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Antiviral drugs proposed for COVID-19: action mechanism and pharmacological data

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Abstract. – OBJECTIVE: As a beta-coronavirus, Coronavirus disease-2019 (COVID-19) has caused one of the most significant historical pandemics, as well as various health and medical challenges. Our purpose in this report is to collect, summarize, and articulate all essential information about antiviral drugs that may or may not be efficient for treating COVID-19. Clinical evidence about these drugs and their possible mechanisms of action are also discussed.

MATERIALS AND METHODS: To conduct a comprehensive review, different keywords in various databases, including Web of Science, Scopus, Medline, PubMed, and Google Scholar, were searched relevant articles, especially the most recent ones, were selected and studied. These selected original research articles, review papers, systematic reviews, and even letters to the editors were then carefully reviewed for data collection.

RESULTS: SARS-CoV-2 is the newest member of the coronavirus family, and there are still no promising therapies or particular antiviral compounds to fight it. After entering the body, SARS-CoV-2 penetrates the cells by attaching to specific lung cell receptors, called angiotensin-converting enzyme-2. Then, by employing cell division machinery, it replicates through a complex mechanism and spreads throughout the patient's body. Various antiviral drugs, including anti-influenza/HIV/HCV drugs, have been applied for treating COVID-19 patients. Due to the similarity of the structure and transcriptional mechanism of COVID-19 to a number of viruses, some of the listed drugs have been beneficial against SARS-CoV-2. However, the effectiveness of others is in an aura of ambiguity and doubt.

CONCLUSIONS: Some of the antiviral medications listed and discussed in this article have been effective in the treatment of COVID-19 patients or preventing the virus from spreading further. However, other drugs have to be investigated to reach a reliable conclusion about their effectiveness or ineffectiveness.

Key Words:
COVID-19, Pharmacology, Coronaviruses, Antiviral drugs, Viral replication.

Abbreviations

WHO = World Health Organization; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SARS = Severe acute respiratory syndrome; MERS = Middle East(ern) Respiratory Syndrome; RNA =Ribonucleic acid; S(P) = Spike protein; Kb = Kilo base pairs; HE = Hemagglutinin esterase; ACE 2 = Angiotensin-converting enzyme-2; $3CL^{pro}$ = 3-chymotrypsin-like protease; PL^{Pro} = Papain-like protease; ACEi = Angiotensin-converting-enzyme inhibitors; ADR = Acute respiratory distress syndrome; C_m = Maximum concentration; RdRp = RNA-dependent RNA-polymerase; DCGI = Drug Controller General of India; AIDS = Acquired immunodeficiency syndrome; US FDA = United States Food and Drug Administration; HA = Hemagglutinin; SPs = Spike proteins; HCV = Hepatitis C virus; ER = Endoplasmic reticulum.

Introduction

The new coronavirus disease, introduced by the World Health Organization (WHO) on February 11, 2020, as Coronavirus Disease-2019 (COVID-19, formerly 2019-nCoV), is the latest health-medical challenge in the world. This novel coronavirus is named Severe Acute Respiratory Syndrome Coronavirus 2019 (SARS-CoV-2) by the International Virus Classification Commission[1]. The first case of COVID-19 was identified in Wuhan, Hubei Province, China, and has since spread to almost all countries. On January 30, 2020, the WHO convened a meeting to introduce the pandemic as an international health emergency[2]. However, the prevalence of coronaviruses in

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the world has not been unprecedented. In the last two decades, SARS and Middle East Respiratory Syndrome (MERS), respectively in 2003 and 2014, have been epidemics of coronavirus[3]. The reproduction number of the 2019-nCoV is estimated between 2 and 3, while its fatality rate is predicted around 0.5-1.5%[4]. The most significant symptoms in COVID-19 patients are fever, dry cough, loss of sense of taste, lethargy, and shortness of breath[5]. Anosmia is also one of the most critical symptoms in recent COVID-19 patients[6]. It is stated that COVID-19 is more contagious than other coronaviruses, and its transmission rate is higher than the closely related strain, SARS-CoV-10[7]. There are some similarities between SARS-CoV-1 and SARS-CoV-2, including genome length, receptor type, and the ability to stimulate cytokine storms[8].

The coronaviruses are ribonucleic acid (RNA) viruses, which have a positive single-strand RNA. This genus of viruses causes disease in humans and a wide range of animals[9]. The "Corona" term means crown in Latin, and the reason for their naming as coronaviruses is the observation of the crown-like protein structures on these viruses under an electronic microscope.

Coronaviruses are categorized into four subgroups: alpha, beta, gamma, and delta. The first two groups originate from mammals and can cause zoonotic diseases in humans, while the last two groups emanate from birds and pigs. SARS-CoV-2 is a beta coronavirus, and its genome length is about 26-32 Kilo base pairs (kb). The genetic material of this virus is bound to nucleocapsid proteins, and the envelope protein structures surround it. Structural proteins, including spike proteins (SP), protein membranes (M), small membrane protein (SM), and another membrane glycoprotein called hemagglutinin esterase (HE), are encoded by the viral RNA[10,11]. The schematic structure of 2019-nCoV is illustrated in Figure 1.

