Preclinical and Clinical Investigations of Potential Drugs and Vaccines for COVID-19 Therapy: A Comprehensive Review With Recent Update

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ABSTRACT: The COVID-19 pandemic-led worldwide healthcare crisis necessitates prompt societal, ecological, and medical efforts to stop or reduce the rising number of fatalities. Numerous mRNA based vaccines and vaccines for viral vectors have been licensed for use in emergencies which showed 90% to 95% efficacy in preventing SARS-CoV-2 infection. However, safety issues, vaccine reluctance, and skepticism remain major concerns for making mass vaccination a successful approach to treat COVID-19. Hence, alternative therapeutics is needed for eradicating the global burden of COVID-19 from developed and low-resource countries. Repurposing current medications and drug candidates could be a more viable option for treating SARS-CoV-2 as these therapies have previously passed a number of significant checkpoints for drug development and patient care. Besides vaccines, this review focused on the potential usage of alternative therapeutic agents including antiviral, antiparasitic, and antibacterial drugs, protease inhibitors, neuraminidase inhibitors, and monoclonal antibodies that are currently undergoing preclinical and clinical investigations to assess their effectiveness and safety in the treatment of COVID-19. Among the repurposed drugs, remdesivir is considered as the most promising agent, while favipiravir, molnupiravir, paxlovid, and lopinavir/ritonavir exhibited improved therapeutic effects in terms of elimination of viruses. However, the outcomes of treatment with oseltamivir, umifenovir, disulfiram, teicoplanin, and ivermectin were not significant. It is noteworthy that combining multiple drugs as therapy showcases impressive effectiveness in managing individuals with COVID-19. Tocilizumab is presently employed for the treatment of patients who exhibit COVID-19-related pneumonia. Numerous antiviral drugs such as galidesivir, griffithsin, and thapsigargin are under clinical trials which could be promising for treating COVID-19 individuals with severe symptoms. Supportive treatment for patients of COVID-19 may involve the use of corticosteroids, convalescent plasma, stem cells, pooled antibodies, vitamins, and natural substances. This study provides an updated progress in SARS-CoV-2 medications and a crucial guide for inventing novel interventions against COVID-19.

KEYWORDS: Antiviral agents, convalescent plasma, COVID-19, drug repurposing, protease inhibitors, SARS-CoV-2, vaccines

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Introduction

Coronaviruses belong to a wide family of viruses associated with a range of illnesses, including the common cold and more severe conditions like Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS).[1] The zoonotic origin of the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in December 2019 in Wuhan, China. The novel SARS-CoV-2, which originated from animals and crossed over to humans, was first identified in December 2019 in Wuhan, China.[2] COVID-19, an extremely transmissible viral illness, is attributed to the virus SARS-CoV-2. Its impact on a global scale has been devastating, resulting in over 6.4 million deaths worldwide.[3,4] Indeed, it has emerged as the most notable worldwide health emergency since the influenza pandemic of 1918. The World Health Organization (WHO) proclaimed SARS-CoV-2 a global pandemic on March 11, 2020 as a result of its quick global spread following the initial instances of this predominantly respiratory viral disease. As of February 27, 2023, the WHO predicted that there will be over 758 million confirmed cases of COVID-19 in more than 228 countries, regions, or territories. A strain of RNA viruses known as SARS-CoV-2 has never been identified in humans previously.[4,5] The virus may affect people, civets, mice, dogs, cats, camels, pigs, chickens, and bats severely due to the wide range of hosts it can infect. In both people and animals, SARS-CoV-2 induces respiratory and gastrointestinal disease.[6,7] Transmission is possible through aerosols, direct/indirect contact, medical procedures, and handling of laboratory specimens. The pathogenesis and progression of the difficulties are significantly influenced by certain structural proteins that may be found on the outermost layer of the virus. Typical medical symptoms of this ailment include high fever, chills, coughing, and shortness of breath or difficulty breathing.[8]

Genetic analysis and whole-genome sequencing research have unveiled that SARS-CoV-2 is a beta coronavirus family, closely resembling bat-originated severe acute respiratory syndrome (SARS)-like coronaviruses (with around 88% genomic similarity) and SARS-CoV-1 (around 79% similarity). A recent proposal suggests that SARS-CoV-2 can be categorized into 2 main genotypes: Type I (further divided into Type IA and IB) and Type II. Type IA most closely resembles the

original SARS-CoV-2 ancestor, while Type IB emerged from Type IA through a novel mutation at position 29 063. In contrast, Type II, which likely evolved from Type I, prevails in current infections.[9,10] In the SARS-CoV-2 genome, the viral replicase segment is encoded at the 5′ end, while the structural proteins are encoded at the 3′ end. The virus possesses 4 major structural proteins: spike, membrane, envelope, and nucleocapsid. Coronaviruses access host cells via the spike protein's interaction with host cell receptors like angiotensin-converting enzyme 2 (ACE2) and CD147.[11,12] Replicase RdRp manages coronavirus replication within host cells, leading to the production of diverse and highly mutable coronaviruses. Subsequent to initial exposure, immune responses are triggered by cytotoxic cells, antibodies, and interferons.[13]

After the initial SARS-CoV-2 outbreak in China and the announcement of the pandemic, experts worldwide have been swiftly striving to discover ways to treat and prevent COVID-19. Mass vaccination is a "checkmate" move to terminate the pandemic. Nevertheless, to achieve lasting and extensive protection, the emphasis has shifted toward crafting vaccines that not only offer individual defense but also significantly curtail disease transmission. This effort is pivotal for reaching "herd immunity"—a point at which the infectious agent can no longer circulate due to a considerable level of population immunity.[14] However, scientists generated numerous possible COVID-19 vaccines across the globe. All vaccines are intended to instruct the immune system to recognize and combat the COVID-19 virus. Vaccine hesitation and skepticism among the global population are regarded to constitute a significant barrier to the fulfillment of this objective. Hesitancy refers to a situation where a notable portion of the global population demonstrates reluctance in either accepting or declining vaccines, even when vaccination services are readily accessible.[15] COVID-19 vaccine hesitancy is associated with factors such as religion, gender, political orientation, and trust in healthcare organizations and scientific institutions. These are the prime obstacles that health care practitioners, politicians, community leaders and governments must overcome to increase the vaccinations' general acceptability.[15,16] In addition, vaccination equity is a global issue in which high- and upper-middle-income countries receive more vaccine doses than low-income nations. So, despite the invention of the vaccine, not all people can get this vaccine now. It is critical to find novel therapeutic agents, repurposed present pharmaceuticals or chemicals, and broad-spectrum antiviral drugs for the treatment of the 2019-nCoV outbreak. To achieve the goal of developing an appropriate antiviral drug, existing antiviral medicines need to be evaluated against SARS-CoV-2. Several medications have been chosen as potential candidates for the therapy of COVID-19, according to the information obtained to date.[12] The aim of this study is to assess the probable and proposed antivirals, antibiotics, and immune modulators, as well as their preclinical and clinical findings, efficacy or inefficacy, and therapeutic regimens for the management of COVID-19.

Mechanism of SARS-CoV-2 Infection

ACE2 (Angiotensin-converting enzyme 2) and TMPRSS2 (Transmembrane serine protease 2) mediated cell entry and infection of SARS-CoV-2

Recent emergence of the new disease-causing SARS-CoV-2 in China and its rapid country and across border dissemination constitutes an international health emergency. SARS-CoV-2 has 2 main ways of entering cells. It can merge with the outer membrane of cells directly, or it can use a process called endosomal membrane fusion.[17] Intriguingly, coronavirus fusion is reliant on proteases enzymes in the virus's nearest environment, indicating the spike (S) proteins of the virus can adjust and interact with different signaling proteins.[18] The process of coronavirus entering cells relies on the binding of the spike (S) glycoprotein, which is present in trimer formations on the cell surface, to a specific cellular target. This interaction is followed by the activation of the S protein through cellular proteases. SARS-CoV-2 recruits angiotensin-converting enzyme 2 (ACE2) as an entrance receptor in this manner. The strength of the bond between the S protein of SARS-CoV-2 and ACE2 is connected to how quickly the virus replicates and the severity of the resulting illness. Additionally, the involvement of transmembrane serine protease 2 (TMPRSS2) activity and cathepsin B/L activity is necessary for SARS-CoV-2 to enter host cells.[19] The S protein can be activated proteolytically by TMPRSS2 or cathepsins B and L.[20] Unlike SARS-CoV, the S1/S2 site of SARS-CoV-2 spike protein depicts a multibasic cleavage site with a minimal furin recognition motif.[21] During viral escape, furin has been demonstrated to be responsible for cleaving the S1/S2 site. This pathway is required for TMPRSS2 to activate S at the S2′ site following receptor binding and is essential for respiratory tract cell infection.[22]

When neither exogenous nor enclosed by the membrane proteases are not present, coronaviruses can internalize cells through endocytosis, either mediated by clathrin or without involving clathrin.[23] Surprisingly, the precise location where SARS-CoV-2's fusion of viral and cellular membranes takes place is still unknown. It is conceivable for fusion to occur at the plasma membrane of the cell, which has been suggested as the main entrance point for cells. Uncovering the cellular components employed by SARS-CoV-2 for entrance could shed light on viral propagation and identify potential treatment targets.[24]

Other mechanisms of SARS-CoV-2 entry and infection

In addition to ACE2, numerous other molecules like C-type lectins, CD209, or DC-SIGN in dendritic cells and CD209L or L-SIGN in liver endothelial cells have been suggested as possible receptors for SARS-CoV-2.[25] Lectins are important for the identification of a wide range of pathogens and in the regulation of intercellular adhesion. They connect to a broad spectrum of viruses by identifying the glycans on the surface of the viral particle, and this typically speeds up viral entry by

enabling the virus to connect to the cells that are being targeted.[26] Besides, heparan sulfate proteoglycans (HSPG) serves as co-receptors for SARS-CoV-2 cell entry. Heparan sulfate, found in the cellular glycocalyx, binds directly to the SARS-CoV-2 spike protein, aiding in the attachment of viral particles to cell surfaces and promoting viral entry. This interaction facilitates the open conformation of the spike protein required for binding to ACE2 receptors, ultimately enhancing the virus's ability to infect cells.[27-29] Similarly, T cell immunoglobulin mucin domain protein 1 (TIM1) and tyrosine kinase receptor AXL have been proposed as alternate SARS-CoV-2 receptors. These receptors belong to the TIM and TAM (Tyro3, Axl, and MerTK) families of phosphatidylserine receptors, which aid the entry of various enveloped viruses by binding to phosphatidylserine on the viral membrane.[30] However, despite the enhancement of viral entry by lectins and phosphatidylserine receptors, they lack specificity and cannot efficiently support SARS-CoV-2 infection in the absence of ACE2.[30,31] Moreover, CD147, a ubiquitously expressed transmembrane glycoprotein on epithelial and immunological cells, has been postulated as an alternative receptor for SARS-CoV-2 infection.[32] Another host factor for SARS-CoV-2, Neuropilin 1 (NRP1), has been identified by 2 research groups. Although NRP1 is found in olfactory and respiratory epithelial cells, its presence is limited in ciliated cells—the main target of SARS-CoV-2 in the airway. On the other hand, its levels are higher in goblet cells, which are less prone to SARS-CoV-2 infection.[33] NRP1 was noted to amplify the TMPRSS2-facilitated entry of the original SARS-CoV-2 virus. However, this enhancement was absent when examining a mutated virus that lacked the furin-cleavage site. Furthermore, research has indicated that NRP1 can attach to the S1 portion via the furin-cleavage site. This attachment prompts the liberation of S1, revealing the S2′ site, which is then susceptible to interaction with TMPRSS2.[34]

Potential Therapies for the Treatment of COVID-19

Drugs being repurposed for use in COVID-19 treatment

The worldwide health emergency triggered by the COVID-19 pandemic has compelled the acceleration of drug discovery and the speedy identification of effective medications and treatment options. Despite the ongoing worldwide distribution of the COVID-19 vaccine, there remains a requirement to create efficient treatments, particularly in countries where vaccine acceptance and availability are poor and in the face of the insidious threat posed by mutations leading to vaccine escape. There's potential to repurpose current drugs for addressing COVID-19, especially if they are already sanctioned for different uses and possess established records of safety. Drug repurposing is a known strategy of discovering new therapeutic uses of an existing drug other than its original purpose. The strategy of repurposing drugs is widely employed to accelerate the research process, reduce associated costs, and mitigate risks.[35] Even though repurposed drugs still need to go through clinical trials, it's evident that this method can quickly unveil effective treatments, even those that initially failed for their original intent. While there are limited approved drugs or vaccines specifically targeting coronaviruses, numerous theoretical avenues exist for combating the disease. These include vaccines, monoclonal antibodies, therapeutics based on oligonucleotides, peptides, interferon therapy, and small-molecule medications (as outlined in Table 1).[35,36] Unfortunately, the identification of medications capable of providing a lasting cure a disease permanently could take several months to years. On the basis of crystallographic findings, several options for controlling or preventing the emergence of SARS-CoV-2 infections have been considered. These primarily encompass COVID-19 vaccination, evaluating the potency, efficacy, and safety of vaccines against COVID-19, non-pharmaceutical interventions (NPI), COVID-19 contact tracing, and recommendations concerning the quarantine of individuals in close proximity to COVID-19 cases, as well as the isolation of COVID-19 patients.[37] Thus, numerous researchers are attempting to repurpose current medications for MERS and SARS. Although no effective medication therapies for COVID-19 have yet been identified, several are being explored including medications for cancer, HIV, and malaria.[38,39] As COVID-19 spreads rapidly over the globe, it is imperative to identify new medications, which might be accomplished by repurposing the drugs. The drugs that are currently being repurposed for the treatment of COVID-19 infection are designed to address various phases of viral infection. These encompass viral entry, translation, proteolysis, replication of viral RNA, assembly of viral proteins, and the release of the virus (Figure 1). The fusion of viral spike proteins with the host's cellular ACE2 receptor leads to the suppression of ACE2. The expression of ACE2 is increased by repurposed drugs such statins, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). Consequently, these drugs might hold potential effectiveness against SARS-CoV-2 infections. Low endosomal pH lyses viral structural proteins after fusion, hence, chloroquine and hydroxychloroquine may be antiviral by disrupting this acidic environment. The viral primary protease enzyme facilitates proteolysis, generating functional RNA-dependent RNA polymerase (RDRP) proteins. Viral protease inhibitors, including lopinavir, ritonavir, and darunavir, show promise in combating the virus. RDRP supports virus replication and transcription. Remdesivir, favipiravir, ribavirin, and arbidol inhibit viral RDRP, consequently may be useful in COVID-19 treatment. After translation, proteolysis, and packaging, intact virions are exocytosed from the cell. Targeting the growth and propagation of each phase in the viral life cycle presents a strategy for managing its infection.

Antiviral drugs

Remdesivir. Remdesivir (RDV) is a nucleoside antiviral medication that was first employed to combat fatal Ebola, Marburg, and Nipah viral infections.[99] I It has broad-spectrum

Table 1. List of potential drug candidates for repurposing to treat SARS-CoV-2 infection.

REPURPOSED DRUG	CATEGORY	POSSIBLE MECHANISTIC BASIS FOR THE ANTI-COVID-19 RESPONSE	ORIGINAL INDICATION	PURPOSE IN COVID-19	CURRENT CLINICAL STATUS FOR COVID-19	ROUTE OF ADMINISTRATION	REFERENCES
Remdesivir	Antiviral	Inhibits viral replication by attaching to the viral RNA-dependent RNA polymerase (RdRp) and functioning as an RNA-chain terminator.	Ebola virus, dengue virus type 2, yellow fever virus, influenza A and para influenza 3	To treat COVID-19	Approved; enrolled in Phase III clinical trial	Intravenous (IV) infusion	Elhusseiny et al[40], Jorgensen et al[41], ClinicalTrials.gov[42]
Ribavirin	Antiviral	Disrupts viral RNA synthesis through the termination of viral mRNA capping by targeting the viral RdRp.	Hepatitis C virus, chikungunya virus, enterovirus 71, canine distemper virus, orthopoxvirus and influenza virus	For the management of individuals with COVID-19.	Enrolled in Phase II clinical trial	Oral route	Tong et al[43], Singh et al[44], ClinicalTrials.gov[45]
Molnupiravir	Antiviral	Hinders viral replication by attaching to the viral RdRp.	Influenza virus, bovine viral diarrhea virus (BVDV), hepatitis C virus (HCV), respiratory syncytial virus (RSV), and Ebola virus (EBOV)	For the management of individuals with mild to moderate cases of COVID-19.	Emergency use authorization (EUA); enrolled in Phase II clinical trial	Oral route	Pourkarim et al[46], Yip et al[47]
Galidesivir	Antiviral	Blocking the viral RNA polymerase and causing premature cessation of RNA transcription.	Ebola virus and Marburg virus	To lower the occurrence and intensity of COVID-19.	Enrolled in Phase I clinical trial	The intravenous and intramuscular route	Julander et al[48], Taylor et al[49], ClinicalTrials.gov[50]
Paxlovid	Antiviral	By blocking the primary SARS-CoV-2 protease, M^{pro}, the virus's replication in the initial phases of the illness is hindered, thereby deterring the advancement toward severe COVID-19.	SARS-CoV-2	For the management of individuals with mild to moderate cases of COVID-19.	Emergency use authorization (EUA); enrolled in Phase III clinical trial	Oral route	Mahase[51], Wen et al[52]
Lopinavir/ Ritonavir	Antiviral	Curbing viral replication through strong binding to the viral protease.	HIV/AIDS, MERS-CoV	For the management of individuals with COVID-19.	Enrolled in Phase II clinical trial	Oral route	Patel et al[53], Magro et al[54], ClinicalTrials.gov[55]
Favipiravir	Antiviral	Selectively inhibits the viral RdRp via tightly binding to the RdRp	Influenza virus, arenavirus, bunyavirus, filovirus, yellow fever virus, enterovirus	Assessing the safety and effectiveness in individuals with COVID-19.	Enrolled in Phase III clinical trial	Oral route	Özlüşen et al[56], Hassanipour et al[57], ClinicalTrials.gov[58]
Griffithsin	Antiviral	Blocks viral infection by attaching to viral surface glycoproteins like glycoprotein 120 (gp-120) and SARS-CoV-2 Spike protein.	HIV/AIDS	To prevent COVID-19	Enrolled in Phase I clinical trial	Intranasal route	Alsaidi et al[59], Decker et al[60]

(Continued)

Table 1. (Continued)

REPURPOSED DRUG	CATEGORY	POSSIBLE MECHANISTIC BASIS FOR THE ANTI-COVID-19 RESPONSE	ORIGINAL INDICATION	PURPOSE IN COVID-19	CURRENT CLINICAL STATUS FOR COVID-19	ROUTE OF ADMINISTRATION	REFERENCES
Umifenovir	Antiviral	Hampers the connection between the virus and its intended host cells by impeding the merging of the viral capsid with the target cell membrane, consequently obstructing the virus's entry into the target cell.	Influenza-A virus, rhinovirus type 14, respiratory syncytial virus, Coxsackie virus B3 and adenovirus type-7	To treat patients with COVID-19 pneumonia	Enrolled in Phase IV clinical trial	Oral route	Huang et al[61], Alavi Darazam et al[62], ClinicalTrials.gov[63]
Thapsigargin	Antiviral	Blocks viral replication	Respiratory syncytial virus (RSV), common cold coronavirus OC43 and influenza A virus	To treat patients with COVID-19	Enrolled in Preclinical trial	Oral route	Shaban et al[64], Al-Beltagi et al[65]
Darunavir	Protease inhibitor	Blocks viral cellular entry	HIV/AIDS	To treat patients with COVID-19	Enrolled in Phase III clinical trial	Oral route	Cattaneo et al[66], Tegeli et al[67], ClinicalTrials.gov[68]
Disulfiram	Protease inhibitor	Inhibiting the viral replication via blocking the protease	HIV/AIDS	To diminish the occurrence and intensity of COVID-19.	Enrolled in Phase II clinical trial	Oral route	Fillmore et al[69], Custodio et al[70], ClinicalTrials.gov[71]
Tocilizumab, Sarilumab, Eculizumab	Monoclonal antibody	IL-6 inhibitor, blocks cytokine storm.	Rheumatoid arthritis, autoimmune rheumatic disease	To treat patients with COVID-19 pneumonia	Enrolled in Phase II clinical trial	Intravenous (IV) injection	Patel et al[72], Shariare et al[73], Esmaeilzadeh et al[74], ClinicalTrials.gov[75]
AZD7442 (Tixagevimab and cilgavimab)	Monoclonal antibody	Inhibits receptor-binding domain (RBD)-ACE2 binding	SARS-CoV-2	To prevent COVID-19	Approved; enrolled in Phase III clinical trial	Intravenous (IV) infusion, intramuscular (IM) injections	Mahase[76], Aisenberg[77]
Sotrovimab	Monoclonal antibody	Blocks the merging of membranes following the virus's attachment to the human ACE2 receptor, achieved by binding to a conserved epitope on the spike protein of SARS-CoV-2	SARS-CoV-2	For the management of individuals with mild to moderate cases of COVID-19.	Emergency Use Authorization (EUA) Enrolled in Phase II clinical trial	Intravenous (IV) infusion	Gupta et al[78], Gupta et al[79]
Bamlanivimab and Etesevimab	Monoclonal antibody	Prevents viral attachment and penetration into human cells, effectively neutralizing the virus.	Mild to moderate cases of COVID-19 in both adult and pediatric patients, including newborns, who have tested positive for active SARS-CoV-2 infection.	To treat mild to moderate COVID-19.	Enrolled in Phase II and III clinical trial	Intravenous (IV) infusion	Dougan et al[80], Gottlieb et al[81]

(Continued)

Table 1. (Continued)

REPURPOSED DRUG	CATEGORY	POSSIBLE MECHANISTIC BASIS FOR THE ANTI-COVID-19 RESPONSE	ORIGINAL INDICATION	PURPOSE IN COVID-19	CURRENT CLINICAL STATUS FOR COVID-19	ROUTE OF ADMINISTRATION	REFERENCES
Chloroquine and hydroxychloroquine	Anti-parasitic	Elevating the pH within endosomes, necessary to prevent virus-cell fusion, while also interfering with the glycosylation process of SARS-CoV-2's cellular receptors.	Malaria, autoimmune disease (e.g. rheumatic diseases), enterovirus 71, zika virus and chronic inflammatory diseases	For the management of mild symptomatic and asymptomatic instances of COVID-19.	Approved; enrolled in Phase III clinical trial	Oral route	Gasmi et al[82], Saghir et al[83], ClinicalTrials.gov[84]
Nitazoxanide	Anti-parasitic and anti-viral	Disruption of pathways regulated by the host that play a role in viral replication, while enhancing the cytoplasmic sensing of RNA and the pathways related to type I interferons.	Influenza virus, hepatitis C virus, respiratory syncytial virus, parainfluenza virus, rotavirus, norovirus and hepatitis B virus	To assess the safety and effectiveness of the combined approach in the context of COVID-19.	Enrolled in Phase III clinical trial	Oral route	Lokhande and Devarajan[85], Blum et al[86], ClinicalTrials.gov[87]
Ivermectin	Anti-parasitic	Binds selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of microfilaria	HIV/AIDS, chikungunya virus, and yellow fever virus	To evaluate the safety and efficacy of the combination in COVID-19	Enrolled in Phase II clinical trial	Oral route	Popp et al[88], López-Medina et al[89], ClinicalTrials.gov[90]
Teicoplanin	Antibacterial	Inhibits the cathepsin L protease through the interaction of the teicoplanin lipophilic moiety with the enzyme and stops the SARS-CoV release from the late endosome	Bacterial infections, Ebola virus, influenza virus, flavivirus, hepatitis C virus and HIV/AIDS	To treat COVID-19 patients	No information	Intravenous (IV) infusion, intramuscular (IM) injections	Vimberg[91], Ceccarelli et al[92]
Azithromycin	Antibacterial	Inhibit viral activity, bacterial protein synthesis inhibition	Influenza virus, dengue virus, zika virus and ebola virus	To prevent COVID-19 disease progression	Approved; enrolled in Phase IV clinical trial	Oral route	Echeverría-Esnal et al[93], Kamel et al[94], ClinicalTrials.gov[95]
Oseltamivir	Neuraminidase inhibitor	Blocks the activity of the viral neuraminidase enzyme.	Influenza A and B viruses	To decrease the mortality rate and shorter length of hospitalization of COVID-19 patients	Enrolled in Phase III clinical trial	Intravenous (IV) infusion	Zendehdel et al[96], Muralidharan et al[97], ClinicalTrials.gov. Hydroxychloroquine[98]

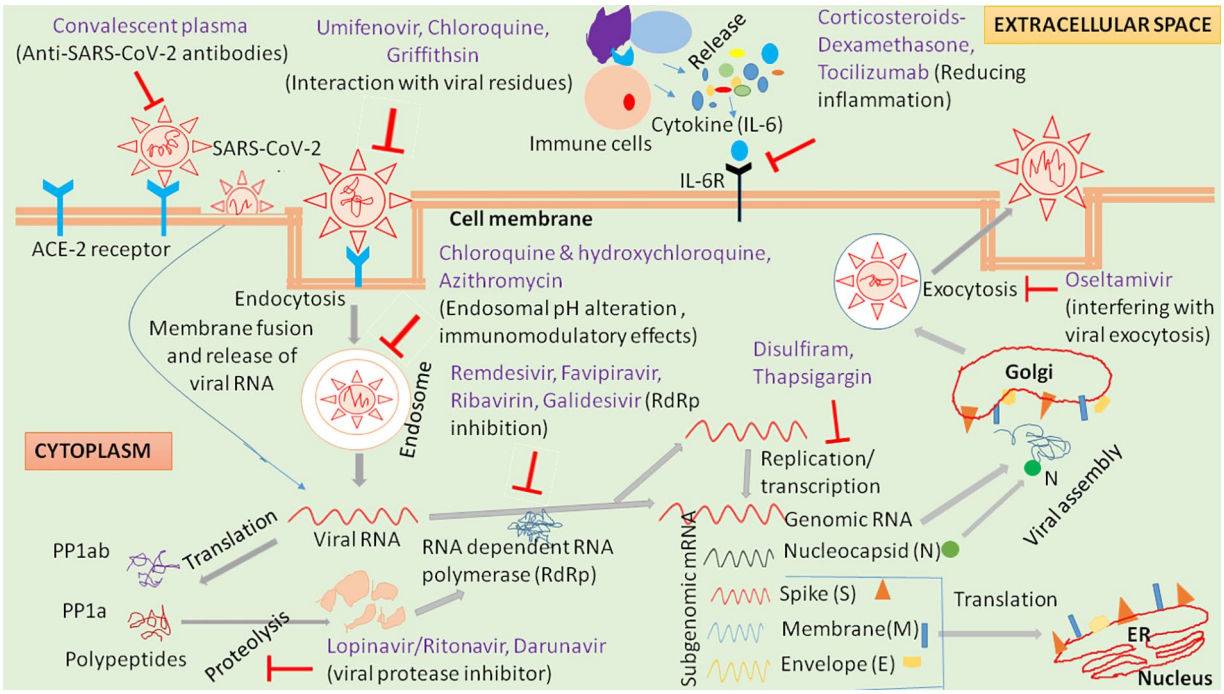

Figure 1. The mechanism of action of potential drugs against SARS-CoV-2. Even though there are no specific drugs for SARS-CoV-2 yet, it has been suggested that a number of drugs used to treat viral diseases, bacterial diseases, parasitic infections, monoclonal antibodies, and different protease inhibitors could be used to treat COVID-19.

anti-coronavirus activity that works against MERS-CoV and SARS-CoV-2, among other viruses.[100] Remdesivir's RdRp inhibitory effect can prevent the reproduction of several coronaviruses in a breathing epithelial cell.[101] Remdesivir has been proven in preclinical trials to be protective against SARS-CoV and MERS-CoV infections by interfering with coronavirus viral polymerase. Remdesivir was also proven to effectively block viral infection in a human cell line (Huh-7 cells from human liver cancer) that is susceptible to 2019-nCoV.[100] The first COVID-19 patient in the United States also saw a dramatic recovery after receiving therapy with intravenous remdesivir.[102] In Korea, the initial patient was administered personalized treatment with remdesivir on the sixth day of hospitalization, followed by intravenous administration on the seventh day, which resulted in no negative responses. Subsequently, vancomycin and cefepime were ceased the following day. Improvement in clinical and respiratory symptoms was observed on the eighth day of hospitalization, accompanied by an increase in oxygen saturation to 94%.[103]

The World Health Organization (WHO) said that remdesivir offered substantial potential as a leading contender for treating COVID-19 at the time of the COVID-19 pandemic's outbreak. Multiple in vivo studies discovered that RDV (remdesivir) led to a decrease in pathological processes, viral load, mild symptoms, and established lung lesions in animals infected with SARS-CoV-2.[104] An intriguing study involved 53 severe COVID-19 patients who received remdesivir treatment. The results indicated clinical improvement in 36 out of the 53 patients (68%). A double-blind, randomized, placebo-controlled trial found that RDV treatment (200 mg on day 1, followed by 100 mg daily for up to 9 days) could help hospitalized patients recover faster with fewer side effects and mortality than the placebo group, as well as evidence of decreased respiratory tract infection.[104] The combination of baricitinib and remdesivir was demonstrated to shorten the duration to recovery within 29 days of beginning therapy as compared to patients who got remdesivir plus a placebo.[105] Notable side effects were observed, including acute respiratory failure, reduced kidney filtration rate, low levels of lymphocytes, fever, high blood sugar, worsened anemia, higher levels of creatinine, and increased liver enzymes.[106] The National Institutes of Health now recommends the combined use of baricitinib and remdesivir only if corticosteroids (such as dexamethasone) cannot be utilized. So, larger studies should be needed to confirm the results. Presently, there are 129 ongoing clinical trials investigating the application of remdesivir in COVID-19 patients.[42]

Ribavirin. The Food and Drug Administration (FDA) has authorized the guanosine analog ribavirin (RBV) as a wide-spectrum antiviral.[107] The hepatitis C virus, enterovirus 71, canine distemper virus, chikungunya virus, Semliki Forest virus, orthopoxvirus, influenza virus, and flavi- and paramyxoviruses have all been demonstrated to be susceptible to this medication's antiviral effects.[108,109] The RNA-dependent RNA polymerase (RdRp) catalyzes RNA synthesis, transcription, and proliferation, as well as virus pathogenesis.[110] Ribavirin is administered intravenously, and targeting the viral RdRp prevents viral RNA formation by stopping viral mRNA production.[111]

This study suggests that ribavirin, RDV, and sofosbuvir may be helpful in the treatment of SARS-CoV-2. In a trial including 115 patients with severe COVID-19 who received intravenous ribavirin, researchers found that ribavirin medication had no effect on mortality when compared to the control group.[43] Elfiky recently recommended using a combination antiviral medication to treat COVID-19.[81] In another trial, RBV was administered alongside lopinavir/ritonavir (LPV/RTV) and IFN-γ to hospitalized COVID-19 patients. This triple treatment was shown to be more effective than LPV-RTV alone at reducing signs and symptoms, reducing viral shedding, and shortening hospital stays in patients with mild to moderate COVID-19. About 400 mg dosage of RBV was evaluated alongside 400 mg/100 mg of LPV/RTV + IFN-γ for 14 days.[112] In one trial, the antiviral medications sofosbuvir/daclatasvir and RBV were compared for the treatment of COVID-19 patients. Sofosbuvir/daclatasvir were more effective than RBV at binding to RdRp and could therefore be utilized to treat COVID-19.[112,113] However, these medications may bind to the COVID-19 RdRp by restricting the protein's activity, resulting in the eventual eradication of the virus. In vivo effects and their safety profile required additional examination. There are now 18 registered clinical studies examining the use of ribavirin in COVID-19 patients.[45]

Molnupiravir. Beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that combats RNA viruses in a variety of ways, is available orally under the name molnupiravir. NHC is taken up by viral RNA-dependent RNA polymerases, which results in virus mutations and deadly recombination.[114,115] Molnupiravir was originally developed for the treatment of influenza at Emory University, USA.[116] The Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for molnupiravir on December 23, 2021. This authorization allows the use of molnupiravir to treat adults with mild to moderate COVID-19 symptoms within 5 days of onset, if they are at a heightened risk of developing severe illness and if other antiviral treatments are not available or suitable from a clinical perspective. A broad-spectrum, orally active antiviral drug called molnupiravir works on the RdRp enzyme by contending with uridine and cytidine triphosphate substrates. This causes A and G to be incorporated into stable complexes in the active RdRp center, which causes mutation and proofreading to be evaded. Molnupiravir's 2-step mutagenesis strategy and "error catastrophe" processes attempt to halt viral reproduction. In other words, it causes the virus to self-destruct.[115] Molnupiravir has shown promise in increasing the frequency of viral RNA mutations and inhibiting SARS-CoV-2 replication in both animal models and humans.[115] Virus mutants might quickly escape not only the immune response within an individual patient but also the antibody repertoire raised in a vaccinated population.[117] However, it also carries the possible risk of inducing mutagenesis in patient DNA, potentially leading to cancer or embryonic damage in pregnant women.[118,119] Due to this risk, pregnant women are not eligible for molnupiravir treatment, and a negative pregnancy test is required before administering the drug.[120]

Several researchers have studied the inhibition of COVID-19 replication by molnupiravir in animal models. In the study conducted by Wahl et al,[121] mice were used to explore the effects of molnupiravir (EIDD-2801) on lung infection. To evaluate the preventative effects, molnupiravir was administered 12 hours prior to infection. The results demonstrated that molnupiravir is more effective at preventing COVID-19 infection if it is administered sooner. Abdelnabi et al[122] studied the impact of EIDD-2801 on the transmission of COVID-19 in ferrets. In this trial, EIDD-2801 was administered 2 times a day (BID)—12 and 36 hours—following oral gavage infection. The impact of molnupiravir on preventing transmission through close contact was also investigated in both the control and treatment groups. The findings indicated that it effectively hinders virus transmission within 24 hours of administration. Another examination of the inhibitory effects of EIDD-2801 on COVID-19 replication in lung epithelial cells of Syrian hamsters exhibited a significant reduction in viral replication, as reported in a separate investigation. In a research effort conducted by Abdelnabi et al,[122] the administration of molnupiravir led to a dose-dependent reduction in viral titer and viral RNA load compared to the control group. Furthermore, this study highlights that delaying the therapy might not completely stop viral replication; however, it could potentially delay the progression of the infection within the hamsters' lungs.

Galidesivir. The antiviral compound galidesivir functions as an analog of adenosine and operates by preventing the function of viral RNA polymerase.[48] It has shown effective against a variety of viruses, including as Zika, Marburg, yellow fever, and Ebola. In vitro assessments have showcased its broad-spectrum efficacy against more than 20 RNA viruses spanning 9 distinct families, encompassing coronaviruses, filoviruses, picornaviruses, togaviruses, bunyaviruses, arenaviruses, orthomyxoviruses, paramyxoviruses, and flaviviruses.[123] BioCryst Pharmaceuticals has initiated a randomized, double-blind, placebo-controlled clinical trial involving individuals with COVID-19 to evaluate the safety, pharmacokinetics (PK), clinical outcomes, and antiviral impacts of galidesivir. Additionally, Brazil is commencing trials with galidesivir in human participants. Consequently, galidesivir presents itself as a promising therapeutic contender for treating severe symptoms of COVID-19 caused by the SARS-CoV-2 virus. Currently, a single clinical study, dedicated to investigating the utilization of galidesivir in COVID-19 patients, has been officially registered.[50]

Paxlovid. Paxlovid, an oral antiviral therapeutic for COVID-19, issued on December 22, 2021, is a combination antiviral drug created by the pharmaceutical company Pfizer. The therapy involves a recently created antiviral medication called nirmatrelvir along with ritonavir, a potent inhibitor of

the enzyme cytochrome P450-3A4 (CYP3A4), which is responsible for processing various types of medications.[124] Ritonavir inhibits the breakdown of nirmatrelvir, raising drug concentrations and delaying elimination. Within 5 days of the beginning of symptoms and as soon as possible after the COVID-19 diagnosis, it should be started. Paxlovid exhibited significant potential in clinical trials, demonstrating an 88% reduction in the risk of hospitalization or death from COVID-19 when administered within 5 days of symptom onset, compared to a placebo.[125] Paxlovid is authorized for managing mild to moderate cases of COVID-19 in individuals aged 12 years and above, weighing a minimum of 40 kg, who have received a positive SARS-CoV-2 test result. This approval is intended for those who face an elevated risk of progressing to severe COVID-19, which could lead to hospitalization or even fatal outcomes. The FDA amended the initial Emergency Use Authorization (EUA) for Paxlovid on April 14, 2022, to permit the presentation of an additional dose pack with the proper dosing for patients with moderate renal impairment within the parameters of the EUA. The U.S. Food and Drug Administration (FDA) authorized paxlovid for emergency use in December 2021, and the government obtained enough of the antiviral medication to treat 20 million people in 2022.[125] Paxlovid is not sanctioned for the prevention of COVID-19 before or after exposure, nor is it approved as an initial treatment for patients who are hospitalized due to severe or life-threatening cases of COVID-19 infection.[51] Paxlovid was finally received full approval by the FDA in May 2023 for the treatment of mild to moderate COVID infection in adults at high risk for severe disease, including hospitalization and death.

By inhibiting a protease needed for viral replication, paxlovid exerts antiviral efficacy. Coronavirus proteases cleave many locations in the viral polyprotein where flexible glutamine replaces pyrrolidone. Due to the coronavirus epidemic, dehydration rates are extremely high. While nirmatrelvir was meant to particularly target SARS-CoV-2 Mpro, in vitro testing revealed that it also inhibited the infectivity of SARS-CoV-1, SARS-CoV-2, MERS, and 229e coronaviruses.[126] When given orally, it also provided protection against SARS-CoV-2 in mice. Pfizer had previously concluded a phase 1 clinical trial involving healthy volunteers and had initiated a phase two-thirds trial for COVID-19 named Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) at the time these findings were disclosed. The phase 1 study explored nirmatrelvir in isolation and in conjunction with ritonavir. Pfizer adopted the combination approach after recognizing that medication levels remained higher for an extended period when used in conjunction, as seen in EPIC-HR, a trial that involved 2246 participants. Among these participants, 1120 received 300 mg of nirmatrelvir and 100 mg of ritonavir, while 1126 received a placebo twice daily for 5 days.[126]

Pfizer disclosed an interim analysis on November 5, 2021, involving 774 patients treated within 3 days of showing symptoms. Among the individuals who received Paxlovid, only 3 out of 389 patients (0.77%) had been admitted to the hospital by the 28th day. In contrast, among the 385 patients who were administered a placebo, 20 had been hospitalized by that time, and an additional 7 had passed away. These 27 individuals constituted 7% of the placebo-administered group. Pfizer eventually released the final data on December 14, 2021, and the findings were subsequently published in the New England Journal of Medicine on February 16.[127] Once more, the main research was restricted to patients who had received Paxlovid within 3 days of the commencement of symptoms. On day 28, 5 of 697 (0.72%) Paxlovid patients were admitted to the hospital. In the placebo group, 35 out of 682 patients had been hospitalized over this period, and 9 had died; these 44 patients represented 6.45% of the placebo group. Upon widening the scope of the analysis to encompass individuals who were administered Paxlovid within 5 days from symptom initiation, the results indicated that out of 1039 patients in the Paxlovid group, eight (0.77%) had been hospitalized due to COVID-19 or had succumbed to any cause by the 28th day. In contrast, among the 1046 patients in the placebo group, 66 (6.31%) had been hospitalized or had passed away within the same timeframe. Unlike molnupiravir, where the comprehensive study findings turned out to be worse than initially stated in a press release by its developers, the interim and final analyses for Paxlovid showcased consistent results.[124]

Paxlovid was approved to treat COVID-19 as it inhibits SARS-CoV-2 3-chymotrypsin-like cysteine protease (3CLpro) also known as main protease (Mpro). The manifestation of SARS-CoV-2 variants with mutations in Mpro further raised the alarm of potential drug resistance. Numerous studies have identified mutations in the Mpro which confer resistance to nirmatrelvir, emphasizing the importance of monitoring their prevalence among circulating strains. Analyzing over 13 million SARS-CoV-2 sequences, approximately 0.5% showed mutations associated with nirmatrelvir resistance, with no significant rise post-Paxlovid approval. The mutations G15S (2070 per million) and T21I (1386 per million) were the most common, and they held dominance in specific lineages of SARS-CoV-2. Other mutations like E166V and S144E, which have been demonstrated to significantly impact nirmatrelvir's ability to inhibit viral replication or protease activity by over 100-fold, were detected in fewer than 1 per million sequences.[128] Another study identified 100 naturally occurring mutations in SARS-CoV-2 Mpro, located at the nirmatrelvir binding site of the Mpro, which could exert resistance to nirmatrelvir and, hence, could impact the effectiveness of Paxlovid. Continued use of Paxlovid may potentially elevate the occurrence of these pre-existing drug-resistant mutants.[129]

Lopinavir/ritonavir (LPV/r). LPV/r is a combined antiviral medication utilized to treat the infection of HIV by blocking the viral protease and acting as a booster for ritonavir.[130] Based on its demonstrated efficacy against SARS-CoV, lopinavir/

ritonavir (LPV/r) is a prospective treatment option for COVID-19 infections.[131] The majority of in vitro investigations have demonstrated that SARS-CoV-2 can be suppressed by lopinavir and that its EC50 is acceptable. In Vero E6 cells, lopinavir exhibited an antiviral activity against SARS-CoV-2 virus with an estimated EC50 of 26.63 μM.[131] The recommended dosage of Lopinavir/Ritonavir is 200 mg/50 mg per capsule, taken twice day by mouth.[132,133]

In a trial conducted in Hong Kong, patients treated with lopinavir/ritonavir plus ribavirin fared better than those treated with ribavirin alone. At 21 days after the onset of symptoms, lopinavir/ritonavir plus ribavirin reduced the probability of acute respiratory distress syndrome (ARDS) or death.[134] Moreover, lopinavir/ritonavir is thought to be a COVID-19 therapeutic option based on clinical research with COVID-19 patients.[133] In alternate research involving 47 COVID-19 patients, the combined therapy of LPV/r alongside the standard of care (SOC) (utilized for 42 patients) exhibited that individuals in the experimental group experienced a quicker return to normal body temperature (4.8 ± 1.94 days) compared to those in the control group (7.3 ± 1.53 days). This is in contrast to the SOC group, which comprised 5 patients treated with arbidol and an IFNα inhaler. According to these findings, patients who received LPV/r and pneumonia-related adjuvant medications had a higher chance of recovering their normal body temperature. Patients in the test group were able to get negative more quickly (7.8 ± 3.09 vs 12.0 ± 0.82 days for the control group).[135] Although lopinavir/ritonavir is suggested as prospective treatment for COVID-19, neither lopinavir nor ritonavir acts as an inhibitor of Mpro.[136,137]

In a randomized study involving 199 severe COVID-19 patients, the inclusion of LPV/r (administered at a dose of 400/100 mg twice a day for 14 days) to the standard treatment regimen did not result in a significant reduction in the duration required for clinical improvement when compared to the sole utilization of standard care. In addition, LPV-RTV treatment was related to a lower mortality rate, a shorter length of stay in the intensive care unit, and fewer gastrointestinal side effects. Due to unfavorable effects, the therapy of 13 patients with lopinavir–ritonavir was discontinued early.[138] In another study, patients with COVID-19 who were given LPV-RTV had a higher risk of bradycardia, which is when the heart rate drops to less than 60 beats per minute for more than 24 hours. Because of this, the amount of LPV-RTV was cut back or stopped. As a result, the patients' bradycardia went away.[139] At the moment, 92 clinical trials have been signed up to look into how LPV/RTV works in COVID-19 patients.[55]

Favipiravir. A novel RNA-dependent RNA polymerase (RdRp) inhibitor called favipiravir (FPV) has been utilized to treat influenza virus.[140] It also stopped the spread of many RNA viruses, like the Arena, Bunya, Flavi, and Ebola viruses.[140,141] The RdRp gene of the 2019-nCoV, a single-stranded RNA beta-coronavirus, is nearly identical to those of SARS-CoV and MERS-CoV. This was found by sequencing the virus's genome.[100,142] Favipiravir is going through a lot of clinical trials and in vitro tests right now to help treat COVID-19 patients.[110] The administration of the treatment is through oral intake, with the initial effective dose being 500 mg on the first day. This is followed by 2 subsequent doses of 600 mg each day for the next 13 days. Additionally, the treatment regimen includes the use of interferon-alpha, which is inhaled through an aerosol. This inhalation is performed twice a day, with each inhalation consisting of 5 million units of interferon-alpha.[110,142]

Patients with SARS-CoV-2 who take high doses of favipiravir have strong antiviral effects. In a Japanese study, FPV was also used to stop COVID-19 patients' inflammatory mediators and pneumonia from getting worse. FPV is also used to improve lung histology in severe or critical COVID-19 patients.[143] In an open-label controlled investigation involving 80 patients, the participants were divided into 2 groups. The first group, known as the FPV group, received oral FPV treatment, which consisted of 1600 mg twice daily on the first day, followed by 600 mg twice daily from days 2 to 14. Additionally, this group received IFN-γ via aerosol inhalation, with each inhalation containing 5 million international units and performed twice daily. The second group, referred to as the control group, was administered LPV/RTV treatment, which involved 400 mg of LPV and 100 mg of RTV taken twice daily from days 1 to 14. Similar to the FPV group, the control group also received IFN-γ through aerosol inhalation, with each inhalation containing 5 million international units and performed twice daily. Their results showed that the FPV group responded better to COVID-19 treatment in terms of disease progression, improvement in chest imaging, and removal of the virus.[144] In another study, however, favipiravir did not seem to stop the SARS-CoV-2 virus in the lab at concentrations below 100 μM.[38]

In a randomized clinical trial, 120 people who got favipiravir and 120 people who got arbidol were compared. Among individuals diagnosed with mild to moderate COVID-19, the percentage of clinical recovery after a span of 7 days was observed to be 55.86% in the arbidol-treated group and 71.43% in the favipiravir-treated group. Even though favipiravir didn't make a big difference in the clinical recovery rate at Day 7, it did make a big difference in how long it took for fever and cough to go away compared to arbidol[142] Antiviral therapy, specifically favipiravir combination with lowered immunosuppression and anti-IL6 receptor antibody, is associated with positive outcomes.[145] Nonetheless, these first clinical data provide valuable information regarding the use of FPV to treat COVID-19 infection. As of now, there are 65 registered clinical trials focused on exploring the utilization of favipiravir in patients diagnosed with COVID-19.[58,145]

Griffithsin. Griffithsin is an antiviral lectin produced from *Griffithsia* sp.[146] It was developed to provide broad-spectrum antibacterial activity as a microbicide. By attaching to the viral surface glycoproteins such as HIV glycoprotein 120, it can

limit human immunodeficiency virus (HIV) infection.[146-148] The phase I clinical trial using griffithsin as an anti-HIV microbicide to prevent sexual transmission of HIV in healthy populations confirmed its human safety.[147] The antiviral activity of griffithsin is likely attributable to the presence of numerous sugar-binding sites that give a vast number of attachment sites for complex carbohydrate molecules present on viral envelopes.[148] Griffithsin blocks viral entrance by binding specifically to the SARS-CoV or MERS-CoV spike glycoprotein.[147] Considering the substantial similarity between the spike proteins of SARS-CoV and the newly identified SARS-CoV-2, it becomes crucial to evaluate the potential effectiveness of griffithsin as a promising antiviral agent for treating patients with COVID-19.[149]

Umifenovir (arbidol). Umifenovir (UFV), commonly known as Arbidol (ARB), is a Russian antiviral medication used to treat influenza and hepatitis C. It is widely used in Russia and China, and to a lesser extent in other nations, but not in the United States.[150,151] ARB works by preventing the virus's communication with its host cells. This is achieved by obstructing the fusion of the viral capsid with the target cell membrane, thereby impeding the virus's ability to enter the target cell. Within the concentration range of 10 to 30 M, ARB has demonstrated the capability to effectively prevent COVID-19 infection.[151] It is administered orally to adults in doses of 200 mg 3 times a day for up to 10 days.[142] According to one trial, ARB monotherapy may be preferable than lopinavir/ritonavir in the treatment of COVID-19 patients.[142] Another open-label randomized controlled trial found that ARB, when compared to lopinavir/ritonavir, significantly improves clinical and laboratory outcomes, such as peripheral oxygen saturation, ICU admissions, hospitalization duration, chest computed tomography (CT) involvements, white blood cell count (WBC), and erythrocyte sedimentation rate (ESR).[152]

Patients with COVID-19 who were administered UFV alongside LPV/RTV exhibited more favorable results compared to those who solely received LPV/RTV treatment.[153] The administration of umifenovir was considered safe and was associated with a heightened rate of negative PCR test results by the 14th day in adults who were confirmed to have COVID-19 through laboratory assessments. However, it was not able to significantly reduce the duration required for nucleic acid negative conversion or the length of hospital stay (LOS). It also couldn't improve symptoms or lower the risk of the disease getting worse. There is no evidence that using umifenovir will improve patient-important outcomes in COVID-19 patients.[61] At the moment, 15 clinical trials have been signed up to look into how COVID-19 patients can use umifenovir.[63]

Thapsigargin. Researchers have identified an antiviral medication derived from plants.[154] The research was conducted at Nottingham University in the United Kingdom. The study shows that thapsigargin is an effective broad-spectrum host-centered antiviral innate immune response against 3 respiratory viruses, including Covid-19 virus (SARS-CoV-2), respiratory syncytial virus (RSV), and influenza A virus, and may have significant implications for how future pandemics are mitigated. Through cell and animal investigations, it was determined that thapsigargin exhibits efficacy against viral infections when administered both before and during active disease. Additionally, it has the capability to hinder the production of new virus copies within cells for a minimum of 48 hours following a single 30-minute exposure.[155] Recent studies have shown that thapsigargin, an inhibitor of the sarcoplasmic/endoplasmic reticulum (ER) Ca^{2+} ATPase pump, at levels that do not cause cell toxicity, triggers a robust innate immune antiviral response within the host. The respiratory syncytial virus (RSV), the common cold coronavirus OC43, the SARS-CoV-2 virus that causes COVID-19, and the influenza A virus are all successfully prevented from replicating by this response.[155] Thapsigargin demonstrated superior antiviral activity compared to remdesivir and ribavirin in inhibiting OC43 and RSV, respectively. The hypothesis posits that thapsigargin, or its derivatives, holds significant potential as a broad-spectrum inhibitor against SARS-CoV-2, OC43, RSV, and the influenza virus. This is grounded in its ability to effectively impede these distinct viruses both prior to and during active infection, alongside its demonstrated antiviral effectiveness that extends for at least 48 hours post-exposure.[155]

Protease inhibitors

SARS-CoV-2 Mpro and PLpro inhibitors. The SARS-CoV-2 produces 2 polyproteins pp1a and pp1ab that are cleaved by the viral main protease (Mpro) and papain-like protease (PLpro) to produce the non-structural proteins (nsp)1 to 16. PLpro cleaves nsp1-3 at its *LXGG* recognition sites while Mpro cleaves the remaining downstream non-structural proteins (nsp4-16).[156] Due to the involvement of viral Mpro and PLpro in regulating viral genomic RNA replication, viral polyprotein processing, disrupting the host immune system by interacting with and modifying host proteins, and being common to most coronaviruses—including SARS-CoV, MERS-CoV, and SARS-CoV-2, Mpro and PLpro stand as crucial therapeutic targets for the development of medications against SARS-CoV-2.[157-161]

In an attempt to develop Mpro and PLpro based drugs against SARS-CoV-2, an in vitro screening was performed using the 2560 compounds from the Microsource Spectrum library. This study identified several compounds as potent inhibitors—2 compounds for Mpro and 8 compounds for PLpro. Among these compounds, the quaternary ammonium compound cetylpyridinium chloride showed inhibitory activity against both enzymes ($IC_{50} = 2.72 \pm 0.09\,\mu M$ for PLpro and $IC_{50} = 7.25 \pm 0.15\,\mu M$ for Mpro). A second inhibitor of PLpro was the selective estrogen receptor modulator raloxifene which also showed dual activity ($IC_{50} = 3.28 \pm 0.29\,\mu M$ for PLpro and $IC_{50} = 42.8 \pm 6.7\,\mu M$ for Mpro). Moreover, several kinase

inhibitors were also tested and, consequently, olmutinib (IC_{50} = 0.54 ± 0.04 μM), bosutinib (IC_{50} = 4.23 ± 0.28 μM), crizotinib (IC_{50} = 3.81 ± 0.04 μM), and dacominitinib (IC_{50} = IC_{50} 3.33 ± 0.06 μM) were identified as PLpro inhibitors. This study suggests that other known kinase inhibitors could be repurposed as potential PLpro inhibitors, hence, could facilitates the COVID-19 treatment opportunities.[162] Recently Hersi et al performed a phenotypic screening using an in-house pilot compounds collection possessing a diverse skeleta against SARS-CoV-2 PLpro. The researchers found SIMR3030 serves as a potent inhibitor of SARS-CoV-2 by exhibiting deubiquitinating activity and inhibition of SARS-CoV-2 specific gene expression (ORF1b and Spike) in infected host cells and possessing virucidal activity. Moreover, the in vitro absorption, distribution, metabolism, and excretion (ADME) assessment of the drug-likeness properties of SIMR3030 demonstrated good microsomal stability in liver microsomes.[163] A synthetic noncovalent PLpro inhibitor Jun12682 inhibited SARS-CoV-2 and its variants, including nirmatrelvir-resistant strains with EC50 from 0.44 to 2.02 μM in vivo. Oral treatment with Jun12682 in a SARS-CoV-2 infected mouse model improved survival and reduced viral loads and lesions in lung, suggesting that Jun12682 PLpro inhibitor could be a promising oral antiviral candidate for the treatment of SARS-CoV-2 infection.[164] Using a FRET-based enzymatic assay, several molecules including boceprevir, GC-376, calpain inhibitor II and calpain inhibitor XII were identified to exert potent inhibitory activity against of SARS-CoV-2 Mpro with single-digit to submicromolar IC_{50} values. Moreover, these 4 compounds (boceprevir, GC-376, calpain inhibitors II and XII) were also found to exhibit antiviral activity against SARS-CoV-2 through inhibiting viral replication in cell culture with EC_{50} values ranging from 0.49 to 3.37 μM.[136] In a study, numerous inhibitors were initially targeted for SARS-CoV-1 PLpro but have shown efficacy against SARS-CoV-2 PLpro, with GRL0617 being a notable example. GRL0617 inhibits SARS-CoV-2 PLpro as a reversible competitive inhibitor. Various other compounds, including repurposed drugs and peptide-based molecules, have been investigated, with many drawing inspirations from GRL0617's structure.[165,166] In another study, several naphthalene-based compounds were synthesized and tested for their potential inhibitory action against SARS-CoV-2 PLpro. One of these compounds (GRL0617) was identified previously as a specific SARS-CoV PLpro inhibitor, and showed good potency and low cytotoxicity in SARS-CoV-infected Vero E6 cells. In this study, 7 compounds were tested through biochemical, whole cell, and high-resolution crystallographic studies which suggest that all the 7 compounds can hinder SARS-CoV-2 PLpro protease activity. The compounds are designated as follows: 1 is 5-amino-2-methyl-*N*-[(1*R*)-1-naphthalen-1-ylethyl]benzamide (GRL0617), 2 is 5-carbamylurea-2-methyl-*N*-[(1*R*)-1-naphthalen-1-ylethyl]benzamide, 3 is 5-acrylamide-2-methyl-*N*-[(1*R*)-1-naphthalen-1-ylethyl]benzamide, 4 is 3-amino-*N*-(naphthalene-1-yl)-5-trifluoromethyl)benzamide, 5 is 5-(butylcarbamoylamino)-2-methyl-*N*-[(1*R*)-1-naphthalen-1-ylethyl]benzamide, 6 is 5-(((4-nitrophenoxy)carbonyl)amino)-2-methyl-*N*-[(1*R*)-1-naphthalen-1-ylethyl]benzamide, and 7 is 5-pentanoylamino-2-methyl-*N*-[(1*R*)-1-naphthalen-1-ylethyl]benzamide.[167] Therefore, the above-mentioned inhibitors of SARS-CoV-2 Mpro and PLpro could serve as the foundation for developing new drugs to combat the COVID-19 pandemic and may pave the way for the development of novel therapeutics for a possible future outbreak of new SARS-CoV-2 variants or other coronavirus species.

Darunavir. An antiretroviral protease inhibitor is darunavir (DRV). It is employed for the treatment and prevention of acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infections.[168,169] Darunavir (300 μM), according to in vitro tests, inhibits viral replication.[170] The third-generation antiviral medicine darunavir, which is used to suppress the viral protease, is advised by international guidelines for the treatment of HIV/AIDS. It may be supplemented with ritonavir or cobicistat. In the treatment of HIV/AIDS, it is more effective and tolerable than lopinavir/ritonavir. Based on in vitro evidence showcasing its potential to combat the disease, darunavir is currently under investigation as a potential treatment for SARS-CoV-2. Ritonavir or cobicistat should be used as a boosting agent when administering DRV because earlier studies of un-boosted DRV showed subtherapeutic drug levels and a higher rate of side events.[168] In vitro tests show that darunavir has potential antiviral action against SARS-CoV-2. At clinically meaningful doses, DRV has minimal antiviral efficacy against SARS-CoV-2 (EC_{50} > 100 μM).[171] Darunavir with cobicistat (DRV/c) failed a single-center, open-label, randomized, controlled trial at the Shanghai Public Health Clinical Center (SPHCC) treating 30 COVID-19 patients.[171] Due to an increase in dispensation during the COVID-19 epidemic, a growing insufficiency of lopinavir/ritonavir was observed in Italy; thus, the use of darunavir/ritonavir 800/100 mg once daily (OD) or darunavir/cobicistat 800/150 mg once daily (OD) was suggested as an alternative treatment in case of lopinavir/ritonavir shortage.[172] Presently, there are 10 registered clinical trials focused on exploring the utilization of darunavir in patients diagnosed with COVID-19.[68]

Disulfiram. Disulfiram (DSF) is a supportive medicine used to treat chronic alcoholism by inhibiting acetaldehyde dehydrogenase and is being studied as a potential treatment for cancer and HIV infection.[173] According to a study from 2018, it was observed that the substance could hinder the PLpro activity of both MERS-CoV and SARS-CoV. It works as a competitive (or mixed) inhibitor for SARS-CoV PLpro while working as an allosteric inhibitor for MERS-CoV PLpro.[174] Disulfiram, an FDA-approved medication utilized for the treatment of alcoholism, has shown promise as a therapeutic option for COVID-19.

It suppresses viral replication by impeding Mpro protease and zinc release and exerts anti-inflammatory effects on SARS-CoV-2 by diminishing cytokine production induced by NF-kB and Nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome.[71] Another study stated that disulfiram is a non-specific Mpro or PL^{pro} inhibitor and its antiviral activity might not involve inhibiting viral proteases in the presence of reducing reagent 1,4-dithiothreitol (DTT) as judged by FRET-based enzymatic assay, thermal shift assay, native mass spectrometry, cellular antiviral assays, and molecular dynamics simulations.[175] According to one study, using disulfiram may help to minimize the occurrence and severity of COVID-19.[176] Although symptoms consistent with COVID-19 were significantly decreased in the disulfiram group, a different study on 1297 patients revealed no significant difference in laboratory-confirmed COVID-19, associated hospitalization, or pneumonia.[177] If disulfiram is successful in clinical studies, it could be a good contender as a generic anti-COVID-19 therapy for global distribution, including to low-income communities. At present, 2 ongoing clinical trials have been initiated to assess the utilization of disulfiram in patients with COVID-19.[71]

Monoclonal antibody

Tocilizumab. Tocilizumab is a genetically engineered humanized monoclonal antibody belonging to the Immunoglobulin G1 class. It has the capacity to attach to both the soluble form of the interleukin-6 receptor (sIL-6R) and the receptor present on cell membranes (mIL-6R), effectively inhibiting both conventional and trans-signals.[178] Interleukin-6 (IL-6) is a cytokine with involvement in numerous diverse biological functions, including the activation of T-cells, tissue fibrosis, and lipid metabolism. Most immune cells and stromal cells, such as B lymphocytes, T lymphocytes, macrophages, monocytes, nerve fiber cells, mast cells, etc., release IL-6.[179] Also, high levels of IL-6 can cause cytokine release syndrome (CRS).[180] This is because IL-6 is involved in the pathogenesis of several anti-inflammatory processes. A complex is created when IL-6 and IL-6R bind to one another. Later on, it interacts to glycoprotein 130 (gp-130) to initiate signaling and gene expression. In the classical signal transduction pathway, IL-6 binds to mIL-6R and then binds to gp-130 to start reactions like anti-inflammatory effects. In the trans-signaling pathway, IL-6 binds to sIL-6R and then to gp-130, which starts signal transduction inside the cell.[181] In the next steps, 2 different signaling pathways were used to make acute reactive protein. The JAK/STAT pathway is one way that IL-6 sends signals, and the Ras/mitogen-activated protein kinase (MAPK)/NF-κB-IL-6 pathway is another.[182] Cytokine storm is a key reason why COVID-19 is spreading so quickly. So, treating a cytokine storm is a very important part of saving the lives of very sick people. There isn't a particular medication available right now to treat SARS-CoV-2 or the COVID-19-induced cytokine storm. Tocilizumab, a medication that hinders the IL-6 receptor, leading to the suppression of the signaling cascade in the downward direction (as shown in Figure 2), has gained approval from the US FDA for the treatment of cytokine release syndrome (CRS).[182]

In a pilot study in China, patients with COVID-19 were given a single dose of tocilizumab 400 mg/iv. If the patients didn't respond well, a second dose could be given. After treatment with tocilizumab, 21 patients in this study showed a significant improvement in their lung function and fever, and their IL-6 level went down.[183] In one study, 3924 people with severe COVID-19 were given tocilizumab early on. Patients who got tocilizumab in the first 2 days were less likely to die (29%) than those who didn't get it (41%).[184,185] In another study with 243 hospitalized people who had moderate COVID-19, tocilizumab did not work to keep people from needing a breathing tube (intubation) or dying. On day 28 of this study, 11% of the people who got tocilizumab had died, while 13% of the people who didn't get the drug had died. No meaningful statistical distinction was found between the 2 groups.[184,185] A number of FDA phase III clinical trials involving tocilizumab for COVID-19 patients are still in progress. Additionally, a recent study by Xu et al[186] has been published, demonstrating the noteworthy improvement of clinical symptoms and a deceleration in disease deterioration among severe COVID-19 patients due to tocilizumab treatment. This suggests that tocilizumab holds effectiveness in treating individuals severely affected by COVID-19. Currently, there are 96 registered clinical trials investigating the application of tocilizumab in COVID-19 patients.[75]

AZD7442 (Tixagevimab and cilgavimab). AZD7442 is composed of 2 entirely human monoclonal antibodies, tixagevimab and cilgavimab, both of which possess the ability to neutralize SARS-CoV-2. These antibodies were derived from B cells that were exposed to SARS-CoV-2 infection.[187] These antibodies feature the L234F/L235E/P331S (TM) alteration, which decreases Fc receptor and complement component C1q binding, and the half-life-extending M252Y/S254T/T256E (YTE) modification.[188] To efficiently eliminate the virus, ixagevimab and cilgavimab bind to distinct, nonoverlapping epitopes of the SARS-CoV-2 spike-protein receptor-binding domain. In addition to having positive preventative and therapeutic effects in nonhuman primates, AZD7442 has been shown in vitro to be effective at neutralizing SARS-CoV-2 and its problematic variants.[189]

Within the ongoing phase 3 trial led by Levin et al,[187] adults aged 18 years and above, who were at a heightened risk of an insufficient response to COVID-19 vaccination, an elevated risk of encountering SARS-CoV-2 exposure, or both, were enrolled. They were then randomly divided into 2 groups at a ratio of 2:1. One group received a solitary dose of AZD7442 (consisting of 2 consecutive intramuscular injections, each containing tixagevimab and cilgavimab) at a dosage of 300 mg, while the other group received a saline placebo. Over a

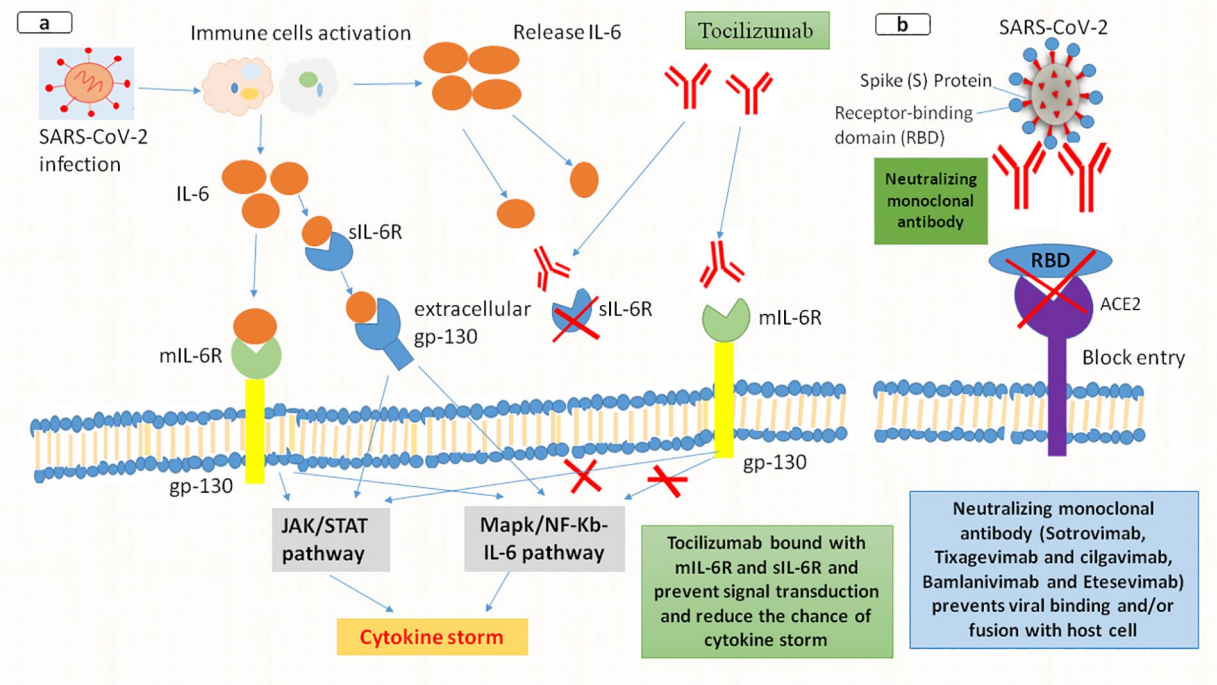

Figure 2. The mechanism of action of monoclonal antibodies against SARS-CoV-2: (a) suppression of SARS-CoV-2 induced cytokine storm by Tocilizumab. It exhibits a strong attraction to the IL-6 receptor, impeding the binding of IL-6 to the receptor and rendering IL-6 ineffective in inducing immune-related harm to target cells. This action subsequently mitigates inflammatory reactions and (b) neutralizing monoclonal antibodies thwart the engagement of SARS-CoV-2 with its target cells. These antibodies impede the virus from adhering to and entering human cells, effectively neutralizing it through their binding to a conserved segment on the spike protein of SARS-CoV-2.

period of up to 183 days, these participants were observed. The development of symptomatic COVID-19 (SARS-CoV-2 infection verified by reverse-transcriptase-polymerase chain reaction test) following the treatment of either AZD7442 or a placebo served as the key indicator of efficacy, and this was tracked up to day 183.[187] Moreover, COVID-19 symptoms were reported by 8 of the 3441 people in the AZD7442 group (0.2%) and 17 of the 1731 people in the placebo group (1.0%). The relative risk goes down by 76.7% because of this effect. Within the placebo-administered group, there were instances of severe or critical COVID-19 observed, totaling 5 cases. Furthermore, 2 fatalities attributed to COVID-19 were recorded in this group.[187]

Sotrovimab. Several sarbecoviruses, notably SARS-CoV-1, the cause of the SARS pandemic 20 years ago, are neutralized by the human monoclonal antibody sotrovimab, formerly known as VIR-7831.[190] In actuality, a SARS-CoV-1 patient provided the parental form of sotrovimab, S309.

The unapproved chemical sotrovimab may be used in an emergency after receiving approval from the US Food and Drug Administration (FDA) through an Emergency Use Authorization (EUA). This approval is for the treatment of mild-to-moderate COVID-19 cases in adult and pediatric patients (12 years of age and older, weighing at least 40 kg), who have tested positive for the SARS-CoV-2 virus directly and are at a high risk of progressing to severe COVID-19, which includes the potential for hospitalization or fatal outcomes.[191] It exhibits a strong binding affinity, with a dissociation constant (Kd) of 0.21 nM, to a remarkably conserved site on the receptor binding domain (RBD) of the spike (S) protein in SARS-CoV-2. Notably, it doesn't hinder the binding of the human angiotensin-converting enzyme 2 receptor. The Fc domain of sotrovimab features amino acid substitutions M428L and N434S (referred to as the LS modification), enhancing the antibody's half-life without influencing the wild-type Fc-mediated effector functions in cell culture.[37]

In a study on sotrovimab, 41 patients were hospitalized (18.6%) after receiving sotrovimab, while 179 patients were not hospitalized (81.4%).[91] This finding is consistent with the findings of Gupta et al.[78] It contained 583 COVID-19 patients who had been treated (sotrovimab, 291; placebo, 292). Compared to the placebo group, which saw 21 (7%) patients advance to the main outcome end-point, COVID-19 progression was decreased by 85% (97.24% interval of confidence), with just 3 (1%) patients in the sotrovimab group. One of the 5 patients brought to the ICU who received a placebo died on the 29th day.[78] his aligns with a study carried out by Verderese et al,[192] wherein 707 individuals confirmed to have COVID-19 were administered NmAb. Participants who received the monoclonal antibody infusion exhibited notable advantages such as a substantially reduced hospitalization rate (5.8% compared to 11.4%), a shorter average length of hospital stay (5.2 days vs 7.4 days), and fewer visits to the emergency department

within the 30 days after the index event (8.1% vs 12.3%) when compared to the control group.This study examined how patients' symptoms changed after taking sotrovimab, finding that shortness of breath (SOB) worsened in 43 patients (19.5%) and improved in 177 patients (80.5%). Cough symptoms worsened in 43 individuals (19.5%) while improving in 177 patients (80.5%). The radiological progression of patients, as observed through chest X-rays, displayed a deterioration in 43 individuals (19.5%) and an improvement in 177 individuals (80.5%).[192]

According to Hurt and Wheatley, the efficiency of mAbs in persons with COVID-19 who are hospitalized varies, highlighting the problem of antiviral drugs in subjects who progressed to severe disease. Conversely, initial observations suggest a promising potential for monoclonal antibodies (mAbs) in providing effective prevention against COVID-19.[193] Chen et al conducted a study aimed at assessing the effectiveness of mAbs in mitigating COVID-19 symptoms. The investigation analyzed the alterations in the baseline symptoms score between the groups treated with LY-CoV-555 and the placebo. The symptoms score ranges from 0 to 24, encompassing 8 domains rated from 0 (absence of symptoms) to 3 (severe symptoms).[194]

Bamlanivimab and etesevimab. Bamlanivimab is a genetically engineered neutralizing monoclonal antibody (mAb) that specifically targets the spike protein of SARS-CoV-2. Its purpose is to hinder the virus from attaching to and entering human cells, ultimately leading to viral neutralization and the potential for treating COVID-19 (Figure 2). A monoclonal antibody called etesevimab eliminates the SARS-CoV-2 surface spike protein. Lilly and AbCellera developed the bamlanivimab antibody, which is used to prevent and cure COVID-19. Bamlanivimab was given an Emergency Use Authorization (EUA) by the FDA on November 9, 2020, allowing it to be used to treat mild to moderate COVID-19 instances in people 12 years of age and older who are at an increased risk of hospitalization.[80] In a study of 577 patients, bamlanivimab lowered viral load, symptoms, and hospitalization rates when compared to placebo.[81] The FDA approved EUA on February 9, 2021 for the combination of bamlanivimab and etesevimab to be used together for mild or moderate COVID-19 in high-risk patients. Another trial found that, compared to placebo, the combination of bamlanivimab (2800 mg) and etesevimab (2800 mg) significantly decreased SARS-CoV-2 viral load at day 11 and also decreased hospitalization and mortality rates at day 29.[81]

Anti-parasitic drugs

Chloroquine (CQ) and hydroxychloroquine (HCQ). Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines that have been utilized for over 50 years to treat malaria and autoimmune illnesses. In addition, these 2 medicines have immunomodulatory properties that allow them to be utilized to treat autoimmune illnesses such as rheumatoid arthritis and systemic lupus erythematosus.[195,196] In addition, this medication is antiviral against SARS-CoV. By increasing the endosomal pH required for virus/cell fusion and obstructing the glycosylation of SARS-CoV cellular receptors, chloroquine has the potential to prevent infection with the virus. The pH of lysosomes is also changed by chloroquine, and it is likely that this suppresses the cathepsins necessary for the formation of the autophagosome that breaks the SARS-CoV-2 spike protein.[100,107] In addition, chloroquine, by inhibiting MAP-kinase, conflicts with SARS-CoV-2 molecular crosstalk, affecting the assembly of virion, sprouting, and proteolytic processing of the membrane protein (M-Protein) concurrently. SARS-CoV-2 employs surface receptor angiotensin-converting enzyme 2 (ACE2), and chloroquine can also inhibit ACE2 receptor glycosylation, hence preventing SARS-CoV-2 adhesion to targeted cells.[100,197]

Recently, a team of Chinese scientists that examined the impact of chloroquine in vitro (using a Vero E6 cell line contaminated with SARS-CoV-2) discovered that chloroquine is particularly effective at reducing viral replication and hospital stays. In this trial, 500 mg of chloroquine was administered twice daily to individuals with mild, moderate, and severe COVID-19 pneumonia.[100,198] According to reports, HCQ eliminates SARS-CoV-2 in vitro better than CQ. It is effective against viruses both before and after the onset of illness. In fact, HCQ might prevent the glycosylation of ACE2. As a result, ACE2 on host cells would have a harder time binding to the SARS-CoV-2 spike protein. Additionally, HCQ may stop the virus from connecting with the host cell by preventing proteases from cleaving coronavirus surface spike proteins.[198,199] Gautret et al[200] did a clinical trial study with people who had COVID-19 infections and took 600 mg of hydroxychloroquine every day. Researchers found that hydroxychloroquine helped to reduce the number of viruses in these COVID-19 people. Most patients felt much better after taking azithromycin and hydroxychloroquine together for 3 to 6 days.[200] Recent in vitro studies have demonstrated that CQ and HCQ may successfully prevent SARS-CoV-2 infections in Vero E6 cells (EC_{50} values of 2.71 and 4.51 mM, respectively).[201] Even in the early stages of COVID-19, low doses of HCQ help patients live longer.[202] Zhou et al[198] made it clear that HCQ may be a better treatment for SARS-CoV-2 infection than chloroquine. By lowering the expression of T cells, HCQ is anticipated to decrease the rapid advancement of COVID-19 toward cytokine storm.[198] Currently, 287 and 94 clinical studies, respectively, have been filed to examine the use of CQ and HCQ in COVID-19 patients.[84]

Nitazoxanide. The antiparasitic drug nitazoxanide has received FDA approval and has been shown to be effective against a number of viruses, including coronaviruses, influenza, hepatitis C, respiratory syncytial virus, parainfluenza, rotavirus, norovirus, and hepatitis B virus.[203] It has not yet been tested on

COVID-19 patients; however, it has previously demonstrated a low in vitro effective concentration (EC50) against the coronaviruses MERS and SARS. Nitazoxanide was consequently considered an attractive candidate for suppressing SARS-CoV-2. To evaluate inhibitory potential, researchers compared the highest serum concentration (Cmax) of nitazoxanide with the in vitro EC50 for nitazoxanide in the course of therapy of SARS-CoV-2. With matching EC_{50} values of 2.12 and 0.80 M, nitazoxanide has considerable in vitro activity against SARS CoV-2 and MERS CoV in Vero E6 cells. This broad antiviral effectiveness is believed to be a result of the mode of action, which involves the inhibition of overall viral replication pathways as opposed to infection-specific processes.[204] In contrast to other proposed medicines, nitazoxanide demonstrated an elevated ratio of maximum plasma concentration (Cmax) to the concentration needed to block 50% of SARS-CoV-2 replication (EC_{50}) (Cmax: EC_{50} roughly comparable to 14:1) after 1 day of administration of 500 mg twice a day.[204] Administration of nitazoxanide may be useful against SARS-CoV-2 to prevent complications, hence lowering the institutional and societal transmission of the virus and mortality. It has been observed that the combination of nitazoxanide with other medications such as azithromycin and hydroxychloroquine could be effective. Moreover, nitazoxanide is known to increase the synthesis of IFN-α and IFN-β that have been demonstrated to possess anti-MERS-CoV and anti-coronavirus action in vitro. Furthermore, when 600 mg of nitazoxanide was administered twice daily for 5 days to patients with acute, uncomplicated influenza, it was shown to minimize the duration of symptoms with few adverse effects.[205] There are currently 31 registered clinical studies examining the use of nitazoxanide in COVID-19 patients.[87]

Ivermectin. Ivermectin is an oral medicine utilized for treating parasitic infections that has FDA approval.[206] It was found to impede the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro.[207] Regarding the replication of HIV-1, ivermectin is a strong inhibitor of the importin-α/β-assisted transportation of viral proteins into the cell nucleus. Research has demonstrated that ivermectin impedes the replication of diverse RNA viruses, including HIV, chikungunya virus, and yellow fever virus, by influencing the importin-α/β-driven movement of viral proteins within the nucleus.[199,206] One study revealed ivermectin to be an efficient inhibitor of the SARS-CoV-2 in vitro, with a single dose of 5 M to Vero-hSLAM cells 2 hours after SARS-CoV-2 infection causing a 5000-fold reduction in viral RNA after 48 hours compared to the vehicle DMSO.[206] Another small study with 280 patients who received ivermectin in Florida between March and May 2020 revealed a lower death rate compared to standard care (13% vs 25%).[208] In a controlled clinical study that followed randomized, double-blind, and placebo-controlled protocols, a total of 72 patients who were hospitalized in Dhaka, Bangladesh, were separated into 3 distinct groups. The first group received only oral ivermectin (12 mg per day) for a span of 5 days. The second group was administered a combination of ivermectin (12 mg) and doxycycline (200 mg) on the initial day, followed by 100 mg of doxycycline every 12 hours for the subsequent 4 days. The third group was given a placebo as a control. In the ivermectin treatment arm, virological clearance occurred earlier than in the placebo group, but not in the ivermectin plus doxycycline treatment arm. And it was safe and effective for treating COVID-19 in adults with moderate disease.[207] The FDA suggested in March 2021 that ivermectin should not be applied to treat COVID-19. However, additional in vitro, in vivo, and clinical experiments are required to determine its relevance and efficacy in COVID-19 treatment. Currently, 90 clinical trials investigating the use of ivermectin in COVID-19 patients have been registered.[90,207]

Antibacterial drugs

Teicoplanin. Teicoplanin is a glycopeptide drug that is approved by the FDA and is often used to treat bacterial infections. It has been shown to stop the first stage of the MERS-CoV virus's life cycle in human cells.[91] Teicoplanin has been added to the list of potential substances that might be used to treat COVID-19 since it was effective in vitro against SARS-CoV.[153] Numerous viruses, including the flu virus, Ebola virus, hepatitis C virus, flavivirus, human immunodeficiency virus (HIV), and coronaviruses including MERS-CoV and SARS-CoV, have been successfully treated with this antibiotic in the past. Currently, it is utilized to treat bacterial infections caused by Gram-positive organisms, mainly staphylococcal infections.[209] In a particular research study, it was found that teicoplanin has the capability to hinder the low-pH cleavage activity of cathepsin L on the viral spike protein within late endosomes. This interference effectively prevents the discharge of genomic viral RNA, halting the progression of the virus replication process in the early phases of the MERS-CoV coronavirus's life cycle.[210]

Recent research has indicated that the IC_{50} concentration of teicoplanin in a laboratory setting is 1.66 μM. However, the recommended teicoplanin concentration in the bloodstream for clinical purposes, to effectively counter Gram-positive bacteria, is 15 mg/l, which corresponds to 8.78 μM. It's worth noting that the typical daily dosage of teicoplanin in practical medical use is 400 mg.[211] Zhou et al[209] have revealed that teicoplanin acts at the beginning of their life cycles of coronaviruses, such as SARS-CoV2. Given the mechanism of action, Zhang et al concluded that employing teicoplanin during the initial phases of COVID-19 infection could be a viable approach.[211] Their research involved contrasting the medical progress of COVID-19 patients admitted to the hospital who were administered teicoplanin with a similar group of patients who were not given the teicoplanin treatment. One trial had 55 patients with severe COVID-19 who were hospitalized in intensive care units (ICUs). Of these, 34 patients (the Tei-COVID

group) got teicoplanin, while the other 21 did not (control group). Although lacking statistical significance ($P = .654$), the unadjusted 30-day mortality rate among individuals in the Tei-COVID group (35.2%) was slightly lower than that of the control group (42.8%). By the 14th day after hospital admission, viral clearance was observed in 64.7% of Tei-COVID patients and 57.1% of the control group, with no noteworthy statistical distinction. In contrast to the control group, the Tei-COVID group exhibited a notable reduction in the serum C-reactive protein level. Teicoplanin usage has no negative side effects. This early finding suggests that the 2019-nCoV virus infection may be treated using the possible antiviral activity of teicoplanin. Therefore, additional clinical research is necessary to confirm the precise function of teicoplanin.

Azithromycin. A semisynthetic macrolide antibiotic called azithromycin (AZM) is frequently utilized to treat bacterial infections like bronchitis and pneumonia.[212] Additionally, it is applied in the prevention of flu, zika, dengue, and Ebola viruses.[213] For SARS-CoV-2 viral elimination, azithromycin combined with hydroxychloroquine was noticeably more effective. In one study, COVID-19 infection in France was treated with hydroxychloroquine (200 mg × 3 daily for a course of 10 days) and azithromycin (500 mg on day one, followed by 250 mg daily for 5 days), the researchers hypothesized that using HCQ and AZM together would help COVID-19 patients survive better.[214] An analysis including 80 patients revealed that COVID-19 patients treated with a combination of azithromycin and HCQ had a significantly lower viral load.[215] According to a retrospective research conducted in the United States, the mortality rate was lower in the group getting HCQ and azithromycin together than it was in the group receiving only HCQ.[216] After 8 days of treatment with azithromycin and hydroxychloroquine, 93% of patients with COVID-19 were free of the virus. In a separate research, the combination of AZM and HCQ was more successful in treating SARS-CoV-2 infection during pregnancy and was linked with a lower fatality rate.[217] In a controlled study, individuals with mild to moderate COVID-19 who received treatment with HCQ alone or in conjunction with azithromycin did not exhibit any enhancement in their clinical condition when contrasted with the control group.[218] In another trial with 1061 patients in France who got HCQ and azithromycin, no COVID-19-related problems occurred, indicating that the patients were safe.[218,219] Nonetheless, according to certain research, the usage of AZM to treat COVID-19 patients had no therapeutic effect. At present, there are 136 registered clinical trials exploring the utilization of azithromycin in patients with COVID-19.[95]

Neuraminidase inhibitors (NAIs)

Oseltamivir. Oseltamivir (marketed as Tamiflu) is an antiviral medication that inhibits the neuraminidase enzyme of influenza A and B virus.[220] It prevents the discharge of viral fragments from host cells, hence limiting their transmission to the respiratory system. Moreover, oseltamivir was utilized in clinical studies to manage COVID-19 individuals during the outbreak in China. It was used with various key treatment candidates, including corticosteroids, antibiotics, chloroquine, and FPV.[221] According to the severity of their illness, 124 COVID-19 patients got varied doses of oseltamivir and methylprednisolone in one of these clinical studies, however there were no appreciable positive effects.[221] Another study found that oseltamivir isn't a good choice for treating COVID-19 in vitro study, and clinical use of oseltamivir (75 mg twice daily for 5 days) did not slow the progression of the disease or improve the signs and symptoms of the patients.[222] There are currently 21 registered clinical studies looking at the use of oseltamivir in COVID-19 patients.[98]

Zanamivir. Zanamivir serves as the active component in the antiviral medication Relenza. This medication inhibits the reproduction of the influenza virus and can shorten the duration of symptoms if administered promptly after the onset of the infection.[223] The mechanism of action of this medication involves attaching to the active site of the neuraminidase protein. This protein must be activated for the influenza virus to escape the host cell prior to its death and infect a new host cell. The antiviral activity of zanamivir obstructs the neuraminidase protein and hinders the virus's ability to infect additional cells. As a result of this impact, zanamivir is able to arrest the progression of the infection. These are administered to ventilated individuals who are resistant to oseltamivir. According to the most recent studies, zanamivir is ineffective against nCoV-2019 and should not be used to treat patients.[224]

Other Potential Treatment Options for COVID-19

Nanobodies for COVID-19 therapeutics

Nanobodies (Nbs) or Variable Heavy-Chain Domains of Heavy-Chain Antibodies (VHHs) are compact, singular antigen-binding fragments obtained from the subgroup of heavy chain-only camelid immunoglobulins. They offer an alternative to traditional antibodies and come with numerous benefits such as minimal toxicity, strong affinity, sensitivity, water solubility, simple production, extended shelf life, among others. Nbs can be introduced through intravenous, intramuscular, or subcutaneous routes, although inhalation delivery stands out as the most promising choice for addressing COVID-19.[225]

Huo et al[226] discovered 3 variants, H11 Nb and 2 enhanced versions of H11 (H11-D4 and H11-H4), which effectively prevented the binding of the RBD and spike (S) protein to ACE2 in vitro. RBD binding of H11-H4 and H11-D4 had KD's of 5 and 10 nM, respectively, by surface plasmon resonance (SPR) and 12 and 39 nM, respectively, by isothermal titration calorimetry (ITC).[226] H11-H4-Fc (IC_{50} = 61 nM), H11-D4-Fc (IC_{50} = 161 nM), and VHH72-Fc (IC_{50} = 262 nM)

inhibited RBD binding in vitro. H11-H4-Fc (IC_{50} = 34 nM), H11-D4-Fc (IC_{50} = 28 nM), and VHH72-Fc (IC_{50} = 33 nM) also found to prevent ACE2 binding in vitro. They were also demonstrated to be able to neutralize live virus, but H11-H4-Fc had higher potency.[226] Nbs can also be fused with human IgG Fc domains.[227] Dong et al generated a variety of Nbs, including 3F, 1B, and 2A, aimed at obstructing the interaction between SARS-CoV-2 and ACE2. By combining 2 of these Nbs, they observed a synergistic effect in blocking this interaction.[227] Importantly, the bi-specific Nb-fc displayed notable improvements at concentrations relevant for therapy. It exhibited enhanced binding to the S protein and effectively blocked the S-ACE2 interaction (with KD = 0.25 nM, IC_{100} ~36.7 nM, IC_{95} ~12.2 nM, IC_{50} ~1 nM), surpassing the performance of monoclonal Nb-Fc.[227] The Ty1 Nb showed both direct prevention of RBD-ACE2 binding by binding specifically with RBD with high-affinity (KD 5-10 nM). It also demonstrated neutralization of pseudotyped viruses (Ty1: IC_{50} = 0.77 μg/mL; Ty1-Fc: IC50 of ~12 ng/mL).[228] Gai et al generated 6 Nbs that displayed strong binding affinity to the spike protein's receptor binding domain (S-RBD), alongside 8 mutations (Q321L, V341I, N354D, V367F, K378R, V483A, H519P, and Y508H). These Nbs effectively hindered the interaction between the modified RBD mutants and ACE2, with inhibition constants (KD) ranging from 21.6 to 106 nM.[229] Nb887 (16.2%), Nb1358 (50.4%), and Nb1159 (98.9%) all exhibited varying degrees of RBD-ACE2 blocking activity. All Nbs had EC_{50} and IC_{50} values less than 0.2 and 1 μg/mL, respectively, for half maximal neutralization.[229]

Pymm et al discovered a group of powerful Nbs with high affinity, including WNb 2, WNb 7, WNb 15, and WNb 36 (with KD values ranging from 0.14 to 19.49 nM), can interfere with the interaction between the receptor binding domain (RBD) and ACE2. These Nbs not only effectively blocked the virus-host interaction but also demonstrated virus-neutralizing properties.[230] The Nb-Fc fusion constructs exhibited binding to various antigenic sites on the RBD, leading to ACE2-RBD interaction inhibition. Furthermore, they showed affinity for a broad range of RBD variants (with EC_{50} values spanning 0.7-14 nM). Although the binding of Nb-Fc (WNb 2, 7, 15, and 36) to the E484K or N501Y variants of RBD was reduced, their binding to the wild-type RBD remained strong (with EC50 values between 0.97 and 2.65 nM).[230]

Cell-based therapy

Various cellular therapy strategies, such as mesenchymal stem cells (MSCs), natural killer (NK) cells, dendritic cells (DCs), engineered lymphocytes, novel cell-based vaccine platforms, and extracellular vesicles, are presently undergoing clinical trials as potential authorized treatments for COVID-19.[231] Shortly following the emergence of COVID-19, scientists specializing in stem cells suggested utilizing MSCs as a promising therapeutic option for treating severe cases of the disease. Subsequently, clinical trials were promptly initiated. Wang et al conducted a comprehensive meta-analysis to evaluate the effectiveness and safety of MSC therapy in COVID-19 patients.[232] The results revealed a notable decrease in adverse events and mortality through the utilization of MSC therapy, exhibiting a statistically significant distinction in comparison to the control group. No noteworthy unfavorable effects were linked to MSC therapy. Positive changes were observed in pulmonary function, radiographic evaluations, and biomarkers related to inflammation and immunity. The researchers concluded that MSC therapy represents a feasible and secure approach for addressing COVID-19-associated pneumonia.[232] However, it's important to note that there exists limited data to gage the role of MSCs in COVID-19 treatment, and no MSC-based treatments have gained approval from the FDA for this purpose.

Novocellbio, based in Incheon, South Korea, has recently disclosed encouraging outcomes derived from the utilization of their autologous NK cell treatment called NOVO-NK. These promising results were observed in both laboratory settings (in vitro) and live organisms (in vivo). In light of these findings, the company is taking the lead in pursuing further preclinical investigations to delve into the mechanisms underlying the effectiveness of NOVO-NK therapy against SARS-CoV-2.[233] In recent times, several clinical trials have been undertaken to examine the safety and immunogenicity of intravenously infusing NK cells sourced from healthy donor peripheral blood mononuclear cells (PBMCs) into patients infected with SARS-CoV-2.

Combination therapy

Combination therapies play a pivotal role in antiviral treatment by enhancing the efficacy of individual drugs and impeding the swift emergence of drug resistance. However, it's important to acknowledge that combining therapies can bring about challenges related to clinical and regulatory development, despite their potential benefits. Recently, combined therapy for COVID-19 patients has demonstrated some promise.[234] According to certain research findings, the implementation of combination therapy or the use of multiple drugs for COVID-19 outpatients could potentially lead to a reduction in hospitalizations and mortality rates by up to 85%. In numerous cases, the combination therapy approach has demonstrated remarkable effectiveness in the treatment of individuals with COVID-19. As highlighted by McCullough et al,[235] the use of combination or multidrug therapy is seen as a crucial necessity for managing COVID-19 patients with severe conditions. For instance, on November 19, 2020, the FDA approved the first Emergency Use Authorization (EUA) for the dual combination of remdesivir and baricitinib for the treatment of hospitalized adults and children with COVID-19.[235]

As previously highlighted, a randomized clinical trial involving hospitalized COVID-19 patients revealed that the

combined administration of baricitinib and remdesivir exhibited higher effectiveness compared to the use of remdesivir alone.[236] Another clinical trial involved the treatment of 1694 COVID-19 patients with 2 medications (remdesivir and dexamethasone) alongside standard care. The results suggest a reduction in 30-day mortality rates.[236] Likewise, an additional randomized clinical trial was carried out, assessing the effectiveness of the combined treatment of etesevimab and bamlanivimab for patients with COVID-19. Patients who received bamlanivimab and etesevimab did not experience any death, while 10 deaths occurred in the placebo group (9 of which were attributed to COVID-19).[80] From March to September 2020, Procter et al[236] assessed the effects of the combined therapy on 922 outpatients. Antiviral compounds such as ivermectin, hydroxychloroquine, and zinc were utilized in the investigation. Three antibiotics were also utilized, including doxycycline, azithromycin, and ceftriaxone. The study's findings indicated that utilizing multidrug or combination therapy is a more viable and secure approach for individuals experiencing early symptoms, especially when managed at home or in non-hospital settings.[236]

Intravenous immunoglobulin therapy

Intravenous immunoglobulin (IVIG) is a pooled antibody that is isolated from the plasma of thousands of healthy donors and contains the naturally therapeutic immunoglobulin G (IgG). It is an immunotherapy approach utilized to treat a range of inflammatory and autoimmune illnesses. Recent data suggest that high-dose IVIG treatment started early may help severely sick COVID-19 patients recover.[237] Cheng et al[238] claimed that SARS-CoV-2 differs from other SARS family coronaviruses by encoding a superantigen-like motif near to its S1/S2 cleavage site. The authors get to the conclusion that this pattern could be what allows SARS-CoV-2 to trigger the cytokine storm seen in COVID-19. IVIG may inhibit T cell activation and cytokine release caused by super-antigens because it includes antibodies that respond to SARS-CoV-2 antigens.[238]

A recent meta-analysis was carried out to evaluate the effectiveness of intravenous immunoglobulin (IVIG) therapy in individuals with COVID-19.[239] This analysis compiled data from 4 clinical trials and 3 cohort studies, which encompassed a total of 825 patients who were hospitalized due to COVID-19. Their findings revealed that the severity of COVID-19 is related to the effectiveness of IVIG. When compared to the control group, IVIG could reduce mortality in patients with critical conditions. Alternatively, due to its wide-ranging anti-inflammatory characteristics, IVIG could potentially be used in conjunction with immunotherapies focused on IL-1 and IL-6, both of which exhibit encouraging outcomes. This combination approach could be explored to assess the potential therapeutic benefits of an additive or synergistic treatment strategy.[240,241]

COVID-19 convalescent plasma therapy

Convalescent plasma (CP) therapy involves transferring plasma components containing antibodies from an individual who has recuperated from COVID-19 (a convalescent COVID-19 patient) into a patient who is currently infected.[168] In March 2020, the FDA released an Emergency Investigational New Drug (eIND) authorization for the therapy of COVID-19 patients using convalescent plasma. Within convalescent plasma treatment, passive immunization takes place, whereby the therapeutic effects of CP antibodies manifest through various mechanisms like virus neutralization, antibody-dependent cellular cytotoxicity (ADCC), and initiation of the complement system.[242] Antibody neutralizes the viral infection by attaching directly to the virus's epitope. This virus includes a domain of receptor binding (RBD) that functions as both an antibody epitope and a binding site for the ACE-2 (angiotensin-converting enzyme-2) receptor, a key entry receptor for COVID-19 pathogenicity. he antibody against SARS-CoV-2 obtained from the plasma of individuals who have recuperated from COVID-19 possesses the ability to vie with ACE-2 receptors in attaching to the receptor-binding domain (RBD) of the virus. This competition thwarts or neutralizes viral infection by obstructing the RBD (Figure 3).[242,243] In addition to their neutralizing impact, the non-neutralizing antibodies IgG and IgM contained in COVID-19 CP boosted the patient's recovery via other antibody-dependent pathways.[244] In August 2020, the FDA granted an emergency use authorization (EUA) for the utilization of convalescent plasma in the treatment of COVID-19 patients who were hospitalized. The first application of CP therapy was against SARS-CoV-2 in China and Italy, and the rapid deployment of CP in numerous countries.[149,245] Duan et al described a series of 10 COVID-19 patients who were all administered a single dose of 200 mL convalescent plasma (CP) carrying neutralizing antibody titers greater than 1:640 a median of 16.5 days after the onset of sickness. The key outcome measure was the safety of CP transfusion, and no significant adverse effects were seen. The secondary objectives aimed to enhance clinical symptoms and laboratory indicators within a 3-day period post convalescent plasma (CP) transfusion. Subsequent to the CP transfusion, there were noted increases in levels of neutralizing antibodies, oxyhemoglobin saturation, and lymphocyte counts, along with decreases in C-reactive protein (CRP), viral load, and lung lesions as evident in chest radiographs.[149] Another trial encompassed 5000 individuals in the United States (US) who were grappling with severe or life-threatening COVID-19. These participants received convalescent plasma during the initial stages of symptom manifestation. This study concluded that convalescent plasma therapy for hospitalized COVID-19 patients was reasonably secure.[246] Several investigations demonstrated the efficacy of CP therapy, whereas certain clinical studies suggested that the utilization of CP did not lead to reduced hospitalization duration, severity of illness,

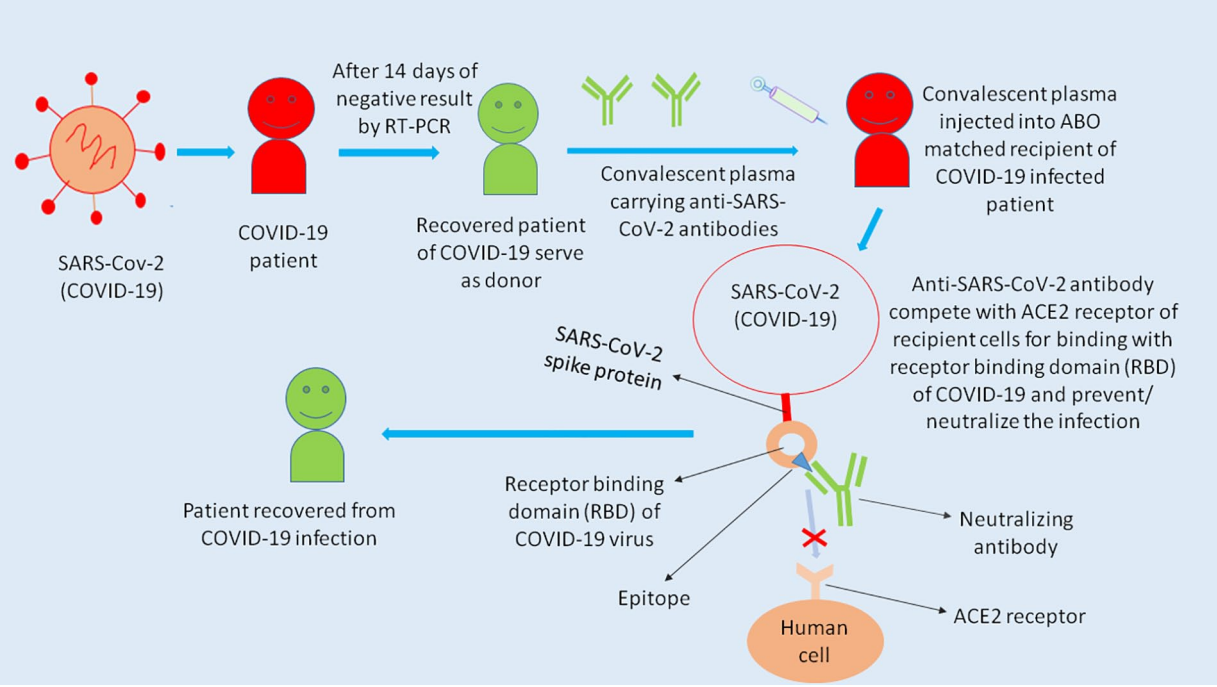

Figure 3. Schematic representation of the convalescent plasma therapy. In 14 days, a person who has recovered from COVID-19 infection produces enough specific antibodies. Plasma with neutralizing antibodies can be delivered to infected individuals to produce prompt immunity. Antibodies against SARS-CoV-2 bind to particular locations on the virus and neutralize it.

or mortality rates in comparison to the control groups.[149,247] A multicenter, randomized, open-label clinical trial involving 103 severe or life-threatening COVID-19 patients in China found no statistically significant difference in the improvement of clinical symptoms between CP-treated patients and those receiving standard treatment alone within 28 days.[248] Another multicenter study of 78 patients from Poland who received convalescent plasma found that 68 (87%) patients recovered from COVID-19 and 10 (13%) patients died within 30 days after CP transfusion, and concluded that convalescent plasma can be applied as a supportive medication for COVID-19 patients because of its accessibility and low incidence of side effects.[249] There are now 201 clinical studies registered looking at the use of convalescent plasma in COVID-19 patients.[250]

Corticosteroid therapy

Corticosteroids, such as dexamethasone, have been utilized for many years to treat a variety of medical ailments, including autoimmune disorders and allergic reactions. As per findings from the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, the administration of a reduced dosage of dexamethasone diminishes the mortality rate among hospitalized COVID-19 patients who require respiratory support.[251] According to the RECOVERY study, the results of 2104 patients who received dexamethasone (at a low dose of 6 mg once day) orally or intravenously for up to 10 days were compared to those of 4321 patients who received either conventional treatment or no dexamethasone at all. Within 28 days of the randomization, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group passed away ($P = .001$). In the dexamethasone group, the mortality rate for patients receiving invasive mechanical ventilation and oxygen without invasive mechanical ventilation reduced (29.3% vs 41.4%) and oxygen alone (23.2% vs 26.2%), however it did not decrease for patients receiving no respiratory assistance at randomization (17.8% vs 14%).[252,253] The World Health Organization (WHO) recommends using dexamethasone (6 mg intravenous or orally) or hydrocortisone (50 mg intravenous every 8 hours) for 7 to 10 days in the most severely ill individuals, but not in those with less severe conditions.[254] If dexamethasone is unavailable, other corticosteroids such as prednisone, acetaminophen, methylprednisolone, or hydrocortisone may be utilized. Acetaminophen is used to treat fevers, and methylprednisolone is an acceptable medication for patients experiencing rapid illness progression.[254,255] All corticosteroids may be harmful if administered for COVID-19 infections of lesser severity. In some instances, tocilizumab or baricitinib may be administered with dexamethasone to mechanically ventilated or oxygen-dependent hospitalized patients. In hospitalized patients who require more oxygen or are on mechanical ventilation, remdesivir is usually used with dexamethasone. When there is uncontrolled viral replication but a low amount of inflammation, only high dosages of corticosteroids should be used as a treatment. However, corticosteroids decrease the immune system, and there are worries regarding COVID-19 patients using these medications.[256] Another study found no significant link between patients receiving corticosteroids and the control group in terms of

recovery in 11 out of 31 COVID-19 patients who got corticosteroid therapy.[257] However, because of the immunosuppression and side effects associated with these medications, proper care must be followed during therapy, and they should not be used to treat 2019-nCoV-induced lung damage or shock outside of a clinical trial.[258] About 101 clinical studies examining the use of dexamethasone in COVID-19 patients have been registered so far.[259]

Vitamin supplements for COVID-19 therapeutics

A variety of adjunctive therapies has recently been utilized in the prevention and management of SARS-CoV-2 infection and associated complications. Due to their immunomodulatory properties, vitamins C and D have drawn more attention in the fight against COVID-19. It is thought that these supplements may support infected patients and strengthen their immune systems.[260] A pilot trial of COVID-19 patients who received large doses of vitamin C demonstrated statistically significant increases in oxygenation from baseline to day 7 in the treatment group compared to the control group.[261] In a controlled and randomized clinical study, it was demonstrated that providing mild to moderate COVID-19 patients who had insufficient vitamin D levels with a 2-week regimen of 5000 IU vitamin D3 supplementation resulted in a shortened duration for recovery from cough and loss of gustatory sensory perception.[262]

Natural compounds for COVID-19 therapeutics

Several natural compounds and their derivatives have reportedly shown promise in combating SARS-CoV-2 infection.[263,264] Emodin, derived from the Polygonaceae plant family, has exhibited the ability to hinder the interaction between the viral S protein and the host ACE2 receptor.[265,266] Myricetin and scutellarein, which are naturally existing flavonoids, have been confirmed to have the potential to hinder the NSP13 helicase of SARS-CoV-2.[267] Moreover, Rhizoma Cibotii, desiccated Cibotium barometz and Dioscoreae rhizoma rhizomes, along with Doscorea batatas tubers, as well as the flavonoids herbacetin, rhoifolin, and pectolinarin, have also been identified in this context,[267,268] and betulinic acid and savinin triterpenes all significantly reduce SARS-CoV 3CL protease activity.[268,269] Due to its significant involvement in the genomic RNA replication of SARS-CoV-2, the papain-like cysteine protease (PLpro) stands as a crucial therapeutic target for the creation of medications against SARS-CoV-2.[157] Tanshinones and hirsutenone, 2 bioactive compounds derived from *Salvia miltiorrhizia* and *Alnus japonica*, respectively, have been shown to inhibit PLpro activity.[270,271] Moreover, extracts from *Ganoderma lucidum* have demonstrