Comprehensive review on repurposing of approved medicine in the management of COVID-19 infection

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Abstract: The SARS-CoV-2 virus, accountable for the COVID-19 pandemic, is now sweeping the globe. As a result, as this disease resists testing and adoption of new treatments, repositioning existing medications may provide a quick and appealing method with established safety, features, and dose used. They are not, however, specific or focused. However, numerous medications have been studied for their efficacy and safety in treatment of COVID-19, with the majority currently undergoing clinical trials. The goal is to rapidly expand novel preventative and therapeutic medications, as well as to apply preventive methods such as early patient identification, isolation, and treatment. Moreover, reducing transmission through physical contact is also important. In the fight against this dangerous disease, finding the proper treatment is crucial. This article summarizes several anti-malarial, anti-parasitic, monoclonal antibodies, immunosuppressant, and immunomodulating agents in clinical trials for COVID-19. The purpose of this article is to evaluate and explore the potential roles of several medications now utilized in COVID-19.

Keywords: COVID-19; SARS-CoV-2; spike protein; drug repurposing; ACE; coronavirus. ©2022 ACG Publication. All right reserved.

1. Introduction

Wuhan, China's capital and the capital of Hubei province, became the epicenter of aggressive influenza of unknown origin in December 20191. The virus is SARS-CoV-2, and the causative agent of the infection is coronavirus disease 2019 (COVID-19)2. SARS-CoV-2 belongs to the beta coronavirus group, including the previously well-known middle east respiratory illness (MERS) virus 3. The overall number of reported cases reached 201 million, with over 42,70,000 fatalities by the 7th of August, 2021 2. Some surveys have indicated that the incubation time for COVID-19 is 3-7 days after initial contact 4. 5. According to the laboratory data, the plasma level of specific pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) increased in severe COVID-19 patients.6 COVID-19's subacute and long-term impacts on numerous organ systems are being studied scientifically and clinically7. Early studies indicated that SARS-CoV-2 infection might...
cause tiredness, chest discomfort, cognitive difficulties, and arthralgia; a decrease in quality of life. Coronaviruses have a spherical shape with a diameter of 80-120 nm. Several club-shaped (17-20 nm) glycoprotein spikes protrude from the surface of the viral envelope. It encodes 16 non-structural proteins (nsp1-16), including 4 or 5 structural proteins, as well as the envelope (E), spike (S), membrane (M), nucleocapsid (N), and hemagglutinin (HE) proteins for HCoV-OC43 and HCoV-HKU1. The ACE2-binding affinity for RBD throughout the S1 subunit of SARS-CoV-2 is 10 to 20-fold more significant than in SARS-CoV-1, which may contribute to SARS-increased CoV-2's infectivity and transmissibility. This M glycoprotein appears to be a pre-glycosylated M polypeptide that gives the viral envelope shape and has a size range of 25–30 kDa (221–262 amino acids). Envelope protein (E) is a small polypeptide with a size range of 8.4–12 kDa that is an integral membrane protein containing 76-109 amino acids (Figure 1).

**Figure 1.** Structure of COVID-19 virus

COVID-19 virus can affect the whole respiratory tract, amongst the surface of the type-II alveolar cell of lungs are the most impacted. The virus enters into the host cell by ACE-2 receptor. Where COVID-19 virus binds to ACE-2 receptor and enters the host cell, it employs a unique surface glycoprotein termed a "spike". Internalization of the virus causes activation of the nuclear factor-kappa B (NF-kB) pathway, which produces a variety of inflammatory factors such as IL-1, IL-17, TNF-α, and INF-γ. Increased cytokines also induce the synthesis of endothelium HA-synthase-2 (HAS-2) in alveolar epithelial cells (type 2) and fibroblasts. Presence of distinct white patches known as ground glass on computer tomography (CT) images of the lungs in patients suffering from acute respiratory distress syndrome (ARDS) may be due to a large amount of fluid in the lungs. According to the most autopsies, infected lungs are filled with transparent jelly liquid, similar to drowning victims' lungs. HA is linked to ARDS, even though the nature of the clear jelly liquid is unknown. In severe and seriously ill hyper inflammation and cytokine storm have been reported, both of which can induce multiple organ failure. Some patients developed rapid progress in combination with acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multi-organ dysfunction syndrome (MODS) due to the presence of ACE-2 receptor in cardiac, renal, and hepatic tissues, which resulted in death in approximately 10% of patients.

Drug repurposing (also known as drug repositioning) is a popular type of drug discovery. It allows authorized medications to treat new ailments, repurposing shelved drugs for additional uses.
indications, and extending patent lifetimes\textsuperscript{29–31}. Drug repurposing is a promising field in researching and developing treatments that identify new therapeutic alternatives for existing pharmaceuticals\textsuperscript{32,33}. When the safety profiles of the drugs being repurposed have been assessed in the context of drug development for another disease, and even faster when the drugs have been accepted for other diseases and post-marketing safety surveillance data are available, drug repurposing can yield new therapies at a faster rate than novel drug discovery\textsuperscript{34,35}. For specific medicines used to treat the present COVID-19 epidemic, pharmacological repurposing has already been recommended\textsuperscript{36}. COVID-19 drug repurposing goes through the same three processes as all other drug repurposing initiatives before it can be considered for advancement along the research pipeline; candidate drug identification, mechanistic examination of drug action in preclinical models, and phase II clinical trial review of candidate medications\textsuperscript{35}. Two ideas underpin drug repurposing. A single medicine interacts with multiple targets, allowing for new target sites of action for existing molecules\textsuperscript{37,38}.

With the sudden surge in COVID-19 cases, there was no time to develop new drugs to work against the SARS-CoV-19 virus. Therefore, various approaches had been investigated to ensure the availability of safe and effective drugs for the treatment of COVID-19 infections. Various research groups investigated several approved drugs with proven safety data against the different molecular targets of the SARS-CoV-19 virus, which produced interruption in the replication of the virus in the body. In the present review, we elaborated on the use of the repurposed drugs to treat COVID-19 infections.

