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Review Article

# Drugs used for the treatment of COVID-19: A Review

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**Abstract:**

COVID-19 is primarily a respiratory disease caused by a newly discovered SARS-CoV-2 virus and identified in the city of Wuhan, China in December 2019. World Health Organization (WHO) has declared this disease as a pandemic, and warned other countries. Presently this has affected 221 countries, areas or territories worldwide, Spreading of this disease is very fast in USA, India, Brazil, and Russia than in the country of its origin China. Like other coronaviruses, this may develop respiratory tract infections in the patients range from mild to fatal illness like pneumonia and acute respiratory distress syndrome (ARDS). Bangladesh, a country of 170 million people, is not an exception regarding COVID-19; it has been reported 5,70,800 confirmed cases with 8690 documented deaths. Still now no effective drug, vaccine, or any procedure is available and experiments are underway. However, empirical therapy is being followed to manage and save the lives of the patients. There is a need for pharmacological alternatives to combat this deadly virus and its complications. Based on the previous experiences with similar coronavirus management and present preliminary data from uncontrolled studies, drugs like Chloroquine, Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, and Favipiravir have been recommended by the researchers to manage COVID-19. This review had assessed the potential mechanisms, safety profile, availability and cost of these drugs. This review concludes that the drugs mentioned above are having different properties and act differently in combating the COVID-19 viruses.

**Key words:** COVID-19, Coronavirus, Hydroxychloroquine, Remdesivir, Favipiravir.

## Introduction:

Respiratory disease caused by a newly discovered coronavirus, SARS-CoV-2 virus was identified in the city of Wuhan, Hubei Province, China in December 2019. WHO declared the official name as COVID-19 in February 2020[1]. Virus isolated from the COVID-19 patients belongs to the genus betacoronavirus, this group of viruses can cause simple/common cold to severe acute respiratory syndrome (SARS) caused by SARS-CoV was identified in 2002, and another syndrome Middle East respiratory syndrome (MERS), caused by MERS-CoV was identified in 2012[2,3]. According to the report of the WHO and China Joint Mission on Coronavirus Disease 2019 (COVID-19), it is a zoonotic virus, based on the data available, bats seems to be the reservoir of COVID-19 virus.

## Epidemiology:

On 21 March 2020, WHO declared this disease as a pandemic, based on its spread to 118,000 cases in 114 countries, and 4291 deaths on that date and warned other countries about its seriousness. Now on 20 March 2021 it affected 221 countries and total confirmed cases are about 12,35,79,918 and total death is 27,24,034 and case fatality is 4%. Its spread and mortality is more in the United States of America followed by India and then Brazil and Russia.

## Virus characteristics and clinical manifestations:

Like other coronaviruses, these are spherical shaped containing genetic material inside and with spike proteins protruding from their surface, which helps to latch onto the human cell followed by fusion and transfer of genes to the host cell. This latest virus can develop respiratory tract infections in the patients range from mild to fatal illnesses like pneumonia and acute respiratory distress syndrome (ARDS). The majority of the patients will experience mild to moderate respiratory illness and recover with supportive treatment and do not need any special care/treatment. Geriatric patients and patients with comorbidities like diabetes, cardiovascular, chronic respiratory disorders, cancer, immunodeficiency and other chronic disorders are more prone to develop serious pathological issues related to COVID-19.

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Symptoms may appear after 2-14 days of infection, which includes fever, cough, shortness of breath, persistent pain or pressure in the chest, new confusion or inability to arouse and bluish lips or face, also associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningo-encephalitis, impaired sense of smell or taste, anxiety, depression and sleep problems. Unfortunately, three types of extra pulmonary complications were reported by the COVID-19 patients, includes liver injury, fulminant myocarditis and acute kidney injury[4,5].

**Pharmacological agents recommended for SARS and SARS-CoV-2 management:**

The exact effective drug, vaccine, or any therapeutic procedure is not available and experiments are underway. However, empiric therapy is being practiced to manage and safe the life of the patient with the known antivirals, antibiotics, corticosteroids, biological and traditional preparations, either alone or in combination based on the patient's condition. As SARS-CoV-2 virus belongs to the SARS-CoV and Middle East respiratory syndrome CoV(MERS-CoV), prescribers are administering the drugs which have shown some promising results in managing similar viral infections[5].