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. As a result of this modification, the virus can attach to the Angiotensin-Converting Enzyme-2 (ACE2) cell receptor, leading to accumulation of clathrin beneath that area and penetration of the virus into the cell. ACE2 receptor has been detected on the cell surface of several tissues, including stomach, liver, and lung[12]. The virus can also trigger inflammatory responses called Acute Respiratory Distress Syndrome (ARDS) that can lead to a deadly severe condition and even death[13]. Two substantial protease enzymes, 3-chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{Pro}) have essential roles in its viral replication process after it enters the host cell via ACE2 receptors[14]. Expression of

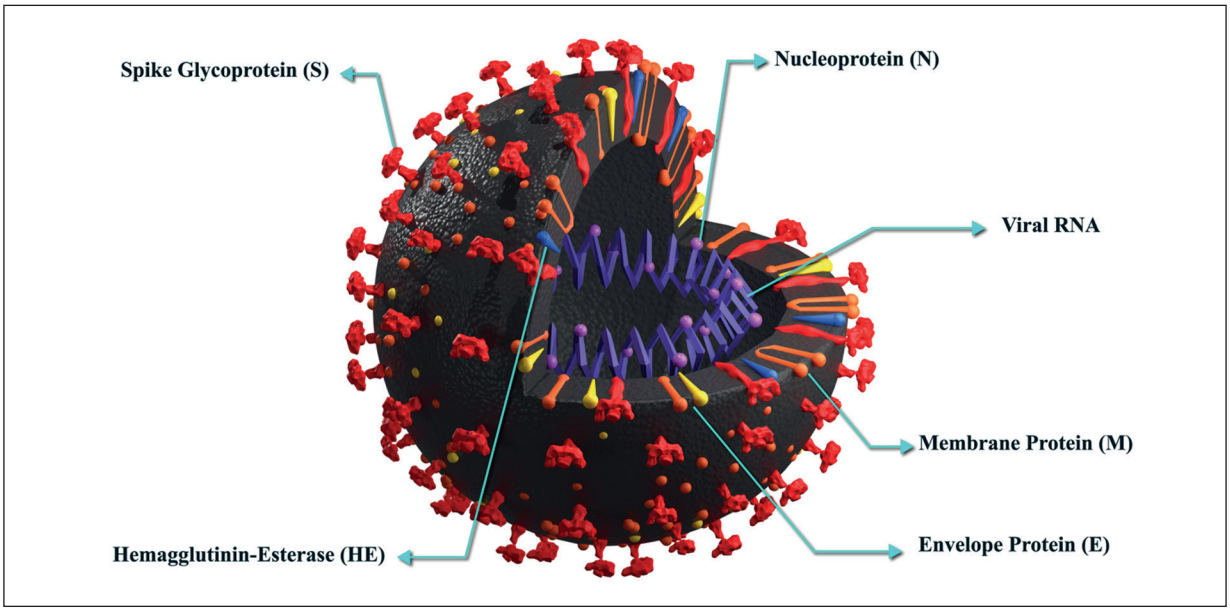

Figure 1. Schematic structure of COVID-19 and various proteins in its composition.

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[15].

Various antiviral agents and adjuvant drugs have been administered to treat COVID-19, and some of them could get emergency approval in different countries. 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[16]. Due to the possibility of secondary infection in these patients, antibiotics have been applied as various protocols. The 10th day upon hospitalization is the most common day for the onset and diagnosis of secondary infections[17]. So far, no fully effective drug compound has been discovered against this virus. The antiviral drugs, usually nucleoside analogues or intracellular proteases, block the virus by preventing its entry into the cell or by interfering with its replication inside the cell. In this study, we aimed to review famous antiviral drugs that have already been used or could be effective against SARS-CoV-2. The names of antiviral agents and other terms that are described in this article are summarized in Figure 2.

Favipiravir

Favipiravir (under the brand name Avigan), also known as the T705 therapeutic compound, is a synthetic agent and antiviral product that was first synthesized and marketed as an anti-influenza drug in Japan. The agent was discovered in the biochemical section of the Toyoma laboratory while studying the effects of several active chemical compounds against the influenza virus. The precursor of this drug is a substance called A/PR/8/34, which was later named T1105. The anti-influenza effects of T1105 and its chemical derivatives were observed during their synthesis. Favipiravir is also a derivative of the precursor T1105, formed by modifying and binding some conjugates to the pyrazine moiety of T1105[18,19]. Favipiravir has desirable pharmacological characteristics. For instance, it has high bioavailability (~94%) and biocompatibility, efficiently binds to about 54% of plasma proteins, and its maximum concentration (C_m) peaks about two hours upon utilization. Its T_{max} and half-life increase after continuous administration of the drug. Drug excretion is through renal elimination and is mainly impacted by aldehyde oxidase and xanthine oxidase. The hydroxylated form of Favipiravir is usually excreted renally. The cytochrome p450 complex enzyme does not metabolize Favipira-

