Review Article:

Proposed Pharmacological Treatments for COVID-19: Previously Confirmed Drugs

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ABSTRACT

Background: The outbreak of severe acute respiratory syndrome coronavirus-2, also called 'coronavirus disease 2019' (COVID-19), first appeared in December 2019 in Wuhan, China. COVID-19 is caused by an enveloped single-stranded RNA virus, which has affected more than 14 million people around the world and caused a high rate of mortality. It is notable that discovering new drugs and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is time-consuming. Therefore, reviewing drugs, which have been previously designed for other purposes can be helpful and effective.

Objectives: Studying the effects of previously approved drugs is important; thus, in this article, we reviewed studies on proposed drugs against COVID-19.

Methods: The articles and information were collected from Google Scholar, ScienceDirect, and Scopus databases. We did our research based on keywords, like "therapeutics", "pharmacology", "Coronavirus", "COVID-19", "SARS", and "MERS-CoV". We also applied some filters, such as title/abstract, and ignored factors that could lead to bias and selective selection.

Results: There is currently no cure for coronavirus, and most treatments have been effective to relieve symptoms. The treatment methods and drugs addressed in this article are chosen either from previous drugs against MERS and SARS, drugs that disrupt the life cycle of the coronavirus, or drugs that have been reviewed in retrospective studies and clinical trials.

Conclusion: Prevention and treatment of COVID-19 remain a challenge, in particular for coronavirus and the treatments based on boosting the immune system and preventing virus replication. Epidemiological studies have shown that COVID-19 and SARS-COV transmission are relatively similar. This can help to select the appropriate drug. Thus, anti-inflammatory and antiviral drugs, such as remdesivir are used. Antimalarial drugs, such as hydroxychloroquine (HCQ) and chloroquine (CQ) along with estrogen receptor inhibitors, such as toremifene citrate, which has shown effective results against SARS and MERS, can influence the treatment process. However, more clinical trials are needed to determine the efficacy and side effects of drugs.

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Introduction

The major outbreak of coronavirus first appeared in Wuhan, China in December 2019. Once it was reported to the World Health Organization (WHO), it was named 2019-novel coronavirus (2019-nCoV) but later, the name was changed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The name, "corona", is selected due to the crown-like spike on the virus's envelope shape. The genome of the virus codes four functional proteins, including spike protein, membrane protein, envelope protein, and nucleocapsid [1, 2]. The genome of SARS-CoV2 consists of a single-stranded RNA [3, 4], which can affect both animals and humans [2]. SARS-CoV2 affects the host by the interaction between spike proteins and angiotensin-converting enzyme 2 (ACE2) on the respiratory epithelium [5, 6]. This virus can involve the respiratory and gastrointestinal tract and central nervous system (CNS) [7]. Attacking the lungs, the virus causes lung injuries in the form of acute respiratory distress [8]. Common symptoms of SARS-CoV2 are fever, dry cough, muscle aches, shortness of breath, dyspnea, and sometimes pneumonia [4, 9]. Since July 19, 2020, over 14 million infected cases and more than 597000 deaths have been reported in the world [10]. The quick prevalence and worldwide spread of SARS-CoV2 led to an alarming situation which was declared a pandemic by WHO [1, 2, 4, 8].

SARS-CoV2 outbreak is considered a huge threat because prevention and treatment of COVID-19 remain a challenge [2]. Therefore, it is important to develop effective drugs and vaccines against SARS-CoV2. There are currently some drugs available, which have been designed for other viral and pathogenic infections. These drugs fall into two groups; the first group targets virus replication directly and the second one works based on inflammatory responses and immunotherapy, like convalescent plasma therapy [11, 12]. SARS-CoV2 is up to 80% similar to severe acute respiratory syndrome coronavirus (SARS-CoV); therefore, we can use drugs, such as interferon and lopinavir/ritonavir that were previously used for the treatment of SARS-CoV and middle east respiratory syndrome (MERS) [9, 13, 14]. The conventional drugs used for SARS-CoV2 include chloroquine (CQ), hydroxychloroquine (HCQ), lopinavir/ritonavir, favipiravir, and remdesivir [11]. CQ is an antimalarial drug, which is considered to be helpful [4].

Recent studies have indicated that using azithromycin and HCQ can be effective against SARS-CoV2 [15]. Lopinavir is an inhibitor of aspartate protease in HIV type 1 that showed inhibitory activity against SARS-CoV and MERS *in vivo* and animal models. Ritonavir increases lopinavir plasma half-life by inhibiting cytochrome p-450 [16]. Favipiravir inhibits RNA-dependent RNA polymerase, and it was approved as the first drug for the treatment of SARS-CoV2 in China due to its efficiency and minimum side effect [11]. Remdesivir can inhibit virus replication by inhibiting RNA-dependent RNA polymerase [13]. Renin-angiotensin-aldosterone system (RAAS) inhibitors can increase the risk of infection with SARS-CoV2 because they increase the expression of ACE2 and its presentation on the cell surface [5]. Discovering new drugs and vaccines takes time. On the other hand, evaluating the effects of antiviral drugs and the drugs that were already confirmed against coronavirus is very important; therefore, in this study, we reviewed studies on drugs used to treat SARS-CoV2.

