INNOVATIONS IN ANTIVIRAL AGENT DESIGN: CHEMICAL STRATEGIES AND THERAPEUTIC APPLICATIONS

Priyanka Rani Sahu[1*], Jitendra Singh Thakur[2], Yogesh Sardul[3], Om Prakash Padhey[4]

Lecturer, Department of Pharmaceutical Chemistry, Danteswari College of Pharmacy, Borpadar, Raipur Road, Jagdalpur-494221, Chhattisgarh, India.

B. Pharm Student, Danteswari College of Pharmacy, Borpadar, Raipur Road, Jagdalpur-494221, Chhattisgarh, India

Corresponding Author*: Priyanka Rani Sahu

ABSTRACT

Antiviral agents are of immense importance in the fight against viral disorders, they have been of great value in the world by halting viral replication and thus slowing the transmission of viral diseases. This article focuses on the advancements in the potency of antiviral compounds and chemistries which have occurred in the recent past including their synthesis, use, mode of action, and problems they solve. New chemical entities are protease and polymerase inhibitors, peptoids and peptides, nanomaterials that augment antiviral activity. Advanced computational techniques in designing and screening of antiviral have become significant breakthrough in the treatment of viral ailment including HIV, influenza, hepatitis, and COVID-19. The review also focuses on the issues of antiviral agents in prevention and treatment of resistant viral strains employing strategies such as combination therapy, drug repurposing, and designing new generation broad spectrum antiviral compounds. An understanding of the molecular interactions between the pathogen and the host, as well as the targeting of the viral life cycle, form the scientific basis of these developments. Nevertheless road maps have been envisioned and notwithstanding these advances there are still a number of existing problems, such as rapid emergence of resistant strains, safety issues and the absence of broad-spectrum antiviral agents. Future directions of antiviral research are discussed in this paper and the call for new developments in chemistry and clinical medicine is emphasized to efficiently respond to constant emergence of viral threats to public health.

KEYWORDS

Antiviral agents, antiviral chemistry, drug resistance, broad-spectrum antivirals, protease inhibitors, polymerase inhibitors, peptoid-based drugs, nanomaterials, computational drug discovery, mRNA vaccines, pre-exposure prophylaxis (PrEP), viral replication cycle, host-pathogen interactions, combination therapies, emerging viral infections.

INTRODUCTION

Antiviral agents are currently acknowledged as the most important weapons that world healthcare systems have at their disposal for the treatment of viral diseases. These drugs are preferentially synthesized to disrupt the virus particle to infect, to replicate and to disseminate within the host. He explained that given the widespread prevalence of various diseases; HIV, Influenza, Covid-19, amongst others; antiviral drugs are potentially critical to decrease mortality and morbidity. However, the development and optimization of these drugs present a number of difficulties which are the development of drug resistant viral strains and viruses genetic variation. Viral infections bring out chemical problems that can be solved to provide efficient drugs for treating the disease, therefore, chemistry is at the core of antiviral innovation

Subsequent sections discuss the general purpose of antiviral agents, its importance, the difficulties faced, and the new developments found within the field in relation to itself.

OVERVIEW OF ANTIVIRAL AGENTS

Definition and Purpose

Specificized substances that interfere with various stages of the virus's life cycle, antiviral agents kill virus. First, their main aim is to obstruct viral replication to curb infection, otherwise, spread can occur. Whereas antibodies target bacteria to kill or destroy them, antivirals are specially fitted to derail particular viral activities. This consists of blockade of the receptor through which the virus binds to host cells; virus replication machinery block, preventing the assembly of new viral particles *(Xu, 2023; Brady et al., 2022).* For example, we can treat drugs that target neuraminidase, an enzyme essential for new influenza virus release, by curtailing the infection.

Importance in Global Health - Antiviral agents are more than a special interest of ce individual patient care; they are key to managing and containing global health crises. This is exemplified by the addition of antiretroviral therapy (ART) to HIV treatment, turning a terminal disease into a manageable chronic one. Like remdesivir and molnupiravir, the labeling for which has become landmarks in the treatment of COVID-19, simply cutting hospitalization rates and reducing severe outcomes in high risk patients *(Sydorenko, 2023; Brady et al., 2022).* These drugs are also crucial to maintenance of the health of the healthcare systems during epidemics and pandemics, and they not only save lives but also offload their burden.

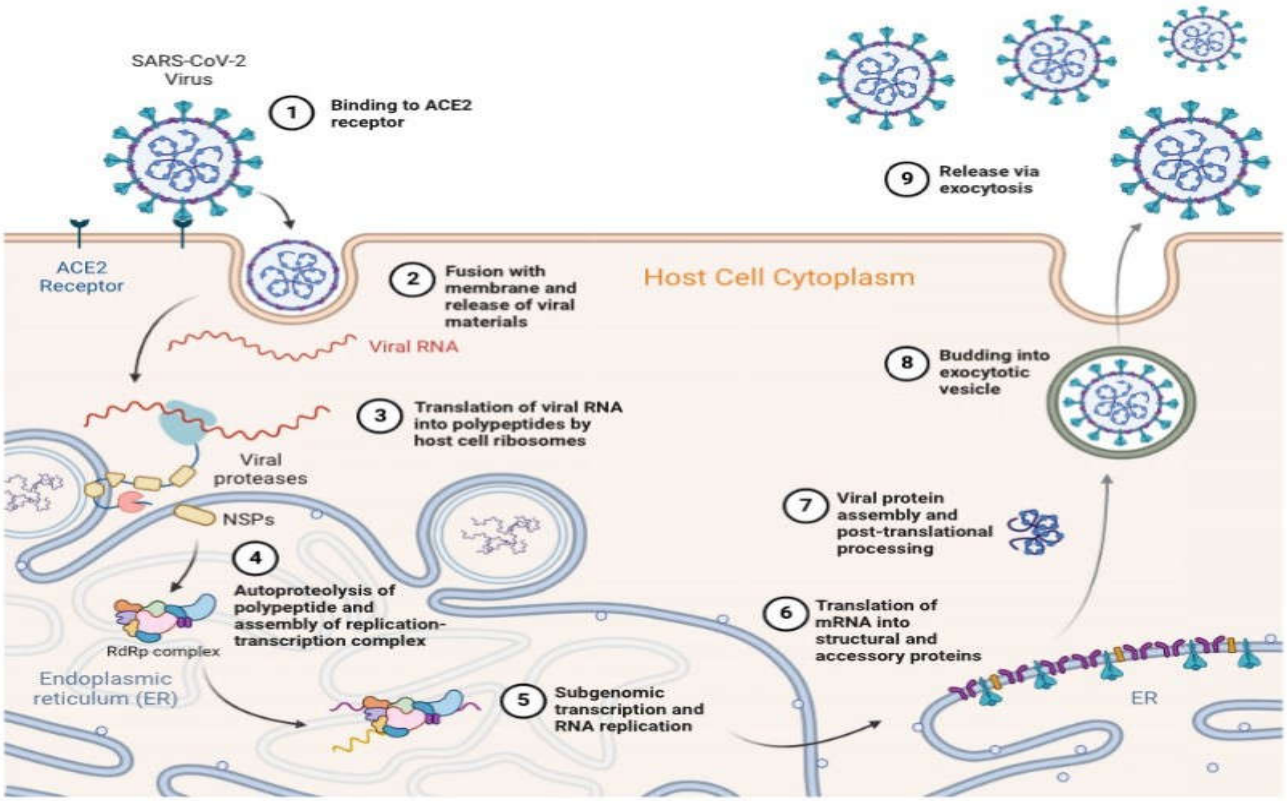

Fig. no. 1 Summarized pathway of the entry into host cell, replication, maturation, and release of the SARS-CoV-2 virus. (Brady et al. 2024)

CHALLENGES IN ANTIVIRAL DRUG DEVELOPMENT

Emergence of resistant strains

Among all the challenges, principal ones are: Viruses have genomic variation potential, low mutation rates and potential resistance to drugs. A virus can change the proteins or enzymes that a cure seeks to interact with when the virus mutates, decreasing the efficacy of medications or making them totally obsolete. This feature is rather typical for HIV, as a long-term treatment with ART results in drug-resistant HIV strains and the need for second or third-line regimes. Influenza viruses present a problem as their genetic makeup means that antiviral drugs, and vaccines, need to be updated frequently *(Săndulescu et al., 2023).* Overcoming the issue of resistance calls for a comprehensive development stream of new drugs and combination products to check a viral evolution.

