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A Chemical Approach on Drugs that are Under Evaluation as Potential COVID-19's Treatment

Abordagem Química de Medicamentos sob Avaliação como Potenciais para o Tratamento da COVID-19

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A novel SARS-CoV-2 coronavirus, the virus responsible for COVID-19, is a public health emergency of international concern since this infection spreads quickly through human-to-human transmission. Several drugs are being studied by researchers worldwide as an effective antiviral agent against this coronavirus. Therefore, most studies are focusing on drugs that have been already used earlier on the treatment of other diseases. Therapies under investigation include azithromycin, chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, and favipiravir. Remdesivir is the only Food and Drug Administration-approved drug for the use in adult and pediatric patients (>12 years old) for the treatment of this disease requiring hospitalization. In this context, the present review summarizes information about these drugs highlighting the chemical standpoint, such as physical-chemical and molecular characteristics, toxicity, history, and main applications, since knowledge about these substances is essential to assist the search for an appropriate treatment.

Keyword: Coronaviruses; azithromycin; chloroquine; remdesivir.

1. Introduction

In late December 2019, an unknown viral infection cause was identified in Wuhan city, Hubei province, central China.[1] Since then, the virus has spread for all China territory, because of its high transmission potential, and 159 countries and territories on six continents, in less than 3 months.[2] The World Health Organization (WHO) has named this viral infection 2019-new coronavirus disease (COVID-19).[3] Additionally, the virus name has been designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), and the species to which the virus SARS-CoV-2 belongs is severe acute respiratory syndrome-related coronavirus.[4] On March 2020, the WHO declared COVID-19 a global pandemic. As of 1 May 2022, over 500 million confirmed cases and 6 million deaths have been reported around the world.[5]

Among humans, the most common symptoms of COVID-19 include fever, headache, nonproductive cough, dyspnea, and fatigue. However, the disease can take on critical forms, and some patients can develop viral pneumonia, acute heart injury, acute respiratory distress syndrome, and sometimes lead to death.[2-5]

Remdesivir is the first Food and Drug Administration-approved drug for the treatment of COVID-19 patients.[6] Therapies that were investigated and/or are currently under evaluation include drugs as azithromycin, chloroquine, hydroxychloroquine, lopinavir, ritonavir, and favipiravir.[7-8] In this context, knowledge about these substances is essential to assist the search for appropriate treatment. Therefore, in this review, we summarize the most common drugs including antiviral agents, antibiotics, and anti-inflammatory agents that have been tested as therapeutic options for SARS-CoV-2 infection, highlighting the chemical standpoint, such as physical-chemical and molecular characteristics, toxicity, their history, and main applications. Since chemistry is part of everything in our lives, it is essential to understand everything related to this virus, from viral structure to the development of therapies.

2. Coronaviruses (CoVs)

Coronaviruses (CoVs) belong to *Coronaviridae* family, which includes viruses with a

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positive-sense, single-stranded RNA genome that typically affects the respiratory system of birds and mammals.[9] When observed under electron microscopy this virus has an appearance similar to a crown (*corona* in Latin word), due to surface projections from the virus membrane and, thus, it was named as a coronavirus.[10-11]

All CoVs share similarities in the organization and expression of their genome and are further divided into four genera according to the difference in protein sequences: *Alphacoronavirus* (α-CoVs), *Betacoronavirus* (β-CoVs), *Gammacoronavirus* (γ-CoVs), and *Deltacoronavirus* (δ-CoVs).[10-12] To date, seven types of CoVs are known to infect humans (HCoVs),[11] including α-CoVs, HCoVs-NL63, HCoVs-229E; β-CoVs, HCoVs-OC43, HCoVs-HKU1, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.[13-14] It is important to note that all seven HCoVs have had origin from animals including domestic animals, bats, and mice.[11-15]

The HCoVs have been known since the '60s and until the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak occasioned by SARS-CoV in 2003 in Guangdong Province, China they were considered harmless.[11-15] This devastating outbreak of SARS-CoV resulted in up to 700 deaths worldwide.[16] In 2012, another infectious outbreak in the Arabian Peninsula caused by MERS-CoV was responsible for over 600 deaths.[15-17] In late December 2019, a novel HCoV (SARS-CoV-2) was responsible for an outbreak in Wuhan, China. Different from the other HCoVs that cause mild symptoms in humans, SARS-CoV, MERS-CoV, and SARS-CoV-2 are associated with severe lower respiratory tract infection, and patients can develop acute respiratory distress syndrome and extrapulmonary manifestations.[15-17]

2.1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2, which causes COVID-19, is a public health emergency of international concern.[17-18] This outbreak originated in Wuhan, Hubei Province, China from mid to late December 2019, in which more than 50 people were infected.[17] The symptoms presented by the patients were very similar to those of viral pneumonia and rapidly evolved to acute respiratory distress syndrome.[11] Initially, it was associated that these patients have consumed infected animals or birds. However, it was soon demonstrated human-to-human transmission of SARS-CoV-2.[19]

In comparison with SARS-CoV and MERS-CoV, the SARS-CoV-2 is more transmissible but less pathogenic.[19] The contamination can occur due to close contact with an infected person, exposure to coughing, sneezing, respiratory droplets, or aerosols.[21-23] Besides, SARS-CoV-2 can be transmitted by asymptomatic carriers, which might contribute to its rapid spreading.[11-12]

