# Review Article

# A comprehensive review of therapeutic options for COVID-19

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**Abstract**

***Introduction:*** COVID-19 is a disease that is induced by severe acute respiratory syndrome coronavirus (SARS). Its viral infection is spread swiftly around the world and causes many restrictions, health problems, and expensive treatment costs worldwide. Due to its high prevalence and mortality rate, there is a global challenge to find an effective therapeutic protocol for the prevention and treatment of COVID-19. No one could disclaim the immediate need for a standardized protocol for COVID-19 treatment.

***Methods:*** Aiming to prepare a comprehensive review of introducing appropriate remedial options for COVID-19, a wide range of investigation on relevant articles established in the English language published through different publications such as PubMed, Medline, Embase, Science Direct, Scopus, and COVID-Evidence . all researchers and clinicians should try to make more precise knowledge about the viral behavior and treatment of COVID-19 to find an effective vaccine to prevent and treatment of this virus. The main objective of the present study is to review and investigate the available evidence for achieving a more precise preventive and treatment protocol to deal with COVID-19.

***Findings:*** many available drugs have been reviewed that include Azithromycin, Lopinavir/ritonavir (LPV/r), Remdesivir, Corticosteroids, Chloroquine, Hydroxychloroquine, Hydroxychloroquine sulfate, Immunoglobulin, Ivermectin, Ribavirin, Favipiravir, Interferon. On the other hand, it is recommended to conduct precise clinical trials on current antimicrobial and antiviral agents that are administered for a long time to find an expeditious and effective response to the COVID-19 pandemic. Although disappointing, it should be noted that there is no effective drug regimen or vaccine against the novel coronavirus. In this regard, using other available antiviral drugs for the treatment of COVID-19 may be effective to some extent. In this study, by investigating some available antimicrobial medicines that may diminish COVID-19 infection, we are trying to introduce a general protocol for controlling this disease. [*Ethiop. J. Health Dev*. 2022; 36(4):000-000]

***Keywords*:** SARS, COVID-19, Pandemic, Antimicrobial drugs, Treatment protocol

## Introduction

After the worldwide prevalence of the infection of novel coronavirus (COVID-19) in late 2019, people of all ages and genders, especially those with underlying diseases affected by the severe symptoms of this disease (1,2). Based on the report of the World Health Organization (WHO), COVID-19 is an international concern for the public health, whose risk is at the highest level. Anyway, it was introduced as a dangerous worldwide epidemic, thus prevention of this epidemic through increasing the knowledge of people is the first aim of health organizations (3). Being highly contagious is the most obvious feature of COVID-19 that after the start of 2020, swiftly involved nearly all countries worldwide.

Based on the data presented on the World Meters' website, COVID-19 is more infectious and fatal than the influenza A virus subtype H1N1 (A/H1N1). Moreover, it declared that in normal condition, the infection and case-fatality rates of COVID-19 are approximately 3.9% and 2.5 (4).

A lot of researchers have worked on the COVID-19 clinical course and its treatment options (8-10). Nearly three-fourths of patients who are presented to health centers have certain symptoms such as cough, fever, dyspnea, or a combination of them. Based on the studies carried out by Siddiqi and Mehra (5), the clinical courses of COVID-19 could be presented based on a three-staged progression model. Stage 1 is also known as a mild phase that coronavirus multiplies and mainly enters the respiratory tract. Then in stage 2, the multiplication rate of viruses' increases and localized inflammation in the lungs is the most common observation. Finally, in stage 3 the syndrome of extra-pulmonary systemic hyperinflammation could be seen as a common symptom. Accurate and rapid diagnosis of the disease and the stage that the patient is in and preparation of the most appropriate treatment strategy could have the greatest outcomes (5).

There are some factors that may worsen overall health conditions such as age, coronary artery disease (CAD), high blood pressure (HBP), diabetes, malignancies, and chronic lung disease (6).

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Due to the lack of precise knowledge about the virus and also available evidence about its treatment, all researchers around the world should work on the main therapeutic options to achieve the most promising treatment protocol. Despite the high number of randomized clinical trials (RCTs), there is not any obvious evidence of the improvement of available therapeutic outcomes in COVID-19 patients. Therefore, more precise clinical trials should be carried out to discover any potential strategies for preventing or treatment of COVID-19 (7). In this comprehensive study, the newest treatment strategies and the data on clinical achievement for COVID-19 are presented. Moreover, this study is mainly focusing on investigating novel protocols and available therapeutic options.

