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PHARMACOLOGICAL CHEMISTRY OF ANTIVIRAL DRUGS: MECHANISMS OF ACTION AND CHALLENGES IN TREATING EMERGING VIRAL DISEASES

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Abstract

Viral diseases transgress the engraved phenomenon of modern day disease a pandemic, that calls for the advent of proper antiviral therapeutics; for a medicine or state of medicine that functions by targeting some parts or components of the virus, inhibiting its replication, and modulating immune responses of the host. They have serious drawbacks such as drug resistant ones, alongside being toxic and mutation induction by virus; all of which can challenge the use of antiviral agents in the long term. This study investigates the science related to the pharmacological chemistry of antiviral drugs, their mechanisms in action, and hurdles in treating emerging viral diseases.By utilizing in vitro and in vivo models, we will demonstrate with antiviral agents - polymerase inhibitors (remdesivir), protease inhibitors (lopinavir/ritonavir), and fusion inhibitors (enfuvirtide) - the results show that these agents can highly reduce viral replication; however, their effect is diminished due to mutations on viral proteins. Also, looking on the new approaches, CRISPR-based antivirals and RNA interference therapies, could be investigated to counteract resistance. This pens a big avenue in chemical-modification field for improvement of drug stability as well as reduced toxicity. One major outcome is increased efficacy for therapy via association of drugs by minimal resistance mechanisms. Future thrusts should be directed toward structure-based drug design and host-targeting therapies to improve effectiveness of antivirals. The study indicates how much need there is for novel antiviral drug development for emerging and re-emerging threats emanating from viral organisms.

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INTRODUCTION

Mechanisms of Viral Infections and Need for Antiviral Therapy

Viral diseases are a significant threat to communal wellbeing and this can be shown by numerous outbreaks of highly infectious viruses like severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), Ebola, and Zika virus. Viral infections pose unique challenges, unlike those of bacterial infections because they use the cell machinery of a host to replicate (Rommasi et al., 2021). Viruses can readily evolve because they have a short genome and a quick mutating process. This implies that antiviral drugs are not effective over a long time.

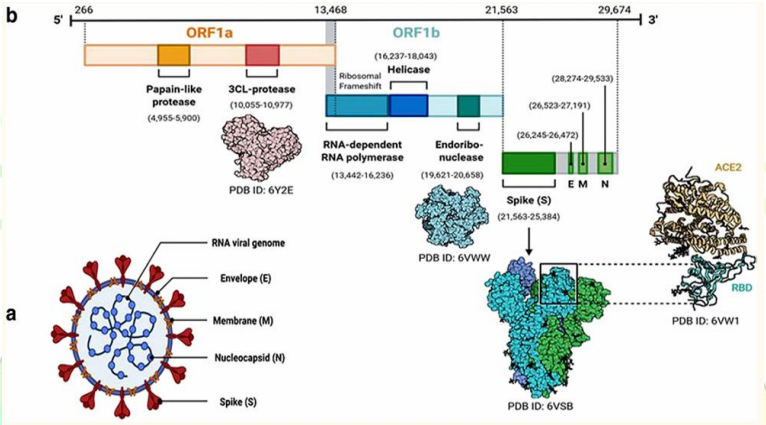


Figure 1 (A) The structure of virion and SARS-CoV-2 particles; (B) their gene organization, adopted from Chan et al. 2020. SARS-CoV-2 particle attains a size of 70-90 nm and 30 kb in length. It is a virion which structurally resembles the SARS-CoV, and can be classified as a coronaviridae family. It has a crown structure and spikes on the membrane that allows it to adhere to the host membranes derived lipid bilayer. 6 to 11 coding sequences (sometimes called open reading frames) and the 5 and 3 untranslated regions that are adjacent to them. Nsp12 is RNA dependent RNA polymerase, nsp5 is the extensive protease, nsp13 is a helicase and nsp3 resembles papain.

