

REVIEW ARTICLE

The Pathophysiology of Repurposed Antiviral Drugs for treatment of COVID-19 Infection

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ABSTRACT

Our planet earth has seen many viral pandemics. The most recent pandemic was Severe Acute Respiratory Syndrome (SARS-CoV-2) commonly called Corona Virus disease (COVID-19). It was first reported in Wuhan Peoples Republic of China, in December 2019. COVID-19 is a positive-sense single-strand enveloped RNA virus mainly found in mammals. To date, a total of six species of coronavirus have been reported that affected humans. These mainly cause respiratory, hepatic, enteric, and neurological complications. Since it is a novel virus, different therapies were used for the treatment. These measures comprised of mostly repurposing of already available drugs, more specifically antiviral drugs. In this review article, we have summarized the virus-host relation and chemical structure and also discussed in detail the proposed mechanism of these repurposed antiviral drugs.

Key Words: Covid-19, Cytokine Storm, Therapeutic Drugs, Virus.

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Introduction

Viruses are the most diverse and abundant form of life that exists. They play a pivotal role in the evolution and ecology of our biosphere.¹⁻³ Almost all cellular organisms nurture distinctive virus reserves which compel intracellular genetic parasites to encase their genome into virions (virus particles).⁴ This ubiquity of viruses is suggestive that genetic parasites will emerge in the replicator system^{5,6} which in turn suggests that the evolution of life is in fact story of Host-Virus Co-evolution.⁷⁻⁹ Moreover, without the elucidation of the virus origin, the evolution of life is impossible to be understood yet their origin is still mysterious.¹

Coronavirus (CoV) is a member of single-stranded RNA viruses and belongs to the order Nidovirales. The order is comprised of Arteriviridae, Coronaviridae, and Roniviridae families. Furthermore, the Coronaviridae is further classified into Coronavirinae and Torovirinae. Coronavirinae is

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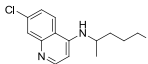
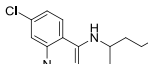
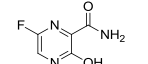
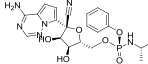
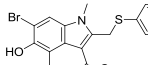
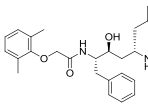
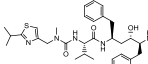
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again subdivided into alpha, beta, gamma, Delta-Corona viruses based on their phylogenetic clustering.¹⁰ Their viral RNA genome length ranges between 26 to 32 kilobases.¹¹ The structure of Coronaviruses is large, enveloped, and has a positive-stranded RNA genome. The nucleocapsid protein (N) forms a helical capsid that entraps the viral genome which in turn is protected/covered by an envelope. With the viral envelop at least three structural proteins are associated. The envelope protein (E) and membrane protein (M) keeps the structure of the virus intact. Whereas, the spike protein (S) helps the virus in attachment and penetration through the host cell membrane. In a few of the coronaviruses, the envelope is associated with hemagglutinin-esterase protein (HE). The role of spike protein apart from entering the host cells is that it determines the interaction between the host and virus and stimulate the immune response of the host.¹² These viruses can be extracted/isolated from various animal species which includes mammals and birds. Their widespread infectivity makes it an important member of the virus family.¹³

The emergence of novel viruses, has posed numerous threats to the health and economy of the countries. One such case is Corona Virus Disease 2019 (COVID-19) or Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) which spread

rapidly around the globe and was declared a pandemic by the World Health Organization (WHO). WHO called it. To date, the virus has claimed thousands of precious lives and have severely affected the world economy. Since the virus is a novel one, therefore, discovery of specific drug for its treatment will take time. In this review article, summary of repurposed drugs, their structure, proposed mechanism, on action will be discussed to help readers understand the structure of the virus, how it affects the host cells as well as the mechanistic effect of the resourced antiviral drugs on the COVID-19.^{14,15}

Table 1: Chemical structure and formula of compounds that interfere with viral replication

Name	Chemical Structure	Molecular Formula	Activity	References
Hydroxy-chloroquine		C ₁₈ H ₂₆ ClN ₃ O	Interfere with Viral entry	16
Chloroquine		C ₁₈ H ₂₆ ClN ₃	Interfere with Viral entry	16
Favipiravir		C ₅ H ₄ FN ₃ O ₂	Inhibit RdRp	17,18
Remdesivir		C ₂₇ H ₃₅ N ₆ O ₈ P	Inhibit RdRp	19
Umifenovir		C ₂₂ H ₂₅ BrN ₂ O ₃ S	Inhibit endosome virus-membrane fusion	20
Lopinavir		C ₃₇ H ₄₈ N ₄ O ₅	Inhibit protease	21
Ritonavir		C ₃₇ H ₄₈ N ₆ O ₅ S	Inhibit protease	22

How does Coronavirus infect cells?

