



Possible Mechanisms of Drugs Used in the Treatment of COVID-19: A Pharmacological Perspective

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Coronaviruses are a type of virus that can infect both animals and humans. Coronaviruses are divided into thirty-nine species and twenty-seven subgenus in the family Coronaviridae, according to the current classification. Seven of these are known to induce respiratory infections, while four others can cause cold-like symptoms on a regular basis. SARS CoV, MERS-CoV, and SARS CoV-

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2 infection are three examples of viral rebound. They are to blame for SARS, MERS, and the most recent Coronavirus epidemic discovered in 2019. (COVID-19). The World Health Organization declared the respiratory sickness caused by the SARS-CoV-2 infection to be a pandemic (WHO). For this COVID-19, there are currently no properly shown managements. The virology of SARS-CoV-2 has yielded a large number of therapeutic targets. Remdesivir appears to be the most promising treatment. Currently, COVID-19 is treated with Dexamethasone, Tocilizumab, Remdesivir, Chloroquine and Hydroxychloroquine, Lopinavir, Favipiravir, Niclosamide, Azithromycin, Sarilumab, Baricitinib, Ruxolitinib, Ribavirin, Nitazoxanide, Umifenovir, Camostat, Ciclesonide, Darunavir. They exert their effects through blocking receptors such as IL 6, TMPRSS2, CD147, and AAKI, as well as RNA dependent RNA polymerase, membrane fusion, endocytosis, and proteolysis. The authors of this study looked at the available literature on the SARS-CoV-2 virus and the COVID-19 virus in terms of therapeutic evidence. This in-depth and thorough examination provides an excellent overview of the most up-to-date information on the medications used to treat COVID-19.

Keywords: COVID-19; remdesivir; coronavirus; favipiravir; azithromycin.

1. INTRODUCTION

Corona viruses belong to the Coronaviridae and Nidovirales families of viruses. In appearance, they resemble myxoviruses. They're massive single-stranded RNA infections with a lipid envelope studded with club-moulded spike proteins that infect birds and a variety of warm-blooded organisms, including humans [1]. People can be infected with a variety of Corona viruses, the deadliest of which are Middle East Respiratory Syndrome Corona Virus (MERS-CoV), Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV), and Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV 2) [2]. On February 11, 2020, the World Health Organization (WHO) designated Novel Corona virus-induced pneumonia as COVID-19; on the same day, the International Virus Classification Commission designated the novel Coronavirus as SARS-CoV-2 [3]. SARS-CoV-2 is extremely contagious and pathogenic. It spreads between people primarily through coughing or sneezing from a contaminated person. People who are asymptomatic may also spread the disease. The mode of transmission, the incubation time, and the duration of infection must all be studied [2]. With age, co-morbid disorders such as hepatic and renal ailments, and a weakened immune system, the chance of contamination increases [4]. According to World Health Organization (WHO), there are around 256, 966, 237 confirmed cases worldwide as of 22nd November 2021.

Fever, cough, myalgia, tiredness, and headache are the most common symptoms; however, some individuals may also experience diarrhoea and nausea a few days before developing a fever.

The patient's lab results may reveal reduced WBC, platelets, or lymphopenia, as well as an extended activated thromboplastin time and a higher C-reactive protein level [5]. Alveolar cells undergo apoptosis as a result, and fibrin hyaline coatings may cause alveolar injury. Scarring and fibrosis may be caused by the wound healing mechanism [6]. Extreme COVID-19 results in coagulation activation and clotting factor consumption. Coronavirus infects humans through ACE2 receptors found in organs such as the heart, lungs, kidneys, and gastrointestinal tract [7]. The reverse transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR) [8,9].

2. DRUGS USED IN THE MANAGEMENT OF COVID-19

2.1 Dexamethasone

Dexamethasone is a steroid with anti-inflammatory effects that is commonly used. It belongs to the corticosteroid class of medicines. It's a glucocorticoid medicine with a traditional action that's used to treat a variety of ailments like joint pain, immune system issues, and hypersensitive skin, eyes, and ears. When the body's immunological response becomes too powerful to even consider managing in COVID-19 patients, dexamethasone suppresses it. The body develops an uncontrolled inflammatory response in many critical condition patients by rapidly producing cytokines to fight the disease, but the cytokines also attack and destroy the body's own cells and tissues. When liquid forms in the air sacs of the lungs, the patient will have difficulty breathing, culminating in acute respiratory distress syndrome (ARDS), which is

fatal. Dexamethasone inhibits the formation of mediators which induced pain and inflammation by suppressing the chemical phospholipase A2 (Table 1). This is why dexamethasone has been found to be effective in individuals who are critically ill and require the use of a ventilator [10]. For the treatment of COVID-19 in patients who are precisely ventilated and in patients who require supplemental oxygen but are not precisely ventilated from Kaplan–Meier survival curves panel recommends using dexamethasone 6 mg once daily for up to ten days in patients who are precisely ventilated and in patients who require supplemental oxygen but are not precisely ventilated [11,12]. This recommendation is based on the preliminary results of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) study. The Panel advises against using dexamethasone to treat COVID-19 in individuals who do not require supplemental oxygen. Dexamethasone or other corticosteroids have not been studied for their

safety and efficacy in the treatment of COVID-19 in children [11].

2.2 Tocilizumab

Tocilizumab is a monoclonal antibody that binds to the interleukin-6 (IL-6) receptor and prevents it from working. Tocilizumab is FDA-approved for the treatment of moderate to severe rheumatoid arthritis in individuals who have had a poor response to disease-modifying anti-rheumatic medications (DMARDs) (RA). It is used to treat inflammatory arthritis in adults and children as an alternative to TNF-blockers [13]. Tocilizumab is an inhibitor of interleukin-6 receptors, a pro-inflammatory cytokine involved in T-cell activation, initiation of hepatic acute stage protein synthesis, and expansion, separation, and stimulation of hematopoietic precursor cells [14]. Tocilizumab has been suggested as a possible treatment for COVID-19 infection (Fig. 1).