3. Drugs and Available Treatment Options

Researchers are testing drugs to effectively treat COVID-19. The studies are mainly focused on drugs that were previously used as a treatment for malaria, chemoprophylaxis, HIV, influenza, Ebola, systemic lupus erythematosus, porphyria cutanea tarda, and arthritis drugs, due to investigation of drug action from results of interaction and molecular affinity between the drugs and the target protein, through the molecular fit test. [2-8]

3.1. Chloroquine (CQ) and hydroxychloroquine (HCQ)

The history of chloroquine (CQ), a 4-aminoquinoline compound, began in 1934, at Bayer Interessen-Gemeinschaft Farbenindustrie A. G. laboratories in Wuppertal-Elberfeld, Germany, where Hans Andersag, in the search for new antimalarial agents, synthesized resochin (1934) and a methylated derivative of it, sontochin (1936).[24-25] Scientists that conducted the *in vivo* testing on these new substances observed that resochin was effective, but considered it too toxic for use in humans. However, sontochin was considered effective and less toxic than resochin.[26]

Bayer, under an international trade agreement, sent samples of the synthesized substances to the Winthrop Chemical Company, in the United States.[24-25] However, this company made no additional clinical advances. Furthermore, sontochin was also sent to Sepia Company, a French pharmaceutical company, in North Africa, which in turn sent the drugs to Tunisia for human trials, which obtained very impressive results.[26]

In 1943, the sontochin was taken to the United States for analysis. Then, this substance was analyzed, and its composition was changed slightly to make it a potent antimalarial medication. In its new formulation, sontochin was renamed chloroquine (Figure 1).[27] However, in 1944, analysis of chloroquine revealed that its chemical composition was identical to the resochin previously synthesized by Hans Andersag in 1934 and analyzed by Winthrop.[28]

In general, chloroquine has been used for malaria treatment, chemoprophylaxis, and the prevention of reinfection in treated patients. In 1955, chloroquine was used in the WHO Malaria Eradication Program successfully, and in 1982, the WHO declare 24 countries to be endemically malaria-free.[25]

A derivative of CQ by introducing a hydroxyl group into CQ, hydroxychloroquine (HCQ), was synthesized for the first time in 1946 by Alexander R. Surrey and Henry F. Hammer in Rensselaer (New York). It has been used in the treatment and prevention of malaria in response to the widespread malaria resistance to CQ. Moreover, the HCQ demonstrated to be less toxic than CQ in animals.[29] Additionally, HCQ is effective for the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid.[2-8]

Chemically, CQ is N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine, with a molecular formula of $C_{18}H_{26}ClN_3$ and molecular weight of 319.88 g.mol^{-1} (Figure 1). Its structural formula has double benzene with a chloride atom at position 7 and an alkyl side chain at the 4-amino site.[30] CQ as chloroquine phosphate, (IUPAC name N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine phosphate (1:2) is a white or almost white, odorless or almost odorless, crystalline powder, with a molecular formula $C_{18}H_{26}ClN_3.2H_3PO_4$ and molecular weight of 515,86 g mol^{-1}, and CQ as chloroquine sulfate, IUPAC name N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine sulfate, is a white or almost white, odorless, crystalline powder, with molecular formula $C_{18}H_{26}ClN_3.H_2SO_4.H_2O$ and molecular weight of 436.00 g mol^{-1}. CQ phosphate is soluble in 4 parts of water and very slightly soluble in ethanol; while CQ sulfate is soluble in 3 parts of water and practically insoluble in ethanol.[30]

HCQ is 2-[[4-[(7-chloro-4-quinolyl)amino]pentyl] ethylamino]ethanol, with molecular formula $C_{18}H_{26}ClN_3O$, and molecular weight of 335.9 g mol^{-1} (Figure 2). HCQ as hydroxychloroquine sulfate (HCQ sulfate), IUPAC name 2-[[4-[(7-chloro-4-quinolyl)amino]pentyl]ethylamino] ethanolsulfate (1:1)[31] is a white or practically white, crystalline powder, freely soluble in water; practically insoluble in alcohol, chloroform, and in ether, with molecular formula $C_{18}H_{26}ClN_3O.H_2SO_4$ and molecular weight of 433.95 g mol^{-1}.[32]

HCQ and CQ have similar structural formulas. However, HCQ has an *N*-hydroxyethyl side chain, which makes it more soluble than CQ.[33]

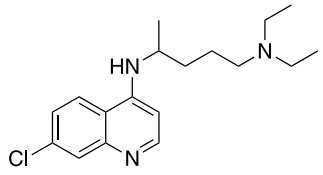

Figure 1. Structural formula of chloroquine

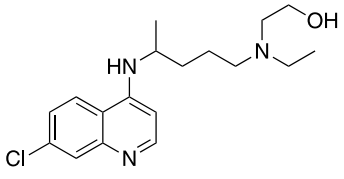

Figure 2. Structural formula of hydroxychloroquine

The CQ is supplied as white, bitter-tasting tablets, containing 100, 250, or 500 mg of CQ phosphate or sulfate and the HCQ is supplied as white to off-white, film-coated, peanut-shaped tablets, containing 200 mg HCQ sulfate.[31]

The acute effects that can occur with the CQ phosphate or sulfate and HCQ sulfate uses include ophthalmic changes, mild diarrhea, nausea, digestive disorders,[2] glucose-6-phosphate dehydrogenases deficiency-related anemia,[7] and more severe cases can lead to heart failure.[2]