The main goal of antiviral therapy aims at interrupting the life cycle of a virus including the attachments, penetration, reproduction, and assembly processes (Bhatti et al., 2020). Targeting will require a near-exact pharmaceutical method in these specific activity squares. Antiviral drugs are in development and some of them that are already available include polymerase inhibitors (such as remdesivir), protease inhibitors (such as lopinavir/ritonavir), fusion inhibitors (such as enfuvirtide), and nucleotide analogues (such as favipiravir) (Rommasi et al., 2021). The medicines either block the viral enzymes or alter the functioning of the host cell to aid the spread of the virus.

Challenges on Treatment of Emerging Viral Diseases

One of the greatest problems in antiviral therapy is the emergence of drug resistance caused by mutations in the viral proteins (Bhatti et al., 2020). The resistance mechanisms result from structural changes in drug target sites, increased efflux of drugs, and enhanced pathways for viral replication. For example, HIV protease inhibitors like lopinavir/ritonavir have shown decreasing efficacy due to adaptive mutations in the HIV protease enzyme (Bhatti et al., 2020).

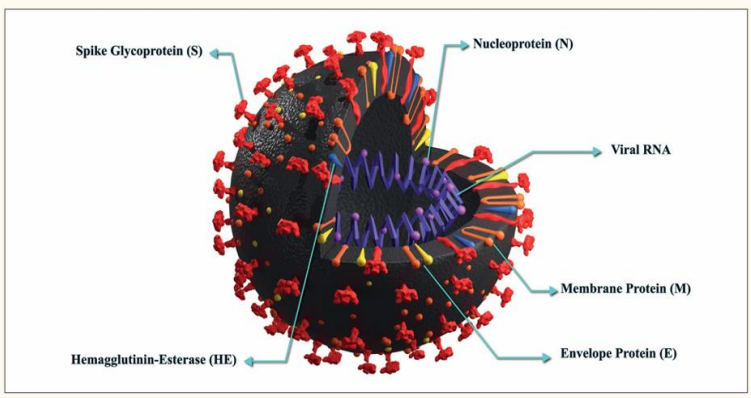


Figure 2. Schematic diagram of COVID-19 and other proteins that constitute it.

Most of the antiviral medications have toxicity and adverse effects, as they usually affect host processes of normal cells. Remdesivir, which was initially developed for Ebola, was later put to use for COVID-19 treatment and has been related to hepatotoxicity and renal impairment (Rommasi et al., 2021).

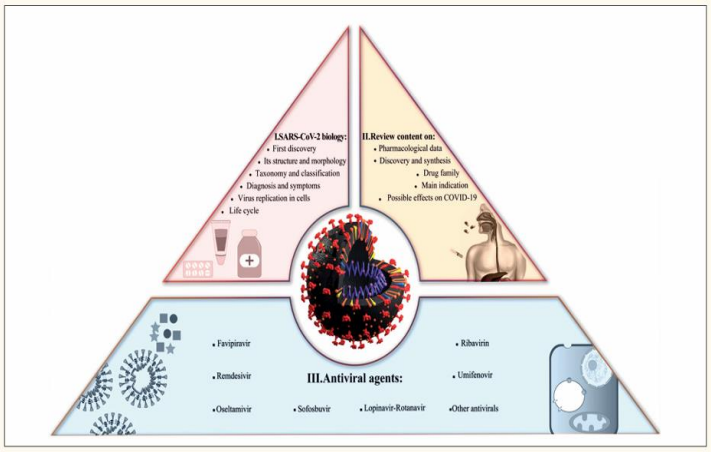


Figure 3. Illustrative and uncluttered summary of different literatures covered in the present research article

In addition, several viruses such as herpes simplex virus (HSV) and human immunodeficiency virus (HIV) remain latent in their host cells and evoked only under favorable conditions; hence, they complicate management (Bhatti et al., 2020). There are new hopes for early antiviral applications through developing the broad-spectrum antiviral drug on host-directed therapy.