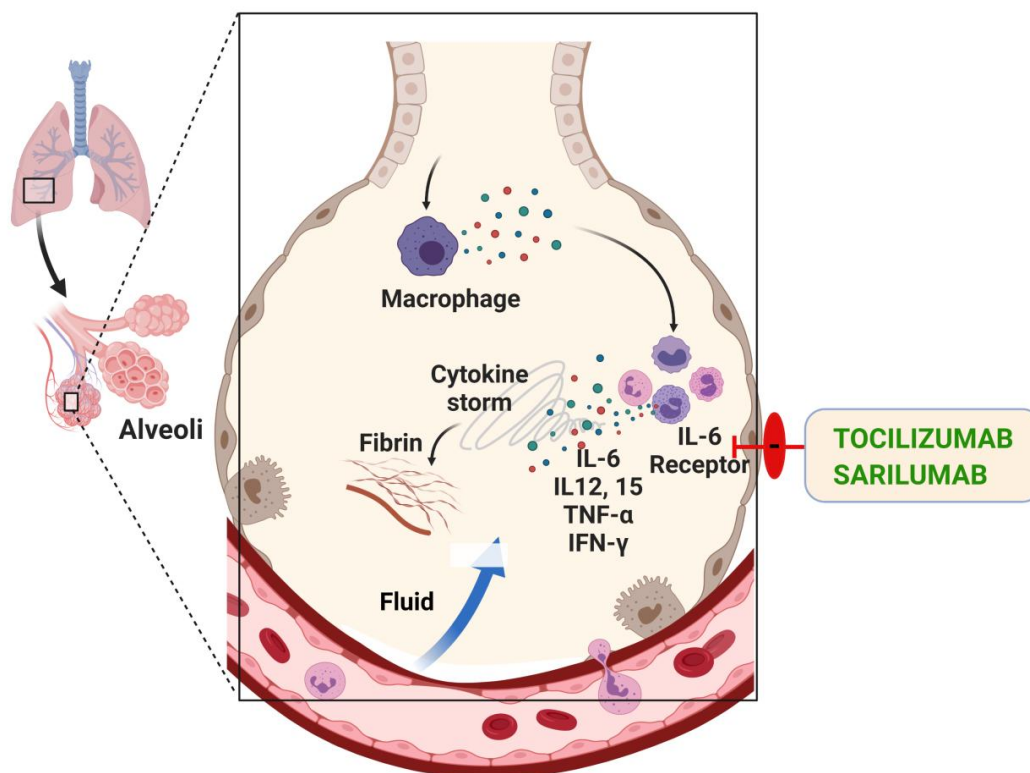


Fig. 1. Mechanism of action of IL-6 antagonists. The figure was created with <http://biorender.com> under a paid subscription

Table 1. Mechanism of drugs used in the treatment of COVID-19 and their doses

Drug	Class	Mechanism of action	Clinical Use	Dose	Route	Risks
Azithromycin	Antibacterial	Inhibits Spike protein binding to ACE2	Anti-Viral and Anti-Bacterial	250 mg, b.i.d/day	Oral	QT-prolongation and cardiotoxicity
Baricitinib	Anti-inflammatory	Inhibits Janus kinase 1 and 2	Rheumatoid arthritis	2 mg/day	Oral	-
Camostat	Serine protease inhibitor	Serine protease inhibitor	Chronic pancreatitis and esophagitis	600 mg/day after 4 days	Oral	Oedema and urticaria at a dose of 900 mg/daily
Ciclesonide	Corticosteroid	Inhibits viral replication by binding to viral NSP15	Anti-inflammatory	400 mg and 800 mg/day for fourteen days	Inhalational	-
Darunavir	Protease Inhibitor	Inhibits HIV-I Protease	Antiviral	800 mg/day	Oral	-
Dexamethasone	Corticosteroid	Supresses Phospholipase A2	Inflammation	6mg/day for 10 days in ventilated patients.	i.v.	-
Ivermectin	Anti-parasitic	Nuclear transport inhibitor	Endo/ectoparasiticide, antiviral, antibacterial, and anticancer	12 mg/day	Oral	Dizziness, pruritis, nausea, or diarrhea.
Mepilazumab	Anti-CD147 IgG2 monoclonal antibody	Inhibition of viral replication	Anti-malarial	10 mg/day	Subcutaneous	-
Nicosamide	Anti-helminthic	Prevent SARS-CoV-2 endocytosis	Anti-helminthic and anti-viral	2 grams orally on day 1 and daily for 6 more days (total 7 days of treatment)	Oral	-
Nitazoxanide	Antiparasitic	Inhibits viral protein formation by changing host enzymes	Antiparasitic and antiviral	500 mg/day	Oral	Abdominal pain, diarrhea, headache, nausea, vomiting, urine

Drug	Class	Mechanism of action	Clinical Use	Dose	Route	Risks
Remdesivir	Antiviral drug	RNA polymerase Inhibitor	SARS-CoV and MERS-CoV	200 mg baseline dose, followed by 100 mg once daily for the next five to ten days	i.v.	discoloration, and, rarely, ocular discoloration.
Ribavirin	Nucleoside analogue	Inhibits Guanosine	Antiviral drug- RSV infection, Hepatitis – B & C, HIV	400 mg for every 12 hours	Oral	-
Ruxolitinib	Anti-inflammatory drug	JAK1 and JAK2 inhibitor	Myelofibrosis (MF) and polycythemia vera	5 mg twice a day	Oral	-
Sarilumab	Monoclonal antibody	Inhibits interleukin-6 (IL-6) receptor	Rheumatoid arthritis	200 mg, single dose of i.v. injection	i.v.	Dose dependent transient and/or reversible elevations in liver enzyme levels
Tocilizumab	Monoclonal antibody	Inhibits interleukin-6 (IL-6) receptor	Rheumatoid arthritis	8 mg/kg/dose once intravenously	i.v.	-
Umifenovir	Antiviral	S protein/ACE interaction and inhibiting viral envelop interaction	Influenza A and B, arboviral infections	200 mg trice daily for 10 days	Oral	Elevation of fever and cough in Cov-19 infection

By inhibiting the IL-6 receptor, it reduces IL-6 accessibility and immunological activity, and hence inhibits IL-6-interceded signal transduction [15]. It was suggested by a few authors that it be used in COVID-19 patients who were critically ill and had high IL-6 levels [16]. The use of Tocilizumab in COVID-19 patients is still controversial. A few studies suggest that individuals with severe symptoms due to COVID-19-related pneumonia treated with a high dose of tocilizumab have a better clinical and radiological outcome [17], whereas other studies found no significant benefit of tocilizumab in serious patients [18]. Furthermore, IL-6 inhibition promotes the onset of viral illnesses [19].

Tocilizumab, which is specifically designed to bind to both mL-6R and sIL-6R and restrain both its classical and trans signaling pathways, controls the impact of IL-6 in severe COVID patients, as it is explicitly intended to bind to both mL-6R and sIL-6R and restrain both its classical and trans signaling pathways. Tocilizumab can be administered intravenously or subcutaneously [20]. The recommended dose for children and adolescents weighing 30 kg or more who have severe COVID-19 pneumonia with symptoms of hyper inflammation is 8 mg/kg/dose once intravenously (Max: 800 mg). Patients may be at risk of contracting bacterial and infectious illnesses. The recommended dose for children and adolescents weighing 30 kg or less is 12 mg/kg/dose once intravenously [21]. Due to a lack of clinical data, the NIH did not recommend or discourage the use of tocilizumab [22]. A total of 324 mg is being assessed via subcutaneous infusion once, coupled with antiviral treatment. Some individuals receive a second dosage 24 to 72 hours after receiving the primary infusion [23]. The US Food and Drug Administration has approved Tocilizumab for use in pediatrics for ARDS/sepsis in stage III clinical trials, although more research is needed [24].

2.3 Remdesivir

Remdesivir (RDV) has been shown to be the most effective treatment for SARS-CoV-2 infection. RDV is an adenosine analogue that exhibits activity against viruses belonging to the families Filoviridae, Paramyxoviridae, Pneumoviridae, and Orthocoronavirinae, including pathogenic SARS-CoV and MERS-CoV. Because of its low EC50 and host polymerase selectivity towards the Ebola virus, RDV demonstrated promising results during the Ebola infection outbreak [25]. RDV is an inhibitor

of RNA polymerase (Fig. 2) [26]. Because RDV is a prodrug, it must be converted to a nucleoside triphosphate that can serve as an alternative substrate for the viral RNA polymerase. Chain termination is caused by nucleoside triphosphate consolidation in the growing viral RNA chain, which stifles viral RNA replication [27]. In vitro and in vivo investigations have shown that RDV and IFN- have superior antiviral activities than lopinavir/ritonavir-IFN- against MERS-CoV than lopinavir/ritonavir-IFN-. Similarly, RDV was found to be efficacious in treating the main case of COVID-19 on day 7 of hospitalization in the United States [28].

On the first day, patients receive a 200 mg baseline dose, followed by 100 mg once daily for the next five to ten days. RDV is given for 4–10 days in the United States, or until respiratory symptoms worsen [29]. RDV should be arranged for use in hospitalized COVID-19 patients who require supplemental oxygen but are not on high-stream oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, according to the panel [22]. A randomized, double-blind, placebo-controlled trial concluded that RDV was superior in terms of reducing recovery time [30]. Despite its strong potency against SARS-CoV-2 and clinical success in COVID-19 therapy, remdesivir has lately been found to have vulnerabilities in terms of side effects and clinical viability [31].

2.4 Niclosamide

For a few decades, individuals have been using niclosamide to kill tapeworm infestations (anti-helminthic) [32]. SARS-CoV, MERS-CoV, ZIKV, Japanese encephalitis infection (JEV), hepatitis C infection (HCV), EBOV, human rhinoviruses (HRVs), Chikungunya infection (CHIKV), human adenovirus (HAdV), and Epstein-Barr infection (EBV) are just a few of the viruses that could be treated with it. Niclosamide has antiviral activities as well, including SARS-CoV (IC50 = 1.56 M). Recently, it was also revealed that In vitro, niclosamide was antiviral against SARS-CoV-2 (IC50 = 0.28 M) [33]. Niclosamide's antiviral activity against SARS-CoV2 replication is thought to be due to its ability to prevent SARS-CoV-2 endocytosis. It prevents SARS-CoV-2 autophagy by limiting the S-Phase kinase related protein 2 (SKP2) [34]. A randomized, open-label, controlled exploratory trial (NCT04372082; HYdiLIC) in France is assessing the dose of niclosamide 2 g on day 1 and 500 mg twice day for 10 days as a treatment for COVID-19. In a

randomized, double-blind trial in Boston, researchers are assessing niclosamide in people with mild to moderate COVID-19 (NCT04399356). In a separate experiment (NCT04436458), niclosamide is tested in people with mild COVID-19 who have GI symptoms and adverse effects [35].

2.5 Azithromycin

Apart from its antibacterial properties, azithromycin possesses anti-inflammatory and immunomodulatory properties [36]. It's used to treat otitis media, pharyngitis/tonsillitis, pertussis, network-acquired pneumonia, and sinusitis, among other respiratory illnesses [37]. The evidence for using azithromycin to treat SARS-CoV-2 is limited and questionable. Quantum physics suggests that constraining the interaction between the SARS-CoV-2 spike protein and the host receptor ACE2 protein is a likely aspect of azithromycin inhibiting viral passage; more research is needed to confirm this model. Azithromycin has a high limiting action and may directly target the SARS-CoV-2 spike's coupling

connection site with ACE2 [38]. The NIH advised against using azithromycin with hydroxychloroquine outside of clinical trials due to the risk of toxicity [22]. Antimicrobial care should be limited to COVID-19 patients where bacterial co-contamination is suspected or proven, according to NICE [39].

Some COVID-19 institutional conventions are using azithromycin. In a trial, hydroxychloroquine was used to regulate 500 mg azithromycin orally on the first day, then 250 mg orally once day for five days. On the sixth day, all patients treated with hydroxychloroquine plus azithromycin (n = 6) were virologically alleviated, whereas 57.1 percent of patients treated with hydroxychloroquine alone (n = 20) were virologically relieved [40]. There is no evidence that azithromycin has antibacterial properties in COVID-19 and has previously been used to treat bacterial superinfection [41]. According to the Italian Drug Agency, treating COVID-19 patients with azithromycin alone or in combination with hydroxychloroquine/chloroquine is not indicated unless bacterial superinfections occur [42].

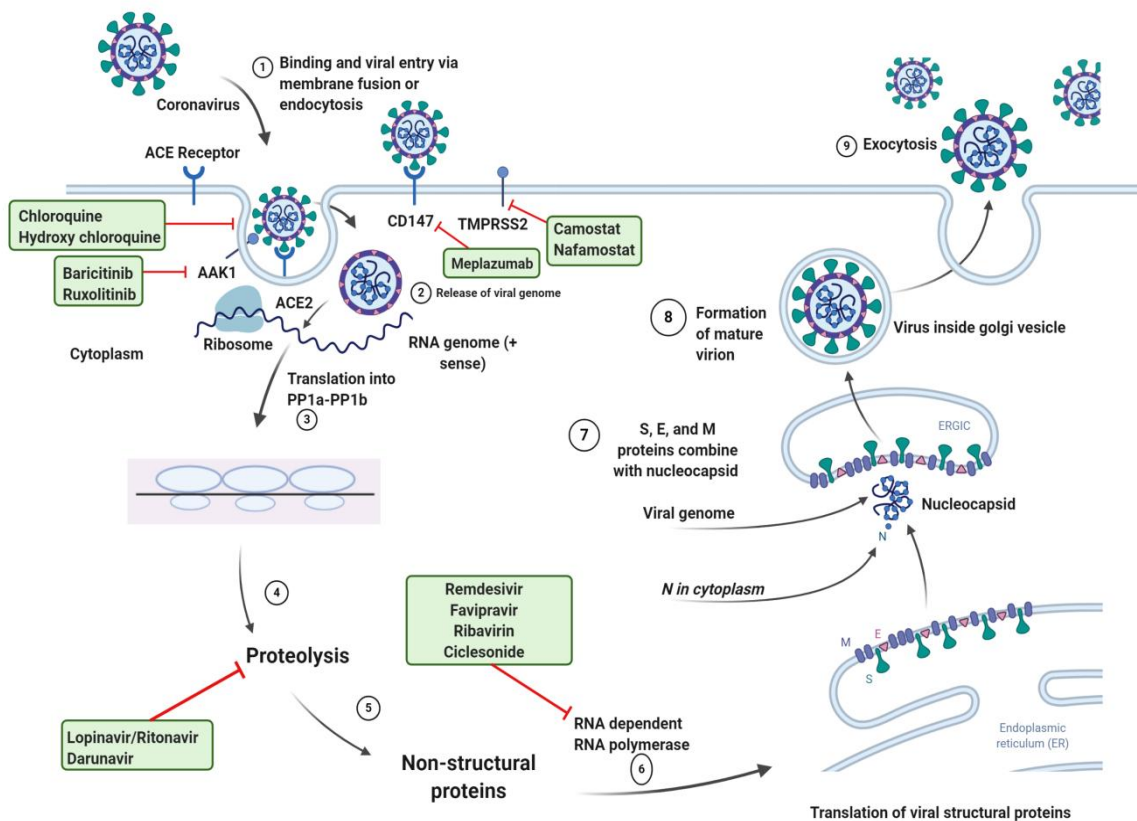


Fig. 2. Mechanism of drugs used in the treatment of COVID-19. The figure was created with <http://biorender.com> under a paid subscription

2.6 Sarilumab

Sarilumab is an inhibitor of the interleukin-6 (IL-6) receptor that is used to treat moderate to severe rheumatoid arthritis. Sarilumab binds to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R and mIL-6R), preventing IL-6-mediated signals from passing through these receptors [43]. IL-6 works through a variety of signaling mechanisms. However, because of the widespread notion of gp130, when IL-6 levels rise, as they do in subgroups of COVID-19 patients, the sign is generally transmitted [44]. CD4+ T lymphocytes infected with SARS-CoV-2 divide into pathogenic Th1 cells, which produce granulocyte-macrophage colony stimulating factor (GM-CSF) and other cytokines that activate monocytes that express IL-6 (Crisaful³). "Cytokine Release Syndrome," or CRS, is a surprise engaged in true COVID-19, in which cytokines such as IL-1, IL-6, IL-12, and IL-18, as well as TNF-, IFN-, and other fiery arbiters, arrive uncontrollably, increasing alveolar-gas trade and decreasing oxygenation in the pulmonary tissue. Some illnesses, such as ARDS, sepsis, Graft-versus-Host Disease (GvHD), essential and auxiliary hemophagocytic lymphohistiocytosis (HLH), and tangling of CAR-T cell managements, could be caused by this condition [44]. Antiviral treatment with 400 mg intravenously is being evaluated. Antiviral therapy at 200 or 400 mg subcutaneously is being evaluated³⁵. The National Institutes of Health (NIH) does not make recommendations for the use of IL-6 receptor inhibitors like sarilumab due to a lack of clinical data [22].

In an open-label study, 400 mg sarilumab was given intravenously along with standard of care in serious COVID-19 pneumonia (PaO₂/FiO₂ 300 mm Hg) with hyperinflammation (increased provocative indicators and serum IL-6 levels). Clinical improvement was seen in 61% of patients treated with sarilumab, but 7% of patients died. Clinical improvement and mortality are not mutually exclusive. Sarilumab was linked to a faster recovery in a subset of individuals who had mild lung solidification at the baseline [45].

2.7 Baricitinib

Janus kinase 1 and 2 are effectively inhibited by baricitinib. The Janus kinase family plays an important role in signaling pathways by triggering the cytokine-induced phosphorylation of STAT, which is then transported to the core for gene

transcription control [46]. Clinical trials have shown that baricitinib is effective in the treatment of rheumatoid arthritis [47]. Because of its preference for Adapter associated kinase-1 (AAK1), a controller of viral endocytosis in alveolar type 2 (AT2) epithelial cells, baricitinib has the best antiviral viability among JAK inhibitors in preventing SARS-CoV-2 from entering and tainting lung cells [48]. The disruption of AAK1 would interfere with viral entrance into cells and prevent viral particles from assembling intracellularly [49].

Baricitinib is used in combination with antivirals such as lopinavir, ritonavir, and remdesivir to reduce viral infectivity, replication, and the inflammatory response of the host. Baricitinib is also linked to a higher risk of microbe-caused severe infections, particularly when used in conjunction with immunosuppressants like corticosteroids [50]. The dose of Baricitinib used in trials for Covid-19 was 2 to 4 mg orally once day for seven to fourteen days [35]. The use of baricitinib (4 mg orally once a day for roughly fourteen days) with lopinavir/ritonavir was evaluated in an open-label research in Italy (NCT04358614). Patients who received baricitinib saw significant improvements in their respiratory capacity bounds, and none of them required ICU care [51]. The National Institutes of Health warns against using JAK inhibitors since their broad immunosuppressive effect outweighs the possible benefit and isn't recommended in people with severe hepatic or renal impairment. When used with solid OAT3 inhibitors, however, a dose adjustment is recommended.