2. Repurposing of Current Drugs in COVID-19

2.1. Chloroquine (CQ) and Hydroxychloroquine (HCQ) – an Anti-malarial Agent

Quinine, an alkaloid compound classified as quinoline methanol, was isolated from the cinchona tree bark native to south and central America as the first anti-malarial\textsuperscript{39}. CQ and HCQ belong to 4-aminoquinolines drugs class. HCQ is derived from chloroquine, and the only difference in chemical composition between HCQ and CQ is that HCQ has a hydroxyl substitution at the amine's ethyl group (Figure 2). Because of hydroxyl (-OH) group, HCQ is more soluble. HCQ/CQ was considerably studied and extensively used to prevent and treat malaria for plenty of decades. It is the concept to boom pH of phagolysosome and, thereby, interrupt virus fusion, and it additionally prevents binding of the virus to cellular floor receptors\textsuperscript{40}. CQ was and nevertheless is, used to prevent malaria in pregnancy even though it is no longer powerful in preventing falciparum malaria\textsuperscript{41–43}. CQ and its spinoff, HCQ, are medications used to remedy and prevent malaria and autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)\textsuperscript{44}.

2.1.1 Role of CQ and HCQ in COVID-19

Chloroquine and Hydroxychloroquine, anti-malarial medications, have been shown to protect against infections caused by various DNA and RNA viruses, including human coronaviruses\textsuperscript{45}. CQ and HCQ are indicated to shorten the span of COVID-19 infection\textsuperscript{46}. CQ is the primary drug suggested to have efficacy COVID-19\textsuperscript{47}. Hydroxychloroquine, a more tolerable chloroquine derivative, has also been demonstrated to exhibit the activity against SARS-CoV-2 \textit{in-vitro}\textsuperscript{44}. The activity of CQ and HCQ against SARS-CoV-2 is attributed to prevent entry of virus, inhibiting replication of the virus, or modulating the immune system to withstand against the spreads of virus\textsuperscript{48}. The pharmacokinetics of CQ and HCQ is complicated; however comparable\textsuperscript{49}. The safety profile of HCQ is better due to less or minimal adverse effects in animals and humans than CQ. CQ and HCQ's pharmacokinetics indicate greater distribution collectively with slow elimination from the body, responsible for causing adverse outcomes of this drug\textsuperscript{50}.

In SARS-CoV-2 patients, CQ and HCQ do not have any clinical benefit in disease incidence or development, nor do they provide any substantial proof of expanded critical aspect consequences\textsuperscript{51}. CQ primarily inhibits the pre-entry stage of the viral cycle and the transport and post-entry stages of SARS-CoV-2 by interfering with viral particles binding to their receptors on the cell surface. It also interferes with glycosylation of the angiotensin-converting enzyme 2 (ACE-2) receptor, raising endosomal pH and
preventing SARS-CoV-1 from attaching to target cells. CQ also inhibits cathepsins, implying that it can obstruct SARS-CoV-2 lysosomal acidification, necessitating a low pH for cleavage of the SARS-CoV-2 spike protein, resulting in autophagosome formation. The whole mechanism of CQ and HCQ in SARS-CoV-2 infection is shown in Figure 3. In THP-1 cells, CQ activates the p38 MAPK by phosphorylating it. Various viruses require this phosphorylation to complete their replication cycles. Inhibition of kinases such as MAPK may have also contributed to the anti-SARS-CoV-2 efficacy. Since the beginning of the current pandemic with COVID-19, a virus linked to SARS, there has been a surge in interest in the potential benefit of CQ and HCQ in treating this infection that is linked to significant morbidity and mortality.

Figure 2. Structure of Chloroquine and Hydroxychloroquine

Figure 3. Role of CQ and HCQ in COVID-19 treatment
2.2. Azithromycin (AZ) – a Macrolide Antibiotic

Azithromycin (AZ) (Figure 4) is a macrolide antibiotic with anti-inflammatory and immunomodulatory properties in a variety of respiratory and infectious disorders through modifying innate and adaptive immune responses\(^{59, 60}\).

![Figure 4. Structure of Azithromycin](image)

2.2.1. Role of Azithromycin in COVID-19

AZ has been proposed as a viable therapeutic for the treatment of SARS-CoV-2 infection due to its anti-inflammatory and immunomodulatory effects, and its superior safety profile\(^{61, 62}\). It prevents bacterial protein synthesis and translation and has additional immunomodulatory activity. It is extensively absorbed by tissue, especially the lungs, tonsils, and prostate\(^{63}\). It has an EC\(_{50}\) of 2.1µM on VeroE6 cells at an MOI of 0.002 for antiviral activity against SARS-CoV-2\(^{64}\). Azithromycin can elevate the pH of the Golgi network and recycle endosomes\(^{65}\), interfering with SARS-CoV-2 activity and reproduction within the cell\(^{66}\). Because the virus is thought to have a furin-like cleavage site in the spike protein, AZ is known to suppress the enzyme furin, which interacts with SARS-COV-2 to enable virus entrance into cells\(^{67}\).

SARS-CoV-2 reaches the cell primarily by glycosylation of hACE2\(^{68, 69}\). During this phase, SARS-CoV-2 uses plasmatic membrane components such as gangliosides (particularly GM-1) as attachment co-factors inside lipid raft membrane platforms\(^{69}\). Recent quantum mechanical simulations of the SARS-CoV-2 virus revealed that AZ may play a role in preventing viral entrance by binding to SARS-CoV-2 spike protein and the host receptor ACE-2\(^{70}\). By inhibiting the interaction points between SARS-CoV-2 and the ACE-2 receptor, AZ prevents SARS-CoV-2 from entering host cells\(^{71}\). AZ has become utilized in a third of sufferers treated for MERS-CoV, even without medical proof of it\(^{72}\). A 500 mg dose of AZ is a common antibiotic used in primary care for bacterial respiratory infections, and it is similar to the dosage used in the early COVID-19 trials\(^{62}\). It is widely distributed throughout tissue, particularly the lungs, where typical concentrations in extracellular fluids and inside cells are significantly higher than in plasma\(^{63}\). AZ is safe, with a lower risk of side effects\(^{74}\).
2.3. Levamisole – an Anti-helminthic Drug

Levamisole (LVM) (Figure 5) is a synthetic anti-helminthic agent with a low molecular weight. It improves cellular immunity depending on the amount and timing of injection, and also enhances the immunological response of T helper type 1 cells.