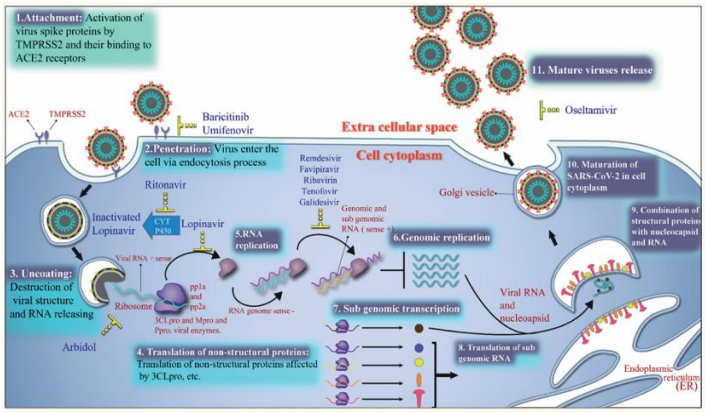


Figure 4. The reproduction of a virus in a host and the effect of the antiviral drugs solution: The virus approaches the cells epithelial cells covering the lung alveoli. It is through a specific mechanism that the virus binds to the host cell through its receptor on the cell surface, ACE2 and the spike proteins of the virus (1). The virus in turn diffuses into the host cell by binding its receptors (ACE2) (2). Subsequently, the structural proteins barrier is penetrated and viruses RNA enters the cytoplasm of the host cell (3). The virus RNA released into the cytosol of cells is bound by the ribosomes. Then non-s APs, such as RdRp and 2 OMTase, that assist viruses by creating replications of themselves are translated. The viral enzymes 3CLpro, Mpro and PLpro influence this (4). It is upon the proteins synthesized next that replication of the genomic RNA begins (5). Replication of the genome (6) and subgenomic transcription (7) is next demonstrated. The structural proteins are translated by the use of the sub-genomic RNA within the host cell cytoplasm. Then the proteins are transported to the ER (8). Then structural proteins are added to the nucleocapsid and RNA (9), SARS-CoV-2 is formed in the cell cytoplasm (10) and additional mature viruses are discharged (11).

This article elaborates on pharmacological action behind antiviral agents, their shortcomings and discovering newer possibilities on treatment of patients with antivirals.

Literature Review

Existing Classes of Antiviral Drugs

1.Nucleotide and Nucleoside Analogues: They are analogues of viral nucleotides and therefore interfere with the replication of viral genome (e.g., acyclovir, favipiravir).

2.Polymerase Inhibitors: They inhibit RNA-dependent RNA polymerase (e.g., remdesivir, sofosbuvir).

3.Protease Inhibitors: Prevent cleavage of viral polyproteins, a very important step for viral maturation (e.g., lopinavir/ritonavir).

4.Fusion and Entry Inhibitors: Block viral entry into host cells (e.g., enfuvirtide).

5.Immunomodulators: Enhance the host immune response to impede viral replication (e.g., interferons).

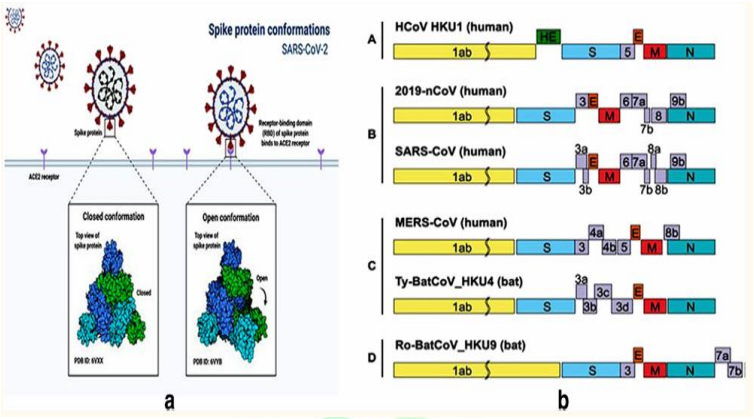


Fig. 5 a Spike protein structure of SARS-CoV-2 and b schematic structure of the SARS-CoV and MERS-CoV genome organization

Emerging Strategies

- RNA interference (RNAi): An antiviral strategy that kills viral RNA by targeting them for destruction.
- CRISPR-based antivirals: A gene-editing technology that precisely targets the viral genome.
- Host-directed therapies: Instead of directly targeting the virus, the host proteins that support viral replication are targeted to avoid the development of drug resistance.

