Review Article

A REVIEW ON ASPECTS OF CURRENT PHARMACOTHERAPIES FOR COVID-19

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ABSTRACT: The novel coronavirus has infected over 609,848,852 individuals throughout the world with a total death of over 6.5 million since its outbreak in December 2019. Since then many therapeutic options have been approached and tested in clinical trials as well to find a potential cure or preventive therapy for the COVID-19 disease. This review summarizes the potential therapeutic options currently available for the treatment of COVID-19 including lopinavir-ritonavir, Hydroxychloroquine, Remdesivir, Ribavirin, dexamethasone, interferon, antibodies, Tocilizumab, Azithromycin, Piperacillin-tazobactam, Moxifloxacin, Ivermectin, Nitazoxanide, Baricitinib, and Arbidol. This study briefly discusses the clinical trials and encompasses the dosage, efficacy, adverse drug reactions, and possible mechanism of action of the potential treatment candidate where applicable. The growing number of reported cases posits an exigent need for a suitable therapy for the prevention and cure of this disease. Therefore, the study aims to provide vital information on each drug to highlight the latest scientific research that could be helpful for better prevention/treatment of COVID-19 disease.

Key words: COVID-19, therapeutic approaches, antiviral drugs**,** mechanism of action.

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INTRODUCTION

The appearance of a new coronavirus i.e. severe acute respiratory coronavirus 2 (SARS-CoV-2) began in China in December 2019 and continues to spread all over the world ever since. In February 2020, World Health Organization (WHO) entitled the disease "COVID-19" and declared it a global pandemic and a health emergency [1]. The novel coronavirus (nCoV) bears genetic similarities to Middle East Respiratory Syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). It is an enveloped, single-stranded RNA retrovirus that has most likely originated from a bat and spread via unknown mechanisms from mammals to humans [1]. The SARS-CoV-2 genome was sequenced quickly after its appearance and isolation followed by the determination of its epidemiological characteristics, preventive measures/treatment strategies. As of February 11, 2021, the death toll of COVID-19 was over 2.3 million, and more than 300 clinical trials and active treatments against COVID-19 are underway. The data from trials does not support any evidence of a final treatment of prophylactic therapy for the COVID-19. This comprehensive review summarizes the randomized controlled trials, repurposed drugs, and proposed treatments for the impediment, management, and retrospective treatment experiences of the COVID-19 pandemic.

PIPERACILLIN-TAZOBACTAM: Piperacillin is a widely used penicillin antibiotic against a variety of infections caused by gram-negative bacteria i.e. *Pseudomonas aeruginosa* and *Enterobacter* spp. it is bacteriostatic, however, most of the commonly occurring pathogens have become resistant to piperacillin [2]. Tazobactum is a β-lactamase inhibitor that protects from various β-lactamases. Combining it with piperacillin not only inhibits the activity of β-lactamase enzymes but also restores the antibacterial activity of piperacillin which would otherwise have been lost [3]. In a case study reported by researchers in Heidelberg University Hospital, five COVID-19 patients over 60 years of age were admitted with respiratory failure. The patients received prophylactic therapy including antibiotic piperacillin/tazobactam. However, no significant improvement was seen in them, instead, they developed severe respiratory distress syndrome [4].

Table 1*:* This Table summarizes list of drugs, repurposed drugs, and proposed drugs and the mechanism of action of each drug used for the novel corona treatment.

Class	Drug	Brand Name	Mechanism of action in SARS-CoV-2	Reference
Antimalarial	Hydroxychloroquine	Plaquenil	It modulates the immune system by inhibiting B-cells and T-cells receptors signaling, toll-like receptor (TLR) signaling, binding with DNA, and inhibiting the production of interleukins (IL-1 and IL-6) and prostaglandins.	(Goldman *et al*., 2000, Kyburz *et al*., 2006, Ruiz-Irastorza and Khamashta, 2008, Bondeson and Sundler, 1998)
Antiviral	Remdesivir	Veklury	Converts to adenosine analog after metabolism and causes premature termination of viral RNA. It incorporates in place ATP and 2 other nucleotides resulting in RNA synthesis blockage and termination. The 3 nucleotides safeguard inhibitor from 3'-5' exonuclease thus inhibiting the viral replication.	(Gordon *et al*., 2020; Nyarko *et al*., 2020)
	Lopinavir-ritonavir	Kaletra	Protease inhibitors of HIV/AIDS (Human Immunodeficiency Virus disease).	(Cvetkovic and Goa, 2003)
	Ribavirin	Ribazole	Ribavirin can cohere with COVID-19 and SARS Human Coronavirus RNA dependent RNA Polymerase and has 50% effective concentration (EC50) against coronavirus disease.	(Elfiky, 2020)
	Umifenovir	Arbidol	Arbidol is an anti-retroviral protease inhibitor. It competitively inhibits the viral protease enzyme by binding to its active site. It also blocks the release of the functional viral particles to prevent their transcription/replication and maturation.	-
Anthelmintic and Antiprotozoal	Ivermectin	Iverlex	Inhibition of transferring viral proteins into host cell nucleus through the (IMP) α/β receptor.	(Heidary and Gharebaghi, 2020)
	Nitazoxanide	Adonid	Inhibits the enzyme for replication of RNA. It also amplifies the innate immune response towards viruses and enhances the cytoplasmic RNA sensing by host cells.	(Jasenosky *et al*., 2019)
Immunotherapies	Interferons	Unipeg	Natural antivirals. Type 1 interferons (IFN-1) are also being used for their antiviral properties against 2019-nCoV.	-
	Antibodies	-	Inhibit the entry of SARS-CoV-2 in a human cell through S-protein which binds to angiotensin converting enzyme 2 (ACE2), preventing the entry of virus from host cells epithelium, therefore preventing its replication.	(Vaduganathan *et al*., 2020, Wan *et al*., 2020)
Antibiotics	Azithromycin	Azomax	Limits the viral replication by genetic shedding of virus from lysosomes and blocks the endosome maturation. AZ might follow a similar pathway like that of IFN by stimulating a signal and activating genes, which leads to viral load reduction.	(Tyteca *et al*., 2002, Li *et al*., 2019, Menzel *et al*., 2016)
	Piperacillin-Tazobactam	Tanzo	The concomitant use of piperacillin/tocilizumab with corticosteroids have been shown to decrease the risk of community acquired pneumonia.	(Nestler *et al*., 2020)
	Moxifloxacin	Moxiaim	Inhibit the SARS-CoV-2 replication by binding to the protease enzyme M_{pro} active site.	(Marciniec *et al*., 2020)