2.8 Ruxolitinib

Ruxolitinib is a JAK1 and JAK2 inhibitor that has been approved for the treatment of myelofibrosis (MF) and polycythemia vera [52]. It's a viable treatment option for steroid-resistant acute graft versus host illness following allogeneic hematopoietic undifferentiated organism transplantation [53]. It is thought to have antiviral activities by preventing viral transit and contamination of pneumonic AT2 epithelial cells by inhibiting AAK1 [54]. The administration of ruxolitinib 5 mg orally at regular intervals for 14 days reduced the number of individuals with severe acute respiratory syndrome [55]. Patients with severe Covid 19 who received ruxolitinib showed faster clinical improvement in a randomized controlled stage II trial. Ruxolitinib has also been found to lower cytokine levels [56].

2.9 Ribavarin

Ribavarin has antiviral properties against HIV, hepatitis B and C, MERS CoV, herpes infections, and respiratory syncytial virus (RSV) (Khali³). It's a prodrug that works by passing through the liver's digestive process, then closely imitating the purine analog guanosine to improve its RNA fusion [29]. It interferes with RNA and DNA replication, as well as RNA covering that relies on normal guanosine, to prevent RNA disruption. Furthermore, it inhibits normal guanosine age by directly inhibiting inosine monophosphate dehydrogenase in a pathway that is required for the creation of the guanine precursor to guanosine, which is required for the destabilization of viral RNA (Fig. 2).

Early triple antiviral management with lopinavir and ritonavir every 12 hours for 14 days, ribavirin 400 mg every 12 hours, and three portions of 8 million worldwide units of interferon beta-1b was found to be superior to lopinavir–ritonavir alone in reducing symptoms and improving recovery by reducing the length of hospital stay in a randomized stage II preliminary trial [57]. Another stage III trial will look at the rate and time of viral clearance in people who take a combination of Nitazoxanide, Ribavirin (200 mg or 400 mg) and Ivermectin for seven days [58].

2.10 Nitazoxanide

Nitazoxanide has been shown to treat parasitic infections (cryptosporidiosis and giardiasis) as well as viral infections (HIV, HCV, hepatitis B infection (HBV), rotavirus, flu infection, and MERS-CoV) [59]. A previous *in vitro* investigation concluded that nitazoxanide, a functional metabolite of nitazoxanide, inhibits virus replication [60]. In human and canine cell lines, the amount of medicine required to suppress viral replication by half (IC₅₀s) is between 0.2 and 1.5 mg/ml. Nitazoxanide is thought to have antiviral potential against Sars-CoV-2 because it interferes with host-directed viral replication pathways, enhancing the finding of cytoplasmic RNA and Interferon type 1 receptors [61]. For COVID-19 therapy, several enrolled trials recommend a nitazoxanide dose of 500 or 600 mg two, three, or multiple times day for five to fourteen days, or 1 g twice daily for fourteen days. Several clinical trials have begun to evaluate nitazoxanide for the treatment of COVID-19-positive hospitalized patients, either alone or in combination with other drugs such as hydroxychloroquine and ivermectin [35]. Except in a clinical trial, the NIH

cautions against using it for SARS-CoV2 postexposure prophylaxis.

2.11 Umifenovir

Umifenovir (Arbidol) is a drug that has been licensed for the prevention and treatment of infections caused by influenza A and B, as well as other arboviruses [62]. *In vitro* antiviral effects of umifenovir were observed in widely spread infection strains such as Ebola, human herpesvirus 8 (HHV-8), HCV, and Tacaribe arenavirus [63]. Umifenovir is a more promising repurposed antiviral specialist, with its activity focusing on the S protein/ACE interaction and inhibiting viral envelope membrane interaction [64]. It inhibits viral cell membrane interface as well as virus endosome interaction with the host cell layer, as well as phospholipid hydrogen holding organization [65]. It is taken orally three times a day for seven to fourteen days.

According to a study, combining umifenovir with Lopinavir-Ritonavir increased the rate of SARS-CoV-2 negative transformation and enhanced the outcomes of chest CT scans [66]. Another study (ChiCTR200030254) found that, when compared to favipiravir, umifenovir has a lower clinical recovery rate and alleviation of symptoms such as fever and cough [67]. A systematic review and meta analysis found that umifenovir was protected and associated with a higher negative PCR rate on day 14 in lab confirmed COVID 19 adults [68].

2.12 Camostat

Camostat is an oral serine protease inhibitor used to treat chronic pancreatitis and esophagitis after surgery [69]. Nafamostat is another designed serine protease inhibitor with anticoagulant and anti-inflammatory effects [70]. Both Camostat and Nafamostat are thought to play a role in COVID-19 control. These drugs can interfere with TMPRSS2's enzymatic activity (Fig. 2) [71]. Three elderly patients with COVID-19 who had pneumonia that was progressing despite antiviral treatment were treated with 200 mg of nafamostat for 24 hours in a trial. The clinical state of patients improves once Nafamostat is administered. Patients are given Camostat (600 mg/day) after 4 days. A negative RT-PCR result was obtained after a few days [72]. Further research on the viability of both camostat and nafamostat is needed. Therapeutic trials are currently underway to determine its clinical efficacy.

2.13 Ciclesonide

Ciclesonide is an inhaled corticosteroid that has been proposed as a possibility for repurposing in the treatment of MERS or COVID-19 patients [73]. Furthermore, despite its inherent anti-inflammatory properties, further screening tests employing FDA-approved drugs have found that ciclesonide acts as an immediate antagonist of viral migration [74]. Ciclesonide binds to viral NSP15, stopping SARS-CoV-2 from reproducing. Viruses convey genomic information in the form of mRNA, which can then be translated into protein. Protease catalysts, notably papain-like proteases (PLpro) and a serine type Mpro (chymotrypsin-like protease (3CLpro) protease encoded in nsp3 and nsp 5, help polyproteins to function better. As a result, cleavage occurs halfway between pp1a and pp1ab, yielding nonstructural proteins (nsps) 1–11 and 1–16. The nsps are involved in a number of infections and host cell cycles.