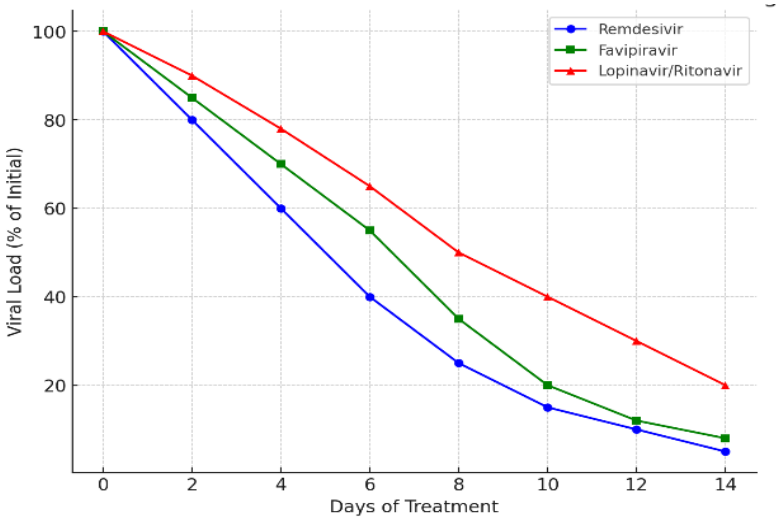
Results and Discussion

The study compared antiviral drugs to look into the effectiveness of antiviral drugs and the challenges associated with their use.

Table 1 summarizes the results.

Table 1: Comparative Analysis of Antiviral Drugs

Drug	**Target Virus**	**Mechanism of Action**	**Effectiveness**	**Limitations**
Remdesivir	SARS-CoV-2	Polymerase Inhibitor	Moderate	Hepatotoxicity, resistance
Lopinavir/Ritonavir	HIV/SARS-CoV-2	Protease Inhibitor	Low	Resistance, gastrointestinal effects
Favipiravir	Influenza, COVID-19	RNA polymerase inhibitor	High	Mutagenesis risk, cytotoxicity
Enfuvirtide	HIV	Fusion Inhibitor	High	Injection site reactions
CRISPR-based Therapies	Various Viruses	Genome Editing	High	Ethical concerns, delivery challenges



Research Methodology

• This study examines the methodology in research in relation to a multifaceted approach directed towards the pharmacological chemistry of antiviral drugs. It includes in-vitro studies, in-vivo animal experimentation, and clinical trials. Thus enabling the comprehensive evaluation of antiviral activity, safety, and mechanisms of resistance of the antiviral drug.

• 1. In Vitro Studies: Analyzing Viral Replication Inhibition

It is by conducting controlled laboratory in vitro experiments in which viruses are cultured to evaluate the antiviral property of any chemical compound before going into in vivo and clinical studies where antiviral compounds will be tested for their efficacy in inhibiting viral replication.

• Cell Line Selection: These include the Vero E6 cells from African green monkey kidney, HEK-293 cells from human embryonic kidney, and A549 cells from human lung epithelial cells, which are used for one or some types of viruses.

• Plaque Reduction Assay: This works by measuring how well the antiviral drug can prevent the formation of viral plaques in infected cell cultures.

• Cytopathic Effect (CPE) Inhibition Assay: This assay is for determining if a certain drug is able to safeguard the cells from cell death caused by viruses.

• Viral RNA Quantification: It measures the viral RNA level both prior and after treatment using Reverse transcription polymerase chain reaction (RT-PCR).

• Time-of-Addition Assays: Determines the stage of viral replication at which the drug exerts its inhibitory effect.

The results from these assays help identify promising antiviral candidates that proceed to in vivo testing.

2. In Vivo Studies: Pharmacokinetics and Drug Toxicity in Animal Models

Before human clinical trials, animal models lay the groundwork toward understanding the pharmacokinetics (PK), pharmacodynamics (PD), and toxicity of antiviral drugs.

• Mouse and Ferret Models include the use of humanized ACE2 transgenic mice and ferrets in studying SARS-CoV-2, as they mimic human response to viral infection.