Materials and Methods

To look for related works we used keywords, such as therapeutics, pharmacology, coronavirus, COVID-19, SARS, and MERS-CoV. Data were collected from Google Scholar, ScienceDirect, and Scopus databases. Five authors collected data on drugs, and two authors sorted and discussed drugs and eliminated useless data. We mainly focused on articles providing information on the mechanism and efficiency of the drug; however, the mechanism is preferred because COVID-19 is a new virus. In addition, knowing about the mechanism of the drug and how they work against the virus helps us understand the life cycle of the coronavirus.

Some filters, like title/abstract, were applied and some articles were chosen randomly. According to keywords and filters, 597 articles were found, of which 67 articles were the most relevant, and information was mainly adopted from 45 articles. In addition, we searched for articles from 2019 to 2020 (it should be noted that two articles from 2014 and 2016 were reviewed in the study due to their high comprehensiveness) and we started to accumulate data since July 4, 2020. The chosen articles included retrospective studies, review research, and *in vitro* studies (clinical trial studies were less available due to the fast outbreak of COVID-19).

We did not consider geographical limitations, and selective (nonrandom)/oriented choices were avoided. Moreover, due to the global compulsion of the pandemic and preparing the lists of probable effective drugs for coronavirus, we did not choose the symmetric process. We tried to provide some tables to make a better decision.

Result

SARS-COV-2 plays a crucial role in increasing pneumonia along with multi-organ disorders. This virus has a fast spreading rate and can be transmitted from person to person in close face-to-face contact. Three types of carriers observed in this disease include asymptomatic, presymptomatic, and symptomatic carriers. This disease, like other diseases, have some symptoms, such as fever, dry cough, and shortness of breath t (the most common symptoms), and abnormal radiographic and laboratory findings, such as Lymphopenia and elevated lactate dehydrogenase. Diagnosis is usually based on reverse transcription-polymerase chain reaction testing. Although the test result is sometimes negative, the person is involved [17].

There is no definitive cure for SARS-COV2 so far [18], and most treatments are based on symptom relief and support [19]. However, randomized trials and laboratory studies are ongoing. In this study, we reviewed published articles and evaluated possible drug therapies. Treatment candidates must influence the life cycle of the coronavirus and host body factors. The development of treatment protocols is based on affecting the virus genome and the physical structure of the SARS-COV-2 virus. However, these protocols may be in a different form or ineffective *in vivo* [20]. At a glance, we included some prevention methods and treatment strategies in Table 1. Our focus was on treatments.

Anti-malaria

Chloroquine (CQ) and Hydroxychloroquine (HCQ): CQ is an amine acid-tropic form of quinine, while HCQ differs from CQ and has a hydroxyl group at the end of the side chain [21]. These drugs have beneficial effects in the treatment and prevention of malaria and are effective in chronic inflammatory and autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE) [20, 21]. The molecular mechanism of action of CQ and HCQ has not been fully defined. Findings from previous studies have suggested that CQ and HCQ may inhibit the coronavirus through a series of steps. First, the drugs can change the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus into the cell membrane. They can also inhibit nucleic acid replication and glycosylation of viral proteins [20], virus assembly, new virus particle transport, virus release, and other processes to achieve their antiviral effects and also interfere with the terminal glycosylation of ACE2 receptor expression that prevents SARS-COV2 to bind its receptor and subsequent spread of infection [20]. Recent studies have shown that these two drugs reduce the viral load of SARS-COV-2 and shorten its viral duration [21].

In vitro studies of CQ have shown that CQ had good antiviral effects. *In vitro*, chloroquine phosphate has anticoronary anti-viral effects and reduces viral load. It can improve cough recovery time. CQ has led to cytotoxic responses to the SARS-COV2 virus in laboratory models. Using CQ before exposure to the virus causes optimal inhibition of virus spread, which can play a preventive role. HCQ has three times higher cytotoxic effects against SARS-COV2 compared to CQ *in vitro*. Analysis of the data collected from clinical trials in China shows the superiority of CQ over the control group in the following cases: Inhibition of exacerbation of pneumonia, improved imaging of the lungs, and promotion of negative virus conversion and shortening of disease duration without complications.

In a recent study in China, CQ improved radiological findings, and an open-label study in France showed that azithromycin improved the effects of using this drug [20]. However, in some patients, HCQ increases interleukin-6 (IL-6), resulting in a cytokine storm. Both CQ and HCQ inhibit the increase of immune factors, prevent the progression of the disease, and prevent the development of a threatening situation for the patient [25].

These two drugs are tolerated well [17, 20]. The side effects include nausea, vomiting, abdominal cramps, and a metallic taste in the mouth. Acute toxicity in dose adjustment causes cardiomyopathy and neuropathy or myopathy. High doses of chloroquine phosphate, 500 mg or higher, increase QT time on the ECG and increase the mortality rate [20, 26]. Retinopathy is the most common complication that occurs due to long-term use of CQ and HCQ [17, 20]. In addition, dermatological complications, such as photosensitivity, lichenoid reactions, drug eruptions with CQ, and acute generalized exanthemata's pustulosis with HCQ are other side effects [17]. They can also lead to hypoglycemia. Furthermore, both drugs are safe in pregnancy and the risk of congenital anomalies is minimal [17, 20].

