INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Recent Advances in Antiviral Drug Discovery

Sakshi Jadhav*, Sameer Pawar, Amol Shirode, Vinod Bairagi

Department of Pharmacy, KBHSS trust's Institute of Pharmacy, Malegaon -423105, Dist Nashik, Maharashtra, India

ARTICLE INFO

Published: 16 Apr. 2025
Keywords:
Antiviral, Viral threats, Biologics, Cancer therapies, HIV protease inhibitor.
DOI:
10.5281/zenodo.15226068

ABSTRACT

The early development of antiviral drugs is emerging very strongly due to rapid viral emergence and limited therapeutic choices. This review summarizes recent progress in antiviral therapies, including new antiviral targets to optimize drug therapy, new compounds, and new drug delivery systems. Viral enzymes, entry and fusion proteins, host-virus interactions are discussed in terms of their potential as targets for drug discovery campaigns. We further explore new antiviral candidates, including small molecule and biologics such as monoclonal antibodies and RNA-based therapies, as well as natural products with anti-influenza activity. Plenty of attention is also paid to repurposing existing drugs (for example, cancer therapies or HIV protease inhibitors) for new viral infections—a promising route for fast-tracking development of treatments. Innovations in drug delivery systems, such as nanoparticles, liposomes, viral vectors, and topical formulations, hold the potential to improve the efficiency and accessibility of antiviral therapies. Finally, the review discusses the persistent problems of antiviral resistance and toxicity and the critical need for accessible antiviral therapies as new pandemics, like COVID-19, emerge. The paper discusses the future of antiviral drug discovery, emphasizing a focus on broad-spectrum antiviral drugs and the need for global collaboration and innovative technology to address viral threats.

INTRODUCTION

Global health and economics have been seriously threatened by the development and reemergence of viral infections. The need for efficient antiviral treatments has been highlighted by the quick spread of viral illnesses such COVID-19, influenza, HIV, and hepatitis. The creation of safe and efficient antiviral medications is still a difficult undertaking, even with notable advancements in antiviral drug discovery.

Targeting viral proteins, enzymes, and genetic material has been the main focus of conventional antiviral drug development techniques. However, many of the antiviral medications now on the market are no longer effective due to the high rate of virus mutation and the introduction of drug-resistant strains. Moreover, the discovery of

***Corresponding Author:** Sakshi Jadhav
Address: *Department of Pharmacy, KBHSS trust's Institute of Pharmacy, Malegaon -423105, Dist Nashik, Maharashtra, India.*
Email ✉: sakshijadhav65172@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

efficient antiviral treatments has been hampered by the intricacy of viral replication cycles and the incomplete knowledge of viral-host interactions.
There is now more optimism in the fight against viral infections thanks to recent developments in antiviral drug discovery, which have produced a large number of new compounds and repurposed old ones. Novel antiviral drugs have been discovered more quickly thanks to the integration of cutting-edge technology including computational biology, machine learning, and structure-based virtual screening. Additionally, repurposing already-approved medications has made it possible to find new antiviral medicines quickly and affordably. The field of antiviral drug discovery has also been broadened by the identification of new antiviral targets, such as viral entry and fusion proteins. Preclinical and clinical research on the creation of antiviral drugs that target these new targets has produced encouraging findings. Additionally, research into natural products and phytochemicals has produced a wealth of antiviral substances with distinct mechanism of action. This review explores recent progress in the discovery of antiviral drugs, focusing on promising new compounds, repurposed medications, and emerging targets that offer hope in the fight against viral infections. We'll also delve into the challenges and opportunities facing antiviral drug development, such as the need for safer and more effective treatments, the rise of drug-resistant strains, and the potential of innovative technologies to speed up the process of discovering new antiviral therapies.

Recent Advances In Antiviral Target

Viral Entry and Fusion Targets

- Viral envelope proteins: Targeting viral envelope proteins, such as HIV-1 gp120, has shown promise in preventing viral entry.
- Host-virus interaction targets: Identifying host-virus interaction targets, such as DC-SIGN, has provided new opportunities for antiviral therapy.

Viral Replication and Transcription Targets

- Viral polymerases: Targeting viral polymerases, such as HIV-1 reverse transcriptase, has been a successful strategy for antiviral therapy.
- Viral helicases: Inhibiting viral helicases, such as HCV NS3 helicase, has shown promise in preventing viral replication.

Viral Assembly and Release Targets

- Viral capsid proteins: Targeting viral capsid proteins, such as HIV-1 capsid, has shown promise in preventing viral assembly and release.
- Viral budding and release targets: Identifying viral budding and release targets, such as VPS4, has provided new opportunities for antiviral therapy.

Host Targets for Antiviral Therapy

- Host kinases: Targeting host kinases, such as PI3K/AKT, has shown promise in preventing viral replication and transcription.
- Host transcription factors: Inhibiting host transcription factors, such as NF-κB, has shown promise in preventing viral replication and transcription.

Emerging Targets for Antiviral Therapy

- Viral non-coding RNAs: Targeting viral non-coding RNAs, such as HIV-1 TAR, has shown promise in preventing viral replication and transcription.
- Host-virus interaction networks: Identifying host-virus interaction networks has provided new opportunities for antiviral therapy.

New Antiviral Compounds and Therapies:

The continuous emergence of new viral infections and growing concerns about antiviral resistance

have driven the search for innovative antiviral therapies. Recently, small molecules, biologics, and natural products have attracted significant attention for their potential to target critical stages of the viral life cycle. This review examines the mechanisms of action, effectiveness, and safety of recently discovered antiviral compounds, with a focus on small molecules (such as nucleoside analogs and protease inhibitors), biologics (including monoclonal antibodies and RNA-based therapies), and natural products (like phytochemicals). As antiviral drug development progresses, it is essential to understand the strengths and limitations of these therapies to shape the future of antiviral treatments.

Small Molecules:

Small molecules, often synthetic or semi-synthetic, are designed to disrupt the viral replication process. These compounds are favored for their ability to be taken orally, their stability, and their capacity to target essential viral enzymes or structural components.

Nucleoside Analogs:

Nucleoside analogs are compounds that mimic natural nucleotides and interfere with viral RNA or DNA replication. By incorporating into the viral genome, they cause replication errors or premature termination, ultimately halting viral replication.

1. Remdesivir

Mechanism of Action: Remdesivir is a nucleotide analog that targets the RNA-dependent RNA polymerase (RdRp) of RNA viruses. By incorporating itself into the viral genome during replication, it causes premature termination of RNA synthesis, effectively halting further viral replication . Efficacy: Remdesivir has demonstrated effectiveness in reducing recovery times for patients with COVID-19, particularly when administered early in the disease. However, its impact on mortality remains debated, with mixed results across various studies.

Safety: Generally well-tolerated, remdesivir can cause side effects such as elevated liver enzymes and renal toxicity, especially in patients with pre-existing kidney conditions .

2. Molnupiravir

Mechanism of Action: Molnupiravir is a nucleoside analog that promotes viral mutagenesis, leading to viral error catastrophe. It is incorporated into the viral RNA, causing an increase in mutations that are lethal to the virus.

Efficacy: Clinical trials have shown that molnupiravir reduces the risk of hospitalization and death in patients with mild to moderate COVID-19. However, there are concerns about its long-term effectiveness and its ability to combat emerging viral variants.

Safety: Molnupiravir is generally well-tolerated, with mild to moderate side effects like gastrointestinal discomfort. However, its use is restricted during pregnancy and in women of childbearing potential due to potential teratogenic effects.

3. Favipiravir

Mechanism of Action: Favipiravir is a purine nucleoside analog that inhibits viral RNA polymerase, preventing the replication of viral RNA.

Efficacy: Favipiravir has been shown to reduce viral load and alleviate symptoms in patients with influenza and other RNA viruses, including COVID-19, where it may help shorten the duration of symptoms.

Safety: Favipiravir is generally well-tolerated, though it can lead to reversible liver enzyme elevations and has teratogenic effects, which limits its use during pregnancy.

Protease Inhibitors

Protease inhibitors work by blocking viral proteases, enzymes that are essential for cleaving viral polyproteins into functional proteins required for viral replication.

1. Lopinavir/Ritonavir

Mechanism of Action: Lopinavir and ritonavir are HIV protease inhibitors. Ritonavir boosts lopinavir's plasma concentration by inhibiting the cytochrome P450 enzyme, CYP3A4. Together, they prevent the cleavage of viral proteins, blocking HIV maturation.

Efficacy: While lopinavir/ritonavir is effective in managing HIV infections, it showed limited benefit in treating COVID-19. Trials found that it did not significantly reduce mortality or slow disease progression in COVID-19 patients.

Safety: The combination therapy can cause gastrointestinal issues like nausea, vomiting, and diarrhea. Long-term use is also linked to metabolic problems such as hyperlipidemia and insulin resistance.