## Methods

Aiming to prepare a comprehensive review of introducing appropriate remedial options for COVID-19, a wide range of investigation on relevant articles established in the English language published through different publications such as PubMed, Medline, Embase, Science Direct, Scopus, and COVID-Evidence were reviewed up to August 2020. Phrases such as severe acute respiratory syndrome coronavirus (SARS-CoV), COVID-19, coronavirus pandemic and pathogenesis, COVID-19 disease, diagnosis of coronavirus, COVID-19 treatment, and treatment protocols in combination with pharmacology. Due to the lack of randomized clinical trials in regard to COVID-19 disease, the authors have used various types of studies including review articles, case series, and reports. Finally, the total amount of included articles reaches 978.

The standard guidelines of PRISMA were used for the specification of inclusions and exclusions criteria. Nearly all the article's titles and abstracts were reviewed independently to be specified for inclusion criteria. Relevant articles were categorized precisely and articles with less relevant content were removed from the study inclusion. The most recent clinical trials were specified and were given special attention. For assessment of the overall quality of selected articles, the Critical Appraisal Skills Program (CASP) checklist was used. For carrying out and writing this review there was not any need for ethical approval. The overall process of selection and deletion of articles in this study is demonstrated in fig.1.

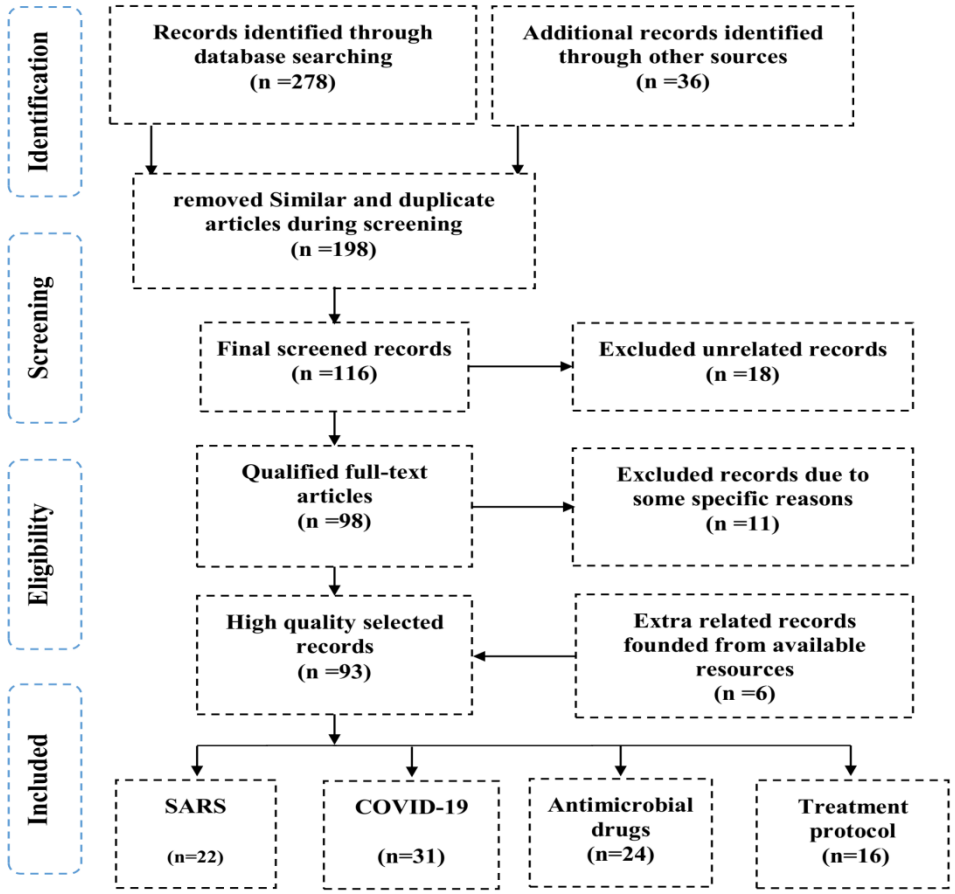


Figure 1: **Schematic diagram of the logic of selection and deletion of articles based on the PRISMA method.**

## Results

***COVID-19 distribution:*** we should not underestimate the overall burden of this disease, due to the low rate of diagnosis and reported cases of acute infections of COVID-19. Worldwide surveys on COVID-19 infectious disease proved that the real rate of its outbreak is nearly more than 10-fold or more of reported cases.

