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Chapter

Antiviral Drugs and Their Roles in the Treatment of Coronavirus Infection

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Abstract

Viruses are the major pathogenic agents that cause various diseases. Antiviral drugs are used for the treatment of viral infections. Emergent advances of antiviral drugs are focused on two different approaches: targeting the host cell factors or the viruses themselves. Antiviral drugs that directly target the viruses include virus entry inhibitors, virus attachment inhibitors, uncoating inhibitors, protease inhibitors, polymerase inhibitors, nucleoside inhibitors, integrase inhibitors, and nucleotide reverse transcriptase. The protease inhibitors, viral DNA polymerase, and integrase inhibitors are the most commonly used antiviral drugs. Still, there are no effective antiviral drugs existing for several viral infections. Coronavirus disease-2019 (COVID-19) or SARS-CoV-2 is the newest member of the coronavirus family. No specific drugs particularly antiviral drugs have been approved for the treatment of COVID-19. Thus, it is extremely crucial to identify new drugs for the treatment of the COVID-19 outbreak. Various antiviral drugs are used for COVID-19 treatment. Currently, various drugs are under investigation to treat COVID-19 patients. Promising clinical outcomes for COVID-19 can be obtained by using alpha-interferon, remdesivir, lopinavir-ritonavir, favipiravir, ribavirin, umifenovir, oseltamivir, etc. Here, we reviewed anti-COVID-19 potencies of currently available antiviral drugs, and some antiviral drugs have been effective or prevent the spread of coronavirus.

Keywords: antiviral drugs, SARS-CoV-2, drug discovery, mechanism of action, pandemic

1. Introduction

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family of Coronaviridae. In this family, there are four types of viruses: α -coronavirus, β -coronavirus, γ -coronavirus, δ -coronavirus [1]. The CoV genome is an enveloped, positive-sense, and single-stranded RNA, and it has the largest genome of known RNA viruses. It is known that α - and β -CoV types cause infections in mammals as δ - and γ -CoVs infect birds [2]. Severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) belonging to β -CoVs are the most

aggressive strains of coronaviruses and cause viral pneumonia outbreaks [3, 4]. SARS-CoV disease is a kind of pneumonia and caused by novel CoV whose genome structure was more than 82% identical to those of SARS-CoV, named coronavirus disease 2019 (COVID-19) [5, 6]. SARS-Cov-2 is a beta gene virus genetically very close to bat-CoVRaTG13, and bat-SL-CoVZC45 Covs can cause severe illness. As the COVID-19 outbreak turned into a global threat, the World Health Organization (WHO) announced it as a global pandemic on 12 March 2020. The COVID-19 pandemic has changed the scenario of the entire world. COVID-19 outbreak started in Wuhan, China, has globally spread to 219 countries and territories [7]. Currently, there are few vaccines for COVID-19. Their acceptance and efficacy are an issue of debate across the whole world. Therefore, there is an urgent need to find drugs or vaccines for the treatment of COVID-19 infections effectively. However, there are some studies related to the use of known drugs such as remdesivir and chloroquine that have proved efficacy on COVID-19 infection. We summarize some antiviral drugs as therapeutic options for the treatment of COVID-19 [8].

COVID-19 mainly attacks the respiratory-tract-associated organs. Additionally, the virus has shown impact various to other organs or systems such as the gastrointestinal system, nervous system, etc. [9]. The most common symptoms in COVID-19 patients are fever, dry cough, loss of taste, lethargy, shortness of breath, dyspnea, chest pain, fatigue, myalgia, whereas headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are less commonly observed [10, 11]. Anosmia is also one of the most critical symptoms in COVID-19 patients [12]. COVID-19 is more contagious than other coronaviruses, and its transmission rate is higher than the closely related strain, SARS-CoV-10 [13]. Currently, new variants of COVID-19 are reported from different regions of the world. Coronavirus interacts with cell surface receptors such as angiotensin-converting enzyme-2 (ACE-2) and neuropilin to gain entry inside the cell. The receptor-binding domain of viral spike protein is essential in SARS-CoV-2 entry into the host cell via surface ACE-2 [14]. Recently, another cell receptor Neuropilin-1 was found to be involved in SARS-CoV-2 entry. After binding to the receptor, the conformational change in the spike protein leads to virus fusion with the host cell membrane. The virus may transfer the RNA directly inside the cells or may proceed through the endosomal pathway [15]. Upon translation of viral RNA, the viral replicase polyprotein PP1a and PP1ab are produced and cleaved into small products by viral endopeptidase [16]. RNA-dependent RNA polymerase (RdRp) produces subgenomic RNAs by discontinuous transcription [16, 17]. This further gets translated into respective viral proteins. After processing through the endoplasmic reticulum (ER), ER-Golgi intermediate compartment (ERGIC), and Golgi complex, the viral RNA and proteins are assembled into virions. These virions are transported through vesicles and exocytosed for transmission. These steps of the viral life cycle are beneficial virus inhibition targets for different drugs. The coronaviruses are ribonucleic acid (RNA) viruses, which have a positive single-strand RNA [14, 18]. When SARS-CoV-2 enters the body and comes in contact with the host cell membrane, some changes occur in the structure of the virus. The human TMPRSS2 protein alters the conformation of the spike glycoprotein in the virus. Two substantial protease enzymes, 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLPro), have essential roles in its viral replication process after it enters the host cell via ACE2 receptors [19]. The expression of several genes, such as AHCYL2, ZNF385B, etc., appears to have a strong correlation with the expression of ACE2 and TMPRSS2 protein receptors in human healthy and normal lung cells [20].

However, repurposing drugs could prove to be beneficial tactics for finding COVID-19 treatment, including cost-effectiveness, elimination of some clinical trial steps, faster on-field availability, combining the drugs with other possible drugs, and the invention of information about the mechanisms of the existing drug. Researchers were able to develop the possible COVID-19 medications using information from previous CoVs therapies, genetic sequences, and protein modeling studies. Antimalarials, antivirals, antibiotics, and corticosteroids are among the most often studied medications, and they have been repurposed based on their ability to neutralize viruses, reduce lung inflammation, or alleviate other illness symptoms. Chloroquine (CQ), hydroxychloroquine (HCQ), and azithromycin (AZM) are the most often utilized antiviral drugs against COVID-19, since they have already demonstrated reasonable antiviral efficacy against SARS-CoV, MERS-CoV, and SARS-CoV-2. Anti-HIV medications lopinavir/ritonavir (LPV/RTV) are being studied for COVID-19 since they were successful in previous CoV epidemics. Furthermore, the anti-Ebola medicine remdesivir (RDV) was evaluated for COVID-19 and garnered further attention.

Similarly, favipiravir (FPV), ribavirin (RBV), umifenovir (UFV), and oseltamivir (OTV) have broad-spectrum antiviral activities and clinically tested against COVID-19. The effective uses of HCQ, RDV, LPV/RTV, or LPV/RTV in combination with Interferon (IFN) β -1a against COVID-19 [21], all these drugs had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay in hospitalized patients. So far, to treat severe and critical COVID-19, only corticosteroids have proven effective [21]. Other drugs, such as Angiotensin-Converting-Enzyme inhibitors (ACEi), have also been used to treat COVID-19. However, no clear correlation was reported between mortality rate and ACEi drugs in hypertension patients with COVID-19 [22]. Due to the possibility of secondary infection in these patients, antibiotics have been used as various protocols [23].