Healthcare systems of different countries have suggested few drugs based on the preliminary data obtained through uncontrolled studies: National Health Commission of the People's Republic of China has recommended favipiravir, chloroquine phosphate, plasma transfusion therapy, remdesivir, and traditional Chinese medicine[6]. The Indian Council of Medical Research (ICMR), New Delhi, has recommended hydroxychloroquine for empirical use for prophylactic purposes in asymptomatic healthcare workers and household contacts of laboratory confirmed patients[7].

According to the guidelines given by the Government of India, Ministry of Health & Family Welfare, Directorate General of Health Services [Emergency Medical Relief (EMR) Division], lopinavir/ritonavir can be given only after proper informed expressed consent from the patient and ensuring all necessary monitoring measures to avoid possible serious adverse reactions.

Spanish Society of Hospital Pharmacy for the management of antiviral treatment in the new coronavirus SARS-CoV-2 disease COVID-19 guidelines has recommended lopinavir/ritonavir, lopinavir/ritonavir (oral) + interferon alfa-2B and beta-1B, remdesivir, hydroxychloroquine, chloroquine, darunavir/cobicistat, tocilizumab[8].

There are no US Food and Drug Administration (FDA)-approved drugs specifically for the treatment of patients with COVID-19. Centers for Disease Control and Prevention have provided information about the currently recommended drugs in the United States i.e. chloroquine, hydroxychloroquine, remdesivir, and lopinavir/ritonavir[9,10].

To date, the Emergency Use Authorization (EUA) authority of the US FDA has issued 2 therapeutic for combating this pandemic: On 28.03.2020, FDA has issued first Emergency Use Authorization (EUA) for the use of hydroxychloroquine sulfate and chloroquine sulfate in certain adolescent and adult hospitalized patients weigh 50kg or more with COVID-19 when a clinical trial is not available or feasible. They also instructed that the prescribers should use the stock supplied from the Strategic National Stockpile. And on 01.05.2020, FDA issued the second EUA for remdesivir to treat severe COVID-19 in both adult and children[7,8].

In Bangladesh , Disease control division of Directorate General of Health Services also prepare a National Guideline for management of Covid-19 with recommendation of following drugs, like Remdesivir, Favipiravir and Tocilizumab.

With this review, few evidence for considering these drugs for managing COVID-19 were assessed through the evaluation of possible mechanism, safety profile, and availability with a note on the cost.

**Pharmacological and clinical aspects of important SARS-COV-2 therapeutic agents**

**1. Favipiravir:** Favipiravir an oral antiviral drug was approved in Japan for influenza infection in 2014. It has also been used for treatment of Ebola virus infection. It acts by direct inhibition of viral replication and transcription through misincorporation in nascent vRNA (viral ribonucleic acid), or by binding to conserved polymerase domains, preventing incorporation of nucleotides for vRNA replication and transcription[6].

1.1. Preclinical evidence: According to the Madelain V et al[7] nonhuman primate (NHP) model study, favipiravir was found to have adaptive immune response in viral clearance, and can become a treatment option for other emerging viral diseases. Other studies have also reported that favipiravir acts by inhibiting RNA dependent RNA polymerase (RdRp) by converting into its active metabolite (favipiravir ribofuranosyl-5'-triphosphate (RTP)) in cells and is recognized as a substrate by viral RNA polymerase. As SARS-CoV-2, is an RNA virus, this drug might be one of the options for treating COVID-19[8,9].

1.2. Clinical evidence: National Medical Products Administration of China has included this drug in the potential treatments for COVID-19. The clinical evidence on the efficacy of this drug was observed in the clinical trial conducted by the third People's Hospital of Shenzhen in Guangdong province, where favipiravir group patients' (n=35) laboratory tests shown negative for COVID 19 after 4 days of treatment, whereas other group patients took 11 days for the same.

In an open-label non-randomized control study conducted by Q Cai et al[10], favipiravir (FPV) 1600mg twice daily as a loading dose and 600mg twice daily plus interferon (IFN)-α 5 million U twice daily by aerosol inhalation were administered to 35 patients with a median age of 43 (35.5-59) years. In another group lopinavir 400mg/ritonavir 100mg (RTV) twice daily plus IFN-α 5 million U twice daily by aerosol inhalation were given in 45 patients {median age was 49 (36-61) years}. They observed a shorter viral clearance time and significant improvement in chest imaging in FPV group with few ADRs. Preliminary results of another comparative study conducted in Wuhan, China, with 120 COVID-19 patients have also supported the efficacy of favipiravir and they also stated that administration of favipiravir tablet is easier.