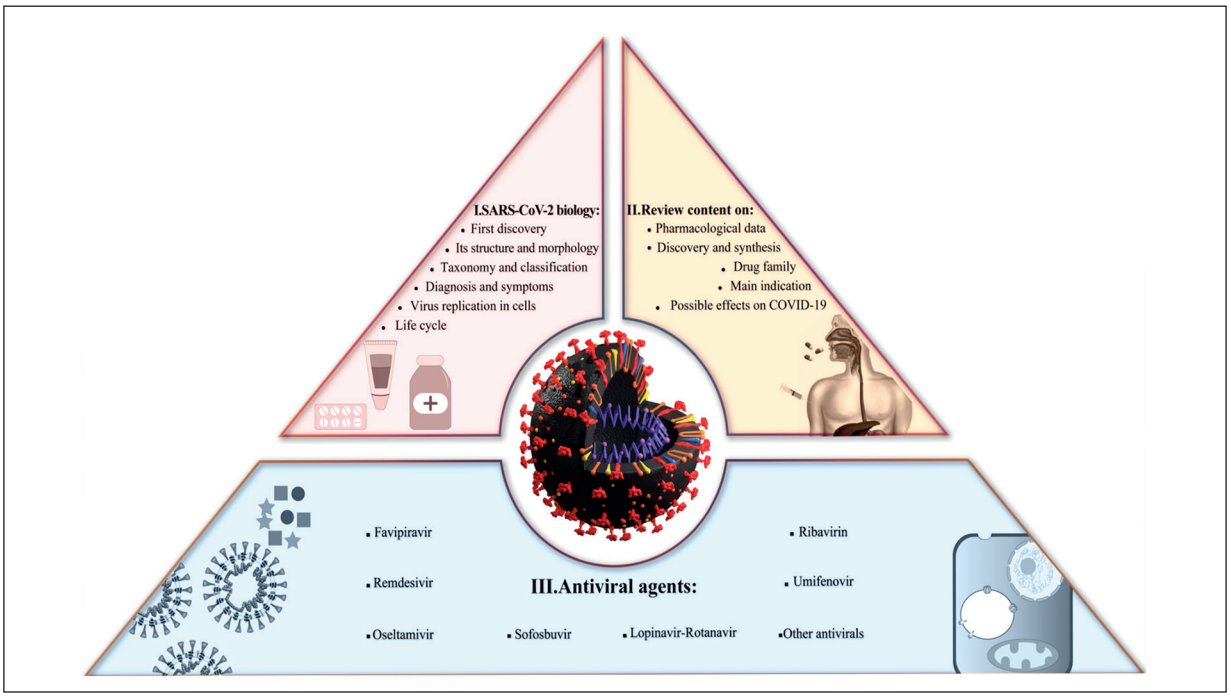

Figure 2. Schematic and straightforward overview of various terms discussed in this review article.

vir, while CYP2C8, a member of this complex, is affected by Favipiravir. The half-life of this drug is short and about 2.5 hours[19,20].

As mentioned, Favipiravir is a prodrug that is phosphorylated upon its entry into the cell and converted to an active antiviral form, Favipiravir-RTP. Due to its similarity to the purine nucleotide, RNA-dependent RNA-polymerase (RdRp) uses Favipiravir-RTP in the synthesis of mRNA strand, which can consequently stop viral protein synthesis via suppressing the translation process[18]. It has recently been noted that lethal genetic mutations in the RNA strand of the virus could be induced in the presence of Favipiravir. This observation was made through clinical trials where Avigan was prescribed against influenza virus[21]. It was also reported that Favipiravir-RTP could inhibit the mRNA strand elongation process[22]. Shannon et al[23] investigated the SARS-CoV-2 RdRp enzyme complex and found that in this virus, it is 10-fold more energetic than the RdRp complex of other viruses. In this study, activated Favipiravir-RTP could suppress the SARS-CoV-2 RdRp enzyme and inhibit viral mRNA elongation and protein synthesis[23].

Avigan was first prescribed in Wuhan, where the pandemic began, to treat patients with 2019-nCoV infection. Different countries, such as Russia, Uzbekistan, Kazakhstan, and Japan have since approved the drug for the treatment of COVID-19 patients. In June 2020, it was approved by the Drug Controller General of India (DCGI) for mild to moderate COVID-19 cases[19]. Favipiravir has been consumed to cure distinct viral diseases and has shown antiviral effects. Even drug-resistant strains of influenza, M2 and NA, were susceptible to Favipiravir. Other influenza strains, such as H5N1, H1N1, H3N2, and H1N2, were also sensitive to this agent[24]. Furthermore, Favipiravir was effective against some of RNA viruses, such as yellow fever virus, Lisa virus, West Nile virus, and Bunyavirus[19]. More clinical trials and investigation are required to evaluate the effect of Favipiravir and understand its exact mechanism of action against 2019-nCoV.

Remdesivir

In 2009, Gilead Sciences, Inc. (Foster City, CA, USA) developed a new antiviral drug called Remdesivir to treat hepatitis B patients[25]. At that time, this compound did not indicate desirable performance against hepatitis in mild to moderate cases[26]. However, further investigations revealed it to be effective against other viruses, including the Nipah virus[27], hepatitis C[28], and Marburg[29]. This drug was modified later in 2014 by the same company and was utilized to treat the Ebola virus, where it demonstrated promising relics[25]. Due to the reported efficacy of Remdesivir against SARS-CoV-1 and MERS-COV viruses, it was also examined against SARS-CoV-2 virus[30]. After penetrating the cell, Remdesivir 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 Remdesivir and convert it to the active form, Remdesivir triphosphate (RDV-TP or GS-441524)[31]. It is a nucleotide analogue that has a similarity to the adenine nucleic acid structurally. After virus entry into the cell cytoplasm, this prodrug gets activated and loses its ability to diffuse to the intercellular space[32].

In terms of pharmacological properties, Remdesivir is more desirable than other drugs already administered for treating COVID-19 infection[25]. The half-life of Remdesivir inside the body is about 20 hours[33], and it is majorly (74%) excreted within the urine, while about 10% remains unchanged[25]. The metabolism of this drug is through getting triphosphorylated. Particular drug interactions between Remdesivir and other therapeutic compounds have not been reported[25].