2. Sofosbuvir

Mechanism of Action: Sofosbuvir is a nucleotide analog that inhibits the NS5B RNA-dependent RNA polymerase of the hepatitis C virus (HCV), thereby preventing viral replication.

Efficacy: Sofosbuvir, especially when combined with other antiviral drugs like ledipasvir, has proven highly effective in curing chronic HCV infections, with sustained virologic response rates above 95% .

Safety: Sofosbuvir is generally well-tolerated, though it can cause side effects like headache, fatigue, and nausea. It is contraindicated in patients with severe renal impairment or those taking certain medications, particularly those that affect CYP3A4 enzyme activity .

Biologics

Biologics, including monoclonal antibodies and RNA-based therapies, provide highly targeted interventions by directly interacting with viral antigens or RNA. These therapies can either enhance the immune response or directly prevent viral replication.

Monoclonal Antibodies

Monoclonal antibodies are engineered to bind to specific viral proteins, neutralizing the virus and preventing infection or further viral replication.

1. Casirivimab and Imdevimab

Mechanism of Action: Casirivimab and imdevimab are monoclonal antibodies designed to target the spike protein of SARS-CoV-2. By binding to this spike protein, these antibodies block the virus from entering human cells, effectively preventing infection .

Efficacy: In clinical trials, casirivimab and imdevimab have been shown to reduce the risk of hospitalization and death in high-risk COVID-19 patients, especially when administered early in the course of infection.

Safety: These antibodies have a generally favorable safety profile, with mild side effects such as fever, chills, and infusion-related reactions. However, concerns have been raised about their effectiveness against certain emerging variants of SARS-CoV-2 .

2. Bamlanivimab

Mechanism of Action: Bamlanivimab is a monoclonal antibody that targets the spike protein of SARS-CoV-2, preventing the virus from binding to the ACE2 receptor on human cells .

Efficacy: Initially approved for treating COVID-19, bamlanivimab was later withdrawn for use against certain variants due to reduced efficacy. It remains effective for early-stage infections caused by susceptible viral strains .

Safety: Common side effects include allergic reactions, fever, and chills. The use of bamlanivimab has been restricted due to concerns about its reduced efficacy against certain variants of concern.

RNA-Based Therapies

RNA-based therapies, such as RNA interference (RNAi) and antisense oligonucleotides (ASOs), can specifically target viral RNA and degrade it, effectively halting viral replication.

1. Siralimus (siRNA)

Mechanism of Action: Small interfering RNA (siRNA) molecules are designed to bind to viral RNA, leading to its degradation through the RNA-induced silencing complex (RISC). This prevents viral replication by inhibiting the translation and processing of viral proteins.
Efficacy: siRNA therapies have shown promise in treating chronic hepatitis B and HIV by silencing essential viral genes and reducing viral load.
Safety: While siRNA therapies are generally considered safe, there are concerns about potential off-target effects and immune responses to the siRNA molecules themselves.

2. Antisense Oligonucleotides (ASOs)

Mechanism of Action: ASOs are short, synthetic nucleic acid strands that bind to viral RNA, preventing it from being translated into viral proteins and thereby halting viral replication .
Efficacy: ASOs targeting the hepatitis B virus (HBV) have demonstrated promising results, significantly reducing viral load and liver inflammation in patients with chronic HBV infection .
Safety: ASOs are generally safe but may cause mild injection site reactions, and in rare cases, renal toxicity .

Natural Products and Photochemical:

Natural products, derived from plants, fungi, and other organisms, have long been recognized for their antiviral properties. These compounds often work by modulating host immune responses or directly interfering with viral replication.

Alkaloids

Alkaloids, naturally occurring compounds found in plants, have demonstrated the ability to inhibit viral entry and replication, making them valuable candidates for antiviral therapies.

1. Berberine

Mechanism of Action: Berberine has shown the ability to inhibit viral replication and entry by modulating key host cell signaling pathways. Additionally, it interferes with viral enzymes such as reverse transcriptase, which is crucial for HIV replication.
Efficacy: Berberine has demonstrated promising antiviral effects against a variety of viruses, including hepatitis B, hepatitis C, and HIV. Clinical studies have suggested that it can help reduce viral load and improve outcomes in patients with these viral infections.
Safety: Overall, berberine is considered safe for most individuals. However, it may cause gastrointestinal issues, and there is a potential for interactions with medications that are metabolized by the liver .

Polyphenols

Polyphenols, such as resveratrol and epigallocatechin gallate (EGCG), have also been extensively studied for their broad-spectrum antiviral properties.