Variability of Viral Pathogens

Viruses are parasites that cause mutations exemplary RNA viruses have high mutational rates with a lot of variation genetically. This makes it difficult to develop antiviral agents that are able to combat any of the different strains. For instance, HCV is made up of separate genotypes, which are likely to produce varying reactions to antiviral drugs. The number one threat in this context is the constant emergence of new advanced viruses such as the influenza virus and SARS-CoV-2 viruses, which place increased demands for constant vigilance and adjustments of strategies against viruses *(Todorovski et al., 2023).* Broad-spectrum antivirals, defining drugs acting against conserved viral components, are a potential approach, but they need more scientific and experimental development.

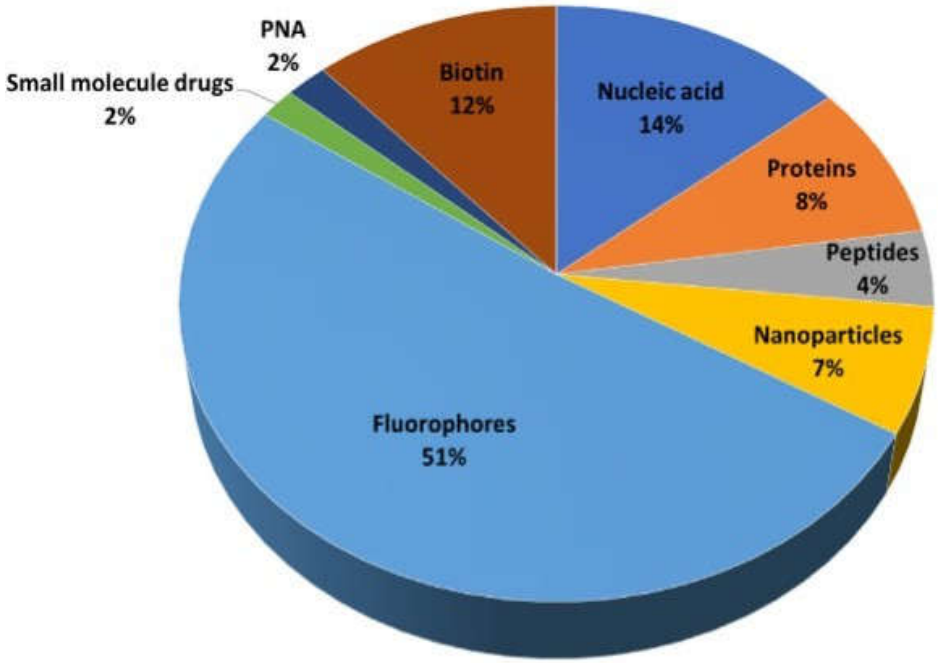

Figure 1. Types of cargoes delivered into cells by CPPs *(Todorovski et al., 2023).*

Need for Rapid and Efficient Drug Development

It will be remembered that the search for antivirals is most of the time made more urgent by a pandemic, and more so nowadays. The conventional approaches of drug development which require long periods of

preclinical and clinical evaluations are incapable of responding to novel viral threats such as COVID- 19. To bypass this, the research community has had to use strategies like drug repositioning in which drugs used to treat other diseases are tested for usability in new viruses. Other techniques such as artificial intelligence (AI) and high throughput screening are also being used to speed up the discovery and the optimization of lead amongst all potential antiviral. *(Alsafi et al., 2022).*

THE ROLE OF CHEMISTRY IN ANTIVIRAL INNOVATION MOLECULAR INTERACTIONS AND DRUG DESIGN

Fundamentally, chemistry is essential for explaining the behavior of antiviral agents with other objects of the virus and the host. This knowledge is important in the development of drugs that are able to readily check on critical viral activities. For example, nucleoside analogs- Acyclovir arrange like a natural nucleotide and incorporate into the viral DNA and stop the further synthesis. Likewise, antiviral protease inhibitors utilised inside HIV remedy attach to the viral proteases to hinder the action of polyproteins required for viral replication (Xu 2023; Peng et al., 2022). These targeted intercessions present that chemistry is useful when it comes to developing efficient and selective antiviral medications.

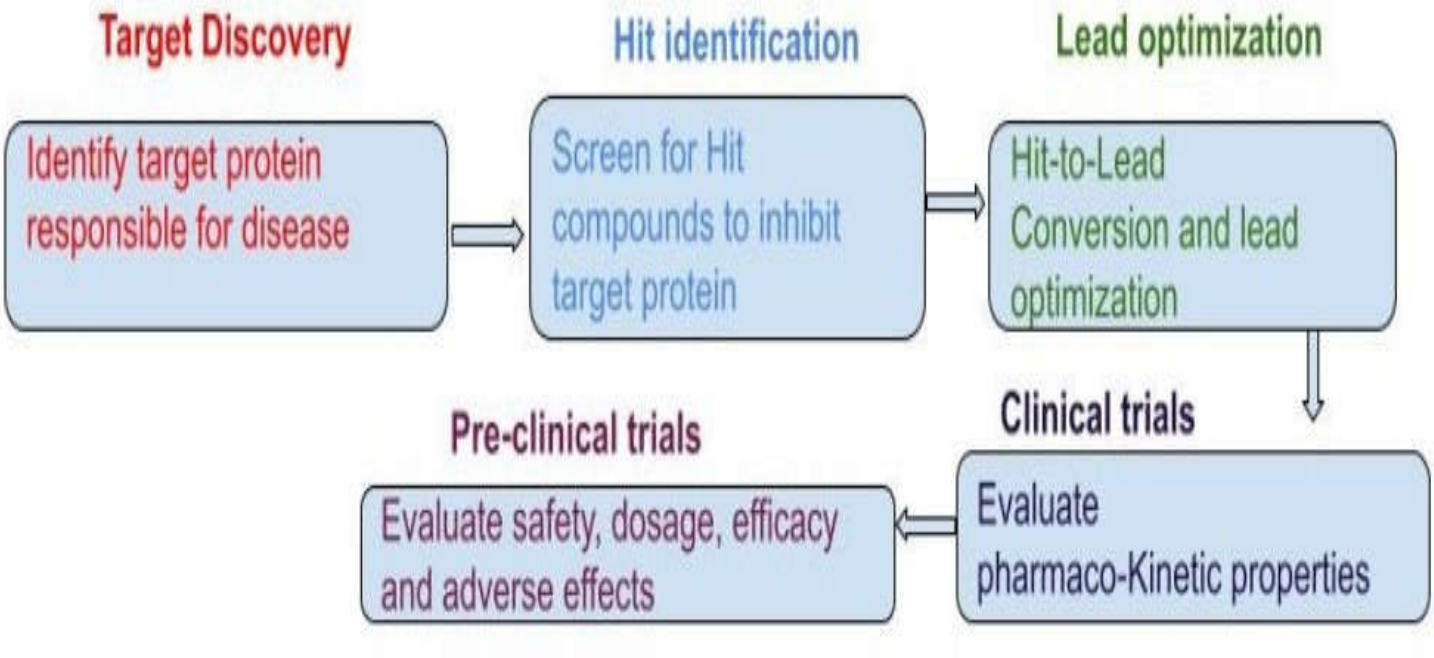

Figure: Flowchart of drug design process. *Choudhuri et al. (2023)*

INNOVATIVE APPROACHES IN MEDICINAL CHEMISTRY

There are new insights and approaches to the discovery of new antiviral agents in medicinal chemistry. One such innovation is the creating of peptide–drug conjugate a delivery system in which therapeutic peptides are bound to the antiviral agents for better targeting. These conjugates enhances the drugs solubility and lessen the undesired systemic side effects and provide more specific treatment methods. Furthermore, structure based drug design enables scientists to design antivirals that achieve a high affinity to the viral proteins, which in turn increases the drugs' efficacy and decreases side effects *(Todorovski et al., 2023). They* extend great prospect in overcoming the weaknesses of conventional antiviral treatments.