Broad spectrum anti-viral drugs

Favipiravir

Its scientific name is T-507 (a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate (RTP) [18]). The effective form of favipiravir is favipiravir-RTP, which prevents virus replication by inhibiting RNA polymerase [18, 26]. A few clinical experiences support

Table 1. Drugs that may be useful for COVID-19 treatment or prevention [22, 23]

Steps	Subclasses	Treatment type	Treatment name
Prevention		Nutritional supplement	Vitamin C [23]
			Vitamin B complex [23]
			Vitamin C [23]
			Vitamin D [23]
			Vitamin E [23]
			Selenium [22]
			Zinc [22]
			Iron [22]
		Immune enhancer	Interfrons [22]
			Gammaglobulin (IV) [22]
			BCG vaccine [22]
		vaccine	Recombinant Vaccine (Adenovirus vector) [22]
			bacTRL-Spike vaccine [22]
			ChAdOx1 nCOV vaccine [22]
			ClGB vaccine [22]
Treatment	Supportive	Corticosteroid	Methyl prednisolone [22]
			BCG vaccine [22]
		Anti-inflammatorie	Colchicine [22]
			Picilidenson [22]
	Symptomatic	NSAIDs	Ibuprofen [22]
	Interventional	Antiviral	Ribavirin [22]
			Lopinavir/Ritonavir [22]
			Remdesivir [22]
			Umifenovir [22]
			Favipiravir [22]
			Nitric Oxide [22]
			Oseltamivir [22]
		Antimalaria	Chloroquine(CQ) [22]
			Hydroxychloroquine(HCQ) [22]
		Kinase inhibitor	Imatinib mesylate [22]
		Protease inhibitor	Camostatemesylate [22]
		Antiparasitic	Ivermectin [22]
			Nitazoxanide [22]

its effective role, but we need more Hospitalized Randomized Clinical Trials (HRCTs). Most of the preclinical data confirm its therapeutic effects on Influenza and Ebola [18]. It is the first approved drug in china [26]. The side effects include hyperuricemia, diarrhea, elevated transaminases, and a reduction in neutrophil count [18]. It should be noted that it affects the QT of the ECG [26].

Ribavirin

Ribavirin (a guanine analog) is a prodrug that mimics the metabolic structure of the purine analogue guanosine, which increases RNA incorporation. Its mechanism of RNA polymerase inhibition depends on RNA. Although *in vitro* studies have shown that rapid resistance occurs if ribavirin is used as monotherapy in the treatment of MERS and SARS, when it is combined with other antivirals, such as lopinavir and ritonavir or CQ analogues, it has potential therapeutic effects. Ribavirin did not have any significant effects on MERS in combination with interferons, but it showed significant effects against SARS-COV if taken with alpha-2 and beta interferons. According to *in vivo* studies, the serum concentration of ribavirin required to prevent blunt viral replication is higher than safe doses for humans; doses, such as 1.2 g to 2.4 g are required. Available pharmaceutical forms of ribavirin are oral capsule, oral solution, and inhaled formulation. While the best efficient method is intravenous, no evidence was observed to support the effects of inhalation.

The ribavirin has some side effects, such as hepatotoxicity, which means an increase in transaminases, as well as hematological problems, such as anemia, which may require blood transfusions and causes problems, like hypocalcemia and hypomagnesemia (hemolytic anemia, hypocalcemia, and hypo-magnesia are most common side effects in the treatment of SARS). It can also cause severe pancytopenia in combination with immunosuppressants, especially azathioprine and interferons20. Ribavirin is a teratogen, that causes fetal toxicity; therefore, it is contraindicated in pregnant women and men with a pregnant partner [18, 20]. If ribavirin is prescribed for men and women of childbearing age, pregnancy should be avoided, and due to the continued active metabolic forms of ribavirin in plasma for up to 6 months, it is necessary to prevent pregnancy during treatment and six months after the end of treatment [20].

Umifenovir (Arbidol)

This substance has a unique function. It exerts its antiviral effects and prevents the virus from entering the target cells by inhibiting the binding of the envelope to the target cell membrane. It also affects the interaction of protein S and ACE and membrane fusion. Arbidol was first recommended by Wuhan union hospital and showed post-exposure prophylaxis (PEP) in COVID-19 patients. It means that arbidol could reduce the risk of COVID-19 infection [27]. It works against a variety of viruses, such as coxsackies, adenoviruses, influenza, and rhinoviruses. Retrospective studies have indicated negative effects on SARS-COV and MERS-COV.

Based on *in vitro* studies, it has inhibitory effects against coronavirus. A non-randomized study in China showed a reduced mortality rate caused by a coronavirus. Besides, its trial has begun in China and has inhibited the pathological effects of the coronavirus. The current recommended dose for this drug is 200 mg for influenza. Some side effects have been reported, including allergic reactions, digestive problems, and elevated transaminases [18].

Anti-viral and anti-retroviral drugs

Lopinavir and ritonavir

Lopinavir is an aspartic acid protease inhibitor and ritonavir potentiates the pharmacokinetic and half-life effects of lopinavir by inhibiting CYP450. These two drugs work based on the inhibition of proteinase 3chemotrypsin. Proteases are essential enzymes for virus genome production and maturation. Antiviral effects of protease inhibitors prevent virus replication and the spread of infection in host cells. These two drugs improve clinical scores for weight loss, reduce symptoms, improve radiological clearance, and reduce viral load in necroscopiclungs [20]. They have antiviral effects in the treatment of HIV-infected people [2, 16, 20].

Retrospective studies on SARS have indicated that it reduces mortality and intubation for patients; however, retrospective studies are not very reliable [11]. The patients who take these drugs are hospitalized for a shorter period in the intensive care unit (ICU) than those who did not [16]. Regarding the efficacy of these two drugs on coronavirus, they are not effective if the treatment is delayed, although they have inhibitory effects when they are used in the early stages of virus replication. The recommended dose is 400 mg twice a day for 14 days [18, 20], but there are side effects, such as anxiety, gastrointestinal problems, and liver toxicity. If these side effects threaten the patient's life, it must be stopped. Hepatotoxicity causes elevated levels of transferases. Due to the mentioned side effects, it is rarely used in experiments to evaluate the performance of lopinavir and ritonavir [21].

Remdesivir

The scientific name is GS-5734 [21]. Remdesivir is a 1′-cyano-substituted adenosine nucleotide analog [20]. It is a phosphoramidate prodrug of an adenine derivate with a chemical structure similar to that of tenofoviealafenamide [28] and the active form is called GS-441524. Its mechanism is based on the inhibition of viral RNA polymerase. Other effective mechanisms of this adenosine nucleotide analog may include lethal mutagenesis and chain termination [20]. Nucleotide analogues reduce viral replication, which is effective against RNA viruses [2]. It was the first successful treatment for Ebola in rhesus monkeys (one daily intravenous administration of 10 mg per kg for 12 days showed 100% protection in animal models). *In vitro* studies on human airway epithelial cell culture have shown its effectiveness against coronaviruses [20]. The onset of effect of remdesivir is fast, and reports indicate its safety and antiviral activity. In addition, it changes the temperature and location of the virus and prevents the virus from settling [28] by considering the possible effects and counteracting SARS-COV and other viruses as treatment candidates. The recommended doses in clinical trials are first 200 mg intravenously and then 100 mg daily intravenously for 5 to 10 days in adults [20]. As there is limited information about the use of remdesivir in humans, we do not know the exact side effects. However, there have been reports of nausea and vomiting, gastroparesis, and rectal bleeding in three patients in the United States [20]. Furthermore, it causes a reversible increase in transaminase and abnormalities in liver function tests. Besides, some adverse effects, such as phlebitis, constipation, headache, and ecchymosis have been reported [29].

Nelfinavir

Nelfinavir is an HIV-1 protease inhibitor that combines with other antivirals that target HIV through alternative mechanisms. Its functional mechanism is to bind to the site of HIV protease activity, which inhibits the cleavage of Gag-Pol polyproteins required for HIV functional proteins. Nelfinavir showed effects against SARS-COV *in vitro* during the SARS epidemic in 2000. The efficacy of this drug in humans for SARS-COV or SARS-COV2 has not been studied. The appropriate dose for HIV treatment is 750 mg orally three times a day or 1250 mg orally twice a day. The effective dose for COVID-19 treatment is not reported. The most important complication is digestion problems, such as diarrhea, nausea, bloating, and nonspecific rashes [20].

The coronavirus genome is very similar to the SARS-COV and MERS-COV virus genomes [28]. Twenty-seven drugs are effective against both MERS and SARS, which act using eight mechanisms. Therefore, effective treatment options against coronavirus can be selected from these drug groups. These drug groups include neurotransmitter inhibitors, kinase signaling inhibitors, protein-synthesis inhibitors, inhibitors of DNA synthesis and repair, estrogen receptor inhibitors, inhibitors of lipid and sterol metabolism, and Anti-parasitic, anti-bacterial, cathepsin inhibitors [30].

Antiparasitic:

Nitazoxanide

Nitazoxanide is a 2- (acetyloxy) -N- (5-nitro-2-thiazolyl) benzamide. Nitazoxanide is metabolized in order to circulate active tizoxanide. Tizoxanide selectively blocks the posttranslational influenza viral hemagglutinin maturation and intracellular movement and blocks protein implantation into the plasma membrane. Nitazoxanide enhances the production of type 1 interferon by host fibroblasts, which exerts its antiviral effects by inhibiting hemagglutinin. It has anti-protozoan effects and treats diarrhea caused by *Giardia lamblia*. It also works against cryptosporidium and *in vitro* studies have shown its effectiveness against anaerobic gram-positive and gram-negative bacteria. It is also used to treat the flu. No clinical benefits have been reported when using this drug in acute and severe respiratory diseases, especially no changes have been reported regarding the length of hospitalization [35]. This drug counteracts the effects of MERS-COV *in vitro*. According to *in vitro* studies on animals, this drug may have effects against SARS-COV2. However, there is limited information about the effects of nitazoxanide on humans. The suitable dose for Giardia lamblia and Cryptosporidium pavrum is 500 mg as oral suspension or tablets, every 12 hours for three days. In patients with acute respiratory problems, treatment lasts up to five days, twice a day, and the dose is determined according to age. The most common gastrointestinal complications are abdominal pain, nausea, diarrhea, and gastroesophageal reflux disease. Problems, such as headache, dizziness, discoloration of the eyes and urine, skin rash, and urticaria have also been reported [20].