The *in vitro* activity of CQ against SARS-CoV was first demonstrated in 2004 and more recently, an expert consensus group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province (2020)[32-35] in China has recommended the use of CQ at a dose of 500 mg twice daily during 10 days in all patients diagnosed with mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to CQ. In another study, the pharmacological activity of CQ and HCQ was tested using SARS-CoV-2–infected Vero cells. HCQ was found to be more powerful than CQ to inhibit SARS-CoV-2 *in vitro*.[37] Therefore, since researchers have found that CQ and HCQ have *in vitro* activity against SARS-CoV-2,[7] both drugs have been approved by the Food and Drug Administration (FDA) to be tested as potential options for treating COVID-19.[2]

In vitro studies demonstrate possible viral inhibition by increasing the endosomal pH, which decreased viral membrane fusion.[7] As CQ and HCQ are both weak bases, when added extracellularly, the non-protonated portion of their molecules enters the cell, where it is protonated and concentrated low-pH organelles, such as endosomes, inhibiting the replication of some viruses.[38-39] Moreover, CQ also interferes with the glycosylation of cellular receptors of SARS-CoV.[8] Also, it was shown that CQ functioned at both entry and post-entry stages of the Vero E6 cells infected by SARS-CoV-2 and that CQ has immunomodulatory effects, improving its antiviral potency *in vivo*.[33]

Brazilian researchers conducted a double-blind trial to assess the CQ efficacy in patients with COVID-19. The study recruited 81 patients who received CQ at a dose of either 600 mg twice daily for 10 days or 450 mg twice daily on day 1 and once daily for 4 days. After 13 days, 39% of patients in the high dose group died versus 15% in the low dose group. Based on the results of the study, they suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards.[40]

Clinical trials on patients with COVID-19 associated pneumonia in ten hospitals in China have demonstrated superior results of CQ to the control treatment of COVID-19 when compared with results obtained with HCQ.[41]

An uncontrolled, non-comparative, observational study in 80 COVID-19 patients treated with a combination of HCQ and azithromycin was conducted at the University Hospital Institute Méditerranée Infection in Marseille, France. Patients received a combination of 200 mg of HCQ, twice daily for ten days combined with azithromycin (500 mg on day 1 followed by 250 mg once daily for 4 days) for at least three days. They observed that almost all patients improved clinically except for two patients. They showed that co-administration of HCQ with azithromycin has beneficial effects and it has potential effectiveness in the treatment of COVID-19.[42]

A retrospective analysis of the treatment of COVID-19 was conducted at University Hospital Institute Méditerranée Infection in Marseille, France. They analyzed 1061 SARS-CoV-2 positive tested patients treated with the combination of 200 mg of HCQ, three times per day for ten days) combined with azithromycin (500 mg on day 1 followed by 250 mg once daily for the next 4 days) for at least three days. They verified good clinical outcomes and virologic cure in 973 patients (91.7%) within 10 days. A poor clinical outcome was verified in 46 patients (4.3%) and 8 died (0.75%), due to respiratory failure. The adverse events reported (2.3% of patients) including gastrointestinal, headache, and transient blurred vision.[43]

In June 15, 2020, the FDA revoked the use authorization that allowed for CQ and HCQ to be used to treat certain hospitalized patients with COVID-19. Additionally, they noted that the potential benefits of CQ and HCQ no longer overcame the potential risks for the authorized use.[44]

3.2. Azithromycin

The invention of azithromycin (Figure 3), the first azalide antibiotic, was in 1980, by a team of Pliva's researchers, a Croatian pharmaceutical company, located in Zagreb. In 1981, Pliva patented it, and in 1986, Pliva and Pfizer signed a licensing agreement, in which Pfizer acquired the right for the sale of azithromycin in Western Europe and the United States, while Pliva maintained the right for the sale product in Central and Eastern Europe. In 1988, Pliva launched azithromycin in this region, and in 1991, Pfizer launched it in the other region.[45]

Azithromycin is indicated for the treatment of several infections caused by bacteria, such as respiratory infections (bronchitis and pneumonia) and *Mycobacterium avium* complex (MAC) infection.[46]

Chemically, the IUPAC name of azithromycin is (2*R*, 3*S*, 4*R*, 5*R*, 8*R*, 10*R*, 11*R*, 12*S*, 13*S*, 14*R*)-13-[2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-ribo-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-hepta-methyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one, with a molecular formula of $C_{38}H_{72}N_2O_{12}$ and a molecular weight of 748.98 g.mol^{-1}.[47] Azithromycin, as dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$ and a molecular weight of 784.98 g.mol^{-1}.[48]

Azithromycin in tablets is manufactured as pink modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 250 mg or 500 mg of azithromycin; and azithromycin for oral suspension after constitution contains a flavored suspension. Azithromycin drug for oral suspension is supplied to provide 100 mg.5 mL^{-1} or 200 mg.5 mL^{-1} suspension in a bottle.[48]

Common azithromycin side effects are mainly gastrointestinal and include diarrhea, nausea, abdominal pain, or vomiting.[48-49]

Azithromycin acts inhibiting bacterial protein synthesis by reversible binding to the bacterial 50S ribosomal subunit susceptible microorganisms.[48] Furthermore, according to Poschet *et al*. (2020)[50] it displays a property of regulating pH levels of endosomes and trans-Golgi network, similar to CQ effect on the respiratory epithelial cell.