Inside the cell, Remdesivir triphosphate, a nucleotide analogue, is utilized as a substrate by the RdRp enzyme, which results in disrupting viral RNA synthesis via a delayed chain termination mechanism. It has been reported that RDV-TP can also compete with adenine nucleotide in binding to the RdRp enzyme within the cell. Ultimately, RDV-TP inhibits viral RNA synthesis by attaching to the RdRp enzyme complex[32]. However, the primary mechanism of action of Remdesivir against SARS-CoV-2 is unclear, and more research is necessary to understand it precisely. Remdesivir has been approved by the US FDA (United States Food and Drug Administration) and is administered to treat COVID-19. However, in October 2020, the WHO removed it from the list of effective drugs in the treatment procedure of COVID-19 patients.

Lopinavir-Ritonavir

Lopinavir is an antiviral therapeutic agent belonging to the family of protease inhibitors. It is commonly used to treat Acquired Immunodeficiency Syndrome (AIDS) infection and prevent

HIV from spreading inside the body. In the initiation of the coronavirus pandemic, when no definitive drug was proposed to treat patients, this medication was applied in several clinical trials. It was administered in combination with another drug called Ritonavir with various brand names. This combination, Lopinavir-Ritonavir branded as Kaletra, is broadly prescribed. 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. As a result, the half-life of Lopinavir is improved and its circulation period is increased[34].

As mentioned, the COVID-19 virus employs the host cell replication machinery for amplifying its RNA after entering host cells[35]. One of the enzymes involved in the replication, accumulation, and preparation of viral RNA is the 3-chymotrypsin-like protease, which possesses a vital role in various processes. Lopinavir inhibits the $3CL^{pro}$ enzyme and is hypothesized to significantly reduce the synthesis of SARS-CoV-2 RNA[36,37]. New coronavirus protease enzymes like $3CL^{pro}$ lack a C2-symmetric enzymatic site, while this site is present in HIV enzymes and is targeted by Lopinavir, which makes doubt on the effectiveness of Lopinavir against COVID-19[38]. The Lopinavir-Ritonavir compound administration has been associated with diverse side effects, mainly in the gastrointestinal tract. Diarrhea, impaired hepatic cell function, and inflammation of the pancreas (called pancreatitis) are some of these crucial side effects. Unlike Remdesivir, there are various drug interactions between Kaletra and other drugs. These drug interactions are due to the inhibitory activity of Lopinavir that disrupts the typical function of the cytochrome p450 enzyme, which is involved in the metabolism of multiple agents[39]. There have been conflicting consequences about the application of this compound against SARS-CoV-2, and for treating new coronavirus. Understanding this drug mechanism against the SARS-CoV-2 requires further clinical studies and laboratory studies.

Oseltamivir

Oseltamivir (branded commercially as 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 its spreading throughout the body. Therefore, Oseltamivir, by targeting neuraminidase, prevents the spread of the influenza virus and its progression inside the body[40,41]. This drug was administered in a research study in Wuhan, to treat COVID-19 infection, which showed an appropriate effect on patients[42]. In multiple clinical trials, Oseltamivir has been applied in concomitant regimens with other drugs like Hydroxychloroquine or Favipiravir. Such studies[43] and trials are still undergoing and the outcomes are unknown yet. In addition to treating influenza A and B patients, this medication may also be utilized 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 major side effects of this drug can be nausea and headache[44]. Neuraminidase inhibitors seem beneficial for COVID-19 patients and can reduce their ventilator requirements[45]. The precise mechanism of action of Oseltamivir against COVID-19 infection is still unclear, and further studies are required.

Umifenovir

Umifenovir (also known as Arbidol) is a non-nucleoside fusion suppressor that interferes with cell-virus interactions[46]. Umifenovir is one of the antiviral medicines approved by China and Russia for therapy and prophylaxis of influenza A and B and other arboviruses. It is a chemical compound derived from indole carboxylic acid that can be subject to various chemical and molecular modifications. The drug was discovered and developed in Russia in 1988 and has since been studied therapeutically[47]. It primarily functions by preventing the fusion of the virus into the host cell. Umifenovir can limit virus contacts with the host cell or the virus-endosome fusion into the cell membrane. The drug exerts this function by influencing the hydrogen bonds of phospholipid molecules in the cell membrane. Moreover, studies have exhibited that this drug can directly impact influenza virus particles. It affects the hemagglutinin (HA) protein of the influenza virus. Umifenovir, by lowering the pH threshold needed for HA to attach the cell, prevents the conformational modifications required for the activation of this protein and causes failure in the virus entry into the cell[48,49]. Because of the structural similarity of the 2019-nCoV 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[46]. Arbidol has been utilized in vitro against other viruses, such as herpes simplex virus, hepatitis C and the Ebola virus. The results of these investigations indicated an appropriate antiviral activity for Umifenovir against these viruses[50]. Furthermore, it has been analyzed to evaluate the influence of Umifenovir, alone or combined with other agents. In a cohort study[51] in Wuhan, the outcomes demonstrated that patients who took daily the Umifenovir with Keltera had a lower virus conversion rate and improved CCT results, compared to patients who only received Keltera. Further studies on the effect of Arbidol on COVID-19 patients and its mechanism of action are still necessary.

Ribavirin

Ribavirin (mostly known as Virazole) is an antiviral compound belonging to the nucleoside analogues family with the chemical formula of 1-Beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. It is a synthetic nucleoside analogue with a guanosine-like structure found in 1972 by Sidwell et al[52,53]. 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, this agent 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 break-down 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[54]. Although Virazole does not entirely inhibit viral RNA synthesis, the synthesis of the viral genetic material is severely impaired in the presence of this agent. It results in significant and persistent mutations in viral RNA, which reduce the viability of the virus in host cells[55]. Besides, the presence of Ribavirin in the patient's body can reduce viral immune evasion and boost immune maintenance[56].