Despite the fact that the pathophysiology of COVID-19 lung injury is unknown, researchers have discovered that the infection replicates in alveolar epithelial cells, producing lung damage and contaminating alveolar macrophages, as seen in MERS and SARS. Ciclesonide's antiviral and calming qualities will be useful in treating Covid-induced lung injury, which is getting more serious. Apart from ciclesonide, no other steroids have been found to exhibit antiviral properties against COVID-19. Steroid therapy for COVID-19 is not suggested due to the danger of prolonged viremia and consequences including diabetes [75]. To keep the virus from reactivating, a routine dose of 400 mg/day and an intense dose of 800 mg/day are given for about fourteen days. In a case study, three patients with mild to mid-stage SARS-CoV-2 sickness were given inhaled Ciclesonide midway through their hospital stay. They were all symptom-free after that, yet efficacy cannot be evaluated because each patient's disease background is unique. Its efficacy has been demonstrated in the elderly. If proved, early administration is regarded to be beneficial [76].

2.14 Darunavir

Darunavir is approved for the treatment of HIV disease in adults and children aged 3 and up, in combination with the HIV medication ritonavir and additional HIV medications (AIDS info). Darunavir binds to the protease enzyme and forms an inhibitor-enzyme complex, which

prevents the dimerization and catalytic activity of HIV-1 protease. Preventing cleavage of the gag-pol polyproteins in particular [77]. Protease inhibitors are one of the proposed strategies for SARS-CoV-2 management, although their use is limited due to their interactions and antagonistic effects. Increased lipase, amylase, hypernatremia and thrombocytopenia, increased prothrombin time, ALP, Cholesterol, and Triglycerides are some of the unfavourable effects (AIDS info).

Darunavir/Cobicistat (800 mg/150mg) was compared to Lopinavir/Ritonavir (200mg/50mg) in a research. 2 pills are administered orally twice daily to compare safety and efficacy in the treatment of COVID-19 pneumonia patients. The use of Darunavir in COVID-19 is not supported by data, as Darunavir did not inhibit viral movement in COVID-19 [78]. In a separate randomized trial, mild COVID-19 patients were randomly assigned to receive Darunavir/Cobicistat for five days with interferon alpha 2b or Darunavir/Cobicistat alone for five days. One of the Darunavir/Cobicistat group members developed critical illness and had to discontinue taking the drug. Finally, despite the fact that Darunavir/Cobicistat was well tolerated, it was assumed that five days of Darunavir/Cobicistat did not build the extent of negative change compared to standard of care alone [79]. In addition, research on the efficacy and safety of Darunavir in the treatment of COVID19 are required.

2.15 Meplazumab

Meplazumab is an anti-CD147 IgG2 monoclonal antibody that is required for Plasmodium falciparum invasion [80]. It is now being tested in phase I trials as a novel malaria treatment [81]. According to a recent study, the SARS-CoV-2 spike protein and CD147 cooperate to allow the virus to enter the body. In Vero E6 cells, meplazumab effectively suppressed SARS-CoV-2 multiplication and virus-induced cytotoxicity in a dose-dependent manner [82]. In light of these findings, a controlled trial was done to see if Meplazumab helps patients with COVID-19 pneumonia by inhibiting infection replication and suffocating inflammation. Their findings suggested that Meplazumab effectively improved the recovery of SARS-CoV-2 pneumonia patients [83]. A phase 2 clinical trial is now underway to assess the safety and efficacy of human Meplazumab for injection in patients infected with 2019-ncov. According on the patient's 2019-

nCoV nucleic corrosive burden, clinical appearances, and the overall assessment of specialists, a 10mg dose is administered on day 1, day 2, and the third dose is authorized 3-5 days following the second. A single dose will be utilized for management, based on the findings of a nonclinical trial (Jianqi NCT04275245).

2.16 Ivermectin

Ivermectin is a macrocyclic lactone that has a broad antiparasitic spectrum [84]. Ivermectin has a wide spectrum of actions, including endo/ectoparasiticide, antiviral, antibacterial, and anticancer properties [85]. Ivermectin works as a nuclear transport inhibitor, interceded by the importin/1 heterodimer, which is responsible for the translocation of viral species proteins (HIV-1, SV40), which is necessary for their reproduction. Furthermore, ivermectin has been shown to be effective against the DNA virus Pseudorabies infection (PRV).

Ivermectin is an inhibitor of (SARS-CoV-2) replication in vitro, according to a study. Its single administration was able to diminish SARS-CoV-2 up to 5000-fold in culture within 48 hours (with 5 M ivermectin). With an increase in time duration up to 72 hours, there is no further decline. The mechanism of antiviral response against SARS-CoV-2 is unknown, although it is thought to work by binding to and destabilizing the Imp/1 heterodimer, blocking entry into the nucleus and resulting in a more efficient antiviral response [86]. According to a study based on population kinetic data, the chances of a successful clinical trial with the permitted dose of ivermectin (200 mg/kg) are slim [87]. A prospective, double-blinded trial was done to assess the efficacy and safety of ivermectin for the treatment of COVID-19, with doses of 600 g/kg daily for five days, and 1200 g/kg daily on an empty stomach with water for five days (Zeno Bisoffi, NCT04438850).

3. CONCLUSION

This in-depth and comprehensive analysis provides an excellent overview of the most up-to-date information on the mechanisms of COVID-19 medicines.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely

no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Coronavirus | Definition of Coronavirus by Merriam-Webster. [Accessed 2021 Oct 29].
2. Ouassou H, Kharchoufa L, Bouhrim M, Daoudi NE, Imtara H, Bencheikh N, ELbouzidi A, Bnouham M. The Pathogenesis of Coronavirus Disease 2019 (COVID-19): Evaluation and Prevention. *J. Immunol. Res.* 2020;2020: 1357983.
3. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J. Pharm. Anal.* 2020;10(2):102–108.
4. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, Sun C, Sylvia S, Rozelle S, Raat H, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. *Infect. Dis. Poverty.* 2020;9(1):1–2.
5. Zu ZY, Di Jiang M, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology.* 2020;296(2):E15–E25.
6. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur. Respir. J.* 2020;55(4):2000607.
7. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host