Currently, azithromycin is under evaluation as a potential drug against SARS-CoV-2,[51]since it was known to inhibit the viral replication of Zika virus *in vitro*[52] and azithromycin could potentiate the effect of HCQ against SARS-CoV-2.[53] Fantini *et al*. (2020)[54] demonstrated that taken together, azithromycin is directed against the virus, whereas HCQ is directed against cellular attachment cofactors.

In Gautret *et al*. (2020)[55] study, twenty patients with COVID-19 were treated with HCQ and azithromycin plus HCQ. At day 6 post-inclusion, 100% of patients treated with azithromycin and HCQ in combination were virologically cured versus 57.1% of patients treated with HCQ only. Therefore, the researchers declared that administrating azithromycin added to HCQ was significantly more efficient for SARS-CoV-2 virus elimination.[55]

On April 1, 2020, a phase 2 randomized clinical trial with the primary purpose of treating 300 hospitalized patients with suspected or confirmed COVID-19 using HCQ and azithromycin was registered at ClinicalTrials.gov (Identifier: NCT04329832) by University of Utah. Patients in the HCQ arm received HCQ 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days. Patients in the azithromycin arm received azithromycin 500 mg on day 1 plus 250 mg daily on days 2-5. Last update posted date was on April 20, 2022. Authors found no suggestion of substantial efficacy for HCQ over azithromycin; HCQ cannot be recommended for patients with COVID-19; and azithromycin may merit additional investigation.[56]

On April 24, 2020, a phase 4 randomized, double-blind, controlled, clinical trial with the primary purpose to treat 40 patients who have a positive test confirming COVID-19 in Shahid Modarres Medical Education Center and Hospital in Tehran, using HCQ and azithromycin was registered at ClinicalTrials.gov (Identifier: NCT04359316) by University of Utah. Patients in the HCQ arm received HCQ 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days. Patients in the azithromycin arm will receive azithromycin 500 mg on day 1 plus 250 mg daily on days 2-5. The

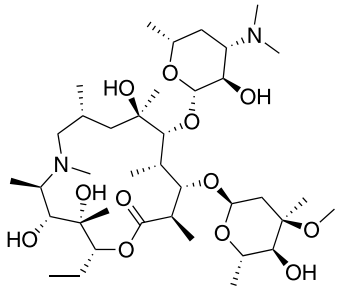

Figure 3. Structural formula of azithromycin

estimated study completion date was May 5, 2020. However, until May, 2022, no results have been published.[57]

Therefore, there is no evidence to support the use of azithromycin to treat COVID-19 outside of the context of clinical trials. Besides, there is limited evidence of the synergy between azithromycin and HCQ.[58]

3.3. Remdesivir

The development of remdesivir (GS-5734) (Figure 4), began in 2009, by the biopharmaceutical company Gilead Sciences, headquartered in Foster City, California, United States. It is an experimental antiviral medication that was originally developed to treat hepatitis C (HCV) and respiratory syncytial virus (RSV).[59]

Remdesivir is a monophosphoramidate prodrug of an adenosine analog, which exhibits broad-spectrum antiviral activity *in vitro* against pathogenic RNA viruses, including filoviruses (EBOV and MARV), and CoVs (eg, SARS-CoV, MERS-CoV); and clinical studies investigating remdesivir safety and pharmacokinetics are ongoing.[60]

In 2014, the drug was tested *in vivo* against Ebola virus (EBOV) disease and Marburg virus (MARV) disease but did not demonstrate clinical efficacy.[60]

Chemically, the name of remdesivir is 2-ethylbutyl (2*S*)-2-{[(*S*)-{[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4] triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl] methoxy}(phenoxy)phosphoryl]amino}propanoate.[62] It has a molecular formula of $C_{27}H_{35}N_6O_8P$ and a molecular weight of 602.6 $g.mol^{-1}$.[63]

Remdesivir for injection is supplied as a lyophilized powder (100 mg) or injection solution (5 $mg.mL^{-1}$). The lyophilized powder is a white to off-white or yellow non-hygroscopic solid, practically insoluble in water and soluble in ethanol. The injection solution is clear, colorless to yellow. The lyophilized powder is reconstituted with 19 mL of sterile water for injection and prior to administration by intravenous infusion, both have to be diluted into 0.9% saline.[64]

Inside cells, remdesivir is metabolized to its pharmacologically active form (nucleoside triphosphate metabolite), an inhibitor of mammalian DNA and RNA polymerases. During replication of viral RNA, it acts as a delayed RNA chain terminator, through competition with the natural adenosine triphosphate (ATP) substrate for incorporation into nascent RNA.[64]

Until October 21, 2020, remdesivir was not approved for any indication of use and its safety profile was incomplete.[64] On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients (>12 years of age) and weighing at least 40 kg for the treatment of COVID-19 at hospitals. On April 25, 2022, FDA expanded the approval of the remdesivir to include pediatric patients (28 days of age and older) weighing at least 3 kg.[65] Remdesivir is the first treatment for COVID-19 to receive FDA approval.[6] There are several ongoing clinical studies aimed to demonstrate the clinical efficacy and safety data to support the compassionate use against viruses as SARS-CoV-2.[6,64] Besides, the approval of remdesivir was supported by the agency's analysis of data from randomized, controlled clinical trials.[6] Since, in tests realized *in vitro* and *in vivo* in animals, remdesivir has demonstrated activity against SARS-CoV and MERS-CoV and *in vitro* activity against SARS-CoV-2.[7]

Remdesivir has proved to be an effective treatment for mice and monkeys infected with SARS-CoV and MERS-CoV, respectively, if administrated on the early stages of the viral infection.[66] A study by Friederike *et al*. (2020)[67] with MERS-CoV infected rhesus monkeys demonstrated that administration of 5 $mg.Kg^{-1}$ of remdesivir 24 hours before and 12 hours after virus inoculation strongly inhibited the virus from spreading to the respiratory system, thus preventing lung failure. Virus inhibition was substantially enhanced with the administration of remdesivir 12 hours after virus inoculation.

On February 6, 2020, a phase3 randomized, controlled, double-blind trial to evaluate the efficacy and safety of remdesivir in 237 participants hospitalized with severe COVID-19, was registered at Capital Medical University (NCT04257656). Patients received 200 mg on day 1, maintenance dosing at 100 mg once daily from day 2.[68] The study demonstrated that the remdesivir use was not related with a difference in time to clinical improvement. The researchers conclude that the dose regimen of remdesivir was adequately tolerated but did not offer significant clinical effects in seriously ill patients with COVID-19. Besides, adverse events were reported in 66% of remdesivir patients and 64% of placebo group. The most common adverse events that occurred in drug group include constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, respiratory failure, or acute respiratory distress syndrome, and increased total bilirubin; and in the placebo group, the most common were hypoalbuminemia, constipation, anemia, hypokalemia, increased aspartate aminotransferase, increased blood lipids, and increased total bilirubin.[69]

On February 21, 2020, a multicenter, adaptive, randomized double-blind, placebo-controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in 1,062 hospitalized adults was registered by the National Institute of Allergy and Infectious Diseases (NIAID). Patients received 200 mg on day 1, maintenance dosing at 100 mg each day while hospitalized for up to 10 days, administered intravenously.[70] Preliminary results indicate that patients who received the drug had a 31% faster time to recovery (11 days) than those who received placebo (15 days), with a lower mortality rate, 8% versus 11.6%.[71] Final report presented that the median time to recovery from COVID-19 was 10 days for remdesivir group compared to 15 days for the placebo group, showing the superiority of remdesivir to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19.[70]

On March 3, 2020, a phase 3 randomized trial to evaluate the efficacy and safety of remdesivir in 4,891 participants with severe COVID-19 was registered by Gilead Sciences (NCT04292899). In the initial phase of the study, 397 patients received 200 mg on day 1, maintenance dosing at 100 mg each day until day 5 or 10, administered intravenously, in addition to standard of care.[72] This study demonstrated that both patients receiving a 5-day and 10-day treatment course of the drug achieved similar improvement in clinical status. The most frequent adverse events occurring in more than 10 percent of patients in either group were nausea and acute respiratory failure.[73]

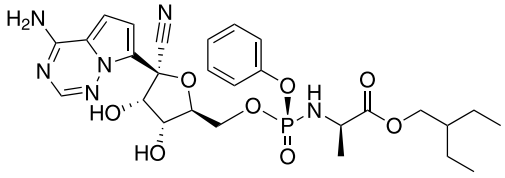

Figure 4. Structural formula of remdesivir

3.4. Lopinavir/Ritonavir

Lopinavir/Ritonavir (Figure 5) is a co-formulation of two structurally related protease inhibitor antiretroviral agents developed by Abbott Laboratories.[74] The development of this drug started with ritonavir (ABT-538), which was discovered in 1995,[75] and the marketed product was available in 1996.[74] Lopinavir (ABT-378) appeared in 1998,[76] and was found to be more active than ritonavir in cell cultures against Human Immunodeficiency Virus (HIV). Moreover, it was found that co-administration with smaller doses of ritonavir improved its poor bioavailability.[77]

Lopinavir is a potent inhibitor of HIV-1 protease which cleaves both structural and functional proteins from precursor viral polypeptide strands, producing non-infectious virions, preventing subsequent waves of cellular infection[78] and ritonavir is a potent CYP3A inhibitor. Therefore, ritonavir increases the plasma levels of lopinavir via inhibition of CYP3A metabolism.[79]

Lopinavir is chemically designated as [1*S*-[1*R*,(R*),3*R**,4*R**]]-*N*-[4-[[(2,6-dimethylphenoxy) acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl) pentyl]tetrahydroalpha-(1-methylethyl)-2-oxo-1(2*H*)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80 g.mol^{-1}. Ritonavir is chemically designated as 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-*bis*(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5*S*-(5*R**,8*R**,10*R**,11*R**)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95 g.mol^{-1}.[80] Ritonavir and lopinavir are a white to light tan powder. They are freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.[81]

Lopinavir/ritonavir received FDA approval for the treatment of HIV-1 infection in combination with other antiretroviral agents.[77] It is available in tablets (200 mg of lopinavir and 50 mg of ritonavir or 100 mg of lopinavir and 25 mg of ritonavir) and oral solution (400 mg of lopinavir and 100 mg of ritonavir per 10 mL oral solution).[82] Commonly adverse events related to lopinavir/ritonavir included diarrhea, vomiting, and asthenia.[79]

Currently, lopinavir/ritonavir has been studied for use in the treatment of COVID-19, since it showed activity against SARS-CoV and was associated with improvement in some patients in 2003.[2] To evaluate the efficacy of this drug against SARS-CoV-2, a randomized, controlled, open-label trial involving 199 hospitalized adult patients with positive infections were conducted at a single hospital in Wuhan, China. Patients received lopinavir/ritonavir (400 mg/100 mg twice daily for 14 days). No improvement above standard care was observed with lopinavir/ritonavir treatment.[83] However, for a 54-year-old man were given 2 tablets of lopinavir (200 mg)/ritonavir (50 mg) and from the next day of the drug administration, the levels of β-coronavirus viral had a significant and substantial decrease.[84]

