly by enzymes, and are poorly absorbed, which reduces their effectiveness. To overcome these problems, researchers use methods like cyclization, PEGylation, and adding D-amino acids to make peptides more stable and effective in the body. At the same time, new drug delivery systems, such as liposomes and polymer nanoparticles, are being studied to protect peptides from degradation and to improve their distribution in the body.

In practice, this means that future work on antiviral peptides should aim to make them not only more effective against viruses but also more stable and easier to deliver. Combining peptide engineering with advanced delivery methods could greatly improve the chances of AVPs being used successfully in clinics.

Another reason for progress in this field is the fast growth of bioinformatics and computer-based peptide design. Tools such as molecular modeling, structure-activity analysis, and artificial intelligence help researchers identify and optimize new peptide sequences with the desired properties more quickly. Using these computer methods, along with lab experiments, can speed up the discovery of new antiviral peptides and increase the likelihood that they will become effective treatments.

5. Conclusions

Antiviral peptides act as a prospective group of molecules being studied for treating viral infections. These peptides can target multiple stages of infection and can be easily modified, which makes them a strong option for developing new antiviral agents.

Although antiviral peptides face challenges such as enzymatic degradation, a short half-life, and difficulty delivering them to target tissues, new research in peptide engineering and drug delivery is helping solve these problems. Recent advances in optimizing peptide structures and using nanocarriers have greatly improved their stability and effectiveness in the body.

At the same time, fast progress in bioinformatics, molecular modeling, and artificial intelligence is helping us design peptides with specific biological effects more easily. Combining these computer-based methods with lab research is speeding up the discovery and improvement of new treatments.

Current evidence shows that antiviral peptides are still a very promising area of research with strong potential for real-world use. Ongoing work to make them more stable, easier to absorb, and better delivered could lead to new and effective antiviral treatments. Moving forward, progress will depend on teamwork across diverse scientific fields and on creative solutions that integrate advances in biology, chemistry, and nanotechnology.

Disclosure

Author's contribution

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive special funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflicts of interest.

Acknowledgements: Not applicable.

Declaration of the use of generative AI and AI-assisted technologies in the writing process. In preparing this work, the authors used ChatGPT for the purpose of assisting with grammar and readability. After using this tool the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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