Ivermectin

Several drugs inhibit viral proteases, such as ivermectin, which is effective in dengue fever, Zika, and the flu. It also has antiviral effects. Ivermectin, which is also a neuraminidase inhibitor, plays an important role in the

Table 2. Proposed drugs against COVID-19

Drugs	Mechanism or Effect	Side Effects	Other Information
CQ and HCQ	Anti-malaria/modulating the interaction of virus and host/IL-6 rising (HCQ)/ inhibiting the increases of immune factors [25]	Gastrointestinal problems [20]	These drugs are used for RA and SLE/CQ is medicated 500 mg oral daily or BD and HCQ is one day 400 mg BD and from 2nd day 200 mg BD for treatment [20]
Ribavirin	Its mechanism of RNA polymerase inhibition is RNA dependent/Ribavirin is a guanine analog [20]	Hepatotoxicity (rising the transaminase as well as anemia) and may need transfusion [20]	No significant effect on MERS but has effect on SARS-COV if taken with α2 and β interferons [20]
Lopinavir and Ritonavir	Reducing the mortality and intubation in SARS patients/shorter ICU stay /Inhibition of proteinase 3chemotrypsin [16, 17, 20]	Anxiety GI problems Liver toxicity [21]	It can be used for AIDS because it can inhibit HIV protease [16]
Umifenovir	Inhibiting the binding of the envelope to target cell membrane/affecting the interaction of protein S and ACE and membrane fusion [27]	Gastrointestinal upset/ Allergic reaction/ Elevated transaminase [18]	It works against coxsackies, adenoviruses, influenza, and rhinovirus. It affects SARS and MERS and reduced mortality of coronavirus [18]
Remdesivir	Inhibition of viral RNA polymerase/ acting early/ preventing the virus from settling [20, 28]	Reversible increase in transaminase/ liver injury [29]	It is a prodrug (the active form is GS-441524) it was successful in the treatment of Ebola in rhesus monkeys [20, 28]
Favipiravir	An active agent that inhibits RNA polymerase and prevents virus replication [18, 26]	Elevated transaminase/ Hyperuricemia/ Diarrhea/ decrease of neutrophil count [18]	It is effective for Ebola and flu [18]
Chlorpromazine hydrochloride and Triflupromazin	Inhibiting neurotransmitters/ these drugs are used for decreasing dopamine/ Traditional antipsychotic agents [30]	Central nervous system problems with chlorpromazine hydrochloride [33]	In addition to mental illness, the use of chlorpromazine hydrochloride causes anesthesia and refractory nausea in pregnant women [33]
Dasatinib and Imatinib mesylate	Treating human cancers, like chronic myelogenous leukemia/ Inhibiting kinase signaling pathway [30]	Pleural effusion and Pulmonary arterial hypertension (more reported from dasatinib) [30, 34]	Effective in treating MERS-COV and SARS-COV [30]

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inhibition of viral protease [34]. Additionally, it plays a crucial part in managing parasitic diseases, like nematodes, arachnids, and insects, and prevents philoviruses from entering the cell [31].

Neurotransmitter inhibitors

Chlorpromazine hydrochloride & trifluprom azine hydrochloride: These two drugs have similar structures and functions (inhibition of dopamine receptor). They are effective against other viruses, such as influenza and West Nile, and have low toxicity [30]. Chlorpromazine can pass the blood-brain barrier and diffuse in CNS where SARA-COV-2 causes encephalitis [33].

Kinase signaling inhibitors

Dasatinib and imatinib mesylate: The kinase signaling pathway plays a crucial role in the replication of viruses by activating the ABL-1 pathway, and it is involved in cell differentiation, cell adhesion, and the cellular stress response. Therefore, these drugs are used to treat human cancers, including chronic myelogenous leukemia. The importance of the ABL-1 pathway is in the replication of viruses. These drugs have low toxicity. Imatinib mesylate controls Ebola, poxviruses, and entry of coxsackievirus. Nilotinib is another signaling kinase inhibitor but is only effective against the SARS-COV virus and has low toxicity [30]. Pleural effusion and pulmonary arterial hypertension (more from dasatinib) have been reported [34].

Inhibitor of DNA synthesis and repair

Gemcitabine hydrochloride, also named deoxycytidine analogue, has an antiviral role against coronavirus. It also has few toxic effects [30].