Coronavirus is an intracellular parasite that exploits the host cells for their spreading and replication. Since the basis of the disease is the interaction between the virus and the host cells, therefore, knowledge about their interplay is of pivotal importance. We have compiled the so far available literature related to the virus-host relationship including virus attachment to the host, translation of the replicase and transcriptase, genome replication and mRNAs transcription, and assembling and budding till the formation of new virions. In the first step, coronavirus attaches itself to the host cell *via*

the S1 domain of their spike protein using the cognate receptor. This triggers the conformational changes in the S2 subunit, an enticing fusion of the virus and host cell plasma membranes. This is followed by the release of the nucleocapsid to the cytoplasm, the viral gRNA is translated *via* ribosomal frameshifting to synthesize polyproteins such as ppla and pplab. Host and viral protease enzymes auto-proteolytically process Ppla and pplab to produce 16 nonstructural proteins which in turn are assembled to form replicase-polymerase enzymes (Table 1). Replicase and polymerase enzymes are responsible for the replication of coronavirus, during this process, the gRNAs are replicated and subgenomic RNAs are transcribed and translated into structural proteins. The newly synthesized viral products get assembled in ERGIC which later on buds out as smooth-walled vesicles to the cytoplasm and leaves cytoplasm *via* exocytosis.²³

The range of coronavirus symptoms varies from asymptomatic, mild to severe state. However, in most of the infected patients, the most common symptoms observed were fever, sore throat, cough, fatigue, headache, breathlessness, and myalgia. Therefore, it is difficult to distinguish between COVID-19 and other respiratory infections. COVID-19 infections lead to pneumonia which in turn lead to the failure of the respiratory system and ultimately causes death. This progression is related to an extreme rise in inflammatory cytokines including IL2, IL7, IL10, IP10, GCSF, MCP1, MIP1A, and TNF α .^{24,25}

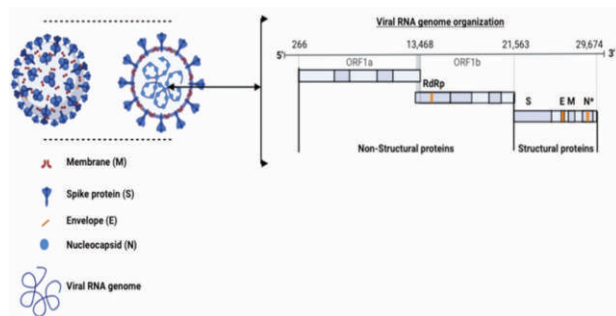


Fig 1: Depicts the structure and genome organization of SARS-CoV2. The virus structure is composed of envelope and membrane proteins with protruding spike protein encapsulating the nucleocapsid with genomic RNA. The viral genome is composed of two open reading frames (ORF), carrying non-structural proteins. The structural proteins encoding region is present at the 3' end of the genome that also express some accessory proteins. Figures courtesy of BioRender (www.biorender.com)

Repurposed antiviral drugs

Remdesivir is a phosphoramidate antiviral pro drug of Adenosine C-nucleotide synthesized by Gilead Science for treatment of the Ebola virus in 2017.^{26,27} Remdesivir is metabolized and activated into its active GS-441524 form, which conceal virus RNA polymerase and dodge viral exonuclease proofreading mechanism, this results in inhibiting viral RNA syntheses. Remdesivir causes chain termination of budding viral RNA. A group of researchers reported that remdesivir has shown efficacy against viral infections by reducing viral load in lungs of mice infected with the MERS-CoV virus. They also reported that remdesivir showed its efficacy in improving the functioning of lungs, and reducing pathological damage to lung tissues caused during viral infection.²⁸ In another study Wang et al. concluded from their obtained results that remdesivir effectively blocks COVID-19 infection at very low concentration (micromolar concentrations) and has high selectivity index (half-cytotoxic concentration (CC50)) > 100 μ M; SI > 129.87), (half-maximal effective concentration (EC50)), 0.77 μ M.²⁹ Similarly, Holshue et al. suggested from their findings that the administration of remdesivir showed enhanced efficacy against COVID19 viral infection in patients while recovering from pneumonia.³⁰ The current recommendation of remdesivir administration against COVID-19 is on the same protocol which was used for the treatment of Ebola, which included 200mg dose on the first day followed by 100mg dose till the next 9 days.³⁰ Furthermore, in one study researchers reported that the administration of remdesivir in the United States of America resulted in almost 70% improved oxygen intake in COVID19 infected patients and many of the subjects were extubated who were previously put on a ventilator. However, their study did not include control subjects,. It is too early to suggest the direct antiviral mechanism of remdesivir in reducing COVID-19 viral load in lungs/respiratory tract but never the less it has exhibited excellent therapeutic efficacy.¹⁹

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have almost the same chemical structure except that hydroxychloroquine has hydroxyl moiety which enables it to be less toxic contrary to chloroquine.