The Bangladesh Society of Medicine (BSM) concluded from a recent study "Study on safety and efficacy for Covid -19" that Favipiravir evidences clear cut safety and effectivity against Covid -19. They studied on 50 positive patients, after 4 days with favipiravir treatment 48% patients were RT-PCR negative for Covid -19 and at the 10$^{th}$ day the result was negative by 96%.

1.3. Adverse drug reactions (ADR), cost and availability: According to the data obtained from the Uppsala Monitoring Centre (UMC)-Global adverse reactions reporting system as on 22.05.2020 only 24 ADRs were reported. The cost of the drug is not found with our extensive search and the global commercial availability of this drug is very less. In Bangladesh it is about 150 USD needed per course of treatment and available throughout the country.

**2. Chloroquine (CQ):** Chloroquine is approved for the prophylaxis and treatment of malaria, to treat extraintestinal amebiasis and chloroquine is also used off label for the treatment of various rheumatic diseases, as well as treatment and prophylaxis of Zika virus11. As per the Emergency Use Authorization (EUA) of US FDA unapproved use of this drug in COVID-19 patients.

2.1. Preclinical evidence: Preclinical data from various studies has confirmed the role of chloroquine in controlling the human coronavirus infection through different mechanisms, which includes; through protease inhibition in SARSCoV; inhibition of sialic acid biosynthesis; inhibition of HCoV-OC43 replication in HRT-18 cells by chloroquine in newborn mice; the activation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) in human coronavirus 229E infection in human epithelial lung cells; Inhibition of viral spread in cell culture through endosomal pH rise and interfering with terminal glycosylation of angiotensin-converting enzyme 2 receptor; Inhibition of the replication of SARS-CoV in Vero E6 cells[12-16].

2.2. Clinical evidence: Chloroquine phosphate tablet 500mg 12 hourly for 10 days might have benefits in controlling the novel coronavirus pneumonia irrespective of their severity[17]. In other studies conducted on COVID-19 patients, researchers have found the superiority of chloroquine over other therapy in terms of both efficacy and safety in reducing the exacerbation of pneumonia[18]. With the support of this data, Chinese government recommended chloroquine along with other therapies for the prevention and treatment of COVID-19 pneumonia.

2.3. Adverse drug reactions (ADRs), cost and availability: The American Academy of Ophthalmology stated that risk of toxicity with the usage of chloroquine/hydroxychloroquine is dose and duration dependent with the normal daily dose for less than 5 years therapy has <1% chance of retinopathy, however regular monitoring is required to prevent retinopathy[12,19]. A total of 6189 ADRs were reported to UMC, Sweden. Of which 1873 were skin and subcutaneous disorders, 1676 were gastrointestinal disorders, 1447 were nervous system disorders, and 738 were eye disorders. This drug is widely available and cost effective.

**3. Hydroxychloroquine (HCQ):** Hydroxychloroquine (HCQ) is an aminoquinoline. It is indicated for both the prophylaxis and treatment of uncomplicated malaria. It is also prescribed for the management of rheumatoid arthritis, chronic discoid lupus erythematosus, and systemic lupus erythematosus.

3.1. Preclinical evidence: Literature confirms that both the CQ and HCQ have similar properties and act in the same way with minor changes in their dosing schedule, researchers also said that the HCQ is their first choice in treating the SARS-CoV-2 infection, as HCQ is showing less toxicity (~40%) in animals than chloroquine[20].

An in-vitro study conducted by Yao X et al[21] using SARS-CoV-2 infected Vero cells, concluded that the HCQ (EC50=0.72μM) at an oral loading dose of 400mg 12$^{th}$ hourly, followed by 200mg twice daily for 4 days is better than chloroquine (EC50μm=5.47μM) 500mg 12$^{th}$ hourly for 5 days for treating SARS-CoV-2 infection, they also quoted that, the immunomodulatory effects of these two drugs can suppress the raised immune factors (cytokines IL-6 and IL-10) as an immune response to SARS-CoV-2 virus and prevents the complications.

Christophe B et al[22] studied the antiviral activity of ferroquine (FQ) derivatives, hydroxychloroquine, and chloroquine in viruses infecting vero cell cultures where they found the better inhibitory activity of hydroxychloroquine than chloroquine (CQ).