***Transmission:*** Unfortunately, our comprehension of transmission risk is not sufficient. Epidemiologic researchers have recognized a primary association between COVID-19 and eating raw bats (8). Anyway, the main transmission mode of COVID-19 has been recognized to be person-to-person spread.

***Person-to-person spread route:*** The main transmission route of COVID-19 infection is through the direct person-to-person spread. There is strong scientific proof that COVID-19 is spread by respiratory droplets in close contact. In close direct contact, when a person with COVID-19 sneezes, coughs, or talks to others the virus could be released from respiratory secretions that after direct contact with the mucosa or eyes of others can easily infect them. Additionally, the COVID-19 virus could be easily transmitted to others through their hands infected with the virus mainly in situations when they touch their eyes, mouth, or nose without washing their hands. The main way of transmission of COVID-19 is through the air by aspiration of small particles. Anyway, all the natural conditions that affect the rate of COVID-19 spread through the air should be investigated more (9,10). Some studies demonstrated that in close contact, respiratory droplets may create a gas cloud or get aerosolized then will be transmitted horizontally with sneezing, coughing, or speaking (11,12). van Doremalen et al [13] in their study declared that coronavirus could remain in tissue culture in an experimentally generated aero-solution for about 3 hours.

***Children and Pregnant Women:*** Children and pregnant women are among people who should be given a special amount of attention. Just like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), COVID-19 is more common among adults in comparison with children mainly those with milder symptoms (14-17). Among children, cough and fever are the most common symptoms. While pharyngitis, dyspnea, stuffy nose, headache, myalgia, and gastrointestinal problems are the symptoms that are reported in some other studies (15,16,18). In pregnant women, the manifestation of clinical symptoms is nearly mild with a lower rate of severe disease and fatal outcomes (19). Based on a study carried out by Elshafeey et al [20], during pregnancy, the clinical symptoms and severity of COVID-19 are nearly similar to the disease represented among non-pregnant adult women. COVID-19 test is done for all pregnant women at their entrance to the hospital delivery. So, this could be an explanation for the lower rate of COVID-19 infection among them in different countries (19). The exact transmission route of COVID-19 through perinatal transmission is not been clearly proved yet (21). Based on the study carried out by Penfield et al (22), there was not any infection among neonates whose mothers presented with positive RT-PCR results. While Zamaniyan et al (23) based on the RT-PCR test results reported that COVID-19 could be transmitted from an infected mother to her neonate.

Researchers believe about coronavirus transmission is the main challenge that should be managed appropriately. By preventing COVID-19 spread the rate of people who are affected and also the mortality rate would be less. Anyway, the prevention of COVID-19 spread precedes treatment and is a kind of the first step of treatment (24). In this regard, conducting public health protocols exactly could be effective in delaying the widespread transmission of coronavirus among people. Consequently, the rate of direct and indirect mortality would decrease and the global spread of the virus slows down (25).

***Etiology:*** As a large group of RNA viruses, coronaviruses could be found in different animal species. Among humans, these kinds of viruses could cause diseases of the gastrointestinal system, nervous system diseases, hepatic diseases, and respiratory diseases. Because of the presence of spike glycoproteins on the envelope of coronavirus, they are similar to a crown. About 5-10% of acute respiratory infections are induced by coronaviruses (26). Among the people who carry coronavirus nearly two percent believe they are healthy. People who have a normal immune response, when infect COVID-19, common cold, and self-limiting respiratory tract infection (RTI) are the most common symptoms. While for the elderly COVID-19 patients and people who have an impaired immune system, the lower respiratory tracts would be involved (27).

***Clinical features:*** The biggest challenge of COVID-19 is that it leads to a broad spectrum of clinical features ranging from asymptomatic individuals to multiple organ dysfunction syndromes (MODS) and septic shock that at least for a while are often asymptomatic. Anyway, the classification of COVID-19 is carried out based on the severity of the presentation (27). In this regard, diseases are classified into four main groups: mild, moderate, severe, and critical, those are presented in table (1). Fever, fatigue, diarrhea, and dry cough are among the most common symptoms represented by COVID-19 patients (28).

Table 1: **Classification of COVID-19 disease severity and its features**.

| Diseases severity | Site | Symptoms | Rare Symptoms | Radiograph Features | Potential of Deteriorate |
|---|---|---|---|---|---|
| Mild (27,28) | Viral upper respiratory tract infections | mild fever, headache, malaise, dry cough, sore throat, nasal congestion, and muscle pain | Dyspnea | In some cases are not available | Patients' condition may deteriorate to severe or critical quickly |
| Moderate (27) | Respiratory system | Shortness of breath, tachypnea, and cough | Severe disease | Available in a lot of cases | High |
| Severe (27) | One or both lungs | Acute respiratory distress syndrome (ARDS), severe pneumonia, septic shock, pulmonary | Fever | Nearly all cases are available | High |

| | | | | | |
|---|---|---|---|---|---|
| | | infiltrates, tachypnea, and severe dyspnea | | | |
| Critical (27,28) | Respiratory system and lungs | Respiratory failure, cardiac injury, SARS-CoV viral load (RNAaemia), MODS, or septic shock | - | In all cases are available | The mortality rate for critical patients is about 50% |

According to investigations carried out by Wang et al (28), COVID-19 patients with comorbidities such as hypertension (HTN), respiratory disease, cardiovascular disease, and Oncologic complications are at a higher risk of mortality. Anyway, a precise diagnosis of COVID-19 patients with different levels of severity could be very effective in making decisions for determining an appropriate treatment protocol.

***Diagnosis:*** The U.S. center for disease control and prevention has developed a standardized protocol for persons who are in close contact with infectious COVID-19 patients that immediate measures should be taken for preventing and controlling the infection (29). Based on this protocol for specifying the laboratory requirements epidemiological factors are used. If someone within two weeks of symptoms has close contact with COVID-19 patients whose infection is confirmed by a laboratory, or previously been present in an infected area has enough epidemiological factors to be suspected of infecting COVID-19 (30). Based on the recommendations of WHO adequate samples should be collected from the lower and upper respiratory tracts. The samples are mainly achieved from bronchoalveolar lavage (BAL), endotracheal aspirate (ETA), and expectorated sputum samples. Then the samples are examined by polymerase chain reaction (PCR) for assessment of viral RNA (29).

***Management strategies:*** After identifying COVID-19 patients, the most effective management solution is to isolate patients with positive test result. Unfortunately, there is not a particular antiviral vaccine or medication for this disease yet (30). Consequently, the main treatment options for COVID-19 patients include symptomatic treatment and supplemental oxygen therapy. Immediate supportive management should be carried out for patients who are detected with mild infections. Appropriate supportive management could be achieved through nutritional supplements, anti-bacterial therapy, acetaminophen, mild therapeutic hypothermia (TH), and oxygen therapy (28).

Patients with a critical level of COVID-19 should be managed via high-flow oxygen (HFO) therapy, convalescent plasma, glucocorticoid therapy, and extracorporeal membrane oxygenation (ECMO). The treatment of acute respiratory distress syndrome (ARDS) with corticosteroids as a systemic steroid hormone is not recommended (28). Additionally, the usage of antibiotics in an unnecessary way is not recommended at all. On the other hand, despite patients who undergo protective ventilation, the ECMO technique should be considered in patients with refractory hypoxemia. In COVID-19 patients who suffer from respiratory failure syndrome, using mechanical ventilation, intubation, non-invasive ventilation (NIV), or high-flow nasal oxygen therapy (HFNOT) is recommended. Supporting dynamics of blood flow using antihypotensive agents is very critical in the treatment of septic shock. Moreover, for patients with MODS, applying multi-organ function support treatment is a compulsory measure (30).

***Treatment Guidelines:*** There are different guidelines available for the treatment of patients with COVID-19 that differ from one country to another. Based on the guidelines of the world health organization the process of management of patients with underlying co-morbidities, pediatric, and pregnant women who are affected with COVID-19 should be carried out with caginess. As a fact, it should be noted that COVID-19 doesn't have any approved treatments yet. Therefore, for any patient, the treatment strategy should be performed based on the clinical requirement of the patient. On the other hand, COVID-19 patients with severe symptoms should be managed with the implementation of mechanical ventilation equipped with experimental antimicrobial therapy based on the clinical condition of the patients (31). There are some general protocols for the treatment of COVID-19 patients that are common worldwide that mainly including Azithromycin, Lopinavir/ritonavir (LPV/r), Remdesivir, Corticosteroids, Chloroquine, Hydroxychloroquine, Hydroxychloroquine sulfate, Immunoglobulin, Ivermectin, Ribavirin, Favipiravir, Interferon (32,33). The differences between the treatment protocols of various countries are shown in table 2. The mechanism of action of all these agents should be outlined exactly as they are the most effective treatment options for COVID-19 patients in the absence of the coronavirus vaccine (34-37).