Umifenovir (UFV) may interact with SARS-CoV-2 surface glycoproteins and lipids and obstruct the interaction with the entry receptor ACE-2. Antibodies against SARS-CoV-2 may prevent the virus from entering the body and causing illness. Chloroquine (CQ), hydroxychloroquine (HCQ), and azithromycin (AZM) can raise endosomal pH, making viral entrance and RNA release more difficult. CQ, HCQ, and AZM all have immunomodulatory properties. RDV, FPV, and RBV are nucleoside inhibitors that impede RNA replication and reduce RNA-dependent RNA polymerase activity. Fraternization of LPV with viral protease may change proteolysis. OTV may interact with components involved in exocytosis, preventing the virus from leaving the cell. Antibodies against cytokine receptors and corticosteroids have been shown to have anti-inflammatory properties in the face of excessive immune responses. Drugs such as CQ are wide-spectrum inhibitors of viral cell entry, and RDV is a wide-spectrum RNA polymerase inhibitor. SARS-CoV-2 infection concurrently triggers the host immune system and an inflammatory cascade response (cytokine storm). These are being targeted in the treatment of COVID-19 patients [23].

So far, no fully effective drug has been discovered against this virus. The antiviral drugs, usually nucleoside analogs or intracellular proteases, block the virus by preventing its entry into the cell or by interfering with its replication inside the cell. Protease inhibitors target certain proteases, whereas fusion inhibitors block the fusion phase of viral entrance. Transcription inhibitors impede viral replication by inhibiting RNA-dependent RNA polymerase during the reverse transcription process. Nucleoside reverse transcriptases are some of the transcriptase inhibitors. M2 channel protein is a target for certain antivirals. In this chapter, we have provided information

about repurposed drugs that are used against COVID-19, the mechanism of activity, therapeutic regimens, pharmacokinetics, and drug-drug interactions [7, 8].

2. SARS-CoV-2 life cycle and potential targets

The rationale major biochemical events and components in the replication cycle of coronavirus are considered as targets for currently developed drugs. These include the spike protein, proteolytic enzymes, and RNA-dependent RNA polymerase [24]. SARS-CoV-2 is transmitted mainly via respiratory droplets. The virus enters the host cells through two pathways, either via endosomes or plasma membrane fusion. In both mechanisms, the viral S protein mediates attachment to the membrane of the host cell and engages ACE2 as the entry receptor [25]. A host protease termed transmembrane serine protease 2 (TMPRSS2) activates the connection between S protein and ACE-2 [26]. S protein is used by the virus to destroy antibodies and make it simpler for it to attach to host receptors [27]. Beta-coronaviruses generally employ hemagglutinin-esterase (HE) to bind to sialic acid on the glycoprotein surface, despite the fact that the fusion machinery of SARS-CoV-2 remains unknown [28]. Fusion inhibitors might be used to prevent these fusion stages.

The envelope is peeled off when fusion is complete, and the SARS-CoV-2 genome, together with its nucleocapsid, penetrates the cytoplasm of the host cell. Its genome comprises the open reading frames 1a and 1b (ORF1a and ORF1b) genes, which create two polyproteins (pp) named pp1a and pp1b, which aid in the viral translation process by hijacking host ribosomes [29]. Main protease (Mpro) and papain-like protease (Ppro) break these polyproteins to create multiple non-structural proteins [30]. Aside from Mpro and Ppro, SARS-CoV-2 has 3C-like cysteine protease (3CLPro), which has a 96% resemblance to SARS-CoV. These proteases are essential for viral replication and transcription, and protease inhibitors inhibiting these proteases are potential antivirals for SARS-CoV-2. The promising clinical outcomes for COVID-19 patients should be obtained by using alpha-interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir, and anti-inflammatory drugs [31–34]. Moreover, clinical trials with these drugs should be performed on COVID-19 patients to prove their efficacy and safety as proposed for tocilizumab (**Figure 1**) [35].

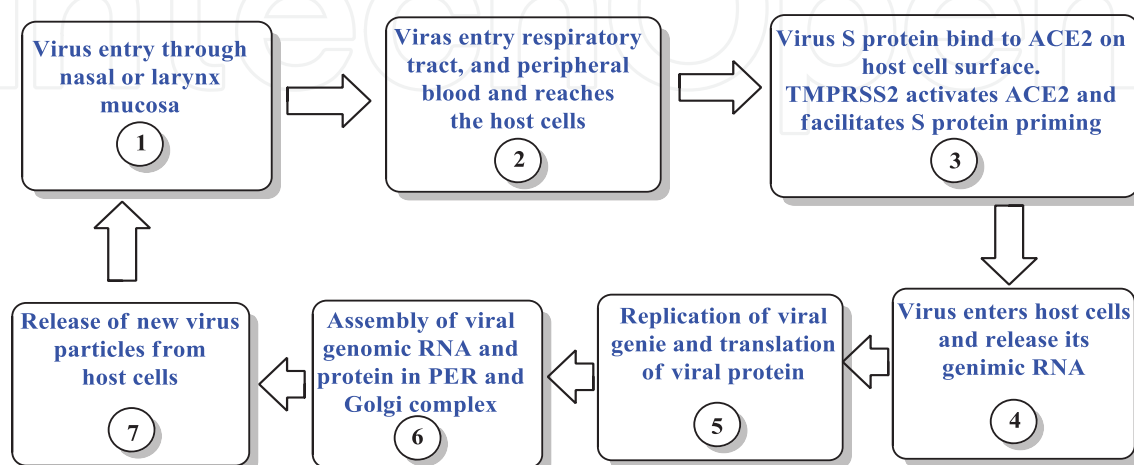


Figure 1. Schematic diagram of the life cycle of SARS-CoV-2.

3. Transmission of SARS-CoV-2

Highest sequence similarity (~96%) was observed for the bat Coronavirus. So, it has been speculated that COVID-19 was transmitted from bats to humans. The intermediary animal host could be a pangolin or dog. COVID-19 illness is spread via intimate contact with an infected individual, as well as minute respiratory droplets emitted during coughing, sneezing, or talking [36]. Small droplets of saliva or sputum emitted from the mouth might carry large amounts of viruses that can linger in the air for lengthy periods of time and function as infection carriers. Even when a person is not in direct physical touch with the infected individual, inhaling these minute droplets causes viral infection to move from the sick to the healthy. The virus enters the human body via the eyes, nose, and mouth and spreads by encountering the virus on infected surfaces and then touching these bodily areas [37]. Environmental factors such as temperature and humidity influence viral propagation across infected surfaces [38]. The binding of homotrimer spike protein (S) on the virus's surface to ACE2 on the host's cell membrane facilitates SARS-CoV-2 entry into host cells [16]. The host cell receptor's credit is a critical predictor of the virus's tissue tropism and pathogenicity. The life cycle of SARS-CoV-2 is similar to the SARS-CoV and MERS-CoV [39]. Different strategies have been adopted to fight COVID-19.