It is worth to stress that nowadays antiviral agents are inalienable part of the world's fight against viral

disease which gives hope and comfort to millions of people all over the world. But resistance, viral variability, and, perhaps, the necessity for a faster development of drugs make this field rather problematic. Chemistry continues to be a leading discipline addressing antiviral needs through offering the relevant technologies and approaches for developing novel antiviral treatments. In this manner the investment of the research into both conventional and advanced technologies, researchers are better placed provide a solution to the dynamic epidemiologic environment of viral infections so as to provide continued protection to global public health through the deployment of antiviral agents.

RECENT INNOVATIONS IN ANTIVIRAL CHEMISTRY

Recent innovations in antiviral chemistry have led to the development of novel chemical classes of antiviral agents, each targeting specific viral mechanisms. These innovations include targeting viral enzymes, utilizing small molecule inhibitors, developing peptoid and peptide-based drugs, employing nanomaterials, and inhibiting viral entry. These approaches aim to enhance the efficacy and specificity of antiviral therapies, addressing challenges such as drug resistance and broad-spectrum activity. Below, each category is explored in detail, highlighting recent advancements and examples.

NOVEL CHEMICAL CLASSES OF ANTIVIRAL AGENTS

Novel chemical classes synthesized are now intended to intervene at precise step in viral replication cycle unlike earlier generations of antiviral compounds synthesized before the discovery of the chemistry of viral replication process. These innovations relate to very important areas of concern such as; Drug resistance and call for the development of a broad spectrum antiviral agents. It has been redirected to the synthesis of very selective and efficient anti-viral agents, such inhibitors of viral enzymes, molecule which disrupt normal functioning of virus, peptides and nanotechnology based products. All these developments show how potential the chemistry is in tackling future threats from viruses in the world.This innovation underscores the flexibility of chemistries in the future, in eradicating some existing diseases caused by virus.

Targeting Viral Enzymes

There are virial enzymes that act in replication life cycle of viruses and existence of the virus. A major aspect of antiviral drug development has been the establishment of inhibitors of these enzymes.

Protease, Polymerase, and Integrase Inhibitors

Nirmatrelvir of the Paxlovid is among the protease inhibitors that work by inhibiting the main protease of SARS-CoV-2 and required for processing viral polyproteins. RNA dependent RNA polymerase (RdRp) known to be an essential component of the replication process. Molnupiravir and remdesivir are such drugs they have been proved effective by inhibiting RdRp thus preventing replication of SARS-CoV-2 *(Ghosh et al., 2022; Hirokazu, 2022).* Likewise, the class of antiretroviral drugs that targets integrase – a protein that catalyses the integration of a viral DNA into the host genome – will hinder the basic processes of viral replication.

Influenza Inhibitors

Such agents, as baloxavir, an endonuclease inhibitor, act on the target that is the viral ribonucleoprotein complex (vRNP) of the influenza virus and affects its transcriptional machinery. This peculiar mechanism overcomes the flaws of current NI and thereby provides the new therapeutic approach *(Bhargav et al., 2022; Hou et al., 2021).*

Small Molecule Inhibitors

These are universal reagents that have diverse effects on viral activities due to interaction with molecules of similar size.

DISRUPTING VIRAL ENTRY AND REPLICATION

Small molecules include remdesivir, which shows effectiveness in inhibiting the replication of SARS-CoV-2 and that of Paxlovid. In particular these compounds exert action at the molecular level – interfere with viral proteins and enzymes. Their design also utilize high specificity so that nearly all that is toxic to the host will not affect the efficacy of the drug *(Ghosh et al., 2022; Hirokazu, 2022).*

Protein-Protein Interaction Inhibitors

Targeting of PPI is a novel approach in antiviral drug discovery Among the identified targets the majority belongs to the viral protein. For instance, small-molecule inhibitors (SMIs) have been proposed to antagonize binding of the SARS-CoV-2 spike protein to the human ACE2 receptor. These SMIs could exclude the virus from the host cells and make up the new tactics for COVID- 19 therapy *(Buchwald, 2022).*

Peptoid and Peptide-Based Drugs

Peptides and peptoids (peptide mimics) are gradually emerging as agents capable of controlling virus infections because of their high specificity towards viral proteins.

SYNTHESIS AND APPLICATION

These compounds are made to improve the binding of a ligand to its target since improved binding is always desirable. These can be designed to act against viral enzymes, structural components or host factors with high tropism for the virus. For instance, compounds that are derived from peptides could potential facilitate the inhibition of SARS-CoV-2 fusion to avoid the viral entry step*(Ianevski et al., 2022).*

ADVANTAGES AND CHALLENGES

As with peptide-based drugs, there is high specificity, but stability and delivery are somewhat problematic. These difficulties have however been overcome with formulation advances including encapsulation and conjugation with stabilizing agents.

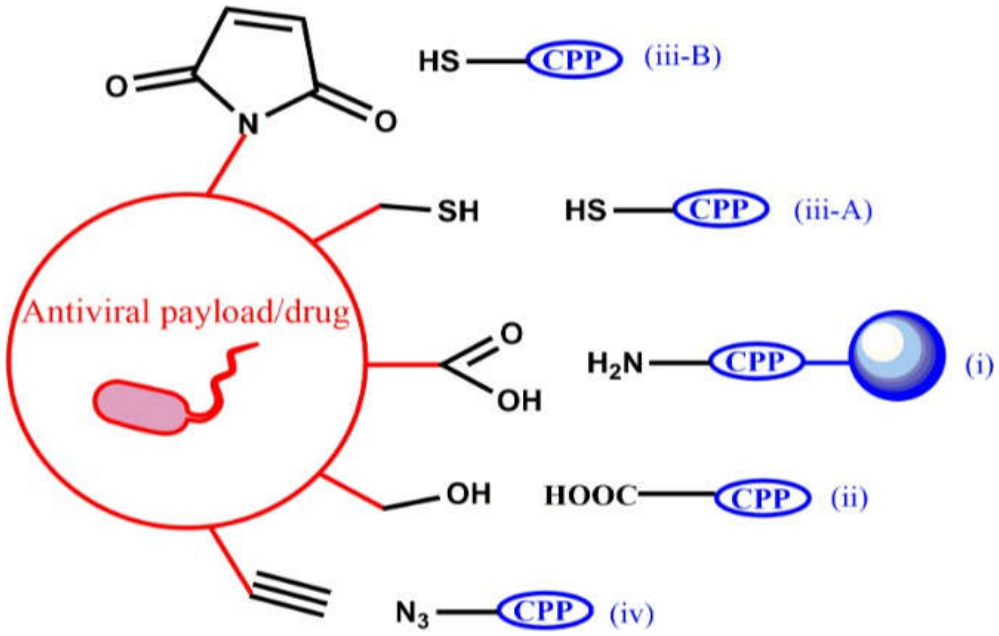

Figure 3. Conjugation chemistries applied in the synthesis of antiviral PDCs.

NANOMATERIALS IN ANTIVIRAL CHEMISTRY

In the present context, nanotechnology brings unprecedented approaches in antiviral drug delivery and virus inactivation.

Nanoparticle Utilization

NPs are currently under consideration due to their capacity for viral interaction, preventing viral attachment to host cells, or enabling more effective targeted delivery of antiviral agents. For instance, functionalized NPs may be designed to imitate a host cell receptor that binds with the virus envelope and neutralizes it or to transport anti-viral drugs to the communicant cells *(Ianevski et al., 2022).*

Innovative Properties

High surface area coupled with versatility of properties of nanoscale materials can be functionalized to suit a particular application to a large extent. Gold nanoparticles and lipid based nanoparticles are some of the most potential candidates for antiviral especially for SARS-CoV-2.

Viral Entry Inhibition

One of the major approaches in avoiding transmission of the virus is to block entry of the virus in the body.

Blocking Entry, Fusion, or Uncoating

Some of HIV enzyme inhibitors like enfuvirtide do not allow the virus to fuse with host cell membranes. In the same manner, entry inhibitors of influenza HA or SARS-CoV-2 S protein have also remained effective according to some preclinical researches *(Hirokazu, 2022).* Antiviral drugs work in stopping the virus before it has a chance to multiply allowing the body's immune system to fight the virus.

ADVANCEMENTS IN DRUG DESIGN AND SCREENING

In the recent world, India has turned to be a key global innovation hub in the production of antiviral pharmaceuticals, through the use of advanced technologies. Molecular modeling, AI, and SBDD have overhauled old school drug designing techniques to cater to the new demands of highly efficient and biologically valid drug candidates. They're all geared towards optimizing pre-clinical drug discovery, increasing the accuracy of hitting viral proteins and dealing with the issues of viral diversity. Subsequent sections discuss these in more detail most with reference to their use in antiviral drug discovery.
Computational Chemistry & AI-Driven Drug Discovery

Machine Learning Algorithms and Computational Models

Machine learning (ML) was of great impact to computational chemistry because it provides fast prediction of large dataset of molecules and their interactions. These tools ease the time and expenses comparative to the reduction levels of conventional drug discovery processes. Currently, Indian researchers have been analyzing the molecular descriptors, physicochemical properties, and bioactivity data to discover the antiviral agents using ML models *(Choudhuri et al., 2023).*

AI-enabled platforms have also posited their contribution regarding the synthesis of covalent inhibitors for SARS-CoV-2. These platforms, applying deep learning algorithms, pinpoint and suggest increased binding affinity to viral targets, Mpro or spike protein, through chemical modifications. For example, there are reports where generative adversarial networks, or GANs, along with reinforcement learning have been employed to develop new small molecules with better targeted profile and fewer side effects by *Kovalevsky et al., 2023.*

Virtual Screening and High-Throughput Screening Technologies

Ligand based virtual screening (LBVS) and structure based virtual screening (SBVS) methods have been used for the identification of potential antiviral compounds. These methods employ computational techniques to predict bindings of viral proteins with potential therapeutic agents. Regarding SARS-CoV-2, LBVS has concentrated on chemical compounds similar to those previously identified as inhibitors, whereas SBVS uses docking predictions to measure the binding energy of compounds to key viral targets *(Delgado-Maldonado et al., 2024).*

Apparently, high-throughput screening (HTS) technologies coupled with artificial intelligence (AI) apply more pressure on drug discovery. These platforms perform virtual screening of thousands of compounds and the estimates of protein-ligand binding affinities are insightful. For instance, AI-based HTS system has been used to enhance the identification of lead compounds for SARS-CoV-2 spike protein inhibitors in congruent with molecular dynamics simulations and enzymatic assays (Saar et al. 2023).

Structure-Based Drug Design

Targeting Specific Viral Proteins

Structure-based drug design (SBDD) refers to the specific use of three-dimensional structures of viral proteins in order to design antiviral agents. This approach entails examining the active sites of viral enzyme or receptor and develop small molecules that would recognize and bind with high selectivity and voluminous binding energy. Recent improvements in computational power, for example quantum mechanics-based modeling have further improved the accuracy of SBDD (Diakou et al., 2022).

Given, SBDD has played a significant position in registering inhibitors for main protease (Mpro) and for RNA-dependent RNA polymerase (RdRp) within the warfare against SARS-CoV-2. These investigations have explained the interaction dynamics, stability, and energetics of the potential drugs, opening up possibilities for fast lead optimization (Dai et al., 2023).

SARS-CoV-2 Spike Protein Inhibitors and ACE2 Receptor Blockers

Interaction of spike protein of the virus SARS-CoV-2 with the human target ACE2 receptor is one of the most important events in virus infection. This interaction has been subjects of inhibitors, as stopping the virus from entering the cells will safeguard the body against infections. Some of the small molecules and pepetides that have been reported to modulate this interaction are shown below. For instance, the computational approach has identified new binding sites of the spike protein and enables one to develop molecules that might interfere with the protein's conformational transformations (Delgado-Maldonado et al., 2024).

Further, inhibitors which act on ACE2 receptor have been considered for their potentiality to prevent effected cells from viral attachment. Sciences suggest that ACE2 receptor blockers work not only to prevent pathogen adherence but also to control overstimulated immune reactions, thus having two-use advantages. However, these all developments have made the way for more challenges in the antiviral drug discovery process. Severe and frequent mutations of RNA viruses including SARS-CoV-2 make it difficult to fully contained them hence the need for different strategies that can track variants. However, theoretical computations have to be effective through experiments in order to prove their effectiveness and safety.

Additionally, complimentary and blending of artificial intelligence and computational chemistry to the conventional drug discovery process needs to accommodate interprofessional practice and sufficient facilities. These challenges are set to be met by India's increasing investment in biotechnology and Artificial Intelligence to enable radical advancements in antiviral therapeutics. In the development of broad-spectrum antivirals that are both efficacious and affordable, these computational tools will most certainly grow indispensable as the tools are adapted.

APPLICATIONS OF ANTIVIRAL AGENTS

Antiviral drugs have been instrumental in the treatment of viral diseases since they come with specific methods to suppress the viruses. Such agents are more relevant in treating diseases caused by virus like HIV, influenza, Hepatitis, COVID-19 among others. The subsequent advancement in combination therapies has further contributed to better treatment result in terms of both effectiveness and resistance. Furthermore, quick changes in tackling viral threats are demonstrated by research as a naturally evolving subject of study. Here, we discuss the use of antivirals in routine community-acquired infections, mechanism of action for new combinations and approaches to future emerging viral infections.

THERAPEUTIC USE IN VIRAL INFECTIONS

HIV Treatment

Haart is essentially the mainstay of treatment in HIV/AIDS alongside with other associated symptoms; HIV/AIDS is inverted from a death warrant to a manageable chronic disease. ART in most cases means that the patient takes several drugs that act at different phases of the viral life cycle in order to avoid drug resistance. There are protease inhibitors like lopinavir and darunavir that prevent the cleavage of viral polyproteins and reverse transcriptase inhibitors such as zidovudine and tenofovir that prevent the conversion of viral RNA to DNA. These therapies have cut down the high HIV-releted mortalities and enhanced the patients' life expectancy *(Tahir, 2024).*

Influenza

Oseltamivir (Tamiflu) class of influenza antiviral agents effectively antagonizes neuraminidase, an enzyme fundamental to release of newly formed viral particles to the extracellular environment. By so doing oseltamivir is effective in decreasing the severity and duration of the disease symptoms, if administered at the right time. They also found out that annual changes of treatment protocols and availability of vaccines add to this therapy *(Tahir, 2024).*

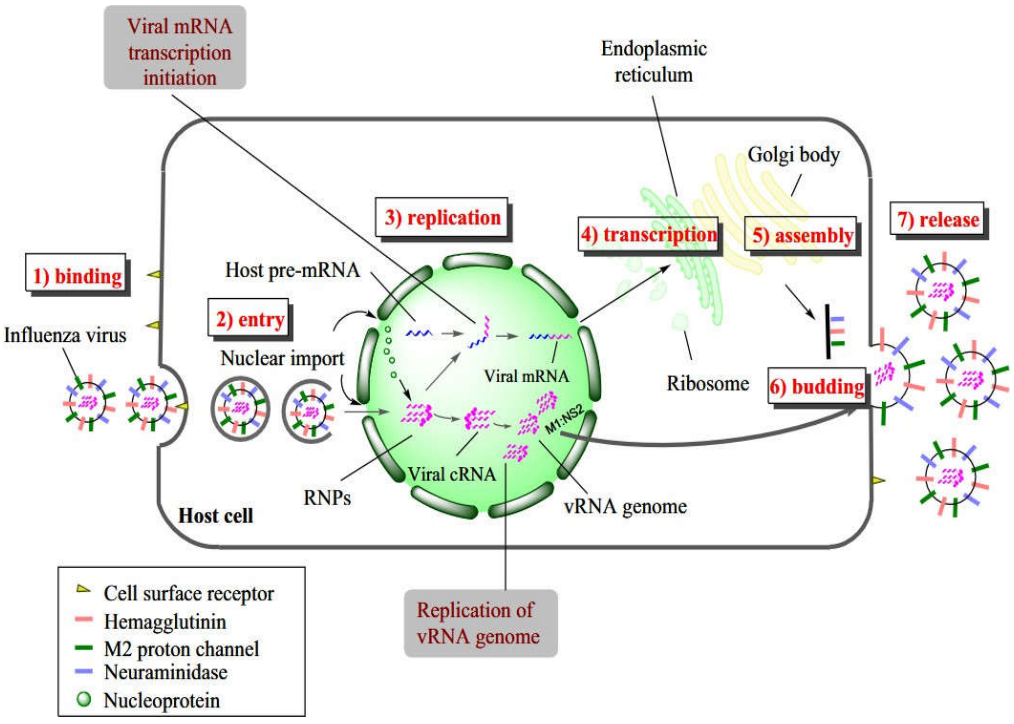

Figure 3: The life cycle of influenza A virus. *Hou et al. (2022)*

Hepatitis

Hepatitis B and hepatitis C exist with the help of antiviral medications nucleoside analogs (background entecavir, tenofovir, and others) and protease inhibitors (glecaprevir and others). These drugs interfere with the viral replicate by binding to the enzymes involved in viral DNA synthesis or the proteases required for viral protein synthesis. Newer oral antiviral agents like sofosbuvir in the DAA class present a far better cure package when it comes to the high rates of sustained virologic response in just a few weeks.