***Azithromycin:*** As one of the most effective bacteriostatic agents, azithromycin is used for the treatment of various types of mycobacterial infections. Based on the studies carried out by Min and Jang [2012], this agent has antiviral activities for instance, can improve the symptoms of viral respiratory infections (VRIs). In their study, Bleyzac et al [38] reported that azithromycin can effectively show antiviral activities on coronavirus through immunomodulatory effects. Anyway, they declared that there should be a lot of clinical investigation on the effect of azithromycin as a monotherapy or in combination with other agents in improving the health condition of COVID-19 patients.

**Table 2**: **A comparison of various guidelines for the treatment of COVID-19 patients in some parts of the world.** (34-37)

| | | Severity | | |
|---|---|---|---|---|
| Various regions | | Mild-to-moderate | Severe | Critical |
| United States (America) | Treatment guidelines | Remdesivir | Chloroquine<br>LPV/r<br>Hydroxychloroquine | Interferon β-1b |
| Europe (Ireland) | | Remdesivir<br>LPV/r<br>Chloroquine<br>Hydroxychloroquine | - | - |
| Africa (Egypt) | | Hydroxychloroquine<br>Chloroquine | LPV/r<br>Chloroquine<br>Hydroxychloroquine | Azithromycin<br>Hydroxychloroquine |
| Asia (Saudi Arabia) | | Chloroquine<br>Hydroxychloroquine | LPV/r<br>Chloroquine<br>Hydroxychloroquine | Remdesivir<br>LPV/r<br>Hydroxychloroquine |

In a similar study, Gautret et al (39) cited that there is not enough evidence in proving the effectiveness of azithromycin in the treatment of COVID-19 alone. It's while a combination of Hydroxychloroquine with azithromycin can relieve the symptoms of the disease. Schwartz and Suskind (40) reported that children with COVID-19 should be examined for the possibility of nosocomial respiratory pathogens. In situations like this, the administration of azithromycin for the treatment of Mycoplasma pneumoniae infections may enhance the rate of morbidity (41). Using azithromycin immediately after the first signs of COVID-19 infection in children is a cost-effective treatment protocol, relatively safe, and easy-to-use (40).

***LPV/r:*** Ritonavir and lopinavir are both protease inhibitors and their combination increases their bioavailability by impeding their metabolic inactivation. Both ritonavir and lopinavir are mainly used for the treatment of HIV infections that slow down HIV infectivity and maturation (42). The combination of LPV/r is a very effective antiretroviral drug, its effectiveness in the treatment of HIV and coronavirus symptoms is declared by various studies (43,44). Studying in vitro replication of coronavirus, demonstrated that the combination of LPV/r and chlorpromazine, loperamide, and chloroquine are capable of inhibiting COVID-19 replication. In their study, Osborne et al (44) investigated the role of LPV/r in the Treatment of COVID-19 in combination with ribavirin could decrease the rate of ARDS or/and mortality.

Additionally, the combination of ribavirin and LPV/r decrease the doses of steroids which could diminish the rate of hospital-acquired infections. Dorward et al (45) have worked on the effectiveness of LPV/r agents against coronavirus and reported that lopinavir is capable of inhibiting COVID-19 in vitro replication. In some similar studies, LPV/r has been introduced as an effective agent in the treatment of COVID-19 (46,47). On the other hand, although Kim et al [48] demonstrated that administration of LPV/r in COVID-19 patients could decrease the viral burden after that viral titers were undetectable, they additionally declared that any decrease in viral titers could be because of the natural development period of the disease in a patient. Administration of antiviral agents in children should be carried out after considering the advantages and disadvantages and their side effects on the children with caution. LPV/r is weighted as a therapeutic choice for the treatment of COVID-19 children. Ribavirin is mainly administrated in combination with the other agent. In children with COVID-19, the combination of more than two drugs simultaneously is not recommended (49). As a consequence, for understanding the direct antiviral effect of LPV/r further studies should be carried out.

***Remdesivir:*** As a nucleoside analogs prodrug, Remdesivir is capable of inhibiting viral RNA-dependent RNA polymerases (RdRPs). RdRPs are enzymes that are conserved structurally which have a critical role in viral replication (50,51). The data presented in Beigel et al (52) studies demonstrated that the administration of Remdesivir in COVID-19 patients could beneficially decrease time recovery and mortality rate. A wide range of diseases such as Marburg hemorrhagic fever, Ebola Virus Disease (EVD), MERS, and recently coronavirus could be treated with Remdesivir. Spinner et al (53) have investigated the effect of Remdesivir on patients with moderate COVID-19 and reported that the administration of this agent did not show any significant difference in patient's clinical status who were under a 10-day course of Remdesivir in comparison with those who were under 11 days of standard care without this agent. While using Remdesivir for patients with a more moderate severity of COVID-19 and a shorter period of hospitalization could yield better results.