There have been several studies on Ribavirin since its synthesis. In vitro investigations have confirmed the effectiveness of this medication against a broad domain of RNA and DNA viruses[54]. which has made it the first broad-spectrum antiviral drug against DNA and RNA viruses. It was also been applied clinically to treat HIV and hepatitis C virus (HCV) patients[57]. Pharmacologically, Ribavirin has desirable bioavailability and is well absorbed via oral administration. Excretion of this drug is renal-urinary, and its maximum serum concentration in blood is 24 μg/ml. T_{max} of Ribavirin in the first dose (1 hour) is diverse from the second (1.7 hours) and multiple (3 hours) doses. Stephens[56] is underway to validate Ribavirin's efficacy in treating COVID-19, and still, more clinical trials are demanded to discover its possible mechanism of action against SARS-CoV-2. All the antiviral medications mentioned so far, with additional details about them are summarized in Table I.

Sofosbuvir

Sofosbuvir is an antiviral drug and RdRp inhibitor that exerts its therapeutic effect by suppressing RdRp enzyme activity. The US FDA approved the drug in 2013 for the treatment of HCV patients. Besides, in 2014, the US FDA approved a combination of Sofosbuvir with Ledipasvir 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 therapeutic agent may help treat COVID-19 patients as well[68]. This medicine disrupts the activity of RdRp by acting like free nucleotides that are essential for viral mRNA synthesis[69,70]. According to our search, only two docking studies, one in 2016 and one in 2020, have been conducted on Sofosbuvir[71]. Therefore, although some studies have suggested Sofosbuvir as a potential option for COVID-19 treatment[72], extensive clinical studies should be performed to verify the effectiveness of this drug.

Other Antiviral Drugs

Other various antiviral agents have been utilized in clinical trials to determine their impacts against SARS-CoV-2. Galidesivir, as a nucleoside analogue and a protease inhibitor, is a remarkable instance[73]. 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 recognized as an anti-influenza drug. It is an antiretroviral agent that targets DNA polymerase and inhibits virus replication[74,75]. The action mechanism of this substance against COVID-19 requires further studies to be comprehended. The replication mechanism of COVID-19 within the host cell, along with the possible action mechanism of antiviral agents, are schematically illustrated in Figure 3.

Table I. Pharmacological information of some promising drugs, which has been purposed against COVID-19 infection.

Medication name	Drug category	Possible mechanism of action against COVID-19	Adverse and side effect(s)	Route of administration	Mainly used for treating	Status (for COVID-19)	R.(s)
Favipiravir	Nucleoside analog antiviral prodrug	Targeting RdRp, preventing viral RNA extension, induction of lethal mutations in the virus	Hyperuricemia and diarrhea, skin rash, abdominal pain	Tablets for oral administration	Influenza virus	Non-approved	19, 58
Remdesivir	Nucleotide analogue antiviral	Targeting RdRp because of its similarity to adenosine	Nausea, worsening of respiratory problems, constipation	Intravenous infusion	Hepatitis C, Ebola virus	Emergency authorization and approval by FDA	25, 59
Lopinavir-Rotanavir	Proteases inhibitor antiviral drugs	Suppressing the activity of 3CLpro, disrupting viral replication	Gastrointestinal disturbance, diarrhea, Dyslipidemia, diabetes mellitus is also reported	Tablets for oral administration	HIV	Non-approved	60, 61
Oseltamivir	Protease inhibitor antivirus	Inhibit the neuraminidase enzyme on the surface of the virus	Nausea, vomiting, diarrhea	Tablet or liquid suspension	Influenza strain A and B	Non-approved	40, 41, 62
Umifenovir	Non-nucleoside HA inhibitor antivirus	Preventing the virus attachment to cell by HA inhibition	Diarrhea and nausea	Tablets for oral administration	Treatment and prophylaxis of influenza or other respiratory infections	Non-approved	63, 64
Ribavirin	Nucleoside analogues antivirals	Disrupts viral DNA and RNA replication because of its similarity to guanosine	Nausea, flu-like symptoms, fatigue and tiredness; low leucocytes in cell counts	Film-coated tablet or capsules	HCV, HBV and respiratory tract viruses	Non-approved	56, 65, 66

Conclusions

The SARS-CoV-2 pandemic is one of the serious medical crises of the last century. It is also probably the most extensive pandemic since the outbreak of Spanish flu in 1918. The magnitude of the current pandemic, along with other factors, such as the lack of time to discover and synthesize 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 importance of examining antiviral agents present in our drug arsenal. Some antiviral drugs that have been synthesized against other pathogenic viruses may be effective against SARS-CoV-2, as well. Therefore, an unbiased summary of available data around these therapeutic agents, their possible mechanism of action, and their pharmacological information can assist scientists in further research and will