4. Diagnosis approach and pathogenesis

COVID-19 diagnosis is a crucial step in tracking the virus and understanding its spread. This aids in the prevention of transmission as well as adequate patient care. COVID-19 is diagnosed in the first instance by observing signs and symptoms such as first loss of smell or taste or both, cough, mild to high fever, myalgia or weariness, and so on [40]. In addition, some people experience gastrointestinal problems such as vomiting, diarrhea, and nausea [41]. However, variations in the development of symptoms ranging from asymptomatic to severe instances, such as septic shock, metabolic acidosis, coagulation malfunction, and acute respiratory pneumonia-like syndrome, have been recorded often [17]. These indications and symptoms should only be used as a starting point for additional testing, not as a diagnostic tool. The recognition of symptoms in clinical conditions is the most important factor in diagnosis. Swabs are used to obtain pathological samples from the upper and lower respiratory areas (throat, oropharyngeal, nasopharyngeal, broncho-alveolar fluid, and sputum). The virus is still absent in the blood and urine of infected people, hence they are not regarded valid clinical specimens. The interlink between the temporal surge of viral load and its bio-distribution in different tissues of the body has a critical implication on the accuracy of various tests for diagnosis, according to reports of inconsistency in RTPCR test results for CoV-SARS-2 in various tissues [42] and temporal variation of test results from the same tissues [43]. SARS-spike CoV-2's surface glycoprotein binds to the ACE2 receptor and then enters the host cell. Viral particles release their DNA after entering the host cell, which is then translated into protein, and additional viral particles are created, which are then released to infect the next cells. Many assays (molecular and immunological assays) or tools have been used for the diagnosis of COVID-19 and many more are currently in development.

5. Therapeutic approaches in COVID-19

SARS-Cov-2 infections currently have no vaccinations or antiviral therapies available [44]. Because developing safe and stable vaccines takes time and the pandemic is still going on, it's critical to test and discover current medications that are already effective against SARS and MERS to determine whether they can be effectively applied to SARSCov-2. Various preclinical studies on other CoVs genetically very close to SARS-Cov-2 suggested that promising clinical outcomes for COVID-19 patients should be obtained by using several drugs including alpha-interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir, and anti-inflammatory drugs. In a large-scale drug screening, nelfinavir has potent antiviral activity against SARS-Cov-2 [45]. Besides, praziquantel, pitavastatin, and perampanel might be effective against SARS-CoV-2. The outbreak of COVID-19 infection is related to the unavailability of specific drugs to combat this viral infection. Despite the challenges related to COVID-19 therapy, there are still several approaches being undertaken that show significant outcomes [5]. Discuss the positive impacts of some of the clinically used drugs for the COVID-19. Some drugs are in clinical trials, and some have shown significant promise in COVID-19 patients [46]. To find the solutions for COVID-19, great efforts have been made and are continued to develop vaccines, small-molecule drugs, or monoclonal antibodies that can prevent the infection [47]. In addition to drugs under clinical trials, some vaccines are expected to play a significant role in controlling the COVID-19 pandemic (Figure 2).

6. Remdesivir (GS-5734)

In 2009, Gilead Sciences, Inc. (USA) developed an antiviral drug called Remdesivir (RDV) to treat hepatitis B [48]. It did not indicate a desirable act against hepatitis. However, it is effective against other viruses, such as the Nipah virus, hepatitis C, and Marburg [49]. RDV is a broad-spectrum antiviral nucleoside analog, and

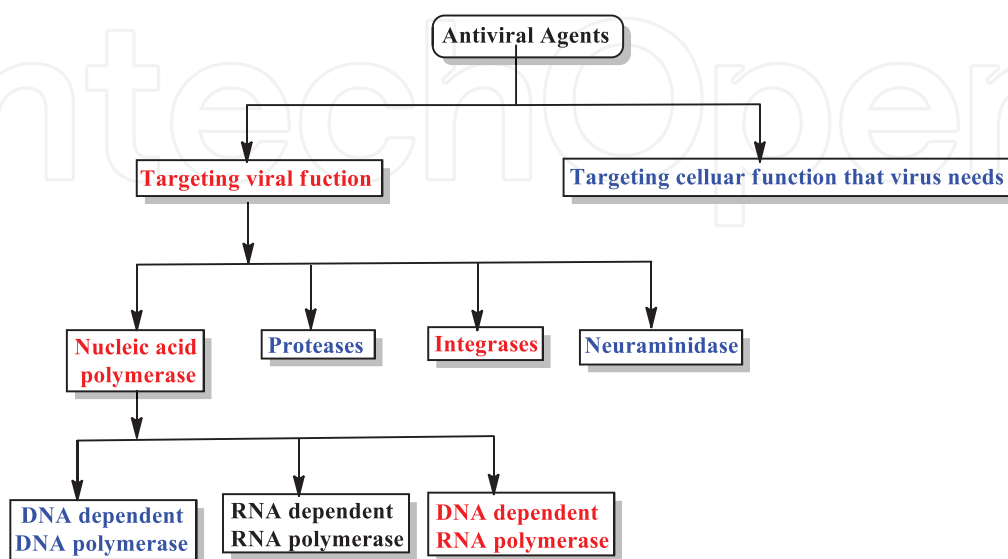


Figure 2.
Common inhibitory action of antiviral drugs.

now it is used as a treatment option for COVID-19 [50]. It is the class of polymerase inhibitors and showed activity against different RNA viruses, including SARS-CoV, MERS-CoV, Lassa fever virus, Junin virus, respiratory syncytial virus, Nipah virus, Hendra viruses, filoviruses, and Ebola viruses. RDV is a prodrug of its parent adenosine triphosphate analog, (2R,3R,4S,5R)-2-(4-aminopyrrolo(2,1-f)(1,2,4)triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)oxolane-2-carbonitrile (GS-441524), and has similarity to the adenine nucleic acid structurally. Both of these drugs are metabolized into the active component as nucleoside triphosphate (GS-443902) after ingestion and show antiviral activity against SARS-CoV [51]. RDV targets the viral genome replication process by acting as an RdRp inhibitor [52], RDV was used to block the RNA-dependent RNA polymerase of SARS-CoV-2. On metabolization of RDV into active nucleoside triphosphate (NTP), which competes with ATP for incorporation into nascent RNA strands, premature RNA synthesis occurs, resulting in RNA strand termination and cessation of growth [51]. RDV when tested through in vitro studies using the Vero E6 cells showed an EC₅₀ value of 1.76 μM that showed its activity against SARS-CoV-2 [53]. Intravenous remdesivir treatment showed significant improvement for COVID-19. RDV and chloroquine are highly effective in the control of SARS-CoV-2 infection. In severe COVID-19 treated with RDV, improvements in the clinical finding were observed in 68% of patients [54]. However, in October 2020, the WHO removed it from the list of effective drugs in the treatment procedure of COVID-19 patients because it failed in the first trials for the treatment of COVID-19 [42]. There are still controversies regarding the results, no benefit in COVID-19 treatment using RDV; whereas, the company claims it as a promising drug for the same. After penetrating the cell, RDV as a prodrug (GS-5734) and like Favipiravir, binds to the triphosphate group under esterase, kinase, and phosphatase enzymatic reactions. These enzymes modify the structure of RDV and convert it to the active form, RDV-triphosphate (RDV-TP or GS-441524) [55]. After virus entry into the cell cytoplasm, this prodrug gets activated and loses its ability to diffuse to the intercellular space [53]. However, the primary mechanism of action of RDV against SARS-CoV-2 is unclear, and more research is necessary to understand it [56]. In an in vitro study, the combination of RDV and chloroquine (antimalarial drug) effectively inhibited SARS-CoV-2 growth in Vero E6 cells [19]. RDV is used to treat COVID-19 cases.