COVID-19

The COVID-19 outbreak has accelerated the process of the creation and the release of antivirals. Like, Sofosbuvir, Remdesivir is also a nucleotide analog that inhibits the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 and thus hinders the viral replication. Likewise, antiviral combination medications including nirmatrelvir-ritonavir (Paxlovid) – target the SARS-CoV-2 main protease and decrease viral load in early-stage patients *(Hejran et al., 2024, Andrews et al., 2023).*

NOVEL COMBINATION THERAPIES

HIV

HAART in HIV uses a cocktail of drugs because each has different mode of working. For instance, integrase inhibitors such as dolutegravir is used jointly with nucleoside reverse transcriptase inhibitors (NRTIs). This strategy raises virus load suppression and brings down causes of resistance, to allow permanent control of the disease *Tahir, 2024.*

COVID-19

Due to the severity of the disease in some patients, treating with more than one drug has been considered. For instance, dexamethasone an anti inflammatory corticosteroid is administered alongside antiviral such as remdesivir in an effort to dampen hyperinflammation as well as inhibit viral replication. Such combinations are most useful in minimizing mortality in severe conditions *(Andrews et al., 2023).*

DEVELOPMENT OF ANTIVIRALS

New and emerging diseases such as Zika, Ebola, and Monkeypox proof a quick development of antivirals is critical. For instance, remdesivir intended for Ebola had been adapted in COVID-19 tiny due to the realization that it interacted with RdRp. Similar maneuvers are used to repurpose such initial anti-viral scaffolds for new pathogens within days *(Tahir, 2024; Hejran et al., 2024).*

Role of Chemists

Chemists are sine qua non in antiviral development, and availing the ultra-modern technologies such as structure-based drug design to come up with molecules that would fit into specific viral proteins. Employing biophysical tools that investigate viral entry mechanisms, replication, and protein interactions, they synthesize inhibitors with optimal selectivity and efficacy. Such a role matters especially in various epidemics that require mass production of antivirals that can prevent the death of millions of people *(Blaskovich and Verderosa, 2023; Tahir, 2024).*

DEVELOPMENT OF ANTIVIRAL VACCINES

mRNA Vaccines

mRNA vaccines can be stated as the major advancement in antiviral vaccine technology. As opposed to more conventional vaccines they depend on introduction of small bits of genetic material into the cells in order to make the body produce viral proteins and incite desired reactions in the immune system. Their application was demonstrated during the COVID-19 pandemic with the use of vaccines created through the

operation of mRNA – such as the Pfizer-BioNTech and the Moderna vaccines. This makes it possible for modifications to address new strains and the use of several antigenic sites that are effective against new viral threats *(Irina, 2023) (Abbas et al., 2023).*

Viral Vectors and DNA Vaccines

Viral vector vaccines in the form of proteins presented on viral vectors are getting popular because of excellent immunogenicity and T cell and antibody responses from the adenoviral based vectors. These platforms have been used in vaccines including the recently developed Johnson & Johnson COVID-19 vaccine. DNA vaccines are also under consideration since they have a stable and ease of manufacturing as a drawback, they require sophisticated delivery mechanisms such as electroporation for the same *(Caplan, 2022) (Khalaf, 2022).*

Bioprocessing Advances

Advanced in bioprocessing have served to improve the production of vaccines more so those of the biologic products such as the antiviral monoclonal antibodies. Issues of scalability touched by complex strategies like the use of single-use bioreactors and the continuous manufacturing method implies faster delivery of vaccines *(Meade et al., 2023).*

Antiviral Agents for Prophylaxis

Pre-Exposure Prophylaxis (PrEP) to HIV

For as a late addition for HIV prevention, PrEP has quickly become a cornerstone, which involves daily use of tenofovir disoproxil fumarate /emtricitabine. Research has shown that when patients adhere to their dosage schedule in the case of PrEP drugs, they can decrease their HIV rates by more than 75%Baroš & Grujicic, 2022). The success rate has been aligned to vulnerable communities including men having sex with men and serodiscordant partners(Paiva et al., 2022) (Sundareshan & Koirala, 2019).

Post Exposure Prophylisis (PEP)

Post-exposure prophylaxis or PEP is the practice of giving antiretroviral medications soon after a healthcare worker or a survivor of sexual assault may have contracted HIV. The study has presented that when PEP is started in the first 72 hours and, the course is complete within 28 days, the HIV transmission risk is decreased by up to 81%(Baroš & Grujicic, 2022).

Resistant Strain Management

Combination Therapies

The combination therapies continue to be considered as the most effective approach to dealing with the drug-resistant viral strains. These therapies are effective to some extent due to the ability which hits several stages of the viral replication cycle and thus, it is inferior to develop resistance. For instance, antiretroviral therapy treatment (ART) of HIV involves the use of drugs such as protease inhibitors and integrase strand transfer inhibitors to boost the treatment outcomes *(Wang et al, 2024).*

Drug Repurposing

The use of drugs used to treat other diseases has been an effective way to make new drugs available to treat resistant forms of the diseases. These included remdesivir originally designed for Ebola but later used effectively against COVID-19(Covid-19) — further showing the possibilities of junk drugs *(Wang et al., 2024).*

Broad-Spectrum Antivirals

New molecules of broad-spectrum antivirals are being created with the aim of having an effective therapy for ranging from one viral family to another. Favipiravir and other related chemicals interfere with conserved viral components that reveal potential treatments for the new generation of viral diseases *(Wang et al., 2024).*

Challenges and Considerations

Mutation and Resistance

Other viruses for instance HIV and the flu virus have especially high mutation rates making resistance to current drugs possible. This is averted by combination therapies but means that there is constant change which means new ideas come in handy. Constant monitoring and DNA sequencing provide the best methods to modify the necessary therapy approaches *(Tahir, 2024; Chalotra et al., 2024).*

Safety and Efficacy

However, some of these antivirals for example favipiravir which has been used in the treatment of Ebola virus have been associated with side effects like toxicity to the liver and teratogenicity. To ensure the benefits of a therapy on one hand outweighs risks on the other a close and intensive study needs to be conducted on samples. Ongoing assessment of patient outcomes continues to help define these therapies as well *(Hejran et al., 2024; Sydorenko, 2023).*

MECHANISMS OF ACTION

The antiviral efficacy of certain reagents is primarily predicated on the ways in which such chemical entities interact with viruses. Particularly, they engage complex processes of interaction with the viral reproduction and host-parasite relationships. These mechanisms concern the recognition of viral targets, interference with critical viral processes, and exploitation of host cell processes to avoid viral replication. The next few sub sections discuss these facets in more detail, while incorporating findings from previous research done in the field.

Viral Replication Cycle and Targeting Mechanisms Stages of the Viral Life Cycle

In order to survive the viruses are organized in a typical life cycle: attachment, entry, replication, assembly, and release. These all steps are significant emergency point for antiviral management.

Attachment and Entry

COVID causing virus, SARS-CoV-2 also uses the spike protein to target

host's ACE2 receptors to allow viral membrane fusion and invasion. An example of such a target is the use of monoclonal antibodies which hinders virus entry and directly inhibits the endpoint interaction and entry blockers *(Golsorkhi, et al., 2020).*

Replication and Transcription

Protease inhibitors, polymerase inhibitors, and nonstructural protein inhibitors are some examples of DAAs as they actively inhibit specific viral enzymes that are vital in the replication process. For example, remdesivir acts upon the RNA-dependent RNA polymerase of SARS-CoV-2 and thus stops the synthesis of new RNA and virus replication (Golsorkhi et al., 2020).