Figure 5. Structure of Levamisole

2.3.1. Role of Levamisole in Covid-19

LVM is one of the suggested drugs used for systemic treatment of COVID-19 because of its broad spectrum of immunological effects, including regulation of neutrophils, macrophages, and T-cell function. It also affects human interferon (IFNs), interleukin-6 (IL-6), and IL-8 levels, and enhances IgA and IgM levels in blood. LMS, as an immunostimulant, is thought to enhance lymphocytes and boost the body's immunity. It also attaches to the virus shell's papain-like protease (PL-pro), which is required for COVID-19 pathogenicity, lowers TNF and IL-6 levels, and introduces the virus to the immune system as a chemical adjuvant. LVM and ascorbic acid aggregate were proven to counteract the stressed helper/inducer subpopulation of lymphocytes in an in-vitro study. Furthermore, in-vitro investigations demonstrated that the lymphocyte abnormalities could be duplicated in lymphocytes treated with LVM. As a result, LVM could be suggested to treat COVID-19.

2.4. Doxycycline (DOX) – a Tetracycline Antibiotic

Doxycycline (DOX) (Figure 6) is classified under tetracycline derivative and used to treat inflammation and immunomodulation. It inhibits bacterial protein synthesis via binding to 30S and possibly 50S ribosomes in an irreversible manner, causing changes in cytoplasmic membrane. DOX is well-known for suppressing metalloproteinases (MMPs), particularly MMP-9, which is thought to be required for initial viral entry into the cell. In addition, DOX inhibits interleukin (IL)-6, which, together with MMPs, is a vital regulator of the cytokine storm that is frequently associated with severe viral pneumonitis.

Figure 6. Structure of Doxycycline
2.4.1. Role of Doxycycline in COVID-19

DOX has no recognized direct specificity for SARS-CoV-2 inhibition. However, DOX in all likelihood, has towards recognized co-receptors DPP4/CD26, via verified inhibition of NF-κB and co-receptor CD147/EMMPRIN, which is needed for SARS-CoV-2 entry into T lymphocytes, even at sub-microbial doses. DOX also inhibits the center-receptor CD147, which is required to have SARS-CoV-2 access into T lymphocytes. It has been shown to have anti-SARS-CoV-2 action in vitro on infected Vero E6 cells. Additionally, It’s in vitro antiviral activity towards a clinical isolate of SARS-CoV-2 established promising outcomes via interacting with the virus at entry and post-entry stages. Docking evaluation confirmed that DOX could firmly bind to the SARS-CoV-2 spike protein (S). Furthermore, DOX and, more broadly, other tetracyclines can bind to the main protease (Mpro) of SARS-CoV-2, also known as 3C-like protease, which is required for SARS-CoV-2 replication by causing the formation of non-structural proteins (NSPs).

2.5 Ivermectin (IVM) – an Anti-Parasitic Agent

Ivermectin (IVM) (Figure 7) is a macrocyclic lactone having broad-spectrum of antiparasitic pharmacological action. It is a combination of 22, 23-dihydro-avermectin B1a (80%) as well as 22, 23-dihydro-avermectin B1b (20%) . It acts by binding to glutamate-mediated chlorine channels to cause cell membrane hyperpolarization, obstructing inhibitory neurotransmission through neurons and myocytes, resulting in paralysis and death. Moreover, IVM significantly reduced the production of inflammatory cytokines such as TNF-α, IL-1, and IL-6 in lipopolysaccharide (LPS)-induced inflammation.

![Figure 7. Structure of Ivermectin](image)

2.5.1. Role of Ivermectin in COVID-19

IVM suppressed severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in-vitro, resulting in a 5,000-fold decrease in viral RNA after 48 hours using IVM at 5 μM. A 50% inhibitory concentration (IC₅₀) of 2 μM (1,750 ng/mL) is more than 35 times higher than the maximum plasma concentration (Cmax) of 0.05 M (46.6 ng/mL), following oral administration of the authorized dose (200 g/kg). At the same time, IVM exhibited little to no action at 1 μM in vitro. Even though IVM is strongly bound to serum albumin (93%), its IC₅₀ orders of magnitude is greater than the unbound plasma Cmax following authorized ivermectin dosages (0.0035 M; 3.26 ng/mL). By binding to the importin-α
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(IMP-α) and importin-β (IMP-β) heterodimer, SARS-CoV-2 protein is translocated into the nucleus via the nuclear pore complex (NPC). The importin-α/β complex releases the SARS-CoV-2 protein once it reaches the nucleus. The SARS-CoV-2 protein then promotes host shut-off, lowering the host's immunological response and allows the virus to replicate. IVM binds to the importin-α/β complex and destabilizes the importin-α/β heterodimer, preventing SARS-CoV-2 protein translocation into the nucleus [Figure (8)]. The IVM treatment most likely promotes the efficient occurrence of host immune responses. Even though these data showed the potential usage of IVM as an antiviral medication in the battle against COVID-19; the dose employed was 200 times higher than that typically being used in clinical applications\textsuperscript{111}. Moreover, a few observational studies and a real-world clinical practice demonstrated that IVM seems effective in treating COVID-19 patients at both mild-moderate and severe stages of the disease, suggesting that IVM may have antiviral but also immunomodulatory activities\textsuperscript{112–115}.

Furthermore, ivermectin-doxycycline had been tolerated well than hydroxychloroquine with azithromycin treatment. Based on this analysis, IVM is feasible for individuals infected with mild to moderate COVID-19 infection\textsuperscript{116}. A total of 140 individuals having COVID-19 were studied in a randomized control trial. In contrast to usual treatment, 70 individuals had oral Ivermectin 200 mg daily for 2 or 3 days and oral doxycycline 100 mg twice daily for 5 to 10 days, while 70 individuals throughout the control group received normal treatment. The IVM group had a lower risk of progression to more severe illness and death, and a considerably shorter time towards recovery\textsuperscript{117}.

![Figure 8. Role of Ivermectin in COVID-19](image)

### 2.6. Thalidomide (TLD) – an Anti-Neoplastic Agent

Thalidomide (TLD), (Figure 9) also known as phocomelia, was launched as an anti-inflammatory medication with extraordinary success in various autoimmune illnesses. Then, because of its multifunctional capabilities such as anti-angiogenesis, anti-fibrotic, immune regulatory effects, and anti-inflammatory, it is widely sold and promoted across the world\textsuperscript{118}. Furthermore, TLD has been demonstrated to stimulate T cell receptors and T cells, improving immunological function\textsuperscript{119}.
2.6.1. Role of Thalidomide in COVID-19

Thalidomide (TLD), a drug known to cause interstitial pulmonary fibrosis, paraquat lung injury, and myeloma, was suggested to function in the therapy of COVID-19. TLD reduces the transcription of IL-1 and IL-6 in human lung epithelial cells, which might also help preventing emphysema. TNFα, IL-1β, IL-6, and transforming growth factor were reduced by TLD. Furthermore, it could enhance interleukin production, like IL-12, thus, activating natural killer cells. In addition, TLD inhibits activated NF-κB, responsible for malignant cell proliferation, inflammation and angiogenesis, including poorly-regulated immunological responses. When used with the COX-2 inhibitor such as celecoxib, TLD has had an immunomodulatory impact; together, these drugs reduce the production of pro-inflammatory cytokines such as TNF-α and interleukin, potentially reducing the activity of the IKB kinase, which inhibits NF-κB. TNF-α, IL-6, IL-1, and TGF-β are the central pro-inflammatory cytokines that underpin the pathogenicity of these diseases, and they are shared by both paraquat and bleomycin-induced pulmonary fibrosis models. Because of its anti-inflammatory and immunoregulatory properties, TLD, combined with low-dose steroids, could treat COVID-19 pneumonia.

2.7. Cyclosporine (CSA) – an Immunosuppressive Agent

Cyclosporine (CSA) is a significant immunosuppressive drug that is frequently used in immunosuppression during organ transplantation. In addition, rheumatologists frequently use it to treat vasculitis.
It is a natural product, which is an 11-amino acid cyclic polypeptide derived from the fungus *Tolypocladium inflatum*. CSA is an immunosuppressant that suppresses or weakens the immune system.

### 2.7.1. Role of Cyclosporine in COVID-19

CSA has been found to suppress the production of various coronaviruses *in vitro*, including SARS-CoV-2, MERS-CoV (Figure 11A)\(^{134-136}\). It has immunosuppressive as well as anti-inflammatory actions *via* reducing interleukin-2 (IL-2) production by inhibiting the activation of the nuclear factor of activated T cells (NF-AT) (Figure 11B)\(^{137}\). Because SARS-CoV-2 non-structural protein might promote IL-2 production *via* NF-AT recruitment, CSA may help in reducing the risk of the cytokine storm in moderate COVID-19\(^{138}\). Cyclosporine seems to be a calcineurin inhibitor that suppresses the synthesis of calcium-dependent interleukin (IL)-2. It inhibits calcineurin activity in the cell by complexing with cyclophilin and decreases IL-2 gene transcription\(^{139}\). At relatively low and non-toxic dosages, CSA has been demonstrated to reduce SARS-CoV-2 viral replication\(^{135, 140, 141}\). NFAT inhibition eventually results in the suppression of cytokine transcription and, as a result, T cell activation\(^{140, 142-148}\). CSA inhibits replicating coronavirus groups (including SARS-CoV-1) in cell cultures at low micromolar and non-cytotoxic doses\(^{140, 144}\). Also, it inhibits cyclophilin-D, which can prevent viral replication\(^{144, 149}\). Moreover, CSA binds CYP-D. It suppresses the opening, including its mitochondrial permeability transition pore (mPTP); essential pathophysiological activity caused by damage (e.g., oxidative stress, hypoxia, and ischemia/reperfusion) which can affect cell function for survival (Figure 11C)\(^{149}\). However, CSA toxicity at concentrations that might be necessary to suppress SARS-CoV-2 cannot be ruled out\(^{140, 144, 149, 150}\). Comprehensive expense analysis should be performed before evaluating CSA for human clinical trials to treat COVID-19, given the diversity of adverse effects such as greater sensitivity to infections, nausea, vomiting, and cancer development, amongst others\(^{151}\).

**Figure 11. Role of Cyclosporin in COVID 19**

### 2.8. Rapamycin (RAPA) - a Macrolide Lactone Antibiotic

Rapamycin (RAPA) (Figure 12) is a hydrophobic macrocyclic lactone antibiotic discovered from *Streptomyces hygroscopicus* by fermentation method\(^{152-154}\). Furthermore, it was detected for its first time in soil actinomycete gathered from Atari region of Eastern Island \(^{155}\). Although RAPA was first considered as an anti-fungal drug, its immunosuppressive characteristics were discovered in 1988\(^{155}\). Furthermore, anti-cancer activity was discovered in the 1990s, which led to the creation and deployment of semi-synthetic rapamycin analogs, exhibiting superior oncology properties (e.g., everolimus, temsirolimus)\(^{156, 157}\).