The combined use of RDV and IFN-β created a higher antiviral activity compared with the lopinavir/ritonavir-IFN-β combination against the MERS-CoV virus. Additionally, RDV could be better pulmonary function, cause fall lung viral loads and severe lung pathology in mice; on the contrary, lopinavir/ritonavir-IFN-β could not [57]. In two clinical studies, the use of RDV has been carried out against severe or mild respiratory infections caused by COVID-19. Recently, RDV for emergency use to treat COVID-19, including five antiviral drugs, ribavirin, RDV, sofosbuvir, galidesivir, and tenofovir, was conducted against SARS-CoV-2 RNA-dependent RNA polymerase (RdRp); these drugs showed promising results against COVID-19. Prominent adverse reactions were an acute respiratory failure, decreased glomerular filtration rate, lymphocytopenia, pyrexia, hyperglycemia, increased anemia, increased creatine, and liver transaminases. RDV given in combination with baricitinib (Janus kinase inhibitor used to hinder intracellular signaling of cytokines) was effective compared with RDV alone in terms of reducing recovery time additionally speeding improvement. RDV's parent nucleotide GS-441524 is superior and less toxic than its prodrug form and has shown efficacy [58].

7. Favipiravir

Favipiravir (Avigan or T705) is a synthetic antiviral agent that was first marketed as an anti-influenza drug in Japan. It is a derivative of pyrazine carboxamide (6-fluoro-3-hydroxy-2-pyrazine carboxamide) [59]. Due to its similarity to the purine (guanine) nucleotide, it is a type of RNA-dependent RNA-polymerase (RdRp) inhibitor. RdRp uses Favipiravir-RTP in the synthesis of mRNA strands, which can consequently stop viral protein synthesis via suppressing the translation process. Activated Favipiravir-RTP could suppress the SARS-CoV-2 RdRp enzyme and inhibit viral mRNA elongation and protein synthesis [60]. Favipiravir acts against RNA viruses by working on viral genetic copying to prevent its reproduction. A phase 3 clinical trial was involved for the treatment of COVID-19 disease using Favipiravir. For the first day, take 1800 mg twice a day, then 600 mg three times a day from the second day onward for a total of 14 days. Normalization of pyrexia, respiratory rate, and cough alleviation for at least 72 h are the key objectives [61]. The precursor of this drug known as T1105 has anti-influenza effects [62]. Drug excretion is through renal elimination and is mainly impacted by aldehyde oxidase and xanthine oxidase [62]. Favipiravir is a prodrug that is phosphorylated upon its entry into the cell and converted to an active antiviral form, favipiravir ibufuranosyl-5'-triphosphate (T-705-RTP). Favipiravir was first prescribed in Wuhan, to treat patients with SARS-CoV-2 infection. In June 2020, it was approved for mild-to-moderate COVID-19 cases in India. Favipiravir has been consumed to cure distinct viral diseases. Favipiravir was effective against some RNA viruses, such as yellow fever virus, Lisa virus, West Nile virus, Bunyavirus, arenavirus, flavivirus, filoviruses, and Ebola virus [63]. The exact mechanism of action is not clear against SARS-CoV-2. Favipiravir is considered a potential drug for COVID-19 and is currently used for COVID-19 treatment in Japan and Indonesia. Besides, its anti-influenza virus action, it stops the replication of RNA viruses such as flavi-, alpha-, filo-, bunya-, arena-, noroviruses [64]. Favipiravir showed a more powerful antiviral activity than lopinavir/ritonavir. Adverse reactions are not observed in a favipiravir therapy group. Compared with the lopinavir/ritonavir group, it had considerably fewer adverse effects. In a Japanese study, FPV was also shown to control inflammatory mediators and pneumonia progression in COVID-19 patients [65]. Severe or critical COVID-19 patients showed improvements after treating with FPV and FPV also led to improved lung histology [66].

7.1 Lopinavir/ritonavir

Lopinavir is an antiviral drug belonging to the family of protease inhibitors. It is commonly used to treat Acquired Immunodeficiency Syndrome (AIDS) and prevent HIV from spreading inside the body. Lopinavir/ritonavir (LPV/RTV) is used in combination with other antiretroviral drugs for the treatment of HIV-1 infection. In the coronavirus pandemic, when no definitive drug was proposed to treat patients, it was used in combination with Ritonavir. This LPV/RTV is branded as Kaletra. Lopinavir has a relatively short half-life in the blood and is affected by the cytochrome p450 enzyme, while Ritonavir is a protease inhibitor and reduces the Lopinavir metabolism by suppressing the function of cytochrome p450. The half-life of Lopinavir is improved, and its circulation period is increased. LPV/RTV acts as a protease inhibitor drug and inhibits the action of 3-CLpro, a chymotrypsin-like protease enzyme, that plays a vital role in the processing and interferes with the process of viral replication and its release from host cells [67–69]. LPV/RTV use is related to diverse side

effects, mainly in the gastrointestinal tract. Diarrhea, impaired hepatic cell function, and pancreatitis are some of these crucial side effects.

The use of lopinavir as an emergency drug in China increased the eosinophil count among COVID-19 patients [70]. In an *in silico* study, LPV/RTV used as HIV protease inhibitors inhibited the main protease (MPro) of SARS-CoV-2 [71]. The LPV/RTV is being used as an emergency treatment for COVID-19 patients in some countries [72]. LPV/RTV alone or in combination with interferon (INF)- β , an inflammation regulator, has been listed by WHO as options for “solidarity” clinical trial for COVID-19. COVID-19 might benefit from LPV/RTV since it reduces viral load and improves clinical symptoms. Lung damage was also significantly reduced when LPV/RTV and umifenovir were used together [73]. A research found that while LPV/RTV therapy was associated with a better result, it did not significantly speed up the clinical progression of severe COVID-19 infection. Although the efficacy of lopinavir for COVID-19 has yet to be determined, LPV/RTV has been employed in the treatment of COVID-19 patients [57]. Now, LPV/RTV and IFN- β 1b are in phase 2 for the MERS therapy. Despite the positive findings, in a recent study performed on patients with SARS-CoV-2 infection, the LPV/RTV did not provide clinical improvement compared with standard care processes [72]. Findings of LPV/RTV clinical efficacy remain limited and primarily anecdotal cases. LPV/RTV in the therapy of COVID-19 is needed as current results contradict. LPV/RTV can ameliorate the outcome of MERS-CoV infection [74]. Moreover, LPV/RTV is assumed as a therapeutic option for COVID-19 pneumonia [72]. Thus, more well-designed clinical studies are necessary to identify their efficacy as therapeutic agents for COVID-19.

7.2 Novaferon

Novaferon has potential as an antiviral drug against COVID-19. It is a synthesized protein consisting of 167 amino acids, designed on the technical basis of DNA shuffling technology. The antiviral effects of novaferon are shown alone and in combination with lopinavir/ritonavir (LPV/RTV) for COVID-19 treatment. Novaferon inhibited the viral replication in infected cells ($EC_{50} = 1.02$ ng/ml) and protected healthy cells from SARS-CoV-2 infection ($EC_{50} = 0.1$ ng/ml). Both novaferon and novaferon plus LPV/RTV groups had significantly higher SARS-CoV-2 clearance rates on day 6 than the LPV/RTV group [8].