3.2. Clinical evidence: The revised advisory report of the Joint Monitoring Group under the Chairmanship of DGHS on the safety and efficacy of prophylactic use of Hydroxychloroquine (HCQ) in India has drawn the following conclusions from the clinical studies:
-A significant dose-response relationship was observed between the number of prophylactic doses taken and frequency of occurrence of SARSCoV-2 infection in symptomatic healthcare workers. The probability of SARSCoV-2 infection in healthcare workers who have taken the prophylactic HCQ was less when compared to those who have not taken. Another study conducted at AIIMS, New Delhi on prophylaxis HCQ (median 6 weeks of follow up) had reported the lower incidence of this infection in healthcare workers. They have also assessed the safety of HCQ prophylaxis among 1323 healthcare workers and found mild adverse effects such as nausea (8.9%), abdominal pain (7.3%), vomiting (1.5%), hypoglycemia (1.7%) and cardio-vascular effects (1.9%). Mehra MR et al[23] have analyzed the multinational registry of 96,032 of COVID-19 in-patients who were admitted during December 20, 2019 to April 14, 2020. A total of 14,888 patients received hydroxychloroquine or/and chloroquine with or without a macrolide along with other treatments. Authors have not found the any evidence of benefit with these drugs, in-spite they noted the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. Results of this analysis suggested not to use these drug regimens without clinical evidence.

3.3. Adverse drug reactions (ADRs), cost and availability: The risk of toxicity with the usage of HCQ is dose and duration dependent. With a normal daily dose for less than 5 years therapy has a <1% chance of retinopathy. They recommend a maximum daily dose, which can lead to this toxicity is ≤5.0mg/kg for HCQ, but with CQ damage may occur at ≤2.3mg/kg weight. But, the duration of the therapy may not be longer in controlling COVID-19, so there is a less possibility of developing retinopathy[19]. No significant elevation of liver enzymes and Liver injury with the HCQ is rare in normal individuals but, it may alter the metabolism of co-administered drugs. This drug is also cost effective and widely available.

**4. Combination of HCQ with azithromycin:** Philippe Gautret et al[24] have studied the efficacy of HCQ in combination with azithromycin confirmed COVID-19 patients received 600mg of hydroxychloroquine daily and depending on their clinical presentation, azithromycin was added to the treatment. A significant reduction of the viral load was observed on day 6 when compared to controls. They concluded that hydroxychloroquine treatment had significantly reduced the viral load in COVID-19 patients and its effect was synergized with azithromycin.

Researchers are investigating the efficacy of this combination in various countries with or without other drugs. Muhammad AR Bhuyan et al[25] have studied the efficacy of combination of HCQ with azithromycin in 33 confirmed cases in a Medical college hospital with the doses of Hydroxychloroquine 400 mg, twice daily on first day, followed by 200 mg, thrice daily from day 2 to 10 and Azythromycin 500 mg on first day, followed by 250 mg daily for 4 days. The patients received hydroxychloroquine and azythromycin and 30 out of 33 patients recovered within a mean period of 14 days. Out of 33 patients, 30 patients were discharged after being negative for SARS-CoV-2 for two times, 24 hours apart. There have been only one mortality and only two referrals.

5. Remdesivir: Remdesivir, or GS-5734, is an investigational adenosine triphosphate analog and used in the treatment for Ebola and coronavirus infections. Remdesivir shuts down viral replication by inhibiting a key viral enzyme, the RNA-dependent RNA polymerase. Based on the preclinical data and preliminary evidence on speedy recovery in clinical trials, on 1st May 2020, Food and Drug Administration (FDA) issued the EUA for its emergency use for the treatment of hospitalized COVID-19 patients.

5.1. Preclinical evidence: Preclinical studies conducted by researchers have demonstrated the antiviral activity through various mechanisms against coronaviruses like MERS and SARS, which are structurally similar to SARS-CoV-2. Dong L et al[8] reported that the remdesivir is a nucleoside analogue with potential and broad-spectrum antiviral activity. Wang M et al[1] concluded that remdesivir acts through incorporation into nascent viral RNA chains and results in premature termination at a stage post virus entry in RNA viruses including SARS/MERSCoV. In 2020, Timothy P S et al[26] observed a potent inhibition in MERS-CoV replication with EC50 of 0.09μM, with no observable cytotoxicity up to 10μM in primary human lung epithelial cell cultures. Lo M K et al[27] have also reported the efficacy of remdesivir in a variety of viruses including coronaviruses. Elfiky A et al[28] stated that remdesivir along with other antiviral binds to the new coronavirus strain RdRp tightly rather than the polymerase. They also suggest GTP as one of the targets in inhibiting SARS-CoV-2.