Ali et al (54) reported that just after one day of administration of Remdesivir the titer of coronavirus in the lung decreased and lung volume improved. Moreover, they proved that in patients whose lung injury is high, the administration of this agent could decrease the mortality rate more and more in various stages of usage. In a similar study, Beigel et al (52) reported that using Remdesivir for the treatment of COVID-19 patients was more effective in comparison with placebo and the patient's recovery time is shorter.

Based on the data presented by Cao2 et al (55), Remdesivir could be used for both adults and children with emergency severe Covid-19 disease. Additionally, for children, the dosage of Remdesivir must be adjusted based on body weight (56).

***Corticosteroids:*** Corticosteroids are a group of anti-inflammatory drugs that reduce the activity of the immune system and inflammation. As an effective adjuvant therapy, and due to its anti-inflammatory effects, Corticosteroids are mainly administered for the treatment of ARDS (57). After the outbreak of COVID-19, the administration of Corticosteroids has been controversial. Several studies on human cases have demonstrated that Corticosteroids could be effectively applied for the reduction of pathological damage. Unfortunately, these agents may cause ARDC as a dangerous side effect (58). In their study, Yang et al (57) reported that despite the availability of some reports about the effectiveness of Corticosteroids in improving COVID-19 patient's symptoms, there is not any confirmed evidence about the potency of this agent in decreasing the mortality rate of COVID-19 patients. Moreover, the administration of Corticosteroid agents in viral infections is still challenging. Therefore, the clinical administration of Corticosteroids for COVID-19 patients should be done carefully.
As one of the most well-known Corticosteroid agents, Dexamethasone was used in a study by Jung et al (59) for the treatment of porcine respiratory coronavirus (PRCV) at earlier stages that was shown to be effective in diminishing pro-inflammatory responses. Anyway, its prolonged administration may cause enhancing viral replication. Additionally, a similar study carried out by Ye et al [60] demonstrated that using Corticosteroids for the treatment of COVID-19 patients is controversial, due to the possibility of SARS and then the increment of viral replication.

The remedial effectiveness and safety of Dexamethasone and some other Corticosteroids for the treatment of pediatric patients with COVID-19 have not been evaluated sufficiently. On the other hand, there are inadequate clinical trials on the effectiveness of Corticosteroids in the treatment of pediatric patients with COVID-19. Additionally, the mortality rate of pediatric patients with COVID-19 is significantly lower than adults with this disease. Therefore, using these agents among children and patients younger than 18 years should be carried out with caution. In pediatric patients with COVID-19, the usage of Dexamethasone may be more beneficial when administered with mechanical ventilation simultaneously (61).

***Chloroquine and its derivatives***: Due to the limitation of effective therapy and a swift outbreak of coronavirus in the world different treatment strategies have been tried in achieving an appropriate treatment for this novel virus that mainly includes antimalarial drugs such as Chloroquine and its other derivatives like Hydroxychloroquine and Hydroxychloroquine sulfate (62).

Because it has immunomodulatory effects, Chloroquine and its derivatives are extensively used in the treatment and diminishing the viral destructive effects (63). Manzo [64] declared that in animal studies, the toxicity of Hydroxychloroquine sulfate is much less than Chloroquine. Due to its antiviral properties, the effectiveness of Chloroquine in the treatment of SARS-CoV infection has been mentioned by Vincent et al (65). The effectiveness of Chloroquine in the treatment of COVID-19 patients has been proved recently (66). Consequently, Chloroquine, Hydroxychloroquine, and Hydroxychloroquine sulfate could be trusted as three of the main potential drugs for improving the health situation of COVID-19 patients (67). Based on a systematic review study carried out by Kapoor and Kapoor (67), there is a lot of in vitro studies that all are powerful evidence for the effectiveness of Chloroquine and its derivatives in the treatment of COVID-19. Kapoor and Kapoor (67) cited that some factors such as low cost, accessibility, and a lower rate of side effects, should be considered for choosing the best therapy for COVID-19 that may contain Chloroquine, Hydroxychloroquine, and Hydroxychloroquine sulfate. Anyway, an international strategy should be prepared to give precise information about the most effective treatments for coronavirus that may contain some therapies such as Chloroquine and its derivatives.