In 1991, the serine-threonine kinase mammalian target of RAPA (mTOR) was identified as a component of the rapamycin mechanism of action\(^{158, 159}\). mTOR is a protein kinase that belongs to the phosphatidylinositol 3-kinase (PI3K)-related kinase family\(^{160}\). The TOR receptor reacts to various
normal and pathological stimuli, thus controlling cell growth and proliferation. The TOR signaling pathway comprises two distinct multiprotein complexes termed TOR complex 1 (TORC1) and TORC2, both responsive and insensitive towards RAPA. Because of the activation of ribosomal protein S6, p70S6K, including 4E-BP1, mTORC1 controls protein synthesis, autophagy, and other cellular activities, whereas mTORC2 is required for maximum stimulation of numerous kinases, including AKT (Protein Kinase B). Furthermore, RAPA binds to the immunophilin, FK-binding protein 12, to form an immunosuppressive complex, which binds to that and inhibits mTOR. Sirolimus seems to be an mTOR inhibitor (rather than a calcineurin inhibitor), reducing cytokine synthesis and T-lymphocyte activation or proliferation.

Figure 12. Structure of Rapamycin

2.8.1. Role of Rapamycin in COVID-19

mTOR pathways within COVID-19 could provide significant targets for controlling cell damage, oxidative stress, or the beginning of hyper inflammation. mTOR generates two complexes: (i) mTORC1 mediates TH1 and TH17 proliferation after viral antigenic transmission by dendritic cells (DC), and (ii) mTORC2 mediates TH2 production, and both ligands inhibit T-cell differentiation. Because the mTOR pathway is vital in many biological activities, it is not unexpected that it governs the growth and response of several immune cells. mTOR regulates their gene expression for myeloid immune cells, which controls its migration and cytokine expression. Inhibiting mTORC1 enhances dendritic cell (DC) T cell stimulatory activity and activates macrophage autophagy. In T cells, mTORC1 action is caused via oxidative stress, which may be prevented as N-acetylcysteine to patients having systemic lupus erythematosus (SLE). mTORC1 activation is engaged with SLE patients that could be inhibited with RAPA, consistent with its function for pro-inflammatory T-cell differentiation.

Moreover, the mTOR pathway is essential for B cell development. mTORC1 controls the fates of B cells throughout the germinal center by regulating BCL6 expression. Following B cell activation,
mTORC1 inhibition lowers the numbers of antigen-specific memory B cells\textsuperscript{171}. RAPA therapy inhibits anti-IgM-stimulated murine B cell proliferation, preventing B cellular proliferation\textsuperscript{172, 173}. In addition, mTOR inhibitors, RAPA, including ATP-competitive inhibitors (INK128, PP242, Ku-0063794, and AZD8055), have been shown to reduce early B-cell generation within germinal centers\textsuperscript{174, 175}. As an mTOR inhibitor, RAPA prevents the cell cycle from progressing from G1 to S. SARS-CoV-2 interaction to human proteins such as LARP1 and FKBP7, regulated by mTORC1 pathway. It was demonstrated that mTOR is a critical route to SARS-CoV-2 infection\textsuperscript{164}. The over-activation, including its immune system caused by infection, induces the cytokine storm through severe COVID-19 patients, resulting in multiple organ failure and death\textsuperscript{176}. Under these situations, IL-2, IL-6, IL-7, IL-10, TNF-\alpha, G-CSF, IP-10, MCP-1 (monocyte chemoattractant protein), or even MIP-1 (Macrophage Inflammatory Proteins) might be implicated with TH17 type reactions. Both TNF-\alpha and IL-1 (TH17 and TH1 cells both express TNF-) increase TH17 responses and vascular permeability and leakage. COVID-19 promotes the development of TH17 cells, which contributes to a TH17-type cytokine storm throughout this disease\textsuperscript{22}. T-cell apoptosis, necrosis, and pyroptosis may also be induced by a cytokine storm, resulting in decreased T-cell numbers\textsuperscript{177}.

RAPA, an immunosuppressant, is known to reduce the production of various cytokines such as IL-6, IL-2, and IL-10, can also regulate a cytokine storm in COVID-19 patients\textsuperscript{164}. As a result of its pleiotropic inhibitory effect in various cytokines and other essential pathways linked to protein synthesis, ageing, and obesity are controlled by mTORC1. Rapamycin provides several benefits\textsuperscript{164}. Furthermore, both the H1N1 influenza virus and now the SARS-CoV-2 virus activate both mTOR but also NLRP3 inflammasome pathways\textsuperscript{166, 178}, resulting in the generation for IL-1\beta, a mediator of lung inflammation, fever, and fibrosis\textsuperscript{166, 179}, as well as pyroptosis, a hyperinflammatory type of cell death\textsuperscript{180}. RAPA suppresses H1N1-induced activation of the mTOR pathway, including IL-1 production\textsuperscript{178}. Furthermore, RAPA might suppress the attachment of SARS-CoV-2 to Toll-Like Receptor (TLR), ultimately leading to IL-1\beta production in COVID-19\textsuperscript{181}. Furthermore, RAPA induces de novo Foxp3 expression in naïve T cells, resulting in Treg proliferation and survival \textit{in vivo} and \textit{in vitro}. As a result, RAPA reduces effector T-cell proliferation while increasing Treg accumulation\textsuperscript{167}. RAPA had been recently discovered as an option for possible usage in COVID-19 in a network-based medication repurposing research\textsuperscript{181}. When administered early in the cytokine storm phase, RAPA may prevent progression toward severe types of COVID-19 by down-regulating a SASP, its mTOR-NLRP3-IL-1 axis, the IL-6 pathway, as well as senescent T-cell population.

2.9. Tocilizumab (TZB) – a Monoclonal Antibody

Tocilizumab (TZB) is a monoclonal anti-IL-6\textit{a} receptor inhibiting antibody used to treat inflammatory disorders\textsuperscript{182}. Numerous genetic indicators, such as FCGR3A, IL6R, CD69, and GALNT18, have been implicated in the effectiveness of TZB through RA\textsuperscript{183–185}. On the other hand, variables of CD69 and GALNT18 are expected to have minor direct impacts on TZB. Variants in these genes are more likely to affect the immune system's downstream, signaling pathways in RA patients, which could limit their use in non-RA patients\textsuperscript{185}. TZB is a recombinantly humanized anti-human IL-6R monoclonal antibody of the IgG1 class. TZB suppresses signal transmission by binding to soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). It is approved to treat rheumatoid arthritis\textsuperscript{186} and systemic juvenile idiopathic arthritis\textsuperscript{187}. In addition, TZB is helpful in diagnosis of patients with severe CRS\textsuperscript{188, 189}.

2.9.1. Role of Tocilizumab in COVID-19

TZB might be used to treat COVID-19-related CRS, similar to how it is used to treat CRS, caused by chimeric antigen receptor T-cell treatment\textsuperscript{180}. In observational studies in the United States and around the world, TZB improved outcomes in patients with COVID-19 pneumonia, pointing to the possible importance of TZB in the therapy of CRS, the critical function of IL-6 in CRS, and the critical role of CRS in the pathogenesis of SARS-CoV-2 ARDS\textsuperscript{191–193}. Randomized studies with TZB, on the other hand, have had mixed results in people with diverse degrees of COVID-19 disease severity and...
populations with varying baseline levels of care\textsuperscript{194-197}. For example, in a trial of 15 COVID-19 patients, 8 were given TZB in combination with prednisolone, and 7 were given TZB separately, frequently, or even more. TZB therapy effectively reduced serum interleukin-6 levels throughout all patients. However, even though the CRP rate quickly recovered the baseline, it was not statistically significant in four critically sick patients who received only one dose of TZB\textsuperscript{198}.

Case reports have mentioned improvements in patients with severe COVID-19 pneumonia who received TZB\textsuperscript{199-201}. Retrospective observational cohort studies have found a rapid reduction in fever, a reduction in the need for oxygen support or mechanical ventilation, and an improvement in lung manifestations\textsuperscript{191, 198, 202}. As a result, IL-6 antagonists such as siltuximab, tocilizumab, and sarilumab have been recommended as supplemental therapy for severe, progressive COVID19. TZB, on the other hand, has been demonstrated to have a putative function in specific case studies\textsuperscript{191, 198, 203-205}.

2.10. Sarilumab (SRB) – a Monoclonal Antibody

Sarilumab (SRB) appears to be a monoclonal antibody that targets interleukin-6 receptor. A biologic response modifier and the disease-modifying antirheumatic drug is a recombinant human IgG1 kappa monoclonal antibody specific for interleukin-6 (IL-6) receptor (DMARD). SRB is a biological medication used to treat moderate to severe active rheumatoid arthritis who have not responded to or tolerated prior treatments. It can be taken on its own or combined with other disease-modifying antirheumatic drugs (DMARDs) like methotrexate\textsuperscript{206}.

2.10.1. Role of Sarilumab in COVID-19

The food and drug administration (FDA) has approved SRB to treat rheumatoid arthritis (RA) and the off-label usage of this medicine for treating COVID-19 has also been studied\textsuperscript{207-210}. Although SRB suppresses both soluble and membrane-bound versions of the IL-6 receptor\textsuperscript{206, 211}, it may reduce pro-inflammatory signaling in pulmonary epithelial or immune cells\textsuperscript{212}. Therefore, COVID-19 patients should be watched for simultaneous infections, particularly severe potentially life-threatening diseases such as tuberculosis (TB), invasive fungal, bacterial, viral, other opportunistic infections, and localized conditions, given the function of IL-6 in the immune system\textsuperscript{206}.

Sarilumab is an anti-IL-6 receptor antibody that was first studied in an open-label trial of 28 patients with COVID-19 pneumonia. No changes in mortality or treatment outcomes found when compared to the standard of care were reported\textsuperscript{213}. In addition, a study of 53 people with acute COVID-19 pneumonia discovered that after a median follow-up of 19 days, up to 90% of patients significantly improved, and 71% was eventually discharged with sarilumab therapy\textsuperscript{214}. There was a 10% risk of significant risk factors resulting in mortality in 29% of sarilumab-treated patients, However, they failed to demonstrate significant improvement in critical and ventilated COVID-19 patients\textsuperscript{215, 216}.

2.11. Nitazoxanide (NTZ) – an Antiprotozoal Agents

Nitazoxanide (NTZ) (Figure 13) is a prototype of a family of chemicals called thiazole derivative, initially synthesized in the early 1970s\textsuperscript{217, 218}. NTZ, also known as 2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide, is an anti-infective medication that suppresses external survival, growth, and proliferation and intracellular protozoa, helminths, anaerobic and microaerophilic bacteria, as well as viruses. NTZ has also been discovered to have anti-inflammatory properties\textsuperscript{219}. NTZ has shown potential as a broad-spectrum antibacterial and antiviral medication in addition to its principal activity as an antiparasitic\textsuperscript{220}. 
2.11.1. Role of Nitazoxanide in COVID-19

Nitazoxanide (NTZ) has previously been found to have antiviral activity against MERS-CoV and other coronaviruses in vitro; it is also known to boost interferon production. NTZ inhibited bovine coronavirus (L9), murine coronavirus, mouse hepatitis virus (A59), and a human enteric coronavirus (4408) cultured in mouse astrocytoma (DBT) and fibroblast (17Cl-1) cell lines with an IC\textsubscript{50} of about 0.3 g/ml. This was achieved via the reduction of viral N protein production. Generally, COVID-19 therapy lasts for 7–14 days. Thus, NTZ is safe to be used for this length of time. The ability of NTZ to balance pro-inflammatory and anti-inflammatory responses in humans could play a key role in COVID-19 by reducing the hyperinflammatory cytokine storm. NTZ inhibits viral infection by upregulating host mechanisms that viruses utilize to overcome host cellular defenses. Although in vitro efficacy of NTZ towards SARS-CoV-2 is promising, additional research is needed to understand its function in COVID-19 treatment. Unfortunately, studies on the effectiveness of NTZ toward human coronavirus are few. Many research groups suggested having efficacy against COVID-19; however, the potential utility is yet to be explored in dose frequency.