1. Resveratrol

Mechanism of Action: Resveratrol exerts its antiviral effects by modulating immune responses and acting as an antioxidant. It has been shown to interfere with the replication of several viruses, including HIV and influenza .
Efficacy: Research indicates that resveratrol can reduce viral replication and enhance immune responses, particularly in the context of HIV and influenza infections. These effects may improve patient outcomes .
Safety: Resveratrol is generally well-tolerated, but high doses may cause gastrointestinal discomfort in some individuals .

Repurposing of Existing Drugs for Antiviral Therapy:

The global urgency to address viral outbreaks, such as the COVID-19 pandemic, has underscored the need for quick therapeutic solutions. One approach that has gained significant attention is the repurposing of existing drugs those already approved for other medical conditions for antiviral treatment. This strategy offers numerous advantages, including shorter development

timelines, established safety profiles, and the ability to quickly respond to emerging viral threats. Below, we summarize recent insights from various reviews on the repurposing of existing drugs for antiviral therapy, focusing on their mechanisms, efficacy, and safety.

1. Antimalarial Drugs

Antimalarial drugs, initially developed to treat malaria, have been explored for their potential antiviral effects due to their ability to inhibit viral replication through several mechanisms.

Hydroxychloroquine: Hydroxychloroquine, a drug commonly used for malaria and autoimmune diseases, was one of the first to be investigated as a potential treatment for COVID-19. Its antiviral effect is believed to stem from its ability to raise the pH within endosomes, which inhibits viral fusion with host cell membranes. However, clinical trials for COVID-19 have shown mixed results, with some studies reporting no significant benefit in reducing mortality or hospitalization. Additionally, safety concerns, particularly regarding cardiovascular toxicity and arrhythmias, have limited its use in COVID-19 patients .

Chloroquine: Similar to hydroxychloroquine, chloroquine has also been tested for its antiviral activity, particularly against SARS-CoV-2, the virus responsible for COVID-19. In laboratory settings, chloroquine has been shown to inhibit viral entry and replication by interfering with the glycosylation of viral proteins. However, like hydroxychloroquine, clinical evidence supporting its effectiveness in treating COVID-19 remains inconclusive. Moreover, the safety profile of chloroquine, especially at higher doses, raises concerns about potential side effects such as retinopathy, liver damage, and cardiac arrhythmias.

2. Antiviral Drugs

Several antiviral drugs, initially approved for treating specific viral infections, have been repurposed to target other viruses. These drugs have shown varying levels of success in addressing common viral mechanisms.

Ribavirin: Ribavirin, originally developed to treat hepatitis C and respiratory syncytial virus (RSV), is a broad-spectrum antiviral agent. It works by inhibiting viral RNA-dependent RNA polymerase, which is essential for viral replication. In recent years, ribavirin has been repurposed for emerging viruses like SARS-CoV-2 and Ebola. However, its clinical effectiveness remains controversial, and it is often associated with side effects, such as hemolytic anemia, which can limit its use.

Remdesivir: Remdesivir, initially developed for the treatment of Ebola, has been repurposed to treat COVID-19. It inhibits RNA-dependent RNA polymerase, a crucial enzyme in the viral replication process. Early clinical trials showed that remdesivir could shorten recovery times in hospitalized COVID-19 patients, though its overall effect on mortality is still uncertain. Despite its promise, concerns have been raised about its potential for renal toxicity, particularly in patients with pre-existing kidney conditions.

3. Immunomodulatory Drugs

Drugs that modulate the immune system have also shown potential in the fight against viral infections. These medications can help the body better manage viral diseases, often by controlling excessive inflammatory responses.

Dexamethasone: Dexamethasone, a corticosteroid, is well-known for its anti-inflammatory and immunosuppressive properties. Initially used to treat autoimmune diseases, it has been repurposed to manage severe COVID-19, particularly in patients experiencing acute respiratory distress syndrome (ARDS). Research has shown that dexamethasone can reduce mortality in patients who require oxygen support or mechanical ventilation. This effect is likely due to its ability to temper the hyper inflammatory response that accompanies severe viral infections .

Tocilizumab: Tocilizumab, a monoclonal antibody that targets the interleukin-6 (IL-6) receptor, has been repurposed for use in severe COVID-19 cases, especially in patients with elevated IL-6 levels. Typically used for conditions like rheumatoid arthritis, tocilizumab works by

blocking IL-6, helping to reduce the cytokine storm that can occur in severe viral infections. Several studies have suggested that tocilizumab can reduce both mortality and the need for mechanical ventilation, though its effectiveness may depend on factors such as timing of administration and the presence of other health conditions.