On February 5, 2020, a randomized, open-label, controlled study of the efficacy of lopinavir/ritonavir and arbidol for treating patients with COVID-19 was performed in China (ClinicalTrials.gov Identifier: NCT04252885). Patients with mild or moderate clinical status, received lopinavir (200 mg)/ritonavir (50 mg), twice daily, for 7-14 days and researchers concluded that this drug might not improve the clinical outcome in treating with mild or moderate COVID-19 and further work is needed to confirm this result.[85]

The antiviral effects and safety of lopinavir/ritonavir and arbidol were evaluated in fifty patients with COVID-19.[86] Patients were divided into two groups: the lopinavir/ritonavir group (34 cases) and the arbidol group (16 cases). Lopinavir/ritonavir group received 400 mg.100 mg^{-1} of lopinavir/

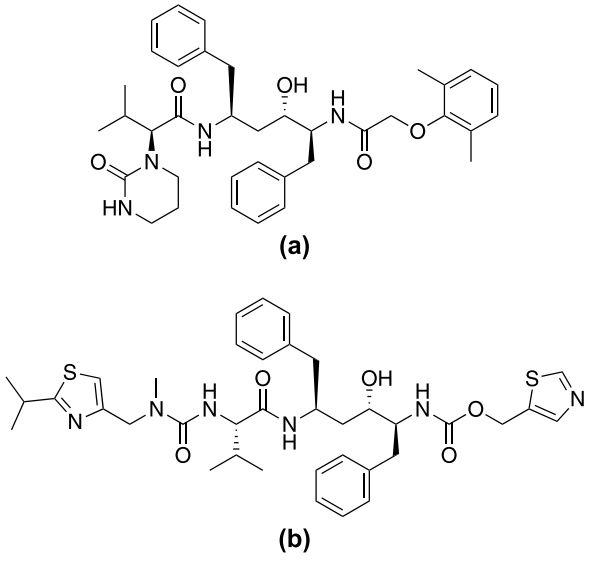

Figure 5. Structural formula of **a)** lopinavir and **b)** ritonavir

ritonavir, twice daily for 7 days, and the results indicated that arbidol monotherapy may be superior to lopinavir/ritonavir in the treatment of COVID-19.

3.5. Favipiravir

Favipiravir (T-705) (Figure 6) is a broad-spectrum antiviral prodrug discovered by Toyama Chemical Co., Ltd., Tokyo, Japan, via chemical modification of a pyrazine analog originally being evaluated *in vitro* for antiviral activity against influenza.[87,88] In Japan, favipiravir was approved in 2014 to treat novel or re-emerging pandemic influenza outbreaks.[87,89]

Interestingly, in addition to influenza, favipiravir's RNA virus's intracellular replication inhibitory effects extend to other positive- and negative-sense single-stranded RNA viruses such as Ebola and Lassa.[87,90]

Favipiravir physicochemical properties are summarized in a report by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).[91] Chemically, Favipiravir name is 6-fluoro-3-hydroxy-2-pyrazinecarboxamide. Its molecular formula and weight are $C_5H_4FN_3O_2$ and 157.1 $g.mol^{-1}$, respectively.[92] It is a white to yellow powder with a melting point between 187 °C and 193 °C and pKa of 5.1. The drug substance solubility is pH-dependent. Favipiravir is soluble in water at pH 5 to 13, but soluble in 1-octanol at pH 2 to 4. Furthermore, favipiravir's lethal dose is >2000 $mg.kg^{-1}$ in mice and rats, >1000 $mg.kg^{-1}$ in dogs.[91]

Regarding favipiravir pharmacokinetics and safety, Du and Chen (2020)[93] discuss that favipiravir maximum plasma concentration is achieved 2 hours after ingesting the prodrug, reaching zero after 2 to 5.5 hours. The parent drug is metabolized in the liver mainly by aldehyde oxidase enzyme, and the inactive metabolite is easily excreted by the kidneys.[87,92] According to Delang *et al*. (2018)[87] favipiravir inhibitory activity towards RNA viruses did not affect DNA-dependent RNA polymerase, nor did it lead to mitochondria toxicity but the latter should not be overlooked.[87] Regarding possible side effects, during its clinical development the most frequent side effects were mild to moderate diarrhea, an increase of blood uric acid and transaminases as well as a decrease in neutrophil.[92]

Favipiravir efficiently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses.[90] The drug is first converted into ribose-5'-monophosphate by the eukaryotic hypoxanthine guanine phosphoribosyl transferase.[87-94] The resulting compound then goes through an intracellular phosphorylation step becoming the drug's active form, favipiravir ribofuranosyl-5'-triphosphate, or simply favipiravir-RTP.[87-90] Favipiravir-RTP is recognized as a substrate by RdRp, thus acting as a competition inhibitor, competing with purine nucleosides for RdRp, consequently interfering with RNA polymerase activity and preventing virus replication.[87-90]

Hence, as favipiravir has shown antiviral activity against an extensive range of single-stranded RNA viruses.[87] The prodrug is considered a potential candidate against COVID-19 and it is under investigation for the treatment of this viruses.[90] Moreover, the antiviral was approved in March 2020 by the National Medical Products Administration of China as the first anti-COVID-19 drug.[94]