Assembly and Release

This group of drugs lock onto the protease enzymes necessary for assembly of viral particles, including the NS3/4A protease inhibitors with HCV *(Williford & McGivern, 2016).*

Key Viral Enzymes and Proteins

Enzymes and viral proteins are important for infection of a virus as well as for replication needs for the virus machinery.

In HCV, the antivirals targeting the NS5A protein and NS5B RNA polymerase are efficient inhibitors of viral replication *(Williford & McGivern, 2016).*

RSV604 an antiviral compound targets the nucleoprotein of respiratory syncytial virus (RSV) inhibiting RNA synthesis and thereby limiting the rate of virus replication *(Challa et al., 2015).*

agents such as Paxlovid for SARS-CoV-2/check the activity of viral protease thereby inhibiting viral polyprotein cleavage thereby halting replication.

Chemical Microbicides

Chemical microbicides target viral structural components, such as the envelope or capsid, disrupting their integrity.

These agents work through the unfolding of viral proteins necessary for attachment and fusion,

thereby inactivating the viral particle's ability to infect others, *(Gerba et al., 2024).*

For instance, some surfactants have shown promise in disrupting viral membrane, especially of lipid enveloped viruses such as coronaviruses *(Lambert, 2012).*

Host-Pathogen Interactions Interfering with Host Cell Machinery

Viruses always take advantage of the host cell equipment to replicate and assemble themselves. In these processes HTAs interact, obtaining an additional level of antiviral protection.

Cyclosporin A (CsA): CsA interferes with post-assembly steps of HCV particles owing to its specificity to cyclophilin A, a host protein that is essential in the replication of HCV thereby significantly decreasing the viral load (Liu et al., 2023). Resistance is well countered in HTAs because they mark the host factors which will not be as prone to mutations like the parts in the viruses.

Modulation of Host Immunity

The antiviral treatments tend to assist with the use of immunologic techniques to destroy viruses.

Interferons

Many of these cytokines have key function in host antiviral reaction, increasing the intracellular defense and stimulating the removal of the virus-infected cells (Antonelli & Turriziani, 2015).

Innate immune responsive with IFNs has been seen to bear potential in taming viral illnesses including hepatitis and COVID-19.

Lipid Metabolism and Signaling

Viral replication requires host lipids with viruses targeting lipid pathways in the formation region to build their membranes.

These pathways' inhibitors prevent the normal formation of virus particles to inhibit viral replication (Antonelli & Turriziani, 2015).

It cited examples such as inhibitors of lipid metabolism that are in active consideration for treatment of flaviviruses and coronaviruses.

Despite these advantages that comes with host-targeting strategies, specific and toxicity issues are some of the problems associated with them. Off-target effects and handling of normal cellular activities are important aspects that determine therapeutic efficacy of kinases. The strategy to achieve a balance between the virus and the host is likely to be critical to achieving breakthroughs in next-generation antiviral therapies.

These combined concepts about the mechanisms of viral replication and host-pathogen bio density are the essential framework for developing new, specific strategies against known and newer viral diseases.

Challenges and Future Directions

Broad-spectrum antivirals are a novelty in managing viral ailments, especially in a world where pandemics and other new viral pressures are arising. In contrast to specific antiviral drugs that treat particular pathogen kinds, broad-spectrum antiviral drugs try to act on the maximum number of virus kinds, including picornaviruses, flaviviruses, coronaviruses and others. But the route to creating these sort of impressive drugs is not without its obstacles based directly on the viruses, their mutation rates, safety concerns, and the fact that agencies regulating these sort of drugs will not accept anything less than perfect. This section expands on such challenges and presents opportunities and innovations that could enable them, here extra chemical and/or pharmacological progress is discerned.

Development of Broad-Spectrum Antivirals

The development of broad-spectrum antiviral drugs is by its nature highly complex because of the enormous morphological, genotypic and functional variation of viruses, the manner in which they reproduce, and their interactions with host organisms.

Diversity of Viruses

Viruses vary widely in genome type (DNA or RNA), mode of replication and the different constituents. For example, while the type of coronaviruses has large and complex RNA genomes with the proof-reading activity, the picornaviruses are of smaller RNA with high rates of mutation. Many of these differences make it challenging to develop a one-size-fits-all antiviral (Robinson et al., 2022).

High Mutation Rates: Some of the diseases are RNA viruses, which are characterised by faster mutation rates, and the development of drug-resistant variants. High genetic variability is not sustainable in the efficacy of a single antiviral agent across different viral species (Robinson et al., 2022).

Host Dependency: Most antiviral targets employ host proteins that are utilized by viruses; this creates a problem because targeting these proteins often proves lethal to the host. Finding out the right combination of effectiveness and safety also requires extra precautions.

Opportunities for Chemical Innovation

New opportunities for broad spectrum antiviral drugs are emerging due to achievements of medicinal chemistry and drug discovery.

High-Throughput Screening: By using automated methods investigators are able to screen thousands of compounds in a short span of time that indicates potentials agents with generalized activity. Small molecules and natural product libraries are searched to find hits with a view to targeting conserved viral components (Azizi et al., 2022).

Computational Tools: Computer-aided drug design and molecular docking simulations inform about the possible ways in which possible drugs will behave when they come into contact with viral and host proteins. These tools enhance the rate by which optimal binders are sourced from these candidates (Azizi et al., 2022).

Targeting Conserved Mechanisms: Chemical innovations are where different viruses belong to different families but the target chemical needs to function against all classes since they are more conserved and less likely to mutate than other elements (Robinson et al., 2022).

DRUG RESISTANCE

Mechanisms of Resistance

Drugs resistance occur when viruses develop certain mechanisms to counteract the effects of the drugs.

Mutation of Drug Targets: Protease inhibitors: The targets for these medications are proteases for which resistance arises when mutations occur in the viral proteins, contributing to the low affinity of the drugs. For example, HCV protease inhibitors have been challenged with patient non- adherence resulting from evolution of NS3/4A protease of the virus.(Robinson et al., 2022)

Drug Efflux and Host Mechanisms: Some viruses may also use the host cellular processes that promote the efflux of drugs out of the infected cell thereby lowering the intracellular concentrations of the drugs to non therapeutic levels.

Strategies to Overcome Resistance

Combination Therapies: Antiretroviral drugs that work through diverse biochemical processes minimise the chance of drug resistance. For instance, there is HIV therapy that uses reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors, all of which work at different stages of the virus replication cycle.

Next-Generation Antivirals: To overcome this , there are investigational agents that have been developed to act on conserved aspects of the virus, less likely to mutate, for example capsid proteins or replication enzymes. Also, host-targeting agents (HTAs) lowers the probability of resistance since they hinder host processes that are mandatory for viral replication (Robinson et al., 2022).

Safety and Toxicity Issues Side Effects and Toxicity

Adverse effects of antiviral agents arise as a result of interactions with other tissues and cause toxicity.

Off-Target Interactions

Some of drugs that may bind target host proteins may interfere with usual functions of proteins within a cell thereby producing side effects. For example, some of the nucleotide analogs when used in antiviral treatment can become incorporated into the host DNA, causing toxicity(Azizi et al., 2022).

Accumulation in Tissues: Some of the antiviral agents can accumulate in important organs like liver and kidney and cause chronic toxicity.

New Directions for Safety

Nanoparticle Delivery Systems: With nanotechnology, drugs can easily be delivered to the infected tissues without affecting the good cells, yet. For instance, liposomal carriers may enhance the bioavailability of encapsulated antiviral agents in addition to decreasing the systemic toxicity(Azizi et al., 2022). Optimizing Drug Selectivity: Progress in methodologies of chemical modifications contributes to the improvement of drug selectivity, thus minimizing the interacting of the viral specific proteins with the host homologues.

Regulatory and Clinical Trials Role of Clinical Testing

Clinical trials are the only ways by which the effectiveness of new antiviral agents , safety of the drugs and the proper dosage can be determined.