7.3 Ribavirin

Ribavirin (Virazole) is an antiviral drug belonging to the nucleoside analogues, (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). It is a synthetic nucleoside analog with a guanosine-like structure. Ribavirin disrupts viral DNA and RNA replication, thereby inhibiting virus proliferation in the cell. Although Ribavirin's primary mechanism of action is suppressing the virus replication, and can also interfere with viral RNA capping, which depends on the presence of natural guanosine in the RNA structure. The natural guanosine in the viral RNA structure prevents the breakdown of RNA strands. Ribavirin reduces the guanosine synthesis in the cell by inhibiting the activity of the inosine monophosphate dehydrogenase enzyme, which negatively impacts virus replication [75]. Although Virazole does not entirely inhibit viral RNA synthesis, the synthesis of the viral genetic material is severely impaired. It results in significant and persistent mutations in viral RNA, which reduce the viability of the virus in host cells [76]. Besides, the presence of Ribavirin in the patient's body

can reduce viral immune evasion and boost immune maintenance [77]. It is the first broad-spectrum antiviral drug against DNA and RNA viruses [75]. It is used clinically to treat HIV and hepatitis C virus (HCV) patients.

Ribavirin, which has been studied for its antiviral effectiveness against SARS-CoV-2, is used to inhibit viral RNA production and viral mRNA capping with a broad range of antiviral activity. It's a prodrug that, when metabolized, looks like purine RNA nucleotide, which prevents viral multiplication by interfering with RNA metabolism. It was discovered in a comparison study of SARS-CoV-2 patients treated with lopinavir/ritonavir (LPV/RTV) and ribavirin combination treatment [77]. Ribavirin is one of the medications used to treat COVID-19 in conjunction with either IFN alpha or LPV/RTV [46]. Using ribavirin in combination with sofosbuvir and remdesivir, docking and modeling studies revealed that ribavirin is a viable candidate medication for COVID-19 therapy [78]. Ribavirin and sofosbuvir are currently part of the therapeutic regimen to treat COVID-19 in some countries.

8. Ribavirin

Ribavirin inhibits the function of inosine monophosphate dehydrogenase, which affects the formation of guanosine triphosphate (GTP), preventing RNA and DNA viral replication. During the SARS outbreak in Hong Kong, ribavirin was utilized. With or without steroids, it was occasionally chosen. The combination of ribavirin and interferon- β , which appears to inhibit SARS-CoV replication, has shown significant efficacy in the inhibition of SARS-CoV [79]. The ribavirin triple antiviral treatment was safe and superior compared with lopinavir-ritonavir combined therapy.

9. Ribavirin

The drug showed antiviral efficacy against canine distemper virus, hepatitis C virus, Enterovirus, Chikungunya virus, and Semliki Forest virus, orthopoxvirus, influenza virus, flavi- and paramyxoviruses [80]. A study observed reduced replication of the MERS-CoV in rhesus macaques upon treatment with IFN- α 2b and RBV [81]. RBV in combination with LPV/RTV was used in SARS-CoV and MERS-CoV trials [82]. In the case of SARS-CoV-2 infection, an *in vitro* study showed the EC_{50} of RBV as 109.50 μ M [31]. A study included RBV along with LPV/RTV and IFN- α in the treatment of hospitalized COVID-19 patients. When compared with those that only received LPV-RTV, the triple treatment was found to be effective in reducing illness symptoms and viral shedding. The RBV dosage was 400 mg bid for 14 days, paired with 400 mg/100 mg of LPV/RTV + IFN- β . A research examined the effectiveness of antivirals sofosbuvir/daclatasvir and RBV in the treatment of COVID-19 patients. COVID-19 patients treated with RBV had a greater death rate (33%) than those treated with sofosbuvir/daclatasvir. A cohort study comparing RBV vs. supportive therapy stated that RBV did not help in reducing the mortality rate in COVID-19 patients [83].

10. Arbidol (Umifenovir)

It is an antiviral widely used to treat the influenza virus. Arbidol can prevent SARS-CoV-2 infection *in vitro* [10]. Lopinavir/ritonavir and Arbidol have been

recommended for dealing with COVID-19 [5]. According to a research, arbidol monotherapy is more successful in treating COVID-19 than lopinavir/ritonavir. On the 14th day of therapy, no viral load was recorded in the arbidol group, compared with 44.1% viral load in patients on lopinavir/ritonavir [84]. Arbidol is used for prophylaxis and therapy of influenza and other respiratory viral infections. Arbidol and its derivative, arbidol mesylate, showed antiviral activity against SARS-CoV because they declined the reproduction of the virus in the cell cultures [85]. Arbidol was tested alone or with some antiviral agents against COVID-19, and certain positive effects were observed [5, 10]. Arbidol is a non-nucleoside fusion suppressor that interferes with cell-virus interactions [86]. The drug exerts this function by influencing the hydrogen bonds of phospholipid molecules in the cell membrane. This drug can directly impact the influenza virus. It affects the hemagglutinin (HA) protein of the influenza virus. Umifenovir, by lowering the pH threshold needed for HA to attach to the cell, prevents the conformational modifications required for the activation of this protein and causes failure in the virus entry into the cell [87, 88]. Because of the structural similarity of the SARS-CoV-2 spike proteins (SPs) to influenza HA protein, researchers speculate that Umifenovir can inhibit the binding of SARS-CoV-2 to the host cell via a similar mechanism to HA inhibition [86]. Arbidol is utilized in vitro against other viruses, such as herpes simplex virus, hepatitis C, and the Ebola virus. The suitable antiviral activity for Umifenovir against these viruses [89] tested the influence of Umifenovir, alone or combined with other agents. The effect of Arbidol on COVID-19 patients and its mechanism of action are still necessary [90]. A study reported that umifenovir monotherapy for COVID-19 patients in China resulted in negative viral conversion where the virus was not detected in 14 days [91]. Arbidol and arbidol mesylate compounds have inhibited SARS virus replication in vitro and are presently being tested in COVID-19 patients to see if they have therapeutic promise in treating pneumonia caused by SARS-CoV-2. Arbidol monotherapy was superior to LPV/RTV against COVID-19 [84]. COVID-19 patients provided with UFV along with LPV/RTV showed better outcomes compared with patients who received LPV/RTV only [46]. The UFV was not beneficial to improve the condition of the patient or viral clearance [92]. Another study suggested that arbidol + LPV/RTV were related to many adverse events. A dosage of 200 mg three times a day was considered in the majority of research. According to a meta-analysis, UFV was ineffective in lowering SARS-CoV-2 removal from infected patients in terms of diagnostic test detection and hospital duration of stay of hospitalized patients [40]. There is no evidence to support the use of UFV for improving patient-important outcomes in patients with COVID-19.

11. Darunavir

Darunavir, an anti-HIV drug, is recommended for COVID-19 treatment in Italy. It is used in a combined regimen along with cytochrome P-450 inhibitors such as ritonavir or cobicistat and confirmed their replication inhibitory effect against SARS-CoV-2. A clinical trial assessed the effectiveness of darunavir combination with other antivirals and hydroxychloroquine for COVID-19 patients. A combination of darunavir and cobicistat is also being tested [93]. PREZCOBIX®, a fixed-dose combination of darunavir and cobicistat, is also used to treat COVID-19. COVID-19 infection was recently discovered in HIV-positive individuals who were already taking darunavir, raising questions about the effectiveness of this HIV protease inhibitor. The darunavir might not be effective in preventing SARS-CoV-2 infection at the dosage of 800 mg [94].