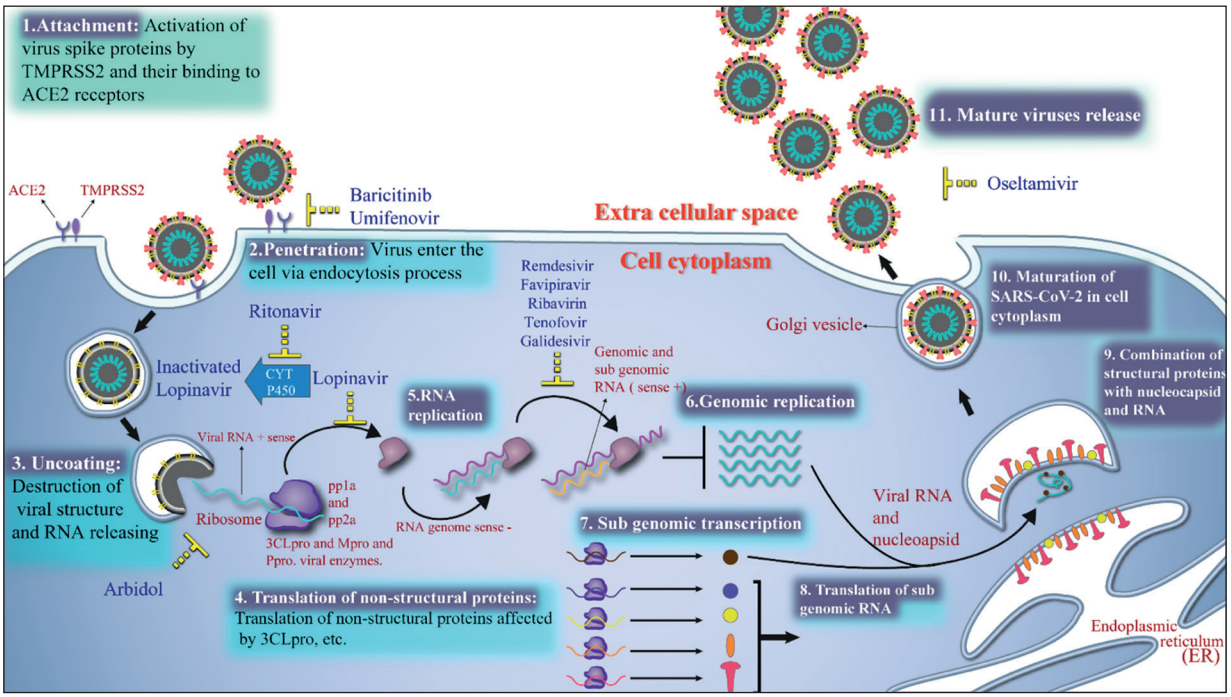

Figure 3. Virus replication in the host cell and antiviral drugs effects: The virus approaches the pulmonary alveoli's epithelial cells. Attachment of the virus to the host cell occurs through a particular binding mechanism between the ACE2 cell receptor and the virus spike proteins (1); the virus attaches to its receptors (ACE2) and penetrates the host cell (2). Next, viral RNA crosses the structural protein barrier and is released into the host cell cytoplasm (3), by binding the released viral RNA to the ribosomes in the cell cytosol. Thereafter, the translation of non-structural proteins such as RdRp and 2'OMTase that are involved in the viral replication process initiates. This process is influenced by $3CL^{pro}$, M^{pro}, and PL^{pro} viral enzymes (4). The produced proteins initiate RNA genomic replication (5). Next, genomic replication (6) and sub-genomic transcription (7) are illustrated. Translation of sub-genomic RNA into structural proteins occurs in the host cell cytoplasm, and then they enter the endoplasmic reticulum (ER) (8). The unification of structural proteins with nucleocapsid and RNA (9), maturation of SARS-CoV-2 in the cell cytoplasm (10), and ultimately release of new mature viruses (11) are also displayed.

help them design better clinical studies to assess the effectiveness or inefficacy of these antivirals against COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

FR and MJN Contributed to the conceptualization and investigations for this article. FR has done the writing-original draft, visualization and figures preparation, and literature search. MJN performed validation and supervision, and project administration. MM contributed to reviewing and editing the article. All authors have read the manuscript intently and approved all of its content.

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References

1) Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020; 10: 102-108.
2) Website JHU. COVID-19 Dashboard by CSSE at JHU. 2021; https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
3) De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14: 523-524.
4) Salzberger B, Buder F, Lampl B, Ehrenstein B, Hitzenbichler F, Holzmann T, Schmidt B, Hanses F. Epidemiology of SARS-CoV-2. Infection 2020; 48: 1-7.