Phase-Specific Trials

Phase I involves only safety and metabolism while Phase II and III deals with efficacy of drugs in larger and correspondingly more diverse populations. The essence of effectiveness of broad-spectrum antivirals involves conducting powerful and exhaustive trial designs when multiple viruses are involved (Robinson et al., 2022).

Adaptive Trial Designs: Changes in the trial characteristics include adaptive protocols which enable changes to the trial in real time based on the results from the trial (Robinson et al., 2022).

Regulatory Hurdles

ER for broad-spectrum antivirals entails weighty assessments because of claim generality.

Real-World Evidence

Using observational data from post-approval utilization can help fill other gaps left by non-real-world evidence methodologies for broad-spectrum antiviral efficacy (Robinson et al., 2022).

Expedited Approvals

LOCs and EUAs illustrated in the current pandemic of COVID -19 indicate how regulatory agencies can flexibly deploy frameworks for prioritizing hurriedly needed antiviral products

CONCLUSION

The improvement in the synthesis of antiviral agents has enriched the possibility of management of viral diseases, giving hope in case of pandemics and appearance of new viral threats. This review focuses on the research gap on the role of chemistry in introducing high added value to antiviral drugs, the accomplishments of current structures in their battle against viruses, well-coordinated viral replication, and ways of handling drug resistance. Main advances in innovation include finding of new chemical entities such as protease and polymerase inhibitors, peptoids and peptide based drugs and the application of nanotechnology and computational intelligence in rational drug design and high throughput screening. Nevertheless, there are still some important issues to solve. New strains that develop immunity to the drugs, the differences in viral agents, and the requirement for development of drugs that can treat a number of diseases at once challenges the contemporary scientific world's resources. In addition, challenges in drug efficacy, toxicity, and safety regulation persist, in taking all the needy and potential antiviral drugs to people. Experimental approaches to antivirals for the future include the integration of conventional and alternative methods. That is, employing AI, and structure-based drug design developing a much-needed targeted and broadly effective therapeutic agents. Vaccines are just as crucial to create, especially mRNA and viral vector platforms that have revolutionized the way we approach diseases that exist including COVID-19. In conclusion, divergence and specialization of chemistry, computation and interdisciplinary consolidation are going to play a significant role in responding to the dynamic problems associated with viral infections. Future availability of the antiviral therapies will remain a key determinant of global health risks, it will therefore require ongoing investment in the research and development of more effective solutions with affordable access.

REFERENCE

1. Payne, S. (2023). Antiviral agents. In S. Payne (Ed.), Viruses (2nd ed., pp. 99–105). Academic Press. https://doi.org/10.1016/B978-0-323-90385-1.00024-8

2. Brady, D.K., Gurijala, A.R., Huang, L., Hussain, A.A., Lingan, A.L., Pembridge, O.G., Ratangee, B.A., Sealy, T.T., Vallone, K.T. and Clements, T.P. (2024), A guide to COVID-19 antiviral therapeutics: a summary and perspective of the antiviral weapons against SARS-CoV-2 infection. FEBS J, 291: 1632-1662. https://doi.org/10.1111/febs.16662

3. Sydorenko, A. (2023). ANTIVIRAL DRUGS IN THE TREATMENT OF COVID-19. Actual problems of modern medicine: Bulletin of the Ukrainian Medical Stomatological Academy , 23 (2.2), 156-159. https://doi.org/10.31718/2077-1096.23.2.2.156

4. Săndulescu, O., Apostolescu, C. G., Preoțescu, L. L., Streinu-Cercel, A., & Săndulescu, M. (2023). Therapeutic developments for SARS-CoV-2 infection—Molecular mechanisms of action of antivirals and strategies for mitigating resistance in emerging variants in clinical practice. Frontiers in Microbiology, 14, Article 1132501. https://doi.org/10.3389/fmicb.2023.1132501

5. Todorovski, T., Kalafatovic, D., & Andreu, D. (2023). Antiviral Peptide-Based Conjugates: State of the Art and Future Perspectives. Pharmaceutics, 15(2), 357. https://doi.org/10.3390/pharmaceutics15020357

6. Agrawal, P.; Bhalla, S.; Usmani, S.S.; Singh, S.; Chaudhary, K.; Raghava, G.P.S.; Gautam, A. CPPsite 2.0: A Repository of Experimentally Validated Cell-Penetrating Peptides. Nucleic Acids Res. 2016, 44, D1098–D1103

7. Alsafi, R., Alghamdi, S., & Asif, M. (2022). Antiviral Drugs and Their Roles in the Treatment of Coronavirus Infection. IntechOpen. https://doi.org/10.5772/intechopen.101717

8. Peng, S., Wang, H., Wang, Z., & Wang, Q. (2022). Progression of Antiviral Agents Targeting Viral Polymerases. Molecules, 27(21), 7370. https://doi.org/10.3390/molecules27217370

9. K. Ghosh, J. L. Mishevich, A. Mesecar, H. Mitsuya, (2022) Recent Drug Development and Medicinal Chemistry Approaches for the Treatment of SARS-CoV-2 Infection and COVID-19 ChemMedChem 17, e202200440.

10. Hou, L., Zhang, Y., Ju, H., Cherukupalli, S., Jia, R., Zhang, J., Huang, B., Loregian, A., Liu, X., & Zhan, P. (2022). Contemporary medicinal chemistry strategies for the discovery and optimization of influenza inhibitors targeting vRNP constituent proteins. Acta Pharmaceutica Sinica B, 12(4), 1805–1824. https://doi.org/10.1016/j.apsb.2021.11.018

11. Buchwald, P. (2022). Developing small-molecule inhibitors of protein-protein interactions involved in viral entry as potential antivirals for COVID-19. Frontiers in Drug Discovery, 2. https://doi.org/10.3389/fddsv.2022.898035

12. Ianevski, A., Ahmad, S., Anunnitipat, K. et al. Seven classes of antiviral agents. Cell. Mol. Life Sci. 79, 605 (2022). https://doi.org/10.1007/s00018-022-04635-1

13. Choudhuri, S., Yendluri, M., Poddar, S., Li, A., Mallick, K., Mallik, S., & Ghosh, B. (2023). Recent Advancements in Computational Drug Design Algorithms through Machine Learning and Optimization. Kinases and Phosphatases, 1(2), 117-140. https://doi.org/10.3390/kinasesphosphatases1020008

14. Joshi, R. P., Schultz, K. J., Wilson, J. W., Kruel, A., Varikoti, R. A., Kombala, C. J., Kneller, D. W., Galanie, S., Phillips, G., Zhang, Q., Coates, L., Parvathareddy, J., Surendranathan, S., Kong, Y., Clyde, A., Ramanathan, A., Jonsson, C. B., Brandvold, K. R., Zhou, M., ... Kumar, N. (2023). AI-accelerated design

of targeted covalent inhibitors for SARS-CoV-2. Journal of Chemical Information and Modeling, 63(5), 1438–1453. https://doi.org/10.1021/acs.jcim.2c01377

15. Delgado-Maldonado, T., González-González, A., Moreno-Rodríguez, A., Bocanegra-García, V., Martinez-Vazquez

16. A. V., de Luna-Santillana, E. d. J., Pujadas, G., Rojas-Verde, G., Lara-Ramírez, E. E., & Rivera, G. (2024). Ligand- and Structure-Based Virtual Screening Identifies New Inhibitors of the Interaction of the SARS-CoV-2 Spike Protein with the ACE2 Host Receptor. Pharmaceutics, 16(5), 613. https://doi.org/10.3390/pharmaceutics16050613

17. K.L. Saar, W. McCorkindale, D. Fearon, M. Boby, H. Barr, A. Ben-Shmuel, , N. London, F. von Delft, J.D. Chodera, A.A. Lee, (2023) Turning high-throughput structural biology into predictive inhibitor design, Proc. Natl. Acad. Sci. U.S.A.120 (11) e2214168120, https://doi.org/10.1073/pnas.2214168120

18. Diakou, I., Papakonstantinou, E., Papageorgiou, L., Pierouli, K., Dragoumani, K., Spandidos, D.AVlachakis, D. (2022). Novel computational pipelines in antiviral structure-based drug design (Review). Biomedical Reports, 17,97. https://doi.org/10.3892/br.2022.1580