Estrogen receptor inhibitor

Toremifene citrate testing against several filoviruses could prevent filoviruses from entering. Its antiviral effect on SARS-COV and MERS-COV is unknown but its inhibitory effect on receptor 1 may be useful. It also has low toxicity [30].

Protease inhibitor

Camostatemesylate (CM)

It was developed in Japan as a protease inhibitor in the 1980s. CM therapy is used for acute symptoms of chron-

Table 3. Drugs or pharmacological classes effective against MERS or SARS or both

Drugs Pharmacological Class	Mechanism	EC50 (SARS vs MERS)
Chlorpromazine hydrochloride and Triflupromazine hydrochloride	NT inhibitors (dopamine) [30]	EC50>EC50 [30]
Toremifene citrate	Estrogen antagonists/Blocking filovirus entry [30]	EC50<EC50 [30]
Imatinib	Kinase signaling inhibitors [30]	EC50<EC50 [30]
Remdesivir	Inhibition of nucleic acid (RNA) synthesis [20]	
Ribavirin	RNA polymerase inhibitor [20]	
Monezin	Inhibition of ions [30]	
Nitazoxanide	Inhibiting 2019-nCOV but approved for diarrhea treatment [28]	

ic pancreatitis and treatment of the pancreas. *in vitro*, it prevents cell entry by inhibiting host serine proteinase. Using 900 mg daily for eight weeks may have some adverse effects, such as edema and urticarial [35]. Studying this drug is another research goal [30].

Disulfiram

It is an anti-parasitic drug. It inhibits protease and prevents the spread of MERS-COV and SARS-COV in culture, but we have no clinical evidence [28]. Disulfiram is usually used for alcohol dependence and probably has some neurological effects [32].

Other drugs

Monezin and Salinomycin Sodium are ion channel inhibitors and can treat MERS-COV but they have no curable effect on SARS-COV. These drugs are also used for human cancers because of the anticancer influence on cancer cells by enhancing their sensitivity to chemotherapy. Monezin is useful in human carcinoma [28]. A wide range of pharmacological classes has been considered as you can see the most important ones in Table 2, 3.

Other methods for treatment

Besides prescribing drugs to control the life cycle of the coronavirus, other methods can be used to manage the length of the disease, such as oxygen therapy and assisted plasma recovery, as well as using other drug classes, such as anti-inflammatory agents. We investigated alternative approaches, including the use of plasma contracting hyperactive immune globulin and monoclonal antibodies, which both target SARS-CoV-2 [17]. When multi-organ damage occurs, anti-inflammatory drugs are taken. However, due to the nature of the coronavirus, which weakens the immune system in severe cases, we must consider the risks and harms of using anti-inflammatory drugs. Additionally, to achieve the most desirable effects, anti-inflammatory drugs should be formulated personally [21].

Monoclonal antibodies

One of the methods was monoclonal antibodies, like tocilizumab. Tocilizumab inhibits interleukin-6 (IL-6) receptors and has also inhibitory effects on membrane-bound organelles. IL-6 released from macrophages can cause symptoms in patients with the cytokine-release syndrome (CRS). Due to its positive effects on cytokines and chronic inflammation, FDA first approved tocilizumab for RA in 2010. Tocilizumab may make patients more sensitive to bacterial infections because of neutropenia. In addition, patients who received tocilizumab due to their chronic illnesses, such as rheumatoid arthritis (RA) or giant cell arteritis, reported thrombocytopeni. In some studies, cytokine storm was reported from COVID-19 infection and that is why tocilizumab is useful [35].

Anti-inflammatory

Colchicine affects chemotaxis of immune cells (neutrophils and monocytes) and intracellular transport. It has some suppressive effects on caspase-1 activation and subsequent release of IL-18. Colchicine had toxic action against pneumocyte microtubules. This anti-inflammatory drug is used for chronic and autoinflammatory diseases, such as gout (the usual adult oral dose is 1.2mg/day and the prophylactic dose is 0.5-1mg/day). In addition, colchicines are useful for inhibiting viral inflammations, such as adenovirus, Epstein-Barr virus, herpes simplex virus type I, and hepatitis virus [37].

Non-specific anti-inflammatory

Patients receiving corticosteroids showed various outcomes. Thus, these data are inconsistent. Large-dose of corticosteroids had a suppressive effect on the immune system, whereas it may cause the clearance of SARS-COV-2 from the body. However, there were a few recovered patients (those with lung injury related to cytokines). Thus, clinicians must weigh out the harms and benefits of corticosteroids [36].

The novel Coronavirus' name is SARS-COV-2. It means that this virus may have some likeness to SARS or possibly MERS; thus, we can use some treatments for SARS and MERS to reach the best cure. Some drugs could influence COVID-19. Monezin and Salinomycin are ion channel inhibitors and can treat MERS-COV, but they have no curable effect on SARS-COV. These drugs also are used for human cancers because of anticancer influence on cancer cells by enhancing their sensitivity to chemotherapy. Monezin is useful in human carcinoma. Toremifene citrate is an estrogen antagonist and has an antagonist effect on estrogen receptor 1. These types of drugs have low toxicity. Its antiviral effect on SARS-COV and MERS-COV is unknown but its inhibitory effect on receptor 1 may be useful [30].