- response. *Diabetes Metab. Syndr. Clin. Res. Rev.* 2020;14(4):407–412.
8. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int. J. Antimicrob. Agents.* 2020;55(5):105955.
 9. Tang Y-W, Schmitz JE, Persing DH, Stratton CW. Laboratory Diagnosis of COVID-19: Current Issues and Challenges. *J. Clin. Microbiol.* 2020;58(6): e00512-20.
 10. COVID-19: What Is Dexamethasone and How Does It Work? - *The Wire Science.* [accessed 2021 Oct 29].
 11. Dexamethasone in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* 2021; 384(8):693–704.
 12. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, Aguilar G, Alba F, González-Higueras E, Conesa LA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir. Med.* 2020;8(3):267–276.
 13. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, et al. 2012 update of the 2008 American college of rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res.* 2012;64(5):625–639.
 14. Actemra (tocilizumab) injection package insert.
 15. Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational Use of Tocilizumab in the Treatment of Novel Coronavirus Pneumonia. *Clin. Drug Investig.* 2020; 40(6):511–518.
 16. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int. J. Antimicrob. Agents.* 2020;55(5):105954.
 17. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, Khatib MY, Aboukamar M, Abukhattab M, Alsoub HA, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J. Med. Virol.* 2020;92(10):2042–2049.
 18. Rimland CA, Morgan CE, Bell GJ, Kim MK, Hedrick T, Marx A, Bramson B, Swygard H, Napravnik S, Schmitz JL, et al. Clinical characteristics and early outcomes in patients with COVID-19 treated with tocilizumab at a United States Academic Center; 2020.
 19. Zhang Y, Zhong Y, Pan L, Dong J. Treat 2019 novel coronavirus (COVID-19) with IL-6 inhibitor: Are we already that far? *Drug Discov. Ther.* 2020;14(2):100–102.
 20. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, Przepiorka D, Farrell AT, Pazdur R. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist.* 2018;23(8):943–947.
 21. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, Behrens EM, Ferris A, Kernan KF, Schulert GS, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. *Arthritis Rheumatol. (Hoboken, N.J.).* 2020;72(11):1791–1805.
 22. National Institutes of Health. COVID-19 Management Guidelines Panel. *Coronavirus Dis.:*19.
 23. Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R, Bonora S, Calcagno A, Cecchi I, Cinnirella G, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin. Exp. Rheumatol.* 38(3):529–532.
 24. Saha A, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Tocilizumab: A Therapeutic Option for the Treatment of Cytokine Storm Syndrome in COVID-19. *Arch. Med. Res.* 2020;51(6):595–597.
 25. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. 2020;323(18):1824–1836.
 26. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn M-Y, Nahass RG, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N. Engl. J. Med.* 2020;383(19):1827–1837.
 27. Delang L, Neyts J. Medical treatment options for COVID-19. *Eur. Hear. J. Acute Cardiovasc. Care.* 2020;9(3):209–214.
 28. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses.* 2020;12(4):372.

29. Barlow A, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, Heavner MS. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. *Pharmacotherapy*. 2020;40(5):416–437.
30. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N. Engl. J. Med.* 2020;383(19):1813–1826.
31. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: The reality and challenges. *J. Microbiol. Immunol. Infect.* 2020;53(3):436–443.
32. Andrews P, Thyssen J, Lorke D. The biology and toxicology of molluscicides, Bayluscide. *Pharmacol. Ther.* 1982;19(2):245–95.
33. Ko M, Chang SY, Byun SY, Choi I, Pham Hung d’Alexandry d’Orengiani AL, Shum D, Min JY, Windisch MP. Screening of FDA-approved drugs using a MERS-CoV clinical isolate from South Korea identifies potential therapeutic options for COVID-19. 2020.
34. Pindiprolu SKSS, Pindiprolu SH. Plausible mechanisms of Niclosamide as an antiviral agent against COVID-19. *Med. Hypotheses*. 2020;140:109765.
35. Home - ClinicalTrials.gov. [accessed 2021 Oct 29].
36. Min J-Y, Jang YJ. Macrolide Therapy in Respiratory Viral Infections. *Mediators Inflamm.* 2012;2012:1–9.
37. Centers for Disease Control and Prevention. Recommended antimicrobial agents for management and postexposure prophylaxis of pertussis. *CDC Guidel. MMWR*. 54(RR-14):1–6.
38. Sandeep S, McGregor K. Energetics Based Modeling of Hydroxychloroquine and Azithromycin Binding to the SARS-CoV-2 Spike (S)Protein - ACE2 Complex. 2020.
39. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital. London (UK): National Institute for Health and Care Excellence (NICE); 2020 May 1. 17 p. (NICE guideline; no. 173).
40. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J. Antimicrob. Agents*. 2020;56(1):105949.
41. Sultana J, Cutroneo PM, Crisafulli S, Puglisi G, Caramori G, Trifirò G. Azithromycin in COVID-19 Patients: Pharmacological Mechanism, Clinical Evidence and Prescribing Guidelines. *Drug Saf.* 2020;43(8):691–698.
42. Italian Medicines Agency (AIFA). Hydroxychloroquine for the management of COVID-19 adult patients.
43. L.L.C. Kevzara (sarilumab) package insert.
44. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J. Autoimmun.* 2020;111:102452.
45. Della-Torre E, Campochiaro C, Cavalli G, De Luca G, Napolitano A, La Marca S, Boffini N, Da Prat V, di Terlizzi G, Lanzillotta M, et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: An open-label cohort study. *Ann. Rheum. Dis.* 2020;79(10):1277–1285.
46. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, Labella A, Manson DK, Kubin C, Barr RG, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* 2020;382(25):2411–2418.
47. Koumaki D, Koumaki V, Lagoudaki E, Bertsias G. Palmoplantar Pustulosis-like Eruption Induced by Baricitinib for Treatment of Rheumatoid Arthritis. *Eur. J. case reports Intern. Med.* 2020;7(1):001383.
48. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30–e31.
49. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565–574.
50. Chen YC, Yoo DH, Lee CK, Li KJ, Won JE, Wu WS, Zhong J, Nicolay C, Walls CD, Tanaka Y. Safety of baricitinib in East Asian patients with moderate-to-severe active rheumatoid arthritis: An integrated