Darunavir is a second generation of HIV-1 protease inhibitors used to prevent SARS-CoV-2 infection in vitro [17] by inhibiting viral replication at 300 μM , and this inhibition efficiency was 280-fold compared with the untreated groups. Darunavir boosted with ritonavir or cobicistat is used in HIV/AIDS treatment. The efficacy of darunavir or ritonavir is enhanced by cytochrome p450 (CYP3A) inhibition [95]. Cell experiments with darunavir showed that the drug inhibited viral replication of COVID-19 in vitro. The lopinavir/ritonavir used in the treatment of HIV/AIDS has more efficacy and tolerability than darunavir, its use in COVID-19 is limited.

11.1 Oseltamivir

Oseltamivir (Tamiflu) is an antiviral agent that is used for patients with influenza A and B. It is a protease inhibitor, which specifically inhibits the neuraminidase enzyme in the influenza virus. This enzyme has a key role in the binding of the influenza virus to the cell membrane and spread throughout the body. Therefore, Oseltamivir, by targeting neuraminidase, prevents the spread of the influenza virus and its progression inside the body [96]. This drug was used in the treatment of COVID-19 infection, which showed an appropriate effect on patients [41]. Oseltamivir has been applied in concomitant regimens with other drugs such as Hydroxychloroquine or Favipiravir [97]. In addition to treating influenza A and B patients, this drug may also be used in severe cases. For the treatment of flu patients, Tamiflu is prescribed in a 75 mg dosage twice a day and once a day as prophylaxis. The main side effects of this drug can be nausea and headache [98]. Neuraminidase inhibitors seem beneficial for COVID-19 patients and can reduce their ventilator requirements [99]. The precise mechanism of action of Oseltamivir against COVID-19 infection is still unclear. Oseltamivir is a synthetic derivative prodrug of ethyl ester [100]. It acts as a neuraminidase inhibitor against the influenza virus and is also effective for various avian influenza virus strains [101]. An in vitro oseltamivir study on H5N1 influenza showed that the IC_{50} was 0.1–4.9 nM [102]. In vivo study involving H5N1 infection required a longer course and higher dosage of Oseltamivir. The COVID-19 originated in China during flu season, and hence earlier, many patients received oseltamivir treatment until the causative agent SARSCoV-2 was discovered. Some current clinical trials have used oseltamivir in combination with other major therapeutic drugs [31, 41].

11.2 Sofosbuvir

Sofosbuvir is an antiviral drug and RdRp inhibitor that exerts its effect by suppressing RdRp enzyme activity. A combination of Sofosbuvir with Ledipasvir is used for treating patients with genotype 1 of HCV67. Because of the similarity in the transcription and replication mechanism of the SARS-CoV-2 with HCV in host cells, physicians speculate that this drug may help treat COVID-19 patients [103]. This drug disrupts the activity of RdRp by acting like free nucleotides that are essential for viral mRNA synthesis [104]. Sofosbuvir is a potential option for COVID-19 treatment [105], and extensive clinical studies should be performed to verify the effectiveness of this drug.

12. Danoprevir

Danoprevir, an HCV N53 protease inhibitor, is authorized in China for the treatment of noncirrhotic genotype 1b chronic hepatitis C in combination with other

medications. In China, only two clinical studies of danoprevir coupled with ritonavir in the treatment of SARS-CoV-2 infection were completed [8].

13. Atazanavir

In a computer simulation, atazanavir bonded more firmly to the active site of SARS-CoV-2 MPro than lopinavir, and atazanavir suppressed SARS-CoV-2 replication in a test tube. A prior trial on HIV-positive individuals found that combining atazanavir with ritonavir enhanced glucose uptake and lipid parameters while also lowering fasting glucose levels more efficiently than lopinavir-ritonavir. The atazanavir might be an alternative for lopinavir when combined with ritonavir for COVID-19 treatment. This antiviral drug is an option for COVID-19 treatment [8].

14. Baricitinib

SARS-CoV-2 penetrates host cells by receptor-mediated endocytosis, just as other viruses. AP2-related protein kinase 1 controls the process of endocytosis (AAK1). As a result, disrupting AAK1 will prevent not just viral entrance but also intracellular viral assembly. Baricitinib is a Janus kinase (JAK) inhibitor that has a high affinity for AAK1 and can inhibit it. SARS-CoV-2 infection can be treated with baricitinib, which inhibits both viral entry and the inflammatory response [106]. JAK inhibitors such as ruxolitinib and fedratinib, which are linked to baricitinib, decreased clathrin-mediated endocytosis at higher dosages, suggesting that they may not be effective at acceptable concentrations in lowering viral infectivity. Neutropenia, lymphocytopenia, and viral reactivation have all been linked to the use of baricitinib for therapeutic purposes. Because individuals infected with SARSCoV-2 had a lower absolute lymphocyte count, baricitinib may increase the risk of co-infection [107].

15. Imatinib

Blocking virus-host fusion is a promising target for the novel antiviral agents that inhibit the Abl kinase pathway [41]. In a study, imatinib, an Abl kinase inhibitor, was observed to block the replication of SARS and MERS viruses by blocking viral fusion in 2016 [108]. COVID-19 utilized the SARS-coronavirus receptor ACE2 as well as the cellular protease TMPRSS2 to get access to target cells; therefore, TMPRSS2, transmembrane serine protease 2, inhibiting medicines such imatinib might be evaluated as COVID-19 disease treatment alternatives [37].

16. Camostat mesylate

Another possible medicine that targets the fusion stage in viruses is camostat mesylate, a serine protease inhibitor. SARS-CoV-2 enters target host cells via ACE-2 receptors and/or TMPRSS2 receptors, with camostat mesylate acting as a TMPRSS2 inhibitor. It inhibits the virus's cellular entrance by downregulating the production of the SARS-CoV-2 spike (S) protein, which prevents surface fusion. SARS-CoV infection in human bronchial epithelial cells was inhibited by camostat mesylate [109]. In vitro testing

revealed that camostat mesylate and E-64d (a cysteine protease inhibitor) effectively blocked SARS-CoV-2 TMPRSS2 binding. Clinical studies are now underway to compare the efficacy of hydroxychloroquine and camostat mesylate vs. hydroxychloroquine alone. Another serine protease inhibitor, nafamostat mesylate, was shown to be 15 times more effective in preventing the SARS-CoV-2 virus from infecting host cells. As a result, nafamostat mesylate can be regarded a preferable option to camostat mesylate due to its more robust antiviral activity and acceptable safety profile [37]. Disseminated