Developing an appropriate treatment protocol against coronavirus is a challenge for physicians. Although the drugs reported in this study have beneficial effects according to the mentioned mechanisms, other factors, such as safety [26], appropriate dosage, method of administration, resistance, availability, and cost [40] should be considered as well as the stage of the disease and patient condition in order to choose the best therapeutic method for each patient

Conclusion

Prevention and treatment of COVID-19 remain a challenge. Basic mechanisms of COVID-19 therapies that are approved for clinical use or evaluated in clinical trials include blocking viral replication, regulating immune function, reducing the inflammatory response, and reducing lung damage [30]. Antiviral and supportive therapies are very important in the treatment of patients with COVID-19. Anti-malaria drugs, CQ and HCQ, immunoglobulin, anti-cytokines, and anti-inflammatory drugs can be considered for different conditions and stages of the disease. It is more efficient to use antiviral therapies, such as remdesivir and lopinavir/ritonavir in the early stages of infection before the peak of virus replication. Therefore, diagnostic methods must be more accurate and sensitive [18]. Side effects of medications must be also considered. Although favipiravir was the first approved drug in China, it has significant cardiac side effects that should be monitored during treatment [26].

Drugs that inhibit the signaling kinase, such as dasatinib and imatinibmyslate, and drugs that inhibit DNA synthesis and repair, such as gemcitabine hydrochloride can be candidates for the treatment of coronavirus due to their inhibitory effects and low toxicity [30]; however, more clinical studies are needed. Some epidemiologic studies have shown that the transmission profile of the coronavirus is similar to the SARS-CoV virus, which is a clue for physicians and scientists to find effective medications [19].

Estrogen receptor inhibitors, for example, toremifene citrate, have contracted SARS and MERS in retrospective studies [30]. Also, Arbidol has been successful in the treatment of viruses, such as SARS and MERS [39]. Therefore, various investigations and clinical trials should be carried out for more detailed examination and efficacy confirmation. New interventions also require lengthy reviews over months, even years [28].

Ethical Considerations

Compliance with ethical guidelines

This article is a systematic review with no human or animal sample. There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed in preparing this article.

Conflict of interest

The author declared no conflict of interest.

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References

[1] Naserghandi A, Allameh SF, Saffarpour R. All about COVID-19 in brief. New Microbes New Infect. 2020; 35:100678. [DOI:10.1016/j.nmni.2020.100678] [PMID] [PMCID]

[2] Manhas S, Anjali A, Mansoor S, Sharma V, Ahmad A, Rehman MU, et al. Covid-19 Pandemic and Current Medical Interventions. Arch Med Res. 2020; 51(6):473-81. [DOI:10.1016/j.arcmed.2020.05.007] [PMID] [PMCID]

[3] Israil A, Ahmed S, Rahman KM, Uddin MJ, Dey SK, Battacharjee M, et al. Efficacy of amitriptyline, pizotifen and propranolol in the prevention of migraine. Mymensingh Med J. 2013; 22(1):93-100. [PMID]

[4] Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: Drug repurposing approach. Life Sci. 2020; 252:117652. [DOI:10.1016/j.lfs.2020.117652] [PMID] [PMCID]

[5] Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med. 2020; 382(25):2441-8. [DOI:10.1056/NEJMoa2008975] [PMID] [PMCID]

[6] McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacol Res. 2020; 157:104859. [DOI:10.1016/j.phrs.2020.104859] [PMID] [PMCID]

[7] Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020; 250:117583. [DOI:10.1016/j.lfs.2020.117583] [PMID] [PMCID]

[8] Sultan OM, Al-Tameemi H, Alghazali DM, Abed M, Ghniem MN, Hawiji DA, et al. Pulmonary ct manifestations of COVID-19: Changes within 2 weeks duration from presentation. Egypt J Radiol Nucl Med. 2020; 51:105. [Link]

[9] Liang C, Tian L, Liu Y, Hui N, Qiao G, Li H, et al. A promising antiviral candidate drug for the covid-19 pandemic: A mini-review of remdesivir. Eur J Med Chem. 2020; 201:112527. [DOI:10.1016/j.ejmech.2020.112527] [PMID] [PMCID]

[10] World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. 2020 [cited 2020 Jul 19]. Available from: [Link]

[11] Yanai H. Favipiravir: A possible pharmaceutical treatment for COVID-19. J Endocrinol Metab. 2020; 10(2):33-4. [Link]

[12] Fleming AB, Raabe V. Current studies of convalescent plasma therapy for COVID-19 may underestimate risk of antibody-dependent enhancement. J Clin Virol. 2020; 127:104388. [DOI:10.1016/j.jcv.2020.104388] [PMID] [PMCID]

[13] Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis. 2020; 35:101647. [DOI:10.1016/j.tmaid.2020.101647] [PMID] [PMCID]

[14] Kim JY. Letter to the editor: Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020; 35(7):e88. [DOI:10.3346/jkms.2020.35.e88] [PMID] [PMCID]