2.12. Interferons – a class of signaling protein

In innate and adaptive immune responses, interferons (IFNs), are a class of signaling proteins that play a critical role in limiting viral reproduction via diverse effector proteins. A cell produces interferon (IFN), a type of cytokine, when it is triggered by a viral infection or another interferon (IFN) inducing agent. It is a secreted protein (primarily a glycoprotein) with a broad spectrum of antiviral and immunoregulating physiologic capabilities and the modulation of innate and acquired immunological responses to infection. Interferon (IFN) is classified into three types; type I, type II, and Type III. Type I interferons (IFN-α/β) have extensive antiviral activity against RNA viruses, generating an antiviral response in various cell types or facilitating adaptive immune response. Humans develop 13 different kinds of IFN-α and a single IFN-β. STING (stimulator of interferon genes, also known as ERIS/MITA) and its downstream effector cyclic GMP–AMP synthase (eGAS) regulate transcription of a broad spectrum of inflammatory mediators type I and type III interferons. The IFN-λ family of cytokines (also known as type III interferons) is a relatively new class of cytokines that binds to various receptor complexes but activate the same JAK-STAT signaling pathway. Furthermore, the IFN-RI receptor is primarily expressed in epithelial cells and organs, including respiratory epithelial cells.

2.12.1. Role of Interferon in COVID-19

IFNs, particularly IFN-1b, have been demonstrated to be effective against SARS and MERS coronaviruses and are now being explored for COVID-19 alone or in conjunction with other medications such as lopinavir and ritonavir. Moreover, COVID-19 pathology, which primarily consists of pulmonary lesions, resembling interferonopathies. This may imply that SARS-CoV-2 produces an overactive IFN-I induced antiviral response, resulting in tissue damage. If this theory is validated, IFN-
I therapy should be confined to the early stages of infection,\textsuperscript{237} Early clinical evidences, demonstrating severe inflammatory biomarkers, are linked with higher mortality\textsuperscript{238}.

Recent research showed that type I IFN and IFN-λ is not generated in COVID-19 patients since they were not identified in the serum of a small COVID-19 group with any unexplained clinical features\textsuperscript{239}. In comparison, another research found that type I IFN is increased in COVID-19 patients, and, therefore, its concentration may be decreased in those severely sick patients\textsuperscript{240}.

A latest study that looked at peripheral blood from patients with COVID-19 of different causes found that IFN-I responses seem to be severely impaired in patients with severe or essential COVID-19, as evidenced by low levels of IFN-I, ISGs and higher production of TNF-α and IL-6 or increased NF-κB-driven inflammatory responses\textsuperscript{240}. However, there have been retroactive investigations on SARS-CoV-2 and MERS-CoV using IFNs in combination with other treatments\textsuperscript{241}. Although IFNs have been indicated for being effective in SARS and MERS-CoV by increasing lung function or delaying death, they have typically neglected to modify the illness in people\textsuperscript{242}. As coronaviruses are so similar, studies have suggested that insufficient IFN production in response to SARS-CoV-2 causes the innate immune response being suppressed, resulting in higher viral levels. As a result, exogenous IFN may be more effective in treating SARS-CoV-2 infection than endogenous IFN\textsuperscript{243, 244}.

2.13 Favipiravir – Flu Virus Multiplication Inhibitor

Favipiravir (FVP) is a purine analog (Figure 14) that is substituted for guanine or adenine\textsuperscript{245}. Favipiravir, also known as T-705, was first created in 2002 as a flu virus multiplication inhibitor\textsuperscript{245}. On February 15, 2020, China authorized FVP to treat the new influenza\textsuperscript{247}. FVP has shown significant antiviral action on cell lines and animal studies against various segmented negative-strand RNA viruses such as arena and bunyaviruses. In addition, FVP has also been shown to have efficacy against positive-strand RNA viruses such as noroviruses and flaviviruses\textsuperscript{248–250}.

![Figure 14. Structure of Favipiravir](image)

2.13.1. Role of Favipiravir in COVID-19

Favipiravir (FVP) is a prospective COVID-19 candidate medicine; however, while delivering it, drug-drug interactions with previously given medications must be examined, as they may change the pharmacokinetics and plasma concentration of favipiravir\textsuperscript{251}. It is a RNA virus-specific and robust inhibitor of RNA-dependent RNA polymerase (RdRp). FVP is integrated into the nascent viral RNA via the error-prone viral RdRp, resulting in viral mutagenesis and chain termination. The presence of RdRp in several kinds of RNA viruses allows favipiravir to have a more extensive range of antiviral action\textsuperscript{118, 252, 253}. FVP - RTP acts as a mutagen after RNA viral inclusion, avoiding coronavirus repair machinery. Although it has been approved for use in such an emergency, large-scale studies are required to assess its role in the ongoing care of COVID-19. Eighty-five percent of COVID-19 patients have mild to moderate illnesses that might be managed at home. Thus, this medicine could help many people. Adults take a loading dosage of 1800 mg followed by 800 mg twice daily for up to 14 days, or a 1600 mg loading dose followed by 600 mg twice daily for up to 14 days\textsuperscript{254}. Due to its teratogenic effects, FVP cannot be given to expectant mothers or those who may become pregnant. In asymptomatic and mild patients, the rate of viral clearance with FVP (1800 mg regimen) was equal in both early (1 day after participation) and late (6 days after participation) treatment groups\textsuperscript{255}. Due to effectiveness of the drug to use for treatment of COVID19 interrupted in many countries.
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2.14 Molnupiravir - Pyrimidine Ribonucleoside Analogue

Molnupiravir (MNP) (Figure 15) was designed to treat alphavirus infections in the first place. Molnupiravir, also known as methyl isobutyrate, is a pyrimidine ribonucleoside analog. EIDD-1931-isopropyl ester; EIDD-2801; MK-4482; uridine, 4-oxime, 50 - (2- methyl propanoate); and -D-N4-hydroxycytidine-50 -isopropyl ester are some of the alternative names for MNP. It is an orally active, directly acting antiviral interventional medicine, and it is a potential forthcoming oral treatment.

![Structure of Molnupiravir](image)

**Figure 15.** Structure of Molnupiravir

2.14.1. Role of Molnupiravir in COVID-19

MNP, a prodrug of the ribonucleoside analog β-D-N4-hydroxycytidine (NHC), is quickly transformed to NHC and subsequently to the active 5’-triphosphate form host kinases in the plasma. The active 5’-triphosphate is a competitive substrate for virally encoded RNA-dependent RNA polymerase (RdRp). If integrated into nascent viral RNA, it causes an antiviral impact by accumulating mutations that increase with each viral replication cycle. Mode of action of MNP is divided into two parts; incorporation and mutagenesis. MNP is a nucleoside analog that incorporates negative sRNA, causing favorable sRNA products to mispair. This mechanism results in fatal mutagenesis or viral inactivation. MNP works by causing a cascade of errors in the coronavirus DNA, and there have been fears that it may affect human genes. However, the panelists were provided data from in vivo studies demonstrating that adult were not at danger at therapeutic levels.

Nevertheless, the medicine will not be approved for use in pregnant or lactating women, and its future in children is unclear. The phase three trial was placed in over 170 locations worldwide, including the United States, Brazil, Italy, South Africa, Japan, Taiwan, and Guatemala. According to the research, the start of symptoms or the existence of underlying risk factors in patients did not affect the efficacy of MNP. It also showed consistent activity against all SARS-CoV-2 variations, including the widely distributed and highly transmissible delta strain. In addition, MNP is an effective inhibitor of SARS-CoV-2 multiplication in cell line studies, with an EC50 in the submicromolar range; a similar viral injection effect has also been reported in animal models.

<table>
<thead>
<tr>
<th>Drugs used in COVID-19</th>
<th>Category</th>
<th>Proposed Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine and</td>
<td>Anti-malarial</td>
<td>↑Lysosomal pH and interfere with viral release</td>
<td>32</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Macrolide Antibiotic</td>
<td>It blocks internalization into host cells during the early phase of infection</td>
<td>264</td>
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<tr>
<td>Levamisole</td>
<td>Anti-biotic</td>
<td>Enhances the cellular immunity; immunostimulatory functions</td>
<td>58</td>
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### Table 1 continued.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Action on Virus</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>Semi synthetic tetracycline antibiotic and sedative drug</td>
<td>↓ Replication SARS-COV2 ↓ IL-6 levels</td>
<td>78</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immunosuppressant and sedative drug</td>
<td>↓ TNF-α ↓ cell surface adhesion molecules involved in leukocyte migration</td>
<td>87</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Immunosuppressant agent</td>
<td>Inhibition of the production of cytokines involved in regulation of T cell activation</td>
<td>101, 102</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Immunosuppressant</td>
<td>Inhibits the secretion of IL-6 and other cytokines</td>
<td>153</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Used to treat parasitic infections</td>
<td>↓ Replication of SARS-COV2</td>
<td>162</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Monoclonal Antibody-IL-6 inhibitor (FDA Granted)</td>
<td>↓ IL-6 interrupts the process of CRS</td>
<td>180, 181, 184</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>IL-6 inhibitor</td>
<td>↓ Immune response ↓ IL-6</td>
<td>183</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Antiviral and antiparasitic - Antiprotozoal agent</td>
<td>Antiviral potential against MERS-CoV and other coronaviruses in in vitro</td>
<td>198</td>
</tr>
<tr>
<td>Interferons</td>
<td>Antiviral</td>
<td>Inhibits varying stages of viral replication including viral entry</td>
<td>208</td>
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<tr>
<td>Favipiravir</td>
<td>Antiviral agent</td>
<td>Inhibits RNA dependent RNA polymerase, which ultimately prevents viral transcription</td>
<td>248</td>
</tr>
<tr>
<td>Molnupiravir</td>
<td>Antiviral</td>
<td>↑ Frequency of viral RNA mutations</td>
<td>258</td>
</tr>
</tbody>
</table>

### 3. Conclusion

There are currently no approved, safe, and effective pharmacologic treatments for COVID-19 infection, and more research into all possible treatments is needed to address the virus. In table 1, we incorporated mechanism of action of some already approved drugs used in COVID 19 viral infection. Also, as outcome, several pharmacologic medicines targeting distinct stages of viral activity have been identified. More clinical trials should be conducted as quickly as possible to evaluate prospective pharmacological medicines and determine the most effective way for reducing the transmission of this virus and the burden of any looming epidemic.

### List of Abbreviations
- COVID-19 – Coronavirus Disease 2019
- SARS-Cov-2 – Severe Acute Respiratory Syndrome Coronavirus 2
- MERS – Middle East Respiratory Syndrome
- IL – Interleukin
- TNF - Tumor Necrosis Factor
- HCoV-OC43 – Human Coronavirus OC43
- ACE2- Angiotensin Converting Enzyme 2
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- NF-KB - Nuclear Factor-Kappa B
- HAS2 – Hyaluronan Synthase-2
- ARDS - Acute Respiratory Distress Syndrome
- CQ – Chloroquine
- HCQ – Hydroxychloroquine
- MAPK – Mitogen Activated Protein Kinase
- AZ – Azithromycin
- MOI – Multiplicity of infection
- LVM – Levamisole
- IFNs - Interferon
- DOX – Doxycycline
- MMPs - Metalloproteinases
- NSPs - Non-Structural Proteins
- TLD – Thalidomide
- CYS – Cyclosporine
- RAPA – Rapamycin
- Mtor – Mammalian target of rapamycin
- SLE - Systemic Lupus Erythematosus
- BCL6 – B-cell lymphoma 6
- IMP -Importin
- IVM – Ivermectin
- NPC -Nuclear pore complex
- TZB – Tocilizumab
- CRP- C-Reactive Protein
- SRB – Sarilumab
- DMARDs - Disease-Modifying Antirheumatic Medications
- NTZ – Nitazoxanide
- JAK-STAT – Janus Kinase – Signal Transducers and Activators of Transcription
- ISGs - Immune Serum Globulin
- FVP – Favipiravir
- MNP – Molnupiravir
- sRNA – Small RNA
- RdRp: RNA dependent RNA polymerase

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications
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