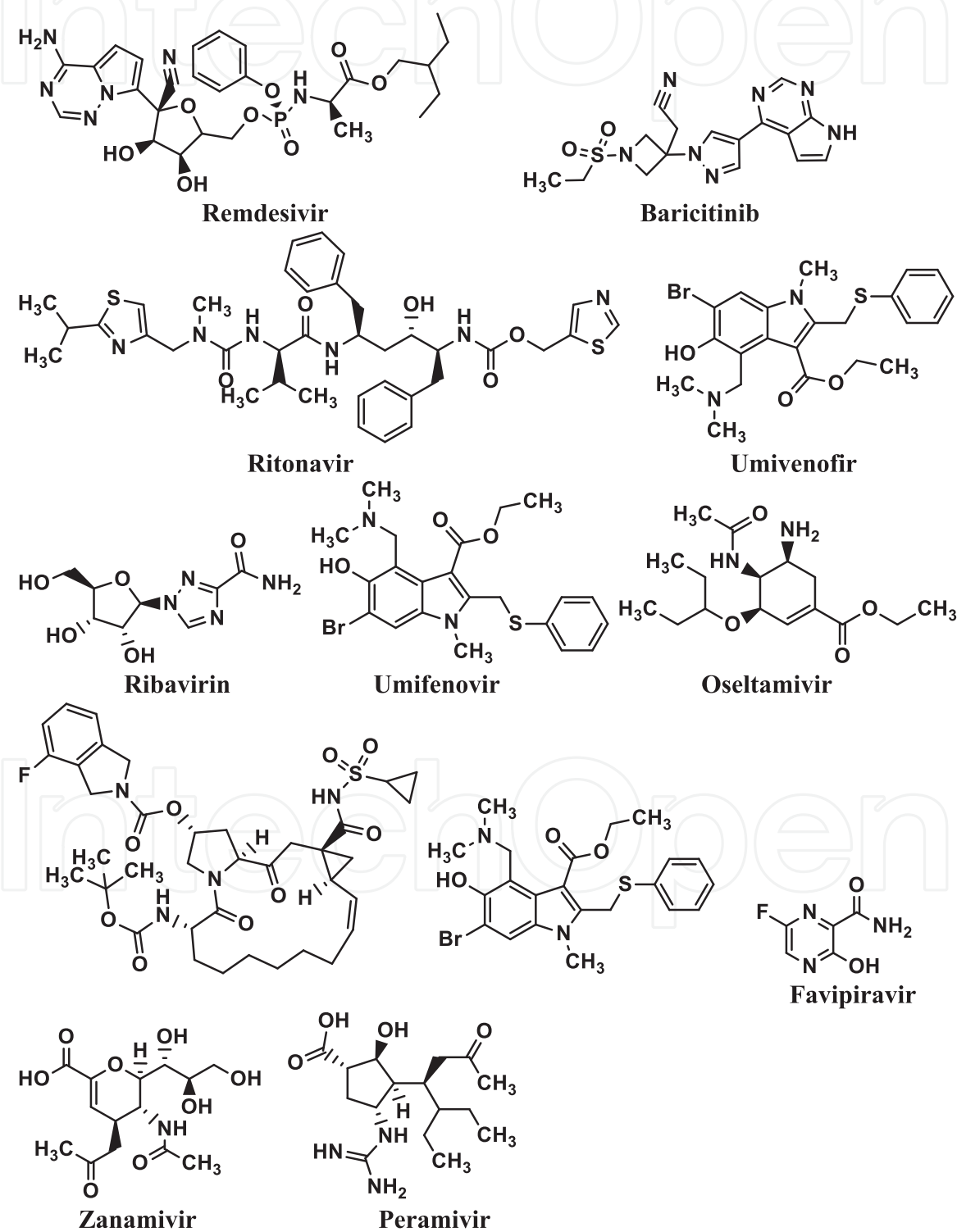


Figure 3.
Chemical structure of antiviral drugs.

intravascular coagulation is also treated with nafamostat mesylate (DIC). It will aid in the management of DIC, as seen by increased fibrinolysis in COVID-19 patients [110].

16.1 Nitazoxanide

In an in vitro research utilizing Vero E6 cells, nitazoxanide and its active component, tizoxanide, showed promise against MERS CoV and SARS CoV-2, with EC₅₀ values of 0.92 and 2.12 μ M, respectively [111]. In addition to coronaviruses, it exhibited action against norovirus, rotavirus, parainfluenza, respiratory syncytial virus, and influenza virus. This antiviral efficacy is due to the fact that the action mechanism is based on interfering with the virus's host-regulated reproduction pathways rather than the virus's particular pathways [112]. Nitazoxanide stimulates innate antiviral systems through amplification of cytoplasmic RNA sensing and type 1 IFN pathways. Nitazoxanide increases the expression of certain host systems that interfere with viral infection, allowing viruses to evade the host's cellular defenses [113]. The nitazoxanide used against influenza viruses blocks the maturation of viral hemagglutinin at the post-translational stage [112]. Even if the findings aren't promising, this medicine is used to treat some acute respiratory infections such as influenza. Although the in vitro activity of nitazoxanide against SARS-CoV-2 is promising, additional research is needed to understand its function in the management of COVID-19 (**Figure 3**).

16.2 Other antiviral drugs

Other various antiviral agents have been utilized to determine their impacts against SARS-CoV-2. Galidesivir is a nucleoside analog and a protease inhibitor [114]. This drug mechanism on COVID-19 is hypothesized to be similar to other antivirals, although its exact action mechanism is unknown. Another antiviral agent for COVID-19 is Tenofovir, which is known as an anti-influenza drug. It is an antiretroviral agent that targets DNA polymerase and inhibits virus replication [115, 116]. The action mechanism of this substance against COVID-19 requires further studies.

17. Mechanism of antivirals for SARS-CoV-2 infection

17.1 Fusion inhibitors

A fusion inhibitor is a group of antivirals that inhibit the fusion process during viral entry into the host cells. Some drugs are available with umifenovir and camostat mesylate representing antiviral activity against SARS-CoV-2 [117].

17.2 Protease inhibitors

Some protease inhibitors such as lopinavir, darunavir, and atazanavir are used against COVID-19 [118]. In a computational study, drugs such as carfilzomib, valrubicin, eravacycline, lopinavir, and elbasvir inhibited the main protease in SARS-CoV-2. Further studies are required to confirm the efficacy of these drugs. Saquinavir and other protease inhibitors such as indinavir, amprenavir, and nelfinavir might also show the same effects against COVID-19 like protease inhibitors, due to resemblance between the structures. In a computer simulation, saquinavir and indinavir were found to suppress 3CLPro activity in SARS-CoV-2 [119]. In vitro

inhibition of SARS-CoV-2 was shown to be inhibited by saquinavir, indinavir, amprenavir, and nelfinavir, with nelfinavir demonstrating the greatest suppression when compared with the others. In Singapore, saquinavir has been used to treat COVID-19 patients. Two other medications, raltegravir and paritaprevir, were shown to have the ability to block 3CLPro activity in SARS-CoV-2 in a computational investigation (**Tables 1** and 2) [120].

17.3 Reverse transcription inhibitors

Another technique for combating SARS-CoV-2 infection is to inhibit RdRp and impede viral replication by targeting the reverse transcription process. Nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase translocation inhibitors are a few examples of possible inhibitors (NRTTIs).

17.4 Other transcription inhibitors

Other NtRTIs with comparable structural properties to remdesivir or ribavirin, such as adefovir, tenofovir alafenamide, tenofovir disoproxil, abacavir, ganciclovir, and didanosine, exhibit antiviral effectiveness against SARS-CoV-2. NRTIs (lamivudine, stavudine, zidovudine, emtricitabine, zalcitabine, and azvudine) and NNRTIs (efavirenz, nevirapine, delavirdine, and rilpivirine) may also have antiviral activity against SARS-CoV-2 [56].