[15] Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020; 35:101738. [DOI:10.1016/j.tmaid.2020.101738] [PMID] [PMCID]

[16] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020; 382(19):1787-99 [DOI:10.1056/NEJMc2008043] [PMCID]

[17] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA. 2020; 324(8):782-93. [DOI:10.1001/jama.2020.12839] [PMID]

[18] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. JAMA. 2020; 323(18):1824-36. [DOI:10.1001/jama.2020.6019] [PMCID]

[19] Abd El-Aziz TM, Stockand JD. Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2)-an update on the status. Infect Genet Evol. 2020; 83:104327. [DOI:10.1016/j.meegid.2020.104327] [PMID] [PMCID]

[20] Barlow A, Landolf KM, Barlow B, Yeung SY, Heavner JJ, Claassen CW, et al. Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019. Pharmacotherapy. 2020; 40(5):416-37. [DOI:10.1002/phar.2398] [PMID] [PMCID]

[21] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clin Immunol. 2020; 214:108393. [DOI:10.1016/j.clim.2020.108393] [PMID] [PMCID]

[22] Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol. 2020; 92(5):479-90. [DOI:10.1002/jmv.25707] [PMID] [PMCID]

[23] World Health Organization (WHO). COVID-19 Landscape of experimental treatments [internet]. 2020 [updated 2020 April 27; 2020 December 2]. [Link]

[24] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect. 2020; 53(3):368-70. [DOI:10.1016/j.jmii.2020.03.005] [PMID] [PMCID]

[25] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020; 71(15):732-9. [DOI:10.1093/cid/ciaa237] [PMID] [PMCID]

[26] Pan X, Dong L, Yang N, Chen D, Peng C. Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. Virus Res. 2020; 286:198057. [DOI:10.1016/j.virusres.2020.198057] [PMID] [PMCID]

[27] Zhang JN, Wang WJ, Peng B, Peng W, Zhang YS, Wang YL, et al. Potential of Arbidol for post-exposure prophylaxis of COVID-19 transmission: a preliminary report of a retrospective cohort study. Curr Med Sci. 2020; 40(3):480-5. [PMCID]

[28] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020; 19(3):149-50. [Link]

[29] Jorgensen SC, Kebriaei R, Dresser LD. Remdesivir: Review of pharmacology, pre-clinical data and emerging clinical experience for COVID-19. Pharmacotherapy. 2020; 40(7):659-71. [DOI:10.1002/phar.2429] [PMID] [PMCID]

[30] Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother. 2014; 58(8):4885-93. [DOI:10.1128/AAC.03036-14] [PMID] [PMCID]

[31] Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: Antiviral levels are not likely attainable with known dosing regimens. Biotechnol Biotechnol Equip. 2020; 34(1):469-74. [DOI:10.1080/13102818.2020.1775118]

[32] Li H, Liu Z, Ge J. Scientific research progress of COVID-19/SARS-CoV-2 in the first five months. J Cell Mol Med. 2020; 24(12):6558-70. [DOI:10.1111/jcmm.15364] [PMID] [PMCID]

[33] Nobile B, Durand M, Courtet P, Van de Perre P, Nagot N, Molès JP, et al. Could the antipsychotic chlorpromazine be a potential treatment for SARS-CoV-2? Schizophr Res. 2020; 223:373-5. [DOI:10.1016/j.schres.2020.07.015] [PMID] [PMCID]

[34] Riou M, Seferian A, Savale L, Chaumais MC, Guignabert C, Canuet M, et al. Deterioration of pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity. Eur Respir J. 2016; 48(5):1517-9. [DOI:10.1183/13993003.01410-2016] [PMID]

[35] Uno Y. Camostat mesilate therapy for COVID-19. Intern Emerg Med. 2020; 15(8):1577-8. [Link]

[36] McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: A review of early and emerging options. Open Forum Infect Dis. 2020; 7(4):ofaa105 [DOI:10.1093/ofid/ofaa105] [PMID] [PMCID]

[37] Parra-Medina R, Sarmiento-Monroy JC, Rojas-Villarraga A, Garavito E, Montealegre-Gómez G, Gómez-López A. Colchicine as a possible therapeutic option in COVID-19 infection. Clin Rheumatol. 2020; 39(8):2485-6. [DOI:10.1007/s10067-020-05247-5] [PMID] [PMCID]

[38] Hemmati F, Saedi S, Hemmati-Dinarvand M, Zarei M, Seghatoleslam A. Mysterious virus: A review on behavior and treatment approaches of the novel Coronavirus, 2019-nCoV. Arch Med Res. 2020; 51(5):375-83. [DOI:10.1016/j.arcmed.2020.04.022] [PMID] [PMCID]

[39] Serafin MB, Bottega A, Foletto VS, da Rosa TF, Hörner A, Hörner R. Drug repositioning is an alternative for the treatment of coronavirus COVID-19. Int J Antimicrob Agents. 2020; 55(6):105969. [DOI:10.1016/j.ijantimicag.2020.105969] [PMID] [PMCID]

[40] Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov. 2020; 6:14. [DOI:10.1038/s41421-020-0153-3] [PMID] [PMCID]

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