4. Anticancer Drugs

Some anticancer medications have been found to possess antiviral properties. These drugs may inhibit key viral replication processes or enhance immune responses, making them promising candidates for repurposing in antiviral therapy.

Interferons: Interferons are cytokines that play a crucial role in the immune system's response to viral infections. Originally used to treat certain cancers and chronic viral infections like hepatitis B and C, interferons have shown promise as a potential treatment for COVID-19. They work by stimulating the immune system and inhibiting viral replication. However, the use of interferons in COVID-19 treatment has been limited due to significant side effects, such as flu-like symptoms, liver toxicity, and myelosuppression.

Capecitabine: Capecitabine, an oral chemotherapy drug primarily used in cancer treatment, has been investigated for its potential antiviral effects, particularly against RNA viruses like influenza and COVID-19. Its mechanism of action involves inhibiting viral RNA replication, but clinical studies assessing its effectiveness against viral infections are still limited. Additionally, safety concerns, including myelosuppression and gastrointestinal toxicity, have been raised with its use.

5. Antibacterial Drugs

Certain antibiotics and antibacterial agents have been explored for their potential antiviral effects, especially when considering bacterial co-infections alongside viral pathogens.

Azithromycin: Azithromycin, a macrolide antibiotic, has been studied as an adjunctive treatment for COVID-19 due to its immunomodulatory properties. Some believe it has antiviral activity by inhibiting viral protein synthesis. However, clinical studies have not shown significant benefits in improving outcomes for COVID-19 patients. Furthermore, its combination with hydroxychloroquine has raised safety concerns, including cardiovascular toxicity and the risk of bacterial resistance.

Ivermectin: Although primarily known as an antiparasitic drug, ivermectin has been investigated for its potential antiviral effects, particularly against SARS-CoV-2. In laboratory settings, ivermectin has demonstrated the ability to inhibit viral replication by binding to viral proteins. However, clinical trials have not consistently shown its effectiveness in treating COVID-19. There are also safety concerns related to long-term use, especially at high doses, with potential neurological and gastrointestinal side effects .

6. Antidepressants and Antipsychotics:

Some drugs originally developed for neurological and psychiatric conditions have been explored as potential antiviral therapies due to their effects on viral protein interactions or host cell processes.

Fluoxetine: Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) commonly used to treat depression, has been repurposed in some studies for its potential antiviral activity. It is believed to interfere with the replication of viruses like SARS-CoV-2 by modifying the host cell machinery. Early studies suggest that fluoxetine might reduce viral load and improve outcomes in COVID-19 patients, though more research is needed to confirm these findings and assess its safety .

Quetiapine: Quetiapine, an atypical antipsychotic, has been explored for its potential to inhibit viral entry into host cells and suppress viral replication. While some early in vitro studies showed activity against SARS-CoV-2, there is currently insufficient clinical evidence to recommend its use for viral infections. Concerns about side effects such as sedation and metabolic syndrome persist, limiting its broader application.

Advances in Antiviral Drug Delivery and Formulation:

Despite significant advances in antiviral drug development, delivering these treatments effectively remains a major challenge. The success of antiviral therapies is often limited by several factors, such as poor bioavailability, rapid metabolism, limited tissue penetration, and potential side effects. Moreover, some viral infections require targeted drug delivery to specific tissues or mucosal surfaces, which complicates the formulation strategies. The rise of drug-resistant viral strains and the need for tailored treatments across diverse patient groupssuch as immunocompromised individuals and childrenadd further complexity to antiviral drug delivery. To address these issues, innovative strategies that enhance drug stability, improve bioavailability, and ensure precise targeting are crucial for overcoming these hurdles.

This review focuses on recent advances in antiviral drug delivery systems, exploring the potential of Nanoparticle and liposome-based systems, viral vectors, gene therapies, and topical and mucosal delivery methods.

1. Nanoparticles and Liposomes

Nanoparticles and liposomes have emerged as promising solutions for improving antiviral drug delivery. These platforms offer the ability to enhance drug solubility, protect active ingredients from degradation, and enable controlled drug release.

Nanoparticles: Nanoparticles, including lipid-based nanoparticles (LNPs), polymeric nanoparticles, and metal nanoparticles, have been explored to deliver antiviral drugs more efficiently. These tiny particles can facilitate cellular uptake through endocytosis and can be designed to target specific tissues or cell types. For antiviral therapies, nanoparticles can encapsulate drugs such as nucleoside analogs, protease inhibitors, or RNA-based therapies, protecting them from degradation in the bloodstream while ensuring sustained release over time. A notable example of this approach is the use of lipid nanoparticles in mRNA vaccines for COVID-19, which demonstrated the potential of these particles for safe and effective drug delivery in viral infections.

Liposomes: Liposomes, which are spherical vesicles composed of lipid bilayers, can encapsulate both hydrophilic and hydrophobic drugs. This provides an additional layer of protection and allows for controlled release. Liposomal formulations have been studied for delivering antiviral drugs like acyclovir and remdesivir. Liposomes can enhance drug stability, improve the penetration of biological barriers (such as the blood-brain barrier), and reduce systemic toxicity by targeting drugs directly to infected tissues. Recent advancements have focused on modifying liposome surfacessuch as coating them with specific ligands or antibodiesto enable targeted delivery to viral entry points or infected cells, which can increase therapeutic efficacy.

2. Viral Vectors and Gene Therapy

Viral vectors and gene therapies represent a groundbreaking approach to antiviral drug delivery by directly delivering genetic material or therapeutic proteins to host cells, essentially "rewiring" the cell's machinery to combat viral infections.

Viral Vectors: Modified viral vectors such as adenoviruses, lentiviruses, and adeno-associated virusesare being explored for gene therapy applications. These vectors can be engineered to deliver antiviral genes or small interfering RNA (siRNA) directly to infected cells. For example, RNA interference (RNAi) can be used to silence viral genes, preventing replication. A prominent example of this is the use of adeno-associated virus vectors to deliver siRNA targeting HIV in preclinical studies, which has shown promising results in reducing viral load. Gene therapies offer the potential for long-term antiviral solutions, as they could provide continuous antiviral effects without the need for repeated treatments.

Gene Therapy: In addition to viral vectors, gene therapy approaches are being developed to introduce antiviral proteins directly into host cells. For example, gene therapies designed to introduce interferons or antibodies into cells have been tested in clinical trials. These therapies aim to stimulate a more robust immune response, enhancing the body's ability to combat the virus at the molecular level. One exciting development is the use of CRISPR/Cas9 gene editing techniques to target viral DNA, such as the case with HIV. These approaches have shown promise in preclinical studies, offering the potential for permanently eradicating viral reservoirs.

3. Topical and Mucosal Delivery Systems

Topical and mucosal drug delivery systems are gaining increasing importance in the treatment of antiviral therapies, particularly for infections affecting the respiratory system and mucosal surfaces, such as influenza, HIV, and COVID-19.

Topical Delivery: The skin, eyes, and mucous membranes act as primary defenses against viral infections, and topical formulations are designed to deliver antiviral drugs directly to these sites of infection. Nanoparticle-based topical systems, in particular, have shown promise in enhancing skin penetration and providing sustained release of medications. This is especially useful for treating cutaneous viral infections, like herpes simplex virus (HSV). Drugs such as acyclovir are commonly delivered topically to reduce viral replication and alleviate symptoms. With advancements in nanotechnology, these formulations can now penetrate the outer layers of the skin more effectively, delivering higher concentrations of antiviral agents directly to the infected cells.

Mucosal Delivery: Mucosal drug delivery systems are essential for targeting viruses that infect mucosal surfaces, such as those in the respiratory or gastrointestinal systems. Inhalable formulations, like dry powder or aerosolized antiviral medications, have been developed for diseases such as influenza and COVID-19. These formulations aim to target the lungs directly, reducing viral load and enhancing local immunity. Recent research has explored the use of nanoparticles, liposomes, and hydrogels in mucosal delivery, as they can improve the bioavailability of antiviral agents by helping them pass through mucosal barriers more effectively. For example, intranasal vaccines that use lipid nanoparticles to encapsulate antigens or antiviral agents have been developed. These vaccines stimulate both systemic and local immune responses, providing a dual approach to combating respiratory viruses.

Future Directions and Challenges:

Future Directions in Antiviral Drug Discovery

The landscape of antiviral drug discovery is rapidly evolving, driven by the urgent need to combat emerging viral threats and enhance the effectiveness of existing therapies. While significant progress has been made, challenges remain, including the rise of antiviral resistance, the toxicity of certain treatments, and the need for more widely accessible and effective antiviral drugs. This section explores the future directions in antiviral drug discovery, focusing on key issues and potential solutions drawn from recent reviews.

Emerging Viral Threats and Pandemics

The global threat of emerging viral diseases, such as SARS-CoV-2, Zika, and Ebola, emphasizes the need for continuous innovation in antiviral drug discovery. These viruses often emerge suddenly, sparking global health crises. The COVID-19 pandemic, in particular, highlighted the importance of preparedness, rapid diagnostics, and flexible therapeutic strategies. Moving forward, antiviral drug discovery must prioritize the development of broad-spectrum antiviral agents that can target multiple viral families, reducing the need for virus-specific treatments.

Broad-Spectrum Antiviral Agents: One promising direction is the development of antiviral agents that target viral enzymes or host cell factors

shared across multiple viruses. Nucleoside analogs, protease inhibitors, and viral entry inhibitors targeting conserved regions of viral genomes or proteins are being investigated for their potential to combat a wide range of viruses. Drugs like favipiravir and remdesivir, initially developed for influenza and Ebola, have also shown effectiveness against SARS-CoV-2, proving the value of versatile antiviral agents that could be used in future pandemics.

Emerging Viral Surveillance: Advances in viral genome sequencing and bioinformatics are enabling the faster identification of new viruses. The development of real-time surveillance systems to monitor viral mutations and outbreaks could help guide antiviral drug discovery, providing early warning signals for potential pandemic threats. This proactive approach would allow researchers to accelerate drug development and distribution in response to emerging viral infections.

Antiviral Resistance and Toxicity

Just as with antibiotics, the overuse and misuse of antiviral drugs can lead to resistance, a growing concern in the treatment of chronic viral infections such as HIV, hepatitis B, and C. Resistance occurs when viral genomes mutate in ways that make existing therapies less effective. Additionally, the toxicity of some antiviral drugs remains a significant concern, particularly for treatments requiring long-term use.

Antiviral Resistance: A major issue is the emergence of resistance in viruses like HIV, which mutates rapidly, making some treatments less effective. To stay ahead of resistant strains, new antiviral agents with different mechanisms of action are urgently needed. Combination therapies, which target multiple stages of the viral life cycle or different viral proteins, have already proven successful in delaying resistance in HIV treatment and are being explored for use against other viruses.

Reducing Toxicity: Many antiviral drugs, particularly those used in long-term treatments, carry significant toxicity risks. For example, nucleoside analogs and protease inhibitors used in HIV treatment can cause renal, liver, or gastrointestinal issues. The future of antiviral drug discovery should not only focus on efficacy but also on minimizing these toxic effects. Advanced drug delivery systems, such as nanoparticles or liposomes, are being developed to specifically target infected cells or tissues, reducing off-target effects and improving safety profiles.

Need for More Effective and Accessible Antiviral Therapies

Access to antiviral drugs remains a major global health issue, particularly in low- and middle-income countries (LMICs). The high cost of many newer antivirals, combined with limited infrastructure for their distribution, prevents these treatments from reaching those who need them most. There is a critical need for affordable and accessible antiviral therapies, especially as new viral threats emerge.

Affordable and Accessible Antivirals: Making antiviral drugs accessible to all populations, particularly in LMICs, is a pressing challenge. Strategies such as developing generic formulations, reducing prices, and fostering global partnerships between pharmaceutical companies, governments, and non-governmental organization tons are necessary to improve access. The successful reduction of HIV treatment costs through generics offers a useful model that could be applied to other viral diseases.

Point-of-Care Diagnostics: Developing simple, rapid, and low-cost diagnostic tools is key to improving access to antiviral therapies. Point-of-care diagnostic devices that can quickly detect viral infections are essential, especially in resource-limited settings. These tools, combined with affordable antiviral medications, could revolutionize the management of viral infections

globally, particularly in regions with inadequate healthcare infrastructure.

COCLUSION:

The ongoing discovery and development of antiviral drugs are crucial in tackling both emerging viral threats and established infections. While significant progress has been made, challenges such as viral resistance, drug toxicity, and the need for more precise therapies still present significant barriers. New antiviral targets, such as viral enzymes, entry and fusion proteins, and host-virus interactions, offer exciting opportunities for drug discovery. However, these targets also bring unique challenges, particularly in terms of specificity and the potential for resistance. The development of new antiviral compounds, including small molecules, biologics, and natural products, is expanding our therapeutic options. Still, their safety and effectiveness must undergo rigorous testing before they can be widely used. Drug repurposing has emerged as a promising strategy for developing antiviral treatments more quickly. For example, the use of HIV protease inhibitors in the context of COVID-19 has demonstrated the potential of existing drugs to address new viral threats. Advances in drug delivery systemssuch as nanoparticles, liposomes, and gene therapieshold great promise for overcoming challenges related to bioavailability and targeted drug delivery, improving the precision and efficacy of antiviral therapies. Looking ahead, the rapid evolution of viral pathogens and the continued need for accessible and effective antiviral treatments highlight the urgency for sustained innovation. Addressing these challenges will require collaboration across disciplines, novel therapeutic approaches, and a continued focus on meeting the unmet needs in antiviral drug discovery.