Class	Drugs	Application	Emergency use for COVID-19
Fusion inhibitor	Umifenovir (Arbidol)	Influenza	Singapore, China
Protease Inhibitor	Lopinavir	HIV	USA, Japan, Singapore, Italy, China, IPC (Lopinavir-Ritonavir fix dose)
	Darunavir	HIV-1	Italy (Darunavir-Ritonavir fix dose)
	Atazanavir	HIV-1	Singapore
	Saquinavir	HIV-1	Singapore
Nucleoside reverse transcriptase inhibitor	Emtricitabine	HIV-1	Singapore (Emtricitabine-Tenofovir fix dose)
	Azvudine	HIV-1	Singapore
Nucleotide reverse transcriptase inhibitor	Remdesivir	Ebola	WHO, IPC, USA, Singapore, Italy
	Favipiravir	(Avigan) Influenza	Singapore, Japan, Indonesia
	Ribavirin	HCV	Singapore, IPC
	Sofosbuvir	HCV	Singapore
Neuraminidase inhibitor (Virus release inhibitor)	Oseltamivir (Tamiflu)	Influenza A & B	IPC, Singapore, Indonesia

International Pulmonologists' Consensus includes the USA, India, Iran, China, Italy, Great Britain, EUA, Colombia, Egypt, Singapore, Romania, Ireland, Malaysia, Saudi Arabia, Sudan, Greece, and Bolivia.

Table 1.
Current use of existing antiviral drugs for COVID-19 [56].

Group	Drugs	Mechanism of action
Viral RNA polymerase inhibitors	Remdesivir (GS-5734)	RdRp inhibitor, prodrug, the analog of adenosine nucleotide
	Favipiravir	RdRp inhibitor, prodrug, the analog of guanosine nucleotide
Viral protein synthesis inhibitors	Ritonavir/Lopinavir	Inhibitor of protease
Inhibitors of viral entry	Hydroxychloroquine Chloroquine	Increase in endosomal pH needed for the virus/cell fusion. Interfere with cellular receptor glycosylation of SARS CoV (ACE-2)
Immunomodulators	Nitazoxanide	Interfere with host regulated pathways of virus replication, amplification of type 1 IFN pathways, and cytoplasmic RNA sensing
	Ivermectin	Inhibition of importin 1 heterodimer to inhibit the nuclear import of host and viral proteins

Table 2.

Mechanism of action of antiviral drugs used for the treatment of COVID-19.

17.5 Neuraminidase inhibitors

Oseltamivir is a neuraminidase inhibitor used in preventing influenza. Neuraminidase inhibitor drugs such as oseltamivir, zanamivir, and peramivir are antiviral drugs that inhibit the viral neuraminidase enzyme and are recommended for influenza and to block the release of viral particles out of host cells. Neuraminidase inhibitors are also used as empirical treatment in MERS-CoV infection [121, 122]. However, a combination of oseltamivir with ganciclovir and lopinavir/ritonavir is used to treat COVID-19 patients [40]. A computational study also supported synergistic effects of oseltamivir-lopinavir-ritonavir combination against SARS-CoV-2 [123]. Oseltamivir is used with ceftriaxone and terbutaline to treat COVID-19 [124]. A study showed that the CT scan of the lungs of a COVID-19 patient showed significant improvement after a three-day course of oseltamivir [19]. Oseltamivir has been used either with or without antibiotics and corticosteroids against COVID-19. In a clinical trial, oseltamivir is tested with chloroquine and favipiravir [93, 125].

18. Conclusion

Nowadays, the rising SARS-CoV-2 turned into a global threat. COVID-19 targets lung cells by connecting to ACE2 protein. This protein is largely produced in some tissues such as the bile duct, liver, gastrointestinal organs, esophagus, testis, and kidney as well as lung tissue. Thus, COVID-19 may damage these organs and tissues. With the global threatening caused by COVID-19, efficient therapy against COVID-19 is quickly necessary. Nevertheless, the development of new drugs for this disease is still a huge problem for people in the world, and we have none formally approved drugs against COVID-19 now. It is very crucial to cut off the extending of this virus owing to epidemic avoidance and checking techniques. We need to develop novel drugs and to find new therapy methods to prevent this outbreak and to treat COVID-19. The extent of the current pandemic, along with other factors, such as the lack of time to develop novel and effective agents against COVID-19, the high mortality rate, possible mutations in its genetic material and severe

economic shocks to societies highlight the value of testing antiviral drugs present in our drug arsenal. Some drugs that have already started with repositioning may be effective against COVID-19 as well. It is essential to address the drug-drug interaction of the drugs in COVID-19 patients with comorbidities. We hope that the continuing studies may provide solutions for the prevention and therapy against the COVID-19.

19. Future perspectives

Despite the fact that specific antiviral medications for COVID-19 have yet to be identified or authorized by the FDA, the usage of some currently existing antiviral agents that target various phases in COVID-19's life cycle might be an alternate therapeutic strategy for combating the pandemic. Fusion inhibitors, protease inhibitors, and transcription inhibitors are just a few of the interesting antiviral medication classes to investigate. Apart from antiviral medicines, various interesting techniques to treating COVID-19 are being employed, such as convalescent plasma, which has been found to reduce viral load and patient morbidity. The effects of interferon (IFN)- α/β and IL-6R inhibitor¹ have also been encouraging [126–128]. The introduction of several new technologies is likely to yield good benefits. The safety of patients should be prioritized while evaluating new SARS-CoV-2 vaccinations. Nanotechnology offers an effective new route for diagnostics and treatment techniques. The more distinctive nanoparticles operate as excellent antiviral medication delivery vehicles, increasing the procedure's effectiveness. Finding appropriate diagnostic and therapeutic strategies for the fast and efficient care of severe COVID-19 patients is urgently needed [129, 130]. Different research on different CoV-induced diseases shows that using α -interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir, and anti-inflammatory medications might result in encouraging clinical results for SARS-Cov-2 patients. Tocilizumab should be used as a therapy approach for severe COVID-19 pneumonia to achieve favorable results. Furthermore, further clinical studies with appropriate medications should be conducted on SARS-CoV-2 patients to demonstrate effectiveness and safety.

Acknowledgements

We are thankful to the Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, 21955, Saudi Arabia, and Glocal School of Pharmacy, Glocal University, Mirzapur Pole, 247121, Saharanpur, Uttar Pradesh, India for providing necessary facilities.

Conflicts of interest

The authors declare no conflicts of interest.

Abbreviations

3CLpro	3-chymotrypsin-like protease
AAK1	AP2-associated protein kinase 1
ACE2	angiotensin-converting enzyme 2

ACEi	angiotensin-converting-enzyme inhibitors
ADR	acute respiratory distress syndrome
AIDS	acquired immunodeficiency syndrome
C _m	maximum concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
DCGI	drug controller general of India
DR	drug repurposing
E	envelope protein
ER	endoplasmic reticulum
ERGIC	endoplasmic reticulum-Golgi apparatus compartment
EVD	Ebola virus disease
HA	hemagglutinin envelope glycoprotein
HAV	hepatitis A virus
HCMV	human cytomegalovirus
HCV	hepatitis-C virus
HE	hemagglutinin esterase
HSV	herpes simplex virus
ICU	intensive care unit
INF- β	interferon
Kb	kilo base pairs
M	membrane protein
MERS	Middle-East Respiratory Syndrome
M _{pro}	main protease
N	nucleocapsid
NNRTI	non-nucleoside reverse-transcriptase inhibitors
NRTTI	nucleoside reverse transcriptase translocation inhibitors
NtRTI	nucleotide reverse-transcriptase inhibitor
PL _{Pro}	Papain-like protease
qRT-PCR	quantitative real-time polymerase chain reaction
R ₀	reproductive number
RdRp	RNA-dependent RNA polymerase
RNA	ribonucleic acid
RVFV	Rift Valley fever virus
S(P)	Spike protein
S	glycoprotein spike
SARS	severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPs	spike proteins
TMPRSS2	transmembrane serine protease 2
US FDA	United States Food and Drug Administration
WHO	World Health Organization

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