Both chloroquine and hydroxychloroquine have a long history of their prescription for the treatment of lupus erythematosus, rheumatoid arthritis and more frequently against malaria infections.³¹ One proposed mechanism of hydroxychloroquine and chloroquine is that both these drugs target lysosome which results in controlling host versus graft infections.³² Chloroquine gets accumulated into lysosomes which causes a significant decrease in the pH level of the lysosomes. This decrease in pH level affects the normal activity of lysosomal protease, which in turn affects glycosaminoglycan and protein degradation.^{32,33} Few studies indicated that Chloroquine inhibits COVID-19 entry into the host cells by hampering the host-virus attachment as it interferes with glycosylation of ACE2 receptor and binding of spike protein to the cell membrane. Based on their findings they reported that chloroquine can be effective during the early stages of infection before COVID-19 suppresses expression and activity of ACE2.^{34,35} Hydroxychloroquine exhibit anti-inflammatory efficacy on Th17-related cytokines (IL-6, IL-17, and IL-22) in normal persons, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients.³⁵ According to one report, the main factor which leads to the death of COVID-19 infected patients is the activation of the cytokine storm. Therefore, there are reports which suggest that both chloroquine and hydroxychloroquine suppresses cytokine storm.³⁶ Furthermore, *In Vitro* studies also suggested that chloroquine and hydroxychloroquine inhibit COVID-19 infections.¹⁶, There is very limited literature available related to the safety and efficacy of chloroquine and hydroxychloroquine against COVID-19, therefore care should be taken by the patients and clinicians during the administration of these drug.³⁷

Arbidol (Umifenovir)

Umifenovir branded as Arbidol is a derivative of indole carboxylic acids. The drug was first developed and launched by Russia in 1988 and since then been approved and administered in China and Russia for the treatment and prophylaxis of infections related to Influenza A and B, and various other arboviruses.²¹ Furthermore, Arbidol showed efficacy in *in-vitro* against viruses such as hepatitis C virus (HCV), human herpesvirus 8 (HHV-8), Tacaribe arenavirus, and Ebola virus.³⁸ Arbidol mechanism of action

against these viruses banks on the fact that it prevents fusion between the cell membrane and the virus by blocking the fusion between endosome and virus *via* interacting and interfering with the hydrogen bonds of phospholipids present in the cell membrane.³⁹ Blaising et al studied the mechanism of action of Arbidol on the virus. They concluded that the dual interaction of Arbidol with aromatic amino acids present in the protein structure and its interaction with membranes is pivotal for making Arbidol broad-spectrum antiviral drugs. These interactions could impact cellular functions or affect the virus itself which makes it a promising host targeting (HTA) or direct-acting antiviral drug (DAA).^{20,40} Furthermore, a retrospective study suggested that compared to the ritonavir-lopinavir (RTV-LPV) combination, the administration of RTV-LPV and Arbidol in combination exhibited enhanced negative conversion of COVID-19 infections and improved chest scan reports.⁴⁰ However, another study suggested that compared to favipiravir, Arbidol has shown lesser relief in cough and fever and recovery rate in the patients infected with COVID-19.⁴¹

Lopinavir-Ritonavir

Lopinavir is known as an inhibitor of the protease enzyme and is highly specific for HIV1 protease enzymes. Lopinavir is specifically administered in combination with Ritonavir. The lopinavir-ritonavir combination was first launched and marketed by Abbot and branded as Kaletra way back in 2000.⁴⁸ Lopinavir and Ritonavir combination is used to overcome the poor oral biotransformation and bioavailability of Lopinavir. Ritonavir enhances Lopinavir exposure. Ritonavir inhibits the enzymes responsible for the metabolism of Lopinavir which leads to increase exposure of Lopinavir and enhances its antiviral efficacy.⁴⁸ Lopinavir is a peptidomimetic molecule having a hydroxy ethylene moiety that imitates peptide linkage targeted by the protease enzyme of HIV-1, which cannot be cleaved on its own, and ultimately results in inhibition of HIV-1 protease enzyme.⁴⁹ A study reported that the administration of Lopinavir-Ritonavir combination with standard care in the individually randomized open-label controlled trial showed no benefits beyond standard care. However, nausea, asthenia, and diarrhea were the observed side effects during

the administration of the aforementioned combination.¹⁵ Another study conducted in South Korea suggested that the administration of Lopinavir and Ritonavir combination significantly inhibited COVID-19 titers. However, the study was conducted on a single patient during the initial phase of the COVID-19 outbreak in South Korea.⁴²