Others	Baricitinib	Olumiant	May inhibit virus invasion along with suppressing the cytokine storm thus preventing the endocytosis hence preventing viral invasion and inflammation.	(Richardson *et al*., 2020; Lu *et al*., 2020,)
	Dexamethasone	Decadron	Inhibition of protective B cells and T cells function and blocking of NK cells and macrophages from clearing the nosocomial pathogens.	(Tsurufuji *et al*., 1980)
Monoclonal Antibody	Tocilizumab	Actemra	It competitively inhibits the IL-6 to its receptor which result in the transduction of the inflammatory mediators, and pro-inflammatory cytokines that signal the T and B cells.	(Nishimoto and Kishimoto, 2008)

The effect of COVID-19 on pneumonia-focused antibiotic use was evaluated in yet another study, where antibiotic days of therapy per 1000 patients were observed. Piperacillin/tazobactam was administered to a group of patients along with other main antibiotics administered in pneumonia. The results revealed no increase in the use of anti-β-lactamases observed when only being given in terms of an empirical therapy [5]. The safety and efficacy of antibacterial agents including piperacillin/tazobactam were evaluated in children with COVID-19 but they were non-beneficial in the absence of any underlying bacterial infection. There was not enough evidences to support the use of piperacillin/tazobactam that contributed to control SARS-CoV-2 infection in children [6]. At present, various clinical trials are being carried out in Germany that is investigating the therapeutic activity of multiple antibacterial agents including piperacillin/tazobactam in randomized multifactorial trials [7].

MOXIFLOXACIN: Moxifloxacin is a fourth-generation fluoroquinolone that acts as the first-line treatment for severe respiratory infections like pneumonia. Fluoroquinolones are broad-spectrum antibacterial drugs which are active against a wide range of bacteria, atypical pathogens, mycobacteria, and anaerobes [8]. Their antibacterial effect is exerted by targeting the DNA gyrase (bacterial topoisomerase II) enzyme which inhibits the bacterial DNA synthesis and stops their growth [9]. In a recent study, the effect of moxifloxacin and ciprofloxacin was observed on the SARS-CoV-2 virus and they exhibited a strong binding capacity for the SARS-CoV-2 main protease (M_{pro}) enzyme. This indicates that the fluoroquinolones may have the ability to inhibit SARS-CoV-2 replication. It is also reported that the fluoroquinolones have a better binding ability to the M_{pro} active site than other antiretroviral agents used in AIDS treatment such as chloroquine and nelfinavir [10]. Levofloxacin is known to exhibit multiple immunomodulatory effects against respiratory viruses like the H1N1 influenza virus and the side effects associated with it such as virus-induced long injury. Studies have shown the effectiveness of fluoroquinolone in animal models for example reduction of oxidative stress from the nitric oxide regulation. It also modulates the inflammatory response by the inhibition of pro-inflammatory cytokines such as TNF-a and IL-1 [10].

The pharmacokinetic properties of fluoroquinolones have been shown to maintain a higher concentration in the lungs as compared to serum levels. Their safety profile is much better than the other antibiotics drugs used for the treatment of respiratory tract infection such as beta-lactams and macrolides [12]. Due to the potential antiviral activity of levofloxacin and moxifloxacin against respiratory viruses, they are being used in conjunction with other immunomodulatory drugs for the treatment/control of COVID-19 patients.

Moxifloxacin is mostly administered in combination with other antibiotics in injectable and tablet form. Community-acquired pneumonia shows the symptoms of respiratory tract infection and radiographic evidence of lung damage. Hence, there is a higher chance of developing infection with the SARS-CoV-2 [8]. It is recommended to administer moxifloxacin as part of the empirical therapy in the patients who present with the lung injury due to infection with or without a confirmed diagnosis of COVID-19 related pneumonia. Moxifloxacin is favorable for such treatment given its safety profile and pharmacokinetics. However, it is being used as an adjunct with other drugs. To further evaluate its safe efficacy against COVID-19 infection caused by SARS-CoV-2 virus, randomized controlled trials are needed to explore the therapeutic potential of moxifloxacin alone and as an adjunct for treating SARS-CoV-2 related pneumonia.

IVERMECTIN: Ivermectin is a multipurpose drug for human and veterinary use. It has been in use as an anthelmintic i.e. for the treatment of parasitic infections in humans for over 30 years [13]. It first came into medicinal practice in 1970 and since then, its antiviral properties have been explored against human viruses many times. It is a macrocyclic lactone structure and derivative of 22, 23-dihydro-avermectin B1 [14]. Currently, Ivermectin has been reported as a drug of choice in humans for the treatment of onchocerciasis and many other parasites as well [15].