19. Dai, R., Gao, H., & Su, R. (2023). Computer-aided drug design for virtual-screening and active-predicting of main protease (Mpro) inhibitors against SARS-CoV-2. Frontiers in Pharmacology, 14. https://doi.org/10.3389/fphar.2023.1288363

20. Eni, D.B., Cassel, J., Namba-Nzanguim, C.T. et al. Design, synthesis, and biochemical and computational screening of novel oxindole derivatives as inhibitors of Aurora A kinase and SARS-CoV-2 spike/host ACE2 interaction. Med Chem Res 33, 620–634 (2024). https://doi.org/10.1007/s00044-024-03201-7

21. Mr. Abu Tahir ,"Antiviral Drugs", Edited Book of Pharmacology-III [According to Latest Syllabus of B. Pharm-VI Semester of Pharmacy Council of India] ,IIP Series, Volume 1, September, 2024, Page no.109-116, e-ISBN: 978- 93-6252-262-7 , DOI/Link: https://www.doi.org/10.58532/nbennurphch12

22. Hejran, A. B., Sarwari, A. A., Hasand, M. H., Monib, A. W., Niazi, P., Basir, A. Q., Sediqi, S., & Kaka, U. M. (2024). IMPACT OF ANTIVIRAL THERAPEUTIC DRUGS ON TREATMENT OUTCOMES AND CLINICAL

23. PARAMETERS IN SARS-COV-2. KazNU Bulletin. Ecological Series , 79 (2), 136–146. https://doi.org/10.26577/EJE.2024.v79.i2-013

24. Payne, S. (2023). Antiviral agents. In S. Payne (Ed.), Viruses (2nd ed., pp. 99–105). Academic Press. https://doi.org/10.1016/B978-0-323-90385-1.00024-8

25. Andrews, H. S., Herman, J. D., & Gandhi, R. T. (2024). Treatments for COVID-19. Annual Review of Medicine, 75, 145–157. https://doi.org/10.1146/annurev-med-052422-020316

26. Blaskovich, M. A. T., & Verderosa, A. D. (2023). Use of antiviral agents and other therapies for COVID-19. Seminars in Respiratory and Critical Care Medicine, 44(1), 118–129. https://doi.org/10.1055/s-0042-1758837

27. Chalotra, R., Singh, A., Chib, S., Gautam, S., Amanat, M., Chaudhary, K., Kumar, M., & Singh, R. (2024). Antiviral medications: Unravelling their significance in context to COVID-19. Volume 5, Issue 4, Article ID: e240124226147. https://doi.org/10.2174/0126667975280977231224175043

28. Sydorenko, A. (2023). ANTIVIRAL DRUGS IN THE TREATMENT OF COVID-19. Actual problems of modern medicine: Bulletin of the Ukrainian Medical Stomatological Academy , 23 (2.2), 156-159. https://doi.org/10.31718/2077-1096.23.2.2.156

29. Muhammad Zahid Ali, Yousra Anwar, Adil Abbas, Noor Ul Ain, Zainab Khalid, Arooj Sattar, Muhammad Usman, Arzoo Nazir, Shah Zeb. (2023). Recent Advances in Vaccine Technology for Viral Infection Management: A Spotlight on Next-Generation Vaccines and Nucleic Acid-Based Platforms. Pakistan Journal of Medical & Health Sciences, 17(05), 261. https://doi.org/10.53350/pjmhs2023175261

30. Vlasova-St. Louis, I., & Abadie, J. (2023). Prophylactic Ribonucleic Acid Vaccines to Combat RNA Viral Infections in Humans. IntechOpen. https://doi.org/10.5772/intechopen.108163

31. Hanke, Tomáša,b. New vector and vaccine platforms: mRNA, DNA, viral vectors. Current Opinion in HIV and AIDS 17(6):p 338-344, November 2022. https://doi.org/10.1097/COH.0000000000000763

32. khalaf, Noorulhuda F. (2022). Viral Vaccine Strategies. Journal of Biotechnology Research Center (JOBRC), 16(2). https://doi.org/10.24126/jobrc.2022.16.2.674

33. Meade, E., Rowan, N., & Garvey, M. (2023). Bioprocessing and the Production of Antiviral Biologics in the Prevention and Treatment of Viral Infectious Disease. Vaccines, 11(5), 992. https://doi.org/10.3390/vaccines11050992

34. Paiva, EBC ., Silveira, CR da ., Kosmiscky, I. de O. ., Gomes , C. da C., Barros, SDG ., Farias, RA da C. ., Saldanha, Z. de O. ., Gomes, ARQ ., Coelho, CS do C. ., & Cartágenes, S. de C. (2022). Pharmacological aspects of pre-exposure prophylaxis (prep) to HIV: a review. Research, Society and Development , 11 (9), e15511924710. https://doi.org/10.33448/rsd-v11i9.24710

35. Sundareshan V, Swinkels HM, Nguyen AD, Mangat R, Koirala J. Preexposure Prophylaxis for HIV Prevention. 2024 Jan 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29939566.

36. Hangyu W, Panpan L, Jie S, Hongyan W, Linmiao W, Kangning H, Yichen S, Shuai W, Cheng W. Advancements in Antiviral Drug Development: Comprehensive Insights into Design Strategies and Mechanisms Targeting Key Viral Proteins. J. Microbiol. Biotechnol. 2024;34:1376-1384. https://doi.org/10.4014/jmb.2403.03008

37. Golsorkhi, M., Ravanshad, Y., Azarfar, A., & Ravanshad, S. (2020). A Review on New Coronavirus Mechanism of Action. Journal of Pediatric Nephrology, 8(2), 1–4. https://doi.org/10.22037/jpn.v8i2.30702

38. Williford, S.E., McGivern, D.R. (2016). Mechanism of Action of Direct-Acting Antivirals: New Insights into the HCV Life Cycle. In: Miyamura, T., Lemon, S., Walker, C., Wakita, T. (eds) Hepatitis C Virus II. Springer, Tokyo. https://doi.org/10.1007/978-4-431-56101-9_11

39. Challa S, Scott AD, Yuzhakov O, Zhou Y, Tiong-Yip CL, Gao N, Thresher J, Yu Q.2015.Mechanism of Action for Respiratory Syncytial Virus Inhibitor RSV604. Antimicrob Agents Chemother59: https://doi.org/10.1128/aac.04119-14

40. Gerba CP, Boone S, Nims RW, Maillard J, Sattar SA, Rubino JR, McKinney J, Ijaz MK.2024.Mechanisms of action of microbicides commonly used in infection prevention and control. Microbiol Mol Biol Rev88:e00205-22. https://doi.org/10.1128/mmbr.00205-22

41. Lambert, P.A. (2013). Mechanisms of Action of Microbicides. In Russell, Hugo & Ayliffe's (eds A.P. Fraise, J.-Y. Maillard and S.A. Sattar). https://doi.org/10.1002/9781118425831.ch5

42. Liu, D., Ndongwe, T. P., Ji, J., Huber, A. D., Michailidis, E., Rice, C. M., Ralston, R., Tedbury, P. R., & Sarafianos, S. G. (2023).

43. Mechanisms of Action of the Host-Targeting Agent Cyclosporin A and Direct-Acting Antiviral Agents against Hepatitis C Virus. Viruses, 15(4), 981. https://doi.org/10.3390/v15040981

44. P.C. Robinson, D.F.L. Liew, H.L. Tanner, J.R. Grainger, R.A. Dwek, R.B. Reisler, L. Steinman, M. Feldmann, L. Ho, T. Hussell, P. Moss, D. Richards, N. Zitzmann, (2022) COVID-19 therapeutics: Challenges and directions for the future, Proc. Natl. Acad. Sci. U.S.A. 119 (15) e2119893119, https://doi.org/10.1073/pnas.2119893119

45. Azizi, M., Kokabi, H., Dianat-Moghadam, H., & Mehrmohammadi, M. (2022). Challenges and future directions. In46. M. Azizi, H. Kokabi, H. Dianat-Moghadam, & M. Mehrmohammadi (Eds.), Targeted cancer imaging (pp. 139– 201). Academic Press. https://doi.org/10.1016/B978-0-12-824513-2.00006-1