5) Conforti C, Giuffrida R, Dianzani C, Di Meo N, Zalaudek I. COVID-19 and psoriasis: is it time to limit treatment with immunosuppressants? A call for action. Dermatol Ther 2020; 33: 1-2.
6) Zayet S, Klopfenstein T, Mercier J, Kadiane-Oussou NdJ, Lan Cheong Wah L, Royer PY, Toko L, Gendrin V. Contribution of anosmia and dysgeusia for diagnostic of COVID-19 in outpatients. Infection 2020; 49: 1-5.
7) Yesudhas D, Srivastava A, Gromiha MM. COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics. Infection 2020; 49: 1-15.
8) Rat P, Olivier E, Dutot M. SARS-CoV-2 vs. SARS-CoV-1 management: antibiotics and inflammasome modulators potential. Eur Rev Med Pharmacol Sci 2020; 24: 7880-7885.
9) Tyrrell D, Bynoe M. Cultivation of viruses from a high proportion of patients with colds. Lancet 1966; 1: 76-77.
10) Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health 2020; 25: 278-280.
11) Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y, Li B, Huang C-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
12) Pashaki PA, Roudkenar MH, Rahim F, Ebrahimi A. From SARS-CoV to SARS-CoV2: a potential guide to better understanding of pathophysiology of the disease and potential therapeutic modality. Eur Rev Med Pharmacol Sci 2020; 24: 7816-7825.
13) Mohammad M, Payam S, Scott D, Orly V. Potential effects of Coronaviruses on the cardiovascular system a review. JAMA Cardiol 2020; 5: 831-840.
14) Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B 2020; 10: 766-788.
15) Hu R, Liu C, Gong J, Cao Z. Gene expression analysis identifies genes associated with SARS-COV-2 receptors, ACE2 and TMPRSS2, in normal human lung tissues. Eur Rev Med Pharmacol Sci 2021; 25: 2409-2414.
16) Rossi L, Malagoli A, Biagi A, Zanni A, Sticozzi C, Comastri G, Pannone L, Gandolfi S, Vergara P, Villani GQ. Renin-angiotensin system inhibitors and mortality in patients with COVID-19. Infection 2021; 49: 287-294.
17) Chong WH, Saha BK, Ramani A, Chopra A. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. Infection 2021; 49: 1-15.
18) Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res 2013; 100: 446-454.
19) Agrawal U, Raju R, Udwadia ZF. Favipiravir: a new and emerging antiviral option in COVID-19. Med J Armed Forces India 2020; 76: 370-376.
20) Madelain V, Nguyen THT, Olivo A, De Lamballerie X, Guedj J, Taburet AM, Mentré F. Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. Clin Pharmacokinet 2016; 55: 907-923.
21) Baranovich T, Wong S-S, Armstrong J, Marjuki H, Webby RJ, Webster RG, Govorkova EA. T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. J Virol 2013; 87: 3741-3751.
22) Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J. The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5′-triphosphate towards influenza A virus polymerase. PLoS One 2013; 8: 1-10.
23) Shannon A, Selisko B, Le N, Huchting J, Touret F, Piorkowski G, Fattorini V, Ferron F, Decroly E, Meier C. Favipiravir strikes the SARS-CoV-2 at its Achilles heel, the RNA polymerase. Nat Commun 2020; 11: 4682-4701.
24) Kerber R, Lorenz E, Duraffour S, Sissoko D, Rudolf M, Jaeger A, Cisse SD, Camara AM, Miranda O, Castro CM. Laboratory findings, compassionate use of favipiravir, and outcome in patients with Ebola virus disease, Guinea, 2015—a retrospective observational study. J Infect Dis 2019; 220: 195-202.
25) Badgujar KC, Ram AH, Zanznay R, Kadam H, Badgujar VC. Remdesivir for COVID-19: A review of pharmacology, mechanism of action, in-vitro activity and clinical use based on available case studies. J Drug Deliv Ther 2020; 10: 264-270.
26) Stephens B. The story of remdesivir. New York Times 2020; 23: 1-10.
27) Lo MK, Feldmann F, Gary JM, Jordan R, Bannister R, Cronin J, Patel NR, Klena JD, Nichol ST, Cihlar T. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. Sci Transl Med 2019; 11: 1-6.
28) Gudipati P, Biswas S. Anti hepatitis C viral drugs remdesivir and uprifosbuvir derivatives are better inhibitors of SARS Cov2 RNA-dependent RNA Polymerase determined by docking studies. ChemRxiv 2020; Preprint: 1-13.
29) Porter DP, Weidner JM, Gomba L, Bannister R, Blair C, Jordan R, Wells J, Wetzel K, Garza N, Van Tongeren S. Remdesivir (GS-5734) is efficacious in cynomolgus macaques infected with Marburg virus. J Infect Dis 2020; 222: 1894-1901.
30) Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020; 11: 220-234.

31) Al-Tannak NF, Novotny L, Alhunayan A. Remdesivir--bringing hope for COVID-19 treatment. Sci Pharm 2020; 88: 29-30.

32) Saha A, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Probable molecular mechanism of remdesivir for the treatment of COVID-19: need to know more. Arch Med Res 2020; 51: 585-586.

33) Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016; 531: 381-385.

34) Shaikh VS, Shaikh Y, Ahmed K. Lopinavir as a potential inhibitor for SARS-CoV-2 target protein: a molecular docking study. SSRN 2020; Preprint: 1-8.

35) Vastag B. Old drugs for a new bug. JAMA 2003; 290: 1695-1696.

36) Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, Becker S, Rox K, Hilgenfeld R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science 2020; 368: 409-412.

37) García-Fernández R, Ziegelmüller P, González L, Mansur M, Machado Y, Redecke L, Hahn U, Betzel C, de los Ángeles Chávez M. Two variants of the major serine protease inhibitor from the sea anemone Stichodactyla helianthus, expressed in Pichia pastoris. Protein Expr Purif 2016; 123: 42-50.

38) Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020; 19: 149-150.

39) Osborne V, Davies M, Lane S, Evans A, Denyer J, Dhanda S, Roy D, Shakir S. Lopinavir-ritonavir in the treatment of COVID-19: a dynamic systematic benefit-risk assessment. Drug Saf 2020; 43: 809-821.

40) McClellan K, Perry CM. Oseltamivir. Drugs 2001; 61: 263-283.

41) Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, Mills RG, Ward P. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001; 20: 127-133.

42) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.

43) Rosa SGV, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam Salud Publica 2020; 44: 1-7.

44) Srinivas P, Sacha G, Koval C. Antivirals for COVID-19. Cleve Clin J Med 2020; 88: 1-5.

45) Pagliano P, Sellitto C, Conti V, Ascione T, Esposito S. Characteristics of viral pneumonia in the COVID-19 era: an update. Infection 2021; 49: 1-10.