Verscheijden et al (68) reported that to improve the effectiveness of Chloroquine in the treatment of pediatric patients with COVID-19, an appropriate dose should be used. The right dose of Chloroquine could provide children with optimal health benefits and enhance their safety. Moreover, they declared that to achieve more appropriate treatment outcomes, the right dose should be driven based on the knowledge that requires precise clinical trials.

***Immunoglobulin:*** Antibodies known as immunoglobulins, are glycoprotein molecules produced by white blood cells. Immunoglobulins have a key role in the immune response that through precise recognition and binding to specific antigens, such as viruses and bacteria can destroy them. In patients who are suffering from antibody deficiencies, intravenous Immunoglobulin (IVIG) could be used as an effective treatment. IVIG is administered in combination with other therapeutic agents for improving the health condition of patients with severe COVID-19. This agent is used as an adjunct and its therapeutic effect is not clarified exactly yet. For achieving significant clinical effectiveness, despite the effectiveness of Immunoglobulin in the treatment of COVID-19, patients should be hospitalized under mechanical ventilation conditions (69,70).

A similar study carried out by Lanza et al (71) yield the same results that, as an adjuvant treatment, Immunoglobulin could be used effectively for the treatment of COVID-19 patients. Additionally, Jiang et al (72) reported that infections induced by severe acute respiratory syndrome coronavirus could be diminished through the administration of polyclonal antibodies (pAbs). The process of immunoglobulin extraction

should be carried out from patients who are on the same diet, and lifestyle to achieve specific antibodies to fight against COVID-19 viral infection.

As mentioned by Zhang2 et al (73), extracted plasma from recovered COVID-19 patients can be used for making two main preparations containing antibodies. The first preparation that is more concentrated is hyperimmune immunoglobulin which is similar to IVIG and contains more antibodies. Another preparation is convalescent plasma which contains fewer antibodies compared with the first one. They reported that hyperimmune immunoglobulin and convalescent plasma have been administered for the treatment of various respiratory viruses successfully. Despite the effectiveness of these treatments, adverse effects can happen. Additionally, due to the lack of adequate information about the therapeutic effectiveness of IVIG in children and pregnant women, further clinical trials and studies should be carried out. Therefore, IVIG can be used with a precise look at its side effects. But in children and pregnant women, it's not recommended to be used (73).

***Ivermectin:*** Ivermectin is a medication that could be used for the treatment of a wide range of parasite infestations. Recently in some clinical trials, it proved that this medicine can inhibit coronaviruses. Ivermectin could inhibit viral proteins such as integrase protein and importin α/β1 heterodimer due to its powerful role in antiviral activity (74,75). Clay et al declared that a combination of Vero-hSLAM cells with Ivermectin at a concentration of 5μM, two hours after being affected with COVID-19 could reduce the viral RNA load after 2 days by 99.98%. Moreover, they proposed that this agent can decrease the viral load in COVID-19 patients, and inhibit the spread and progression of the disease. In children with COVID-19, it's recommended to use Ivermectin based on the bodyweight. Higher or inadequate doses of Ivermectin in children or/and adults may cause toxicity. In vitro activity of Ivermectin against coronavirus has been known, but its administration in vivo should be investigated more accurately (76).

***Ribavirin:*** Ribavirin is classified as an antiviral agent that is mainly used for the treatment of respiratory Syncytial Virus (RSV) infections, viral hemorrhagic fevers (VHFs), and hepatitis C. Since Ribavirin is easily supplied and has a trusted supply chain is a priority in the treatment of COVID-19. Based on the investigation carried out by Khalili et al (77), Ribavirin proved to be effective against the antiviral activity of coronavirus in vitro, so it may be effective in inhibiting COVID-19 in vivo too. Several studies have demonstrated that Ribavirin has been used for the treatment of patients with SARS and MERS (78,79). It's while Arabi et al [80] declared that the administration of Ribavirin for the treatment of COVID-19 could not decrease the mortality rate effectively or would not increase the clearance speed of coronavirus.

Khalid et al (81) reported that the combination of corticosteroids with Ribavirin in patients with SARS could result in lung opacities and resolution of fever after about 14 days. Additionally, the combination of Interferon-beta-1a with Ribavirin is capable of inhibiting the replication of SARS-CoV in vitro (82). In a similar study Beigel et al (52), demonstrated that Ribavirin has antiviral effects against SARS-CoV in vitro. Since Ribavirin is capable of inhibiting the function of the polymerase enzyme, it is recommended to be administered for the treatment of COVID-19 symptoms (83). Anyway, more clinical trials should be carried out for clarifying the antiviral potential of Ribavirin. Moreover, it is recommended to use Ribavirin in combination with LPV/r to decrease the viral activities of SARS-CoV.