Ivermectin exhibits its action in the invertebrates by chloride ion influx by opening the glutamate-gated chloride channels which cause the membranes to hyperpolarize, thus paralyzing the target organism. In

humans, its mechanism of action is poorly understood especially, in use against the SARS-CoV-2 [16].

Many *in-vivo* and *in-vitro* drug trials are under observation to check the effectiveness of ivermectin in the COVID-19 patients. During an in vitro study, Vero/hSLAM cells were made infected of SARS-CoV-2 and then treated with ivermectin in a concentration of 5μM for 48 hours. The result revealed a significant (5000-fold) reduction in the RNA of virus in comparison to the control and destroyed all the viral particles within 2 days [17]. The possible anti-retroviral mechanism could be the inhibition of transferring viral proteins into the host cell nucleus through the (IMP) α/β receptor [18].

Recently, a control trial of one hundred sixteen patients treated with the combination of ivermectin and doxycycline was performed. The results showed that this combination provided better symptomatic relief, reduced recovery duration, and a better success rate with fewer side effects. The authors' concluded the ivermectin is a suitable choice for treating patients with mild COVID-19 disease [19]. In another trial containing 280 patients with COVID-19, patients were divided into two groups with one of them (n=173) receiving ivermectin as a treatment. A low mortality rate was observed in the ivermectin treated group as compared to the standard group (n=107) [20].

Many drug trials for ivermectin against COVID-19 infection are under observation. Five trials of ivermectin are ongoing to treat SARS-CoV-2 infection in Europe [21]. In India, at least five clinical trials include ivermectin [22] and 38 clinical trials are registered in the USA from various countries and are in different stages of evaluation and completion [23]. The ivermectin dose has been used in varying ranges from 200 to 1200 μg/kg for 3 to 7 days. Different doses result in hopeful positive effects in terms of symptomatic relief and reduction in a viral load.

Ivermectin has shown itself to be more effective in comparison with hideout hydroxychloroquine and azithromycin combination. Yet, the safety evaluation of ivermectin at high doses has insufficient evidence especially, in children less than 15 kg and pregnant women [22]. The clinical efficiency of ivermectin and the COVID-19 patients is still unpredictable and its repurposing is an astute usage for treating life-threatening COVID-19 infection.

DEXAMETHASONE: Dexamethasone is a steroidal anti-inflammatory drug. It is a hydrocortisone derivative approved by the FDA in 1958 [24]. It is an immunosuppressant and a pro-inflammatory signaling compound. It has a longer duration of action and 30 times more activity than that of cortisone [25]. The mechanism of action of dexamethasone takes place by inhibition of prostaglandin synthesis or its release by the suppression of phospholipase A2. The immunomodulatory effect of dexamethasone takes place by inhibition of protective B cells and T cells function. It also blocks the NK cells and macrophages from clearing the nosocomial pathogens [26].

Dexamethasone has been actively used in clinical trials against SARS-CoV-2 infection. In a clinical trial performed on 2104 COVID-19 patients, 6mg dexamethasone was given once a daily. The mortality rate in those patients was 8-25% low daily than those who received standard care (n=4321). Based on the findings some changes were made in the NHS treatment protocol of COVID-19 patients [27].

The use of dexamethasone Nano-medicine has been observed in a RECOVERY trial where 6 mg per day administered intravenously or orally for ten days. The deaths of COVID-19 serious patients (who were on mechanical ventilation) in the ICU was reduced up to 35 % after receiving this treatment [28]. It also decreased the hospitalization time in non-ventilated patients by one day i.e. 12 days instead of 13 standard care days and the mortality rate was reduced to 20%. Another study reported similar findings in which dexamethasone has significantly shown to improve survival in acute respiratory distress syndrome (ARDS) [29].

The corticosteroids have wide effects on adaptive and innate immunity. The immunopathology of ARDS relates to a specific antibody that appears temporarily against SARS-CoV-2 infection. In a surveying study performed in China, the patients treated with methylprednisolone presented a lower mortality rate than those who did not receive it [30]. The dexamethasone dose used during the RECOVERY clinical trial was nearly half that is used in the management of severe pneumocystis pneumonia and prevention of treatment-induced ARDS. Therefore, the question remains unresolved whether the dose and route for the steroids used in the clinical trials against SARS-CoV-2 infection were optimal or not. Besides, it cannot be determined if it worked on a few hundred patients, it will serve to be the best option for all the patients. Different factors including co-morbidity and age have remarkable impact in determining the efficacy of a drug in the COVID-19 patients. The effects of dexamethasone on the older age groups were not quite beneficial in that trial and its benefits and risk remained unclear. Therefore, keeping these factors into account, long-term follow-up is required to assess the risks and benefits associated with the use of corticosteroids in the COVID-19 patients [27].

TOCILIZUMAB: Tocilizumab is a recombinant novel monoclonal antibody that acts as an agonist on the interleukin IL-6 receptor. It competitively inhibits the IL-6 to its receptor which results in the transduction of the inflammatory mediators that signal the T and B cells [31]. Interleukins are a group of cytokines that regulate inflammatory reactions and immune responses. The development of autoimmune diseases has been associated

with the overproduction of IL-6 leading towards juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA). Therefore, blocking the binding of the IL-6 to its receptors can alleviate its effects [32].