5.2. Clinical evidence: Holshue M L et al[29] have reported the first case of a 35-year-old man who was confirmed with novel COVID-19. Intravenous remdesivir was initiated from the evening of day 7, as the patient's condition was worsen and continued till the discharge day. On 11th day the viral loads were decreased in respiratory fluid specimens and on the 12th day, specimen tested negative for 2019-nCoV and the patient's clinical condition improved. And no adverse events were observed in association with the remdesivir infusion. They also mentioned the need for extensive clinical investigation on the usage of remdesivir. A randomized, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China on 237 COVID 19 patients, Remdesivir in a dose of 200mg on day 1 followed by 100mg on days 2-10 in single daily infusions was given in158 patients and remaining received placebo. The non-statistical significant clinical improvement at a faster time was observed with remdesivir.

5.3. Adverse drug reactions, cost and availability: A total of 74 ADRs were reported to UMC, Sweden of which, majority were related to the investigations (28), followed by renal and urinary disorders (14), skin and subcutaneous tissue disorders (14), infections and infestations (11), and respiratory, thoracic and mediastinal disorders (9). The cost of the remdesivir 1mg is USD 220 and 5mg USD 550. As of now, this drug is not widely available globally.

6. Lopinavir-ritonavir: Lopinavir and low dose of ritonavir are antiretroviral protease inhibitors; together they work effectively in the treatment of HIV infection, in the year 2000 this combination was released by Abbott under the brand name Kaletra. The metabolism of lopinavir is inhibited by ritonavir and enhances the half-life and antiviral activity.

6.1. Preclinical evidence: Chymotrypsin-like protease (3CLpro) and a papain-like protease (PLpro) are important for the replication of SARS-CoV. These proteases are important targets for the development of antiviral drugs. In-vitro/animal studies conducted in 2020 have revealed the inability of this drug to bind to major targets like 3CLpro, PLpro, RdRp, and a comparative study between the remdesivir and lopinavir/ritonavir (LPV/RTV), and interferon-beta (IFN-b) against MERS-CoV in mice found slight reduction in viral loads and improved the pulmonary function but not reduced the viral replication or severe lung pathology[26].

6.2. Clinical evidence: According to the case report published by Han W et al[30] this combination has shown efficacy in a 47 years old male SARSCoV-2 patient in 800/200mg dose along with, methylprednisolone 40mg (for 2 days only), recombinant human interferon alfa-2b 10 million IU per day, patient was recovered on the 10th day and tested negative for the virus and discharged. In Qione H et al[31] case series, lopinavir and ritonavir tablets (800/200mg daily) were given to 54 patients along with other treatments based on the severity, all the patients become negative for SARS-CoV-2 (range 4-11 treatment days). The average days of hospital stay were 9 for the recovery from the lung lesions, as well as from the clinical symptoms. Fortunately, no deaths were reported during the treatment period and authors concluded that effective treatment should include the combination of traditional Chinese and western medicine.

6.3. Adverse drug reactions (ADRs), cost and availability: A total 10,786 ADRs reported to UMC Sweden of which, the majority were related to injury, gastrointestinal disorders (3117), followed by general disorders and administration site conditions (1913), injury, poisoning and procedural complications (1544), investigations (1483) metabolism and nutrition disorders (1267), skin and subcutaneous tissue disorders (1189), nervous system disorders (1083). The cost of this drug combination is around 100-150 INR for one tablet of 400mg/200mg composition and the availability is not much.

7. Other drugs: Apart from these drugs, Ivermectin and Nitazoxanide have also shown the some evidences of becoming promising drugs for treating the COVID-19 patients.
Ivermectin is a broad spectrum anti parasitic. In 2012, it was approved for lice infestations. Preclinical studies recommend the ivermectin's anti SARS-CoV-2 activity in Vero-hSLAM cells where drug has reduced the viral RNA at 48h and impede the viral replication in Bovine herpesvirus1 (BoHV-1) through the inhibition of DNA polymerase nuclear Import. Ivermectin also inhibits the entrance of DNA polymerase UL42 into the nucleus of pseudorabies virus and itsproliferation[32-34].

As on 26.05.2020, around 14 clinical trials are at the initial stage of development either in alone or combination with other drugs for COVID 19, among them majority are being conducted in combination with Nitazoxanide.

Nitazoxanide is a first line broad spectrum antiparasitic and antiviral drug and also used in influenza patients. Preclinical studies have reported the anti MERS-CoV and other coronaviruses. It acts by different mechanisms i.e. by inhibiting N protein expression of the virus; suppression of pro-inflammatory cytokines and interleukin-6 production; inhibition of the broad spectrum RNA and DNA viruses' replication. According to the review of Pepperrell T et al, a superior safety profile was observed with approved doses of nitazoxanide. They have also suggested further investigation to confirm the hepatorenal, cardiovascular, and teratogenicity effects. And opinioned the possibility of becoming a promising drug for COVID-19[35-37].

**Discussion:**

Scientists have developed 3 strategies in the development of drugs to combat this deadly virus, which includes: Testing of the existed antiviral drugs, screening of chemical libraries against the targets and knowing their properties and discovery and development of the new molecules requires the genomic and pathological characteristics of different coronaviruses. Though it is a promising strategy, it may take around 10 years to develop one promising molecule.

As COVID-19 is a pandemic disease with the high transmission rate, the best strategy is to the testing of marketed antivirals empirically and developing the specific molecules based on the outcomes. So, this review tried to find the properties of recommended molecules for the treatment of this pandemic, especially their mechanisms, efficacy and safety through preclinical and clinical literature in combating coronaviruses and similar viruses, cost, and availability.

Favipiravir has been recommended by the National Health Commission of the People's Republic of China against the SARS-COV-2 virus. It may act at two stages after the virus has entered into the host cell, i.e. inhibition of RNA-dependent RNA polymerase and inhibiting the incorporation of nucleotides for vRNA replication and transcription. Some more clinical evidence on this drug is required for considering this drug the treatment of COVID-19 either in alone or in combination with other drugs, and it is not a widely available drug globally.

Both chloroquine and hydroxychloroquine may act at different stages of the virus life cycle and interferes with the viral entry through endosomal pH rise and interfering with terminal glycosylation of ACE2 receptors, translation, proteolysis, and replication. Among these two, HCQ may be more effective than CQ. Though, the early positive clinical outcomes, less possibility of severe adverse effects, might draw the attention of the prescribers to use these drugs empirically, but latest evidences are not supporting the use of these two drugs either in alone or combination and also with or without macrolide, especially in curing the infection. But, prophylaxis use of hydroxychloroquine in Indian healthcare workers has been producing the beneficial effects with mild adverse effects.

On 22.05.2020, Ministry of Health and Family Welfare in India has reported the efficacy of prophylaxis hydroxychloroquine in healthcare workers, but WHO has announced the temporary pause of the hydroxychloroquine arm within their solidarity trial.

Another promising drug is remdesivir, which acts at more than one site of viral life cycle i.e. through incorporation into nascent viral RNA chains and results in premature termination at a post virus entry stage. Interfere with RNA dependent polymerase and inhibits the replication and targeting the proofreading exoribonuclease and acts through the incorporation of the active triphosphate into viral RNA. And clinical evidence in around 15 patients has shown positive results with minimal or no adverse reactions and deaths. This drug has got US FDA emergency use authorization in COVID-19 patients and also recommended by more national healthcare organizations as a potential option against COVID-19.

Although the in-vitro data of lopinavir-ritonavir may not support its mechanism of action i.e. proteolysis, the clinical evidence suggests that it is an effective drug in combination with interferon as this combination has managed the more than 100 SARS patients with a moderate rate of ADR occurrence.

As of now, it is early to suggest ivermectin and nitazoxanide as the available data is limited to confirm the role of these drugs in COVID-19 patients and clinical trials are at initial stage.

Apart from these drugs, some other biological, chemical and traditional drugs are also showing promising results in uncontrolled studies.

**Conclusion:**

This review concludes that the drugs mentioned above are having different properties and act differently in combating the COVID-19 viruses. No drug may be superior or inferior, however, the use of single drug may not be effective enough to control this deadly virus, so use of combination of antivirals with different mechanism of action may be more effective and at the same time their adverse events should not be underestimated.

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