- analysis from clinical trials. *Int. J. Rheum. Dis.* 2020;23(1):65–73.
51. Cantini F, Niccoli L, Matarrese D, Nicastrì E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J. Infect.* 2020;81(2):318–356.
 52. Jakafi (ruxolitinib) [package insert. Wilmington, DE: Incyte Corporation.
 53. Meng G, Wang J, Wang X, Wang Y, Wang Z. Ruxolitinib treatment for SR-aGVHD in patients with EBV-HLH undergoing allo-HSCT. *Ann. Hematol.* 2020;99(2):343–349.
 54. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect. Dis.* 2020;20(4):400–402.
 55. Marcelo I, Clinica Z. Ruxolitinib in the Management of Covid19, *ClinicalTrials.gov* Identifier.
 56. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Huang L, Wang N, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J. Allergy Clin. Immunol.* 2020;146(1):137-146.e3.
 57. Hung IFN, Lung KC, Tso EYK, Liu R, Chung TWH, Chu MY, Ng YY, Lo J, Chan J, Tam AR, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet.* 2020;395(10238):1695–1704.
 58. New Antiviral Drugs for Treatment of COVID-19 - Full Text View - *ClinicalTrials.gov*. [Accessed 2021 Oct 29].
 59. Pepperrell T, Pilkington V, Owen A, Wang J, Hill AM. Review of safety and minimum pricing of nitazoxanide for potential treatment of COVID-19. *J. Virus Erad.* 2020;6(2):52–60.
 60. Calderón JM, Zerón HM, Padmanabhan S. Treatment with hydroxychloroquine vs hydroxychloroquine + nitazoxanide in covid-19 patients with risk factors for poor prognosis: a structured summary of a study protocol for a randomised controlled trial. *Trials.* 2020;21(1):1–3.
 61. Trindade AG, Caxito SMC, Xavier AREO, Xavier MAS, Brandão F. COVID-19: Therapeutic approaches description and discussion. *An. Acad. Bras. Cienc.* 2020;92(2):1–15.
 62. Boriskin Y, Leneva I, Pecheur E-I, Polyak S. Arbidol: A Broad-Spectrum Antiviral Compound that Blocks Viral Fusion. *Curr. Med. Chem.* 2008;15(10):997–1005.
 63. Pécheur E-I, Borisevich V, Halfmann P, Morrey JD, Smee DF, Prichard M, Mire CE, Kawaoka Y, Geisbert TW, Polyak SJ. The Synthetic Antiviral Drug Arbidol Inhibits Globally Prevalent Pathogenic Viruses. *J. Virol.* 2016;90(6):3086–3092.
 64. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc. Natl. Acad. Sci. U. S. A.* 2017;114(2):206–214.
 65. Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and other Drugs for the Treatment of the New Coronavirus. 2020.
 66. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, Hong Z, Xia J. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. *J. Infect.* 2020;81(1):e1–e5.
 67. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, et al. Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. 2020.
 68. Huang D, Yu H, Wang T, Yang H, Yao R, Liang Z. Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *J. Med. Virol.* 2021;93(1):481–490.
 69. Yamamoto M, Matsuyama S, Li X, Takeda M, Kawaguchi Y, Inoue JI, Matsuda Z. Identification of nafamostat as a potent inhibitor of middle east respiratory syndrome Coronavirus s protein-mediated membrane fusion using the split-protein-based cell-cell fusion assay. *Antimicrob. Agents Chemother.* 2016;60(11):6532–6539.
 70. Kim HS, Lee KE, Oh JH, Jung CS, Choi D, Kim Y, Jeon JS, Han DC, Noh H. Cardiac arrest caused by nafamostat mesilate. *Kidney Res. Clin. Pract.* 2016;35(3):187–9.
 71. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271–280.
 72. Jang S, Rhee JY. Three cases of treatment with nafamostat in elderly

- patients with COVID-19 pneumonia who need oxygen therapy. *Int. J. Infect. Dis.* 2020;96:500–502.
73. Matsuyama S, Kawase M, Nao N, Shirato K, Ujike M, Kamitani W, Shimojima M, Fukushi S. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15; 2020.
 74. Jeon S, Ko M, Lee J, Choi I, Byun SY, Park S, Shum D, Kim S. Identification of Antiviral Drug Candidates against SARS-CoV-2 from FDA-Approved Drugs. *Antimicrob. Agents Chemother.* 2020;64(7):e00819-20.
 75. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395(10223):473–475.
 76. Iwabuchi K, Yoshie K, Kurakami Y, Takahashi K, Kato Y, Morishima T. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: Report of three cases. *J. Infect. Chemother.* 2020;26(6):625–632.
 77. Davis DA, Soule EE, Davidoff KS, Daniels SI, Naiman NE, Yarchoan R. Activity of human immunodeficiency virus type 1 protease inhibitors against the initial autocleavage in Gag-Pol polyprotein processing. *Antimicrob. Agents Chemother.* 2012;56(7):3620–3628.
 78. De Meyer S, Bojkova D, Cinatl J, Van Damme E, Buyck C, Van Loock M, Woodfall B, Ciesek S. Lack of antiviral activity of darunavir against SARS-CoV-2. *Int. J. Infect. Dis.* 2020;97:7–10.
 79. Chen J, Xia L, Liu L, Xu Q, Ling Y, Huang D, Huang W, Song S, Xu S, Shen Y, et al. Antiviral activity and safety of darunavir/Cobicistat for the treatment of COVID-19. *Open Forum Infect. Dis.* 2020;7(7):241.
 80. Drożdżal S, Rosik J, Lechowicz K, Machaj F, Kotfis K, Ghavami S, Łos MJ. FDA approved drugs with pharmacotherapeutic potential for SARS-CoV-2 (COVID-19) therapy. *Drug Resist. Updat.* 2020;53:100719.
 81. I.U.P.H.A.R./B.P.S. Guide to Pharmacology. 1944;2(4380):793–793.
 82. Wang K, Chen W, Zhou Y Sen, Lian JQ, Zhang Z, Du P, Gong L, Zhang Y, Cui HY, Geng JJ, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein; 2020.
 83. Bian H, Zheng ZH, Wei D, Zhang Z, Kang WZ, Hao CQ, Dong K, Kang W, Xia JL, Miao JL, et al. Meplazumab treats COVID-19 pneumonia: An open-labelled, concurrent controlled add-on clinical trial; 2020.
 84. Rizzo E. Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. *Naunyn. Schmiedeberg's Arch. Pharmacol.* 2020;393(7):1153–1156.
 85. Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R, Singh BR, Sah R, Bonilla-Aldana DK, Rodriguez-Morales AJ, Leblebicioglu H. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. *Ann. Clin. Microbiol. Antimicrob.* 2020;19(1):23.
 86. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787.
 87. Schmith VD, Zhou J, Lohmer LRL. The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. *Clin. Pharmacol. Ther.* 2020;108(4):762–765.

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