46) Vankadari N. Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking the trimerization of viral spike glycoprotein? Int J Antimicrob Agents 2020; 56: 105998-105998.

47) Boriskin Y, Leneva I, Pecheur EI, Polyak S. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem 2008; 15: 997-1005.

48) Villalaín J. Membranotropic effects of arbidol, a broad anti-viral molecule, on phospholipid model membranes. J Phys Chem B 2010; 114: 8544-8554.

49) Leneva IA, Russell RJ, Boriskin YS, Hay AJ. Characteristics of arbidol-resistant mutants of influenza virus: implications for the mechanism of anti-influenza action of arbidol. Antiviral Res 2009; 81: 132-140.

50) Pécheur E-I, Borisevich V, Halfmann P, Morrey JD, Smee DF, Prichard M, Mire CE, Kawaoka Y, Geisbert TW, Polyak SJ. The synthetic antiviral drug arbidol inhibits globally prevalent pathogenic viruses. J Virol 2016; 90: 3086-3092.

51) Costanzo M, De Giglio MA, Roviello GN. SARS-CoV-2: recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. Curr Med Chem 2020; 27: 4536-4541.

52) Witkowski J, Robins RK, Sidwell RW, Simon LN. Design, synthesis, and broad spectrum antiviral activity of 1-. beta.-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide and related nucleosides. J Med Chem 1972; 15: 1150-1154.

53) Sidwell RW, Huffman JH, GP Khare L, Allen B, JT Witkowski R, Robins K. Broad-spectrum antiviral activity of virazole: 1-f8-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide. Science 1972; 177: 705-706.

54) Graci JD, Cameron CE. Mechanisms of action of ribavirin against distinct viruses. Rev Med Virol 2006; 16: 37-48.

55) Crotty S, Cameron CE, Andino R. RNA virus error catastrophe: direct molecular test by using ribavirin. Proc Natl Acad Sci U S A 2001; 98: 6895-6900.

56) Khalili JS, Zhu H, Mak NSA, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID-19. J Med Virol 2020; 92: 740-746.

57) Prusiner Pt, Sundaralingam M. A new class of synthetic nucleoside analogues with broad-spectrum antiviral properties. Nat New Biol 1973; 244: 116-118.

58) Goldhill DH, Te Velthuis AJ, Fletcher RA, Langat P, Zambon M, Lackenby A, Barclay WS. The mechanism of resistance to favipiravir in influenza. Proc Natl Acad Sci U S A 2018; 115: 11613-11618.

59) Godman B. Combating COVID-19: Lessons learnt particularly among developing countries and the implications. Bangladesh J Med Sci 2020; 19: 103-108.

60) Dorward J, Gbinigie K. Lopinavir/ritonavir: a rapid review of effectiveness in COVID-19. 2020; https://www.cebm.net/covid-19/lopinavir-ritonavir-

a-rapid-review-of-the-evidence-for-effectiveness-in-treating-covid/.

61) Wu R, Wang L, Kuo H-CD, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z. An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep 2020; 6: 56-70.

62) Aoki FY, Doucette KE. Oseltamivir: a clinical and pharmacological perspective. Expert Opin Pharmacother 2001; 2: 1671-1683.

63) Blaising J, Polyak SJ, Pécheur EI. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res 2014; 107: 84-94.

64) Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clin Microbiol Infect 2020; 26: 917-921.

65) Alvarez D, Dieterich D, Brau N, Moorehead L, Ball L, Sulkowski M. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. J Viral Hepat 2006; 13: 683-689.

66) Martin P, Jensen DM. Ribavirin in the treatment of chronic hepatitis C. J Gastroenterol Hepatol 2008; 23: 844-855.

67) Schinazi RF, Shi J, Whitaker T. Sofosbuvir (Sovaldi): the first-in-class HCV NS5B nucleotide polymerase inhibitor. Innov Drug Synth 2016; 1: 61-79.

68) Nourian A, Khalili H. Sofosbuvir as a potential option for the treatment of COVID-19. Acta Bio Medica: Atenei Parmensis 2020; 91: 239-240.

69) Zuccaro V, Lombardi A, Asperges E, Sacchi P, Bruno R. PK/PD and antiviral activity of anti-HCV therapy: is there still a role in the choice of treatment? Expert Opin Drug Metab Toxicol 2020; 16: 97-101.

70) Pockros PJ. Nucleoside/nucleotide analogue polymerase inhibitors in development. Clin Liver Dis 2013; 17: 105-110.

71) Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci 2020; 248: 117477-117478.

72) Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, Levi J, Hill A, Shamshirian A. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. J Antimicrob Chemother 2021; 76: 753-757.

73) Zumla A, Chan JF, Azhar EI, Hui DS, Yuen K-Y. Coronaviruses--drug discovery and therapeutic options. Nat Rev Drug Discov 2016; 15: 327-347.

74) Drosu NC, Edelman ER, Housman DE. Tenofovir prodrugs potently inhibit Epstein–Barr virus lytic DNA replication by targeting the viral DNA polymerase. Proc Natl Acad Sci U S A 2020; 117: 12368-12374.

75) Clososki GC, Soldi RA, Silva RMd, Guaratini T, Lopes JN, Pereira PR, Lopes JL, Santos Td, Martins RB, Costa CS. Tenofovir disoproxil fumarate: new chemical developments and encouraging in vitro biological results for SARS-CoV-2. J Braz Chem Soc 2020; 31: 1552-1556.