Review Article

Possible mechanisms of drugs used in the treatment of COVID-19: A Pharmacological perspective

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-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, Ribavarin, Nitazoxanide, Umifenovir, Camostat, Ciclesonide, Darun 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.

Key-Words: Covid-19, Remdesivir, Coronavirus, Favipiravir, Azithromycin

Introduction

Corona viruses belong to the Coronaviridae and Nidovirales families of viruses. A group of virologists coined the name, which was published in Nature's "News and Views" section as a brief piece titled "Corona viruses." In appearance, they resemble myxoviruses. They're massive single-abandoned 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]. The infection has a diameter of 65-125 nm and a length of 26 to 32 kilo bases (kb). The family's sub-groupings include alpha (α), beta (β), gamma (γ), and delta (δ). 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].

The China Seafood Market has been linked to the COVID-19 outbreak, however, the source of transmission remains unknown. Bats, pangolins, or ocean depths could be the COVID-19's host. 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]. On December 29, 2019, a few cases of an acute respiratory infection were reported in Wuhan City, China, among people who work at a nearby fish market. Adult patients range in age from 25 to 89 years of age. With age, co-morbid disorders such as hepatic and renal ailments, and a weakened immune system, the chance of contamination increases[4]. Currently, there are around 23.9 million cases worldwide, with the majority of instances in the United States (5.85 million), Brazil (3.67 million), and India (3.67 million) (3.23 million).

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. A patient with a respiratory rate of thirty times per minute, an SpO2 of 93 percent at rest, and a

PaO2/FiO2 of 300 mm Hg is considered severely ill [5]. COVID-19 pathology can be divided into three stages. The inhaled virus enters the nasal cavity, bonds to epithelial cells, and duplicates in stage I, also known as the asymptomatic stage (first 1-2 days of sickness). Nasal swabs can be used to detect the viral infection at this time. Despite the low viral burden, individuals who are infected at this time may become carriers. Stage II - the virus migrates down the respiratory tract; swabs can detect the infection even at this stage. At this point, the clinical symptoms are displayed. CXCL10, also known as IP10/little inducible cytokine or Interferon gamma instigated protein, could be used as a key indication for SARS. It escalates to Acute Respiratory Distress Syndrome (ARDS) in Stage III, and patients suffer pneumonic pneumonia. Around 20% of patients move from stage II to stage III. When the virus enters the lungs, it infects alveolar type II cells, which are precursors to type I cells. Virus spreads and delivers viral particles in alveolar type II cells. 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. Micro thrombin production in lung tissues and pulmonary endothelial cells can lead to thrombotic problems.

Coronavirus infects humans through ACE2 receptors found in organs such as the heart, lungs, kidneys, and gastrointestinal tract. The virus's entry into the host cell cycle is initiated by the attachment of the S glycoprotein to the ACE2 receptor in the host cell. This connection is found in the S protein of the SARS-CoV-2 receptors' coupling area and is obviously connected to human ACE2. Following the combination, TMPRSS2, which is found on the host cell's surface, clears the ACE2 and activates S proteins. When the S proteins are activated, they undergo conformational changes, allowing the virus to enter the cells. The proteins ACE2 and TMPRSS2 are required by SARS CoV-2 [7]. The reverse transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loopmediated isothermal amplification are all used to diagnose Coronavirus (RTLAMP). The sensitivity of rRT-PCR and RT-LAMP are the same. Additionally, antibody-based techniques are given. For detecting early COVID-19 infection, nasopharyngeal and oropharyngeal swab tests have become the gold standard. A single nasopharyngeal swab is chosen since it is less painful for the patient and more secure for administration. Sputum collection or Bronchoalveolar lavage should be utilized to

discover the infection late. Despite negative RT-PCR results, COVID-19 should be diagnosed using routine chest computed tomography (CT) [8,9].

Drugs used in the management of Covid-19

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 by suppressing the chemical phospholipase A2. 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, the 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].

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 (Figure 1).