***Favipiravir:*** Favipiravir is purine nucleoside analog (PNAs) that have a critical role in inhibiting RdRPs (84). The initial emergence of Favipiravir in the form of an oral antiviral drug was in Japan for influenza infection (85). Furuta et al [84] reported that Favipiravir has been used for inhibiting Ebola Virus Disease (EVD). The mechanism of action of Favipiravir is such that it inhibits viral transcription and replication by binding to conserved polymerase domains. Favipiravir acts strongly against influenza A and B, which include inhibiting properties such as preventing Zanamivir and Oseltamivir influenza viruses, preventing VHFs, and SARS-CoV in vitro [66,86]. The outcomes of primary treatment of COVID-19 patients with Favipiravir are promising. Cai et al (87) demonstrated that the administration of Favipiravir could have a significant role in SARS-CoV viral clearance. Using Favipiravir for the treatment of COVID-19 patients could induce a lower rate of side effects in comparison with LPV/r (88). Aiming to achieve more precise information about the effectiveness of Favipiravir in the treatment of COVID-19 patients, further investigations should be carried out in both adults and children.

***Interferon:*** Interferons are a group of proteins that occur naturally, that are made and secreted by the immune system cells. Interferons are mainly such as epithelial cells, white blood cells, fibroblasts, and natural killer cells. Interferons are classified into three main categories of alpha, beta, and gamma (89). Interferons are administered for the treatment of different kinds of cancers such as AIDS-related Kaposi's sarcoma, melanoma, and leukemia. Additionally, they are used for inhibiting various kinds of infections such as condylomata acuminate, chronic hepatitis B, and chronic hepatitis C. Interferons have a critical role in the nervous system to benefit the health of your nervous system and play pathological roles. Endogenous interferons could diminish the viral infection of the nervous system and could have a significant therapeutic role in the treatment of multiple sclerosis (MS) (90). In their study, Channappanavar et al (89) proposed that interferons may be effective in the treatment of autoimmune, neoplastic, and viral diseases. Type I interferons that include Interferon-I, interferon-α, and interferon-β act in both paracrine and autocrine manners. This type of interferon includes a wide range of interferon-stimulated genes (ISGs) that enable host cells to have antiviral activities (91).

Many kinds of viruses such as SARS-CoV are capable of developing mechanisms that could evade the antiviral activity of Interferon-I. Blanco et al (92) reported that the therapeutic response of Interferon-I to coronavirus was limited. In another related study, Hadjadj et al (93) investigated peripheral blood cells of COVID-19 patients and reported that the remedial response of Interferon-I is weak mainly in patients with a severe level of disease. Consequently, further clinical trials should be carried out for achieving more detailed knowledge about the remedial effect of recombinant IFN-I on coronavirus.

**Conclusion**

Due to the lack of effective therapies for COVID-19 treatment, the COVID-19 pandemic seriousness has become a global challenge. Therefore, comprehensive clinical trials and academic investigations should be carried out. Making precipitant decisions about an appropriate treatment protocol could have serious consequences. Based on the case reports and studies reviewed in the present comprehensive study, several agents were recognized to be useful in the diminishing or/and treatment of coronavirus. Chloroquine and its derivatives, and Remdesivir could be administered effectively due to their effective remedial properties in the treatment of COVID-19. Additionally, Azithromycin alone or in combination with Remdesivir, Chloroquine, and its derivatives is a promising treatment option for patients with milder levels of COVID-19. Reviewed studies declared that using type I interferons could be an effective agent against MERS and SARS. While coronavirus is more sensitive to Interferons-I. Interferon-β-1 is a safe and accessible choice for the treatment of coronavirus in the initial stages of infection. In this regard, further clinical trials should be carried out. In severe levels of COVID-19, immunoglobulin, and atlizumab seems to be more effective in diminishing coronavirus.

Recently it's proved that using LPV/r for the treatment of coronavirus wouldn't be an effective option. Therefore, more trials should be done to evaluate the efficacy of this agent. Despite the initial effectiveness of some agents such as Dexamethasone and Remdesivir in the treatment of COVID-19 symptoms, the administration of these drugs should be based on the severity of the patient clinical status. So, safe and sufficient data from many clinical trials are required urgently. Despite the availability of various therapies for this pandemic, there is not any special protocol for the treatment or prevention of COVID-19 disease. Anyway, applying strict quarantine in crowded places is one of the most viable interventions to prevent and decrease the contagion rate of COVID-19.

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