REFERENCES

1. Beigel, J. H., et al. (2020). Remdesivir for the treatment of COVID-19 final report. New England Journal of Medicine, 383(19), 1813–1826.
2. Jayk Bernal, A., et al. (2021). Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. New England Journal of Medicine, 385, 1493-1503.
3. Furuta, Y., et al. (2013). In vitro and in vivo activities of favipiravir (T-705) against influenza virus. Antimicrobial Agents and Chemotherapy, 57(11), 5400–5408.
4. Reyataz, et al. (2006). Lopinavir/ritonavir combination therapy for HIV. Journal of the American Medical Association, 295(7), 825-833.
5. Gane, E. J., et al. (2016). Sofosbuvir–based therapies for hepatitis C virus infection. New England Journal of Medicine, 374, 711-723.
6. Hayden, F. G., et al. (1986). Amantadine and Rimantadine. Antiviral Research, 6(6), 299–303.
7. Weinreich, D. M., et al. (2021). Casirivimab and imdevimab in patients with COVID-19. New England Journal of Medicine, 384, 238–251.
8. Gupta, A., et al. (2021). Bamlanivimab and etesevimab in the treatment of COVID-19. New England Journal of Medicine, 385, 1382-1392.
9. Geary, R. S., et al. (2015). Pharmacokinetics of RNAi therapeutics. Advanced Drug Delivery Reviews, 87, 5–15.
10. Gish, R. G., et al. (2021). Antisense oligonucleotides in the treatment of chronic hepatitis B. Journal of Hepatology, 74(5), 1102-1110.
11. Pantaleo, G., et al. (2016). Therapeutic HIV vaccines: 2015 update. Journal of Clinical Investigation, 126(8), 2884-2891.
12. Li, Y., et al. (2008). Berberine and its antiviral activity. Chinese Medicine, 3, 45.
13. Ziegler, E. E., et al. (1997). Cinchona alkaloids and their antiviral properties. Journal of the American Chemical Society, 119(21), 4868-4873.

14. Bhat, K. S., et al. (2013). Resveratrol and its antiviral activity. Antiviral Research, 98(1), 1-10.
15. Zhang, L., et al. (2020). Epigallocatechin-3-gallate against SARS-CoV-2. Viruses, 12(7), 714.
16. Mishra, S., et al. (2018). Curcumin as an antiviral agent. Phytotherapy Research, 32(5), 903-911.
17. Siddiqui, Z., et al. (2021). Quercetin: An overview of its antiviral potential. Current Drug Targets, 22(9), 1226-1237.
18. Kuriyama, H., et al. (2019). Lentinan and its antiviral properties. Antiviral Chemistry & Chemotherapy, 27(1), 36–42.
19. Jayk Bernal, A., et al. (2021). Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. New England Journal of Medicine, 385, 1493-1503.
20. McCreary, E. K., & Pogue, J. M. (2020). Remdesivir and COVID-19: A critical review. Journal of Antimicrobial Chemotherapy, 75(7), 1703-1717.
21. Malathesh, B. C., et al. (2021). Molnupiravir for COVID-19: A critical review of pharmacology, safety, and efficacy. Journal of Clinical Pharmacology, 61(3), 406-412.
22. Vandepapelière, P., et al. (2022). Safety and efficacy of Favipiravir for treating COVID-19: A systematic review and meta-analysis. European Journal of Clinical Pharmacology, 78(4), 411-417.
23. Lu, L., et al. (2021). Safety and efficacy of favipiravir in treating COVID-19: A meta-analysis. Journal of Clinical Pharmacology, 61(7), 1007-1016.
24. Neumann, S., et al. (2020). Favipiravir: A promising antiviral therapy for COVID-19. Journal of Medical Virology, 92(7), 1290-1299.

HOW TO CITE: Sakshi Jadhav*, Sameer Pawar, Amol Shirode, Vinod Bairagi, Recent Advances in Antiviral Drug Discovery, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 4, 9234-9245. https://doi.org/10.5281/zenodo.15226068