The first pathological reports obtained from the patients infected with the SARS-CoV-2 virus revealed that the concentration of pro-inflammatory cytokines was remarkably high. The overproduction of the pro-inflammatory cytokines resulted in a cytokine storm which was observed in patients critically ill with the COVID-19. Those patients suffered from multiple organ dysfunction, cardiovascular collapse, and rapid death. One of the most important cytokines observed in the recent clinical reports of the COVID-19 patients is the IL-6. Therefore, tocilizumab has been suggested to be used among serious ill patients in the COVID-19 related pneumonia [33].

In a retrospective study performed in China, the treatment response of tocilizumab was observed among 15 patients. Different doses were administered in those patients who showed different responses. The levels of IL-6 initially spiked and then decreased in 10 patients after receiving tocilizumab therapy. Four patients who were severely ill and failed the treatment presented a consistently high level of IL-6. In such patients repeated dose of tocilizumab is recommended [34]. Another clinical trial was performed on 21 patients who presented a confirmatory test for the diagnosis of COVID-19. The retrospective evaluation of the patients treated with tocilizumab was performed in comparison to those treated with the Standard of Care [35]. At first tocilizumab was administrated @ 8mg/kg through an intravenous route. If no side effects were observed afterwards the first dose, then it was repeated after 12 hours. This study also reported similar results for the patients who were admitted to the ICU. The treatment did not provide any significant benefit to the critically ill patients and their pathological reports also showed an interaction between the C-reactive protein and alanine transferase (ALT) enzyme.

The number of cases reported which received the tocilizumab treatment is still not enough to be recommended for all patients suffering from SARS-CoV-2 infection. As it is evident from the clinical trials and studies, it is not suitable to be given alone to those patients who are at an acute and critical stage of COVID-19 related pneumonia. Moreover, the evidence of co-morbidity, age, and gender-related factors are also insufficient. The laboratory reports are showing only a few parameters that could be possibly showing its decreased activity, that's why it is challenging to conclude. The treatment duration is also very less and there is still a need for supporting evidence to make a final finding about the usage of tocilizumab in COVID-19 patients.

REMDESIVIR: Remdesivir conventionally known as GS-5734 is a monophosphate prodrug with broad-spectrum antiviral properties against RNA viruses [36]. It is effective against SARS-CoV and MERS-CoV in in-vitro studies. It is equally efficacious in animals and humans against these viruses. In murine models, initial stage treatment with the drug results in remarkably reduced pulmonary viral load and also exhibits improvement in pulmonary functions besides suppressing the disease [37]. In a trial study, two groups of rhesus macaques with 6 in each were infected with the SARS-CoV-2 strain. After 12 hours, group1 was injected 10 mg/kg remdesivir and group 2 was given the same dose of solvent injection (2ml/kg). After that, a dose of 5mg/kg remdesivir and 1ml/kg solvent was injected to group 1 and group 2, respectively after every 24 hours. Group 1 showed constant improvement in the condition of the animals whereas Group 2 showed no response. Only 1 animal from Group 1 showed dyspnea compared to Group 2 in which all animals exhibited dyspnea and tachypnea. Radiography also showed less lung infiltration and viral load was also lower in group 1 as compared to group 2 [38].

A study was done on 53 Hospitalized Covid-19 patients whose oxygen saturation level 94% or less were selected for the trial. Out of these patients, 30 were on assisted ventilation whereas 4 were given extracorporeal membrane oxygenation. 75% of patients were male with age more than 60 years along with other disease conditions. Patients were given a calculated dose of remdesivir for 10 days. Patients were given 200mg remdesivir intravenously on day 1 and 100 mg intravenous dose for the remaining days of the trial. After 18 days 68% of patients exhibited improved oxygen levels and the mortality rate was 13% whereas 17 out of 30 patients were able to breathe without assisted ventilation. Keeping in the notice the fact of the severity of the condition along with the coexistence of other diseases 68% recovery rate is commendable [39].

Remdesivir converts to adenosine analog after metabolism and causes premature termination of viral RNA [40]. It incorporates in place of ATP and 2 other nucleotides resulting in RNA synthesis blockage and termination. The 3 nucleotides safeguard inhibitor from 3'-5' exonuclease. Combining all effects results in higher efficacy of the drug against the virus [41]. In a trial of remdesivir on 175 patients for the cure of Ebola virus disease, no one reported any side effects [42].

LOPINAVIR-RITONAVIR: Lopinavir-Ritonavir is a protease inhibitor used together for the treatment of Human Immunodeficiency Virus disease [43]. A 54 years old patient residing in Wuhan developed COVID-19 after initial symptoms of chills and muscle pain. He was shifted to a negative pressure isolation room. He started coughing by day 5 and developed fever by day 7.

Two tablets of lopinavir-ritonavir were given to the patient orally twice a day from day 10 of infection. Surprisingly by the next day, no viral load was detected in the patient and he recovered completely. Later on patients reported signs of depression and also had suicidal thoughts which might have resulted from negative pressure in his isolation room [44]. Combination therapy of Lopinavir-ritonavir notably improves clinical symptoms of patients with SARS-CoV [45]. Eighteen people were diagnosed with COVID-19 via PCR in Singapore. Out of these six patients needed oxygen supplements and two were in a critical situation. Five patients out of these six were given lopinavir-ritonavir in 200mg-100mg formulation orally BID for up to two weeks. The initial dose of the drug resulted in a decreased need for oxygen support within 3 days and PCR was negative for three patients whereas 2 patients' condition worsened. Four out of five patients reported nausea, vomit, and diarrhea, and in three patients the liver function was also affected by the drug. Variable results were observed with this drug therapy [46].