Wang *et al*. (2020)[95] investigated *in vitro* antiviral activity against SARS-CoV-2 of favipiravir and other drugs in Vero E6 infected cells by quantifying viral copy number in the cell supernatant. In this study, despite results showing the antiviral activity of favipiravir against the virus, a high concentration of the drug (half-maximal effective concentration of 61.88 μM) was necessary to decrease viral infection. However, the authors recommend further *in vivo* studies to determine the prodrug efficiency. Conversely, a study by Choy *et al*. (2020)[96] showed that *in vitro* antiviral activity of favipiravir against SARS-CoV-2 in Vero E6 infected cells at concentrations under 100 μM was unnoticeable.[95-96]

The potential of favipiravir against SARS-CoV-2 in a prospective, randomized, controlled, open, multicenter study was conducted in three hospitals in Wuhan, China, involving 240 adult patients diagnosed with COVID-19 (ChiCTR2000030254). Patients were separated into two groups to receive conventional therapy plus Arbidol (200 mg three times daily) or favipiravir (1600 mg twice daily on day 1 followed by 600 mg twice daily) for 10 days.[97] Although favipiravir did not improve the clinical recovery rate at Day 7 when compared to the Arbidol group, it significantly improved the latency to relief for pyrexia and cough. Interestingly, a post-hoc observation identified that in moderate COVID-19 cases, patients treated with favipiravir showed superior clinical recovery rates than those treated with Arbidol. Moreover, a reduction in auxiliary oxygen therapy and noninvasive mechanical ventilation rates was attributed to treatment with favipiravir.[97]

On February 14, 2020, a clinical trial to assess favipiravir's efficacy against SARS-CoV-2 was initiated at The Third People's Hospital of Shenzen. The open-label, nonrandomized, control study aimed to compare the clinical outcomes of patients treated with favipiravir plus interferon-α and patients treated with lopinavir/ritonavir plus interferon-α. A total of 90 patients who tested positive for SARS-CoV-2 were included either in the favipiravir arm or the lopinavir/ritonavir arm (control arm). Favipiravir was given orally, 1600 mg twice daily on day 1, changing to 600 mg twice daily on days 2-14. The control arm dose was 400.100 mg^{-1} of lopinavir/ritonavir twice daily, remaining unchanged through the 14 days. All patients received interferon-α 60 μg twice daily via aerosol inhalation. Patients of favipiravir arm exhibited significantly shorter viral clearance time than patients from the control arm (4 days versus 11 days, respectively). Moreover, favipiravir arm also demonstrated a significant improvement in chest imaging over the control arm (91.43% versus 62.22%) as well as fewer adverse events.[98]

A randomized, open-label, parallel-arm, multicenter,

phase 3 study (CTRI/2020/05/025114; 7 sites in India) evaluated the efficacy and safety of favipiravir against SARS-CoV-2 in 150 patients diagnosed with mild-to-moderate symptoms of COVID-19. One group was treated with favipiravir (1.8 g twice daily on day 1, followed by 800 mg twice daily from day 2 to 14) plus standard supportive care while the other only received standard supportive care. Although adverse events were observed mainly in the favipiravir arm, patients in this group exhibited decreased time to clinical cure, which indicates that early administration of the prodrug may help to reduce duration of clinical signs and symptoms.[99]

A prospective, randomized, open-label, multicenter trial with 89 patients was conducted from 25 hospitals in Japan. The patients enrolled in this study were diagnosed either as asymptomatic or with mild COVID-19. The trial divided the patients in 2 groups, which received either early (day 1) or late (day 6) treatment with favipiravir. As results, authors observed that there was no substantial improvement in viral clearance in the first six days, however a trend towards early viral clearance was observed with the favipiravir treatment.[100]

An adaptive, multicenter, open label, randomized, Phase II/III clinical trial (ClinicalTrials.gov Identifier: NCT04434248) on patients with COVID-19 pneumonia also reported promising results for favipiravir. This study enrolled 60 patients, which were equally separated into three groups. Patients were treated with either 1600 mg of favipiravir twice a day on day 1 followed by 600 mg twice daily from day 2 to 14; or 1800 mg of favipiravir twice a day on day 1 followed by 800 mg twice daily for the last 13 days; or standard care. Favipiravir demonstrated promising results, with viral clearance of favipiravir groups being twice as high as in the control group.[101]

In contrast with the promising results previously described, an exploratory single center, open label, randomized, controlled trial (ChiCTR2000029544) reported no evidence supporting the addition of favipiravir to the standard existing treatment. The percentage of adult patients who tested negative for viral RNA within 14 days was substantially higher in the control group (100%) compared to the favipiravir group (77%).[102]

Clinical trials conducted to assess the effectiveness of favipiravir against SARS-CoV-2 indicated that the side effects associated with treatment were diarrhea, liver damage, stomach discomfort and increased serum uric acid concentration.[97-100] However, studies stated that the side effects were tolerable, and the treatment was not interrupted. Favipiravir is severely contraindicated for women, due to the risk of teratogenicity and embryotoxicity.[86]

Favipiravir demonstrated potential against SARS-CoV-2.[95-101] However, additional studies are needed to confirm it clinical benefit, and the prodrug pharmacokinetics needs to be further investigated to develop adequate treatment for patients diagnosed with distinct cases of COVID-19.[103] Besides, due to the lack of concrete evidence

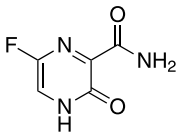

Figure 6. Structural formula of favipiravir

regarding the efficiency of favipiravir as a treatment for COVID-19, the WHO recommended in a guide released on May 2020, the use of this drug exclusively inside clinical trials.[104]

3.6. Other drugs

In view of the dimension taken by the COVID-19 pandemic and the urgency for effective drugs to combat the disease, other drugs in addition to those already reported were also evaluated even with lesser repercussions, including colchicine, ivermectin, methotrexate, nafamostat mesylate and camostat mesylate.