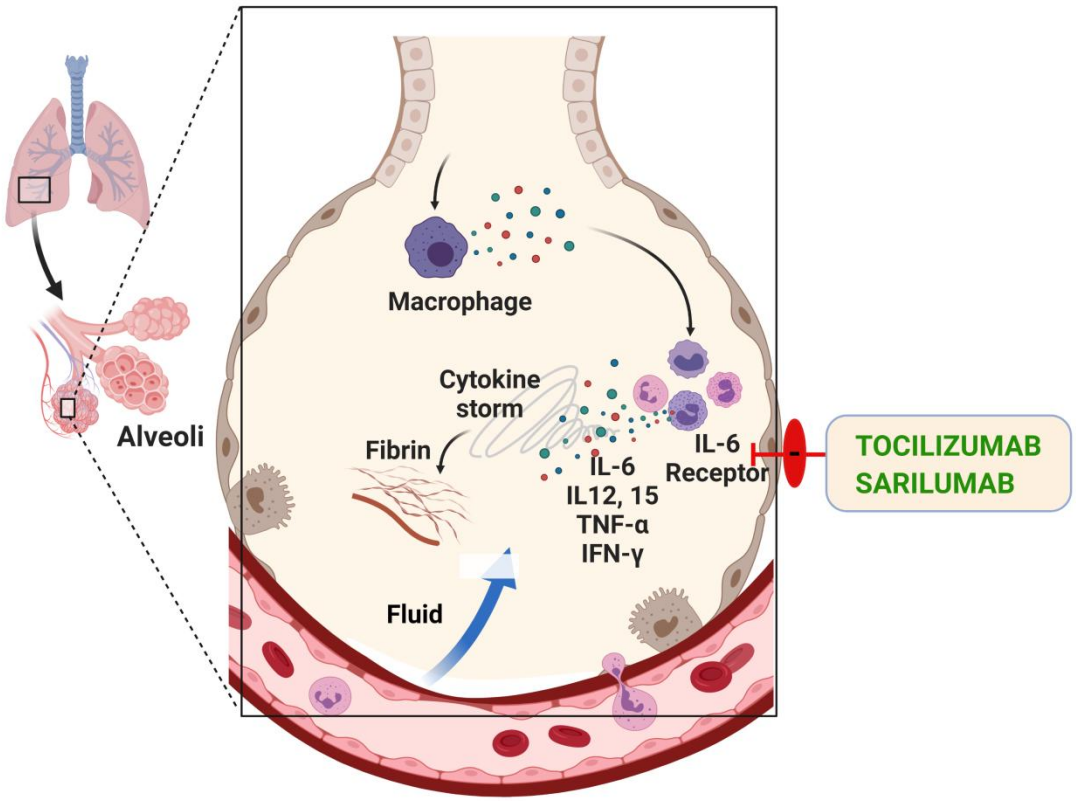

Figure 1: Mechanism of action of IL-6 antagonists

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 mIL-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 mIL-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].

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 (Figure 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].

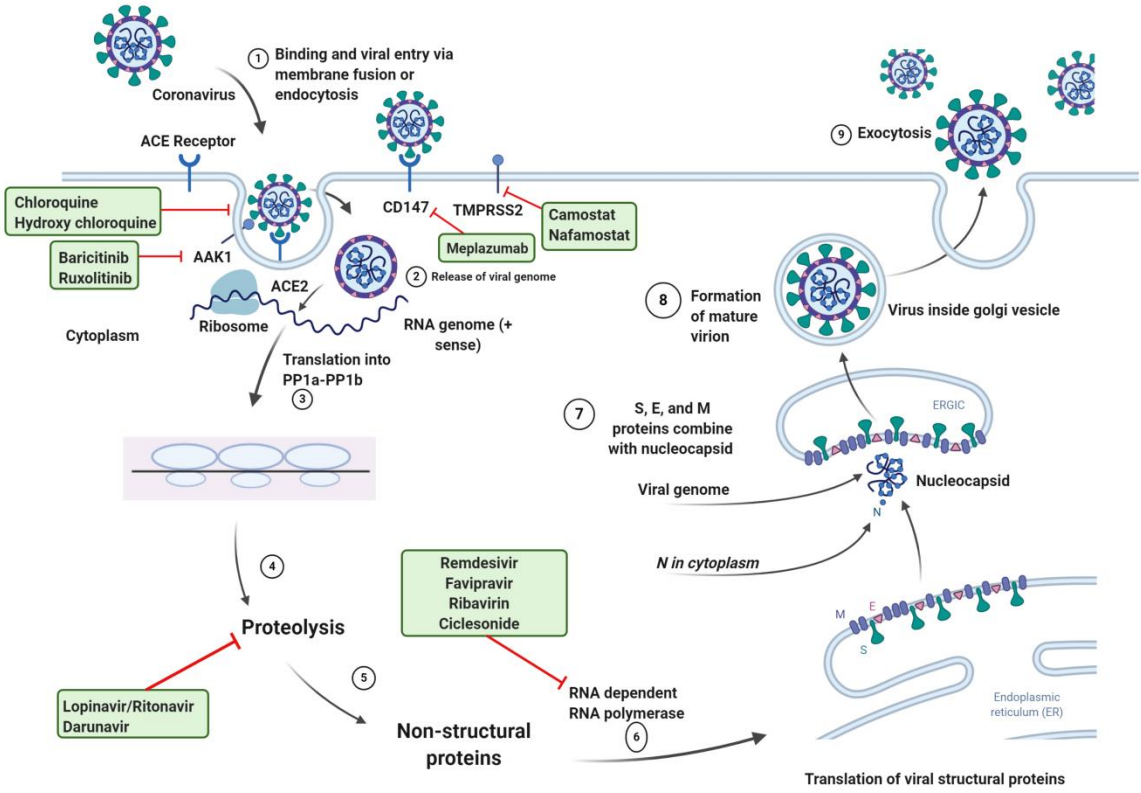

Figure 2: Mechanism of drugs used in the treatment of COVID-19

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].

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].

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 (Crisaful[3]). "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 evaluated[35]. 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].

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.

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].

Ribavarin

Ribavarin has antiviral properties against HIV, hepatitis B and C, MERS CoV, herpes infections, and respiratory syncytial virus (RSV) (Khali[3]). 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 (Figure 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].

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 tizoxanide, 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.

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].

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 (Figure 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.

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. Cilesonide'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].

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.

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).

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).

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.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

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