Avigan (Favipiravir)

Favipiravir, manufactured by Fujifilm Toyama in 2014 (branded as Avigan), is used for the treatment of novel influenza (Avian influenza) which is resistant to neuraminidase inhibitors. It is an analogue of guanine with pyrazine carboxamide moiety. The antiviral efficacy of Avigan gets lower due to competition in the presence of purine nucleosides.¹⁸ The Avigan *via* endocytosis first enters the cell and converts into active favipiravir ribofurannosyl phosphate *via* phosphorylation and phosphoribosylation.^{17,18} The proposed mechanism of action of Avigan is such that during viral RNA replication, it interrupts nucleotide incorporation by selectively targeting the catalytic domain of RdRp (RNA dependent RNA polymerase).¹⁸ Such phenomena results in causing mutation. Adenine (A) replaces guanine (G), thymine replaces cytosine, and in some cases, cytosine (C) is replaced by thymine (T) or uracil (U) in viral RNA, which leads to the triggering of destructive mutagenesis in viral RNA.¹⁸ Avigan is administered against various viral RNA viruses such as norovirus, ebola, and influenza.⁴³ Avigan was repurposed along with other antiviral drugs for assessing and exploring their potential efficacy against the COVID-19 virus. Among the tested drugs Chloroquine and Remdesivir have shown a suitable selectivity index. Furthermore, Avigan when tested against Covid-19 virus-infected Vero E6 cells exhibited half cytotoxic concentration over 400 μ M and half-maximal concentration for 61.88 suggesting that for safe and effective use, a higher concentration of Avigan is required.²⁹ Japan and China conducted randomized clinical trials on COVID-19 infected patients. and their analysis showed, relief time in fever and cough was significantly reduced in Avigan administered group as compared to Umifenovir administered group. Furthermore, the recovery rate in the Avigan administered group was higher (71.43%) than the Umifenovir administered group (55.86%).⁴¹ Few

other studies are in process in various countries assessing the safety and efficacy of Avigan against COVID-19 infections.²⁶

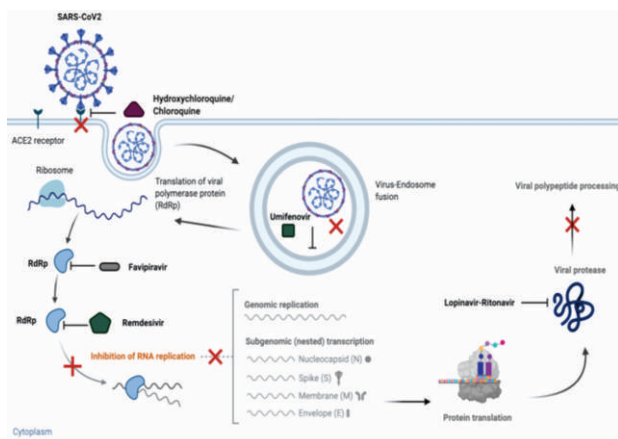


Fig 2: Illustrates the schematic representation of different inhibitors blocking SARS-CoV2 replication. The virus enters the cell *via* its spike interaction with the human ACE2 receptor, hydroxychloroquine/chloroquine inhibits this interaction by interfering with ACE2 glycosylation. The virus infects the cell and releases genomic RNA through endosome formation and fusion, Umifenovir inhibits this membrane-virus fusion and blocks RNA release. Once the RNA is released in the cytoplasm, RNA dependent RNA polymerase (RdRp) is translated for replication of genomic RNA. Favipiravir and Remdesivir inhibit RdRp and block genome replication. The viral genome encodes protease responsible for viral polyprotein processing, Lopinavir-Ribonavir inhibits these proteases to stop polyprotein processing. Figures courtesy of BioRender (www.biorender.com)

Conclusion

Many drugs approved by WHO has been repurposed for treating COVID-19 infection. Among the various prescribed drugs, antiviral drugs got pivotal importance and prominence. This review article, have summed up the literature available on the repurposed antivirals drugs, their proposed mechanism through which it interacts with host cells against the COVID-19 virus.

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