Ivermectin is a popular antiparasitic and antiviral drug with studies showing some *in vitro* activity against a broad range of viruses, including HIV, dengue, influenza, and Zika virus. Its molecular formula is $C_{48}H_{74}O_{14}$ and shows molecular weight of 875.1 g.mol^{-1}. It can be chemically designated as 22,23-dihydroavermectin B1a.[105-106] Some studies such as Caly *et al*. (2020)[105] and Rajter *et al*. (2020),[106] reported that ivermectin, *in vitro*, is an inhibitor of the viral replication of the virus SARS-CoV-2. According to Caly *et al*. (2020)[105] study, the single treatment of this drug was able to reduce the virus up to 5000-fold in culture within 48 h. However, no further reduction was related with further increase in period i.e up to 72 h. Moreover, no toxicity was seen with the drug at any point of time. In Rajter *et al*. (2020)[106] study the ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support. However, they emphasize that these findings should be evaluated later with randomized clinical trials, since these data are for *in vitro* experiments.

Colchicine intended for the treatment of acute gout attacks and the prevention of acute attacks in patients with chronic gouty arthritis. It has been also used for Familial Mediterranean Fever (FMF) prophylaxis, Sweet's syndrome, and Behçet's disease. Originally, it was extracted from the *Colchicum autumnale* plants. It prevents microtubule assembly and thereby disrupts inflammasome activation, microtubule-based inflammatory cell chemotaxis, generation of leukotrienes and cytokines, and phagocytosis.[107- 108] According to IUPAC its chemical nomenclature is N-[(7*S*)-1,2,3,10-tetramethoxy-9-oxo-6,7-dihydro-5*H*-benzo[a]heptalen-7-yl] acetamide. Its molecular formula is $C_{22}H_{25}NO_6$, and its molecular weight is 399.4 g.mol^{-1}. Currently, several clinical trials are under development investigating colchicine efficiency in combating SARS-CoV-2.[109] However, even with preliminary

research showing possible results of efficacy, there is still a lack of clinical evidence to support such studies.[110]

Another drug that has also been tested to combat the symptoms of COVID-19 is methotrexate. It is used clinically for rheumatoid or psoriatic arthritis and systemic lupus erythematosis with good therapeutic results.[111] The name of this active principle by IUPAC is (2*S*)-2-[[4-[(2,4-diaminopteridin-6-yl) methyl-methylamino] benzoyl] amino] pentanedioic acid, and the molecular formula is $C_{20}H_{22}N_8O_5$ with molecular weight of 454.4 g.mol^{-1}. Caruso *et al*. (2020)[111] reported that methotrexate efficiently inhibits viral replication at the post-entry stages of the SARS-CoV-2 infection *in vitro*.

Biological drugs, in turn, such as monoclonal antibodies, interferons, specific proteins and anticoagulants, were evaluated in several clinical trials to define their role in disease therapy. Nafamostat mesylate and camostat mesylate are drugs that belong to the group of synthetic serine protease inhibitors and have been useful in the first phase of infection with the SARS-CoV-2 virus. Nafamostat mesylate is named according to IUPAC for 6-amidino-2-naphthyl-4-guanidinobenzoate dihydrochloride, and it shows the molecular formula of $C_{19}H_{17}N_5O_2$ molecular weight of 347.4 g.mol^{-1}. Normally it is used for acute pancreatitis and intracellular coagulation. Camostat mesylate has the name of [4-[2-[2-(dimethylamino)-2-oxoethoxy]-2-oxoethyl] phenyl] 4-(diaminomethylideneamino) benzoate; methanesulfonic acid, according to IUPAC nomenclature, it shows the molecular formula of $C_{21}H_{26}N_4O_8S$, and molecular weight of 494.5 g.mol^{-1}. It is commonly used to treat acute pancreatitis. However, the application of nafamostat and camostat for COVID-19 prevention or treatment still requires clinical trials.[112-114]The highly toxic compound oleandrin, produced by the oleander plant (Nerium oleander), has been investigated in cells infected with Sars-CoV-2, but there is still no clinical evidence that indicates its safety and efficacy for the treatment of Covid-19. The proposal is based on the anti-inflammatory effects of apremilast, in combination with the reduction of fluid in the lungs of icatibant, and with the blocking of the immune system of cenicriviroc. These drugs will also be tested in combination with remdesivir and dexamethasone.[115]

4. Conclusion

In addition to the therapies discussed in the current review and that are being investigated for safety and efficacy against SARS-CoV-2 (azithromycin, CQ, HCQ, remdesivir, lopinavir/ritonavir, and favipiravir), other drugs have been explored for COVID-19 treatment as colchicine, ivermectin, methotrexate, nafamostat mesylate and camostat mesylate. To date, the studies presented inconclusive results and further work is needed to confirm the safety and efficacy of these drugs as anti-SARS-CoV-2 treatment. Moreover, several clinical trials are underway to ensure the effectiveness of single and combined treatments.

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