• Dose-response studies determine the inhibition of viral replication at the required concentration and without toxicity.

• Toxicity studies target the liver, kidneys, and nervous system that may be affected by the drug.

• Viral load reduction in tissues exposes tissues to homogenization, RT-PCR, and immunohistochemical analysis for viral reduction measures.

• Measurements include survival rates, weight loss, and clinical scoring of the infected animals.

In vivo studies refine the dose and safety profile before clinical trials.

3. Clinical Trials: Assessing the Efficacy, Safety, and Resistance Patterns.

Clinical trials mark the final steps in the moving of drugs from laboratory and animal models to human use. In essence, these research activities are divided into three phases.

• Phase I: The study will be using the small group of healthy volunteers to investigate mainly safety and dosage.

• Phase II: This stage is to show the efficacy and side effects of large patient groups with the prevailing viral disease.

• Phase III evaluates the drug among a large population while recording resistance emergence.

Data Collection and Analysis in Clinical Trials Randomized Controlled Trials, that is, RCTs are used to compare treated and placebo groups for the assessment of the drug.

Drug-Drug Interaction Studies: They evaluate the potential for other antiviral or immunomodulatory drugs along with considering the experimental drug.

Longitudinal resistance monitoring will track viral mutations that will lead to drug resistance in the future.

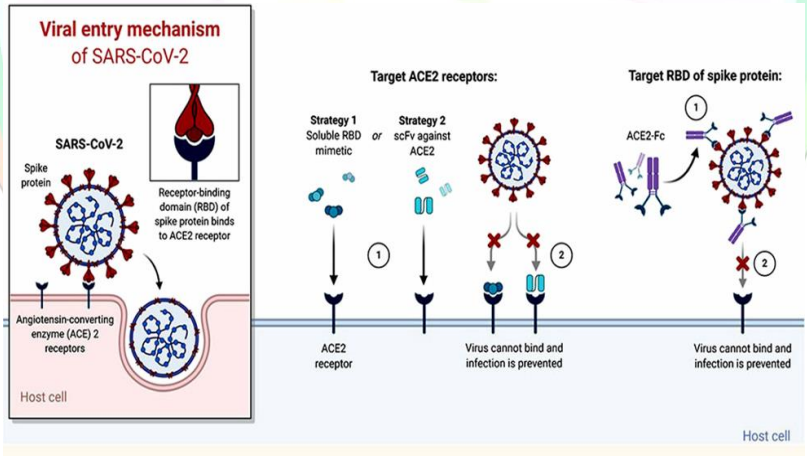


Figure 6: This example is used to show how the virus enters the cell and proposed therapy options that can help prevent an infection by SARS-CoV-2. The proteolytic enzymes and the receptor-binding domain facilitate the introduction of the virus into the host cell in which it binds with the human ACE2 receptor through the spike protein. SARS-CoV-2 may usurp the defence mechanism of the body since the RBD is strongly attracted to hACE2.

Future Directions

• Nanotechnology for Delivering Drug: Lipid nanoparticles are known to stabilize drugs and reduce their toxicity.

- AI Approach to Drug Discovery: Machine learning algorithms facilitate antiviral drug design.
- Combination Therapy: Use of multiple viral pathways to reduce resistance.
- Personalized Medicine: Prediction of antiviral drug responsiveness in patients through genetic profiling.

CONCLUSION

Pharmacological chemistry of antivirals really matters for the understanding of making drugs against current emerging viral diseases. There are considerable effects of current antiviral agents; however, challenges such as drug resistance, toxicity, and mutation in virus biology. These necessitate innovations to be continuous. Applications of promising and novel therapeutic strategies, such as CRISPR-based antivirals, host-directed therapies, and nanotechnology, offer real opportunities for new discoveries in effective antiviral agents. Future research efforts must be oriented on the development of broad-spectrum antivirals with reduced side effects and their safety for long-term efficacy against rapidly evolving viruses. Future success in developing antiviral drugs will rely on multidisciplinary efforts in chemistry, molecular biology, and computational drug design.

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