Coronavirus-19 almost has 79% genetic data similar to SARS-CoV and initially, both viruses were detected in bats [47]. Lopinavir showed good efficacy against the virus as compared to ritonavir but its *in vivo* bioavailability was poor as a result combination therapy was tried which resulted in enhanced effectiveness of the drug. Ritonavir besides being effective against viruses also inhibited cytochrome P450 3A4 which was metabolizing Lopinavir previously resulting in more efficacy plus longer bioavailability [48]. Lopinavir also exhibits antiviral activity against SARS-CoV and MERS-CoV with EC50 between 6.6 and 17.1 μM [49]. Side effects linked with this drug therapy include diarrhea, nausea whereas cholesterol, triglyceride, and amylase levels are also adversely affected which is an indication of its damaging effects on the liver [50].

RIBAVIRIN: Ribavirin is an antiviral drug with a wide range of activity against many viruses including human immunodeficiency virus disease, influenza, herpes simplex, and hepatitis C. Its frequent use is restrained because it exhibits cytotoxicity in living beings [51]. In an In-Vero cell study conducted on cells isolated and infected with h-CoV-EMC 2012, therapy of ribavirin and IFN- α2b was found effective against the viral infection. Ribavirin and IFN- α2b minimal effective concentration was 100μg/ml and 250 U/ml respectively whereas the maximum dose for complete eradication of virus was 200 μg/ml and 1000 U/ml respectively. Subsequently, evaluation of viral load on days 1, 3, and 5 showed a continuous reduction in viral load with a minimal viral concentration on day 5. 50% inhibition concentration for ribavirin was 41.45 g/ml and for IFN- α2b 58.08 U/ml. Later on, the combination of the two drugs resulted in similar efficacy with almost 8-16% decreased drug dose that proved this drug combination beneficial [52].

In cohort research done on 20 patients with MERS-COV in Riyadh, Saudi Arabia patients were treated with combination therapy of ribavirin and interferon. Patients received 180 μg interferon two times in two weeks subcutaneously whereas ribavirin was given orally and its dose was adjusted according to the creatinine clearance level of each patient starting with an initial dose of 2000mg. Results showed a 70 % survival rate compared to the controlled group which showed only a 7 % survival rate by day 14 of the treatment. Patients which were given combination therapy reported reduced hemoglobin level as a side effect by end of the therapy [53]. Ribavirin is an FDA-approved drug against hepatitis C. Ribavirin can cohere with COVID 19 and SARS Human Coronavirus RNA dependent RNA Polymerase and has 109.5 μM 50% effective concentration (EC50) against coronavirus disease whereas its 50% inhibition concentration (IC50) is 8 μM against dengue [54].

In another case where both husband and wife developed the COVID-19 infection were medicated with a combination of ribavirin and interferon- α2b. The male patient was admitted after developing severe shortness of breath along with a high fever. After an initial antibiotic dose of azithromycin and ceftriaxone patient was given Ribavirin and interferon-alpha 2b. By day 2 patient's condition became worse and was shifted on a ventilator however, later on by day 4 the condition started to improve. The patient was discharged by the 18th day as his results showed that he was no more affected by the virus. His wife who also developed the virus due to close contact with the patient recovered by day 6 of the infection and didn't reach the worse stage because of the early start of combination therapy treatment [55].

UMIFENOVIR: Arbidol (umifenovir) is a potent broad spectrum antiviral drug. It is a derivative of indole molecule, manufactured in Russia by JSC Pharmstandard [56]. It has demonstrated antiviral activity against many enveloped and non-enveloped viruses. It is mostly used against the influenza viruses where it acts by inhibiting the fusion of the virus and the host membrane, therefore, preventing the entry of the virus into the targeted cells [57]. The use of arbidol for the prevention of SARS-CoV and MERS-CoV provided a foundation to be used in COVID-19. In a retrospective study in China, the discharge rate of the patient was increased after being treated with ardibol [58].

Arbidol has been given in along with Lopinavir/ritonavir to treat the acute respiratory syndrome presented due to COVID-19 disease. But it also possesses the individual antiviral activity against many viruses infecting the respiratory tract. In a study, the antiviral effects of arbidol were evaluated where 50 patients were divided into 2 groups, out of which 16 received 0.2g arbidol TID and 34

patients received 400mg/100mg of Lopinavir/ritonavir twice a day for 1 week. After 14 days, the patients of arbidol did not test positive for any viral load, but it was detected in 15 patients treated with lopinavir/ritonavir. The results of the study showed the arbidol monotherapy is more effective than lopinavir/ritonavir in treating COVID-19 disease [59]. Similar results were obtained in another study performed in China, where the antiviral effect of ARB was superior to lopinavir/ritonavir against SARS-CoV-2 [60].

Arbidol is an anti-retroviral protease inhibitor. It competitively inhibits the viral protease enzyme by binding to its active site. It also blocks the release of the functional viral particles to prevent their transcription/replication and maturation [61]. Arbidol is believed to inhibit the 3CLpro coronavirus protease enzyme and contribute to decreasing its viral effects [62]. The efficacy of arbidol in treating COVID-19 has been observed in many preclinical and clinical trials [63]. Although, it does seem to provide relief against COVID-19, its definitive mechanism of action against coronavirus is not clear. Given the fact that this public health emergency, more evidence is required to declare arbidol as definitive therapy for the treatment of COVID-19 and future nCoV strains.

INTERFERONS: Interferons are naturally occurring signal molecules that perform various biological functions such as antiviral, immunomodulatory, anti-proliferative, and developmental activities [63]. They are also artificially synthesized by recombinant DNA technology. There are many clinically effective interferons being used for the treatment of COVID-19. The primary site of SARS-CoV-2 attack are lungs, therefore interferon-λ is administered as it activates the antiviral genes in alveolar epithelial cells (AECs). It has been shown to decrease the viral load when administered in the early infection [63]. The antiviral response of interferon-λ in the in-patients who were already sick was fairly disappointing, and it remains a challenge to screen the asymptomatic patients of COVID-19 [64]. Another group of cytokines known as Type 1 interferons (IFN-1) is also being used for their antiviral properties against COVID-19. They are divided into α- and β-subgroups which are activated at different sites.

The INF-1 treatment was administered in MERS-CoV and SARS-CoV as well [65]. Since they are closely related to 2019-nCoV and present similar pathological symptoms, there have been several *in vitro* and *in vivo* experiments to evaluate the antiviral effects of IFN-1 against preventing/treating COVID-19. IFN-α and -β appeared to be systemically efficient in exhibiting antiviral properties in vitro and also in certain animal models but did not show any significant effect in humans [66]. The efficiency of IFN-1 increases against coronaviruses when given in combination with other drugs such as lopinavir/ritonavir, remdesivir, corticosteroids, and ribavirin [67]. In a study, combination therapy of ritonavir with IFN-α against MERS-CoV infection showed a significantly improved survival rate after 2 weeks of treatment [68]. The IFN-1 can show a drastic improvement if the COVID patient is not suffering from any other co-morbidity. The mechanism of the IFN inhibition signaling pathway used by MERS-CoV and SARS-CoV is efficient in preventing acute respiratory distress syndrome (ARDS) in COVID-19infections. However, the optimization of therapy to completely treat COVID-19 is still required. Currently, the safety and efficacy of the IFN-1 treatment for COVID-19 are under assessment in many clinical trials. A clinical trial conducted in China early in 2020 related to IFN based treatment for 2019-nCoV is expected to give relevant results for this therapy.

AZITHROMYCIN: Azithromycin (AZ) is a broad-spectrum macrolide antibiotic, which is primarily used for the treatment of enteric, respiratory, and urinary tract bacterial infections. It has a large volume of distribution and can be easily absorbed from plasma. It is essentially an antibacterial agent which has not been approved for treating viral infections [69]. However, there have been reports of clinical trials to evaluate AZ therapy against COVID-19. A non-randomized, single-arm clinical trial of hydroxychloroquine (HCQ) alone and in combination with AZ to decrease the viral load of SARS-CoV-2 in COVID-19 was conducted in Marseilles, France. 26 patients were given 600mg HCQ alone OD for 6 days and a subset of patients received AZ to prevent the bacterial superinfection. The patients who refused the treatment were kept in unmatched control. On day 6, the patients treated with HCQ and AZ showed a 100% decreased in viral load, a negative polymerase chain reaction (PCR) test for SARS-CoV-2. Comparatively, 57.1% of patients treated with HCQ alone, and 12.5% control patients showed a viral load reduction. The results of this showed that HCQ decreased the viral load and AZ seems to complement it. Similar results were obtained in another trial of 80 patients where HCQ was used alone and in combination with AZ and there was a significant decrease in the viral load in patients of the combination group. It was evident that the use of AZ was effective in the treatment of COVID-19 [70].

The exact mechanism of antiviral action of AZ is unknown, however, one explanation is that AZ limits the viral replication by genetic shedding of virus from lysosomes and blocks the endosome maturation. Since an acidic environment is required to do so, AZ being a weak base increases the pH levels and accumulates in intracellular lysosomes, and causes hindrance for the viral DNA replication [71]. The enveloped viruses e.g. HIV and influenza also require an acidic environment for their uncoating, a similar mechanism may be in action for the

coronaviruses [72]. A few other studies suggest that AZ might follow a similar pathway to that of IFN by stimulating a signal and activating genes, which leads to viral load reduction [73]. A quantum mechanical model specific to SARS-CoV-2 suggests that AZ could interfere with host receptor angiotensin-converting enzyme 2 (ACE2) and viral spike protein, thus preventing its entry into the target cell [72,73]. This is a proposed mechanism, but further studies and experimental work is required for the confirmation of this model.

ANTIBODIES: Antibodies are immunoglobulin proteins that are produced by the plasma cells as an immune response to a foreign particle (antigen) entering the host body. The antibodies tend to neutralize the effect of pathogens i.e. virus and bacteria. There are specific neutralizing antibodies that may bind to the viral surface proteins, preventing the entry of virus from host cells epithelium, therefore preventing its replication. The non-neutralizing antibodies also act as antiviral agents by binding the virus, which activates the phagocytic immune cells. These macrophages engulf the virus and decrease or in some cases completely clear the viral load. The non-neutralizing antibodies are effective in the early stages to clear the virus, but later, it may cause lung damage due to pro-inflammatory factors with a possibility of sepsis.

The entry of SARS-CoV-2 in a human cell takes place through S protein which binds to angiotensin-converting enzyme 2 (ACE2) [75]. The cellular surface of ACE2 is down-regulated after the entry to the virus, which activates the renin-angiotensin-aldosterone system and causes lung injury [76]. According to a study, only two neutralizing antibodies were found effective against SARS-CoV-2 out of 42 monoclonal antibodies generated from a few sources like llamas, plasma B cells of recovered patients, ribosome libraries of phage and yeast. The antibody activity was tested in an animal model of transgenic mice with human ACE2 receptors [77].

The development of antibodies is taking place by Regeneron Pharmaceuticals from transgenic mice. The use of VelociSuite technology is developing antibodies from the immune system of humanized mice to treat sepsis-related to viral infection [78]. An attempt is being made to develop monoclonal antibodies against the C5a molecule. The antibodies binding to the C5a molecule can limit the intracellular lysozyme and chemotaxis of macrophages which can decrease inflammation. This C5a antibody has been developed by a German company Inflarx, but to ensure its safety and effectiveness it is under clinical trials in China [78].

NITAZOXANIDE: Nitazoxanide (NTZx) is a thiazolide anthelmintic agent mainly used to treat diarrhea induced by *Giardia intestinalis* and *Cryptosporidium species* [79]. It performs its anti-parasitic activity by inhibiting the pyruvate-ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction thus inhibiting anaerobic energy metabolism in parasites. [25] NTZx synergizes the efficacy of neuraminidase inhibitors against the influenza virus. A study published in 2014 revealed that a dose of 600 mg of NTZx, twice a day for 5 days, was found to be effective in reducing the duration of symptoms in patients with acute uncomplicated influenza [80]. Nitazoxanide is another potential candidate in the treatment of SARS-CoV-2 [81]. In a previous study, it was found to exhibit *in vitro* activity against the Middle-eastern respiratory syndrome (MERS) along with other coronaviruses [82]. Clinical trials are already underway to evaluate the effect of nitazoxanide when given in combination with hydroxychloroquine. A clinical trial of nitazoxanide along with its active metabolite, tizoxanide, has shown to be effective against coronaviruses. A dose of 500 mg per oral was given two to four times a day for 6 days. NTZx performs this action by inhibiting the replication of RNA. It also amplifies the innate immune response towards viruses and enhances the cytoplasmic RNA sensing by host cells [83]. In addition, NTZx is a potent inducer of interferon-alpha (IFN-α) and interferon-beta (IFN-β). The use of NTZx in treating patients with SARS-CoV-2 was also recommended by Société de Réanimation de Langue Française (SRLF) on March 9, 2020 [84]. NTZx is very well tolerated in children and adults. The drug only displays mild symptoms of the gastrointestinal system such as abdominal discomfort, headache, nausea, etc [85]. Although NTZx manifests a positive effect in the management of COVID-19, it may exhibit its maximum efficacy when given in conjunction with hydroxychloroquine or azithromycin.

HYDROXYCHLOROQUINE: Hydroxychloroquine (HCQ) is a synthetic quinine derivative that is classically used in the treatment of malaria [86]. Besides its antimalarial activity, HCQs are also administered in a ranging number of diseases including lupus, rheumatic, and skin diseases [87]. Multifaceted immunomodulatory roles of HCQs have made them a valuable treatment alternative for many diseases and also brought it as a focal point in the treatment of COVID-19 [88][89]. Although the mechanism of immunomodulation of HCQ is widely under investigation and to some extent still unknown. It modulates the immune system by inhibiting B-cells and T-cells receptors signaling [90], toll-like receptor (TLR) signaling binding with DNA [91,92], and inhibiting the production of interleukins (IL-1 and IL-6) and prostaglandins [93]. Since the emergence of COVID-19, hydroxychloroquine has been in the spotlight and its efficacy against SARS-CoV-2 is a pertinent question. An *in vitro* study suggested that HCQ is more potent than chloroquine in its activity against SARS-CoV-2 [94].

Many clinical trials are still underway regarding the SARS-CoV-2 treatment with HCQ [95]. In a pilot study of 30 patients, the dose of 400 mg of HCQ for 5 days

along with other conventional treatment therapies was found to improve the patient outcomes of moderately ill individuals [96]. In a randomized control trial (RCT), it was found that HCQ when given at a dose of 400 mg for 5 days resulted in a good prognosis of the patient by significantly decreasing the time to clinical recovery [97]. Similarly, two other studies evaluated that HCQ when administered with azithromycin has led to exceptionally improved disease outcomes for all of the patients enrolled in the study [98,99]. HCQ may perform its action by inhibiting the T-cells and hence, alleviating the storm of cytokines released during the infection. The drug may also exhibit the progression of SARS-CoV-2 by inhibiting the glycosylation of the angiotensin-converting enzyme 2 (ACE-2) receptor with the spike protein. This may result in decreasing the viral load as well as improving disease outcomes [100].

In contrast to the above, most recent researches propose conflicting evidence. An observational study of patients with COVID-19 suggested that no patient improvement was observed with the HCQ treatment moreover the use of HCQ was conditioned with evidence-based clinical trials. However, the study also negated the risk of intubation or death associated with HCQ use [101]. No evidence of reduced risk of mechanical ventilation was found in a study of veterans infected with COVID-19 and administered HCQ along with azithromycin. Furthermore, the same study suggested increased mortality following the treatment with HCQ alone [102]. Similar outcomes were reported for the use of HCQ in an RCT where no significant improvement was found in patients with COVID-19 and more adverse reactions were reported among the patients receiving HCQ [103]. Overall, the evidence of HCQ in the treatment of COVID-19 is still premature. The clinical use may lead to severe adverse effects including QT-prolongation [100,104]. Although, HCQ is cost-effective, easily available and has widely been used in other diseases with well-known pharmacological properties. However, more studies are required to address the safety and efficacy of hydroxychloroquine used in COVID-19 patients [105].

BARICITINIB: Baricitinib is a Janus-associated kinase (JAK) inhibitor used to treat immune-mediated disorders. It is used orally in patients with rheumatoid arthritis who fail to respond to classical disease-modifying anti-rheumatic drugs (DMARDs) [106]. Baricitinib is also suggested as one of the potential candidates in the fight against COVID-19 as the drug may inhibit virus invasion along with suppressing the cytokine storm. The virus mainly enters the host cells via AP2-associated protein kinase 1 (AAK1) mediated endocytosis [107]. The baricitinib may inhibit the virus entry by preventing the endocytosis hence preventing viral invasion and inflammation [108]. The efficacy of the medicine was analyzed using an artificially intelligent platform, BenevolentAI. However, only a few studies were found to evaluate its use in COVID-19. In a pilot study, the baricitinib when co-administered with ritonavir-lopinavir was found to downregulate the release of cytokines associated with COVID-19. A dose of 4mg/day for 2 weeks also resulted in better clinical and laboratory outcomes of the patients without any adverse effects [109]. No other evidence of the effectiveness of baricitinib against SARS-CoV-2 was available.

Despite its safety profile, the treatment with baricitinib may result in the reactivation of various latent infections hence the use of the drug in the treatment of COVID-19 still poses a threat in the management of patients with comorbidities [110]. Since baricitinib is a recently discovered drug. Therefore, rigorous clinical studies are required to evaluate its efficacy against COVID-19. (Figure).

Conclusion: This review summarized fifteen drugs that are being used in clinical trials for the treatment of COVID-19. The antiviral drugs ivermectin and remdesivir seem to be quite effective against the virus whereas moxifloxacin which is an antibiotic also exhibits antiviral properties by binding to the main protease enzyme of SARS-CoV2. Hydroxychloroquine in conjunction with azithromycin or Nitazoxanide also shows promising results against the virus and more research need to be done on antibodies and Baricitinib for their efficacy against the virus. Whereas, Piperacillin-Tazobactam, lopinavir-ritonavir, and interferons lack any evidence regarding their efficacy against the virus. This data may prove to be beneficial for future researches which need to be done for a better understanding of drugs' effectiveness against the COVID-19.

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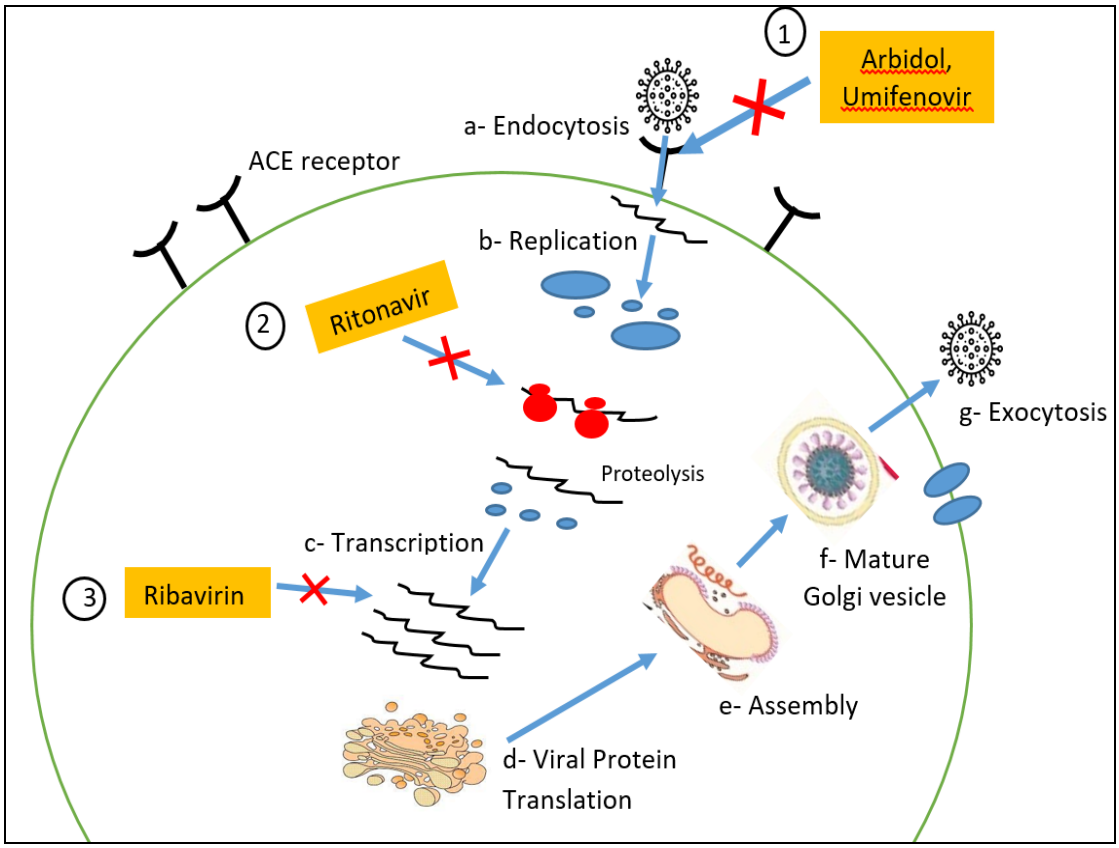

Figure 1: Schematic diagram of entry of SARS-CoV-2 and infection mechanism. a- Endocytosis of the virus from angiotensin converting enzyme (ACE) receptor and release of viral RNA particles. b- Replication of the viral particles. c- Transcription of the viral proteins. d-e Translation and assembly of the viral proteins. f- Release of the mature Golgi vesicle and g-exocytosis of the virion particle. The effect of drugs which block different mechanisms of SARS-CoV-2 include (1) Arbidol inhibits the viral protease enzyme by binding to its active site. (2) Ritonavir blocks the protein transcription by causing its proteolysis and (3) Ribavirin blocks the transcription of viral proteins by blocking RNA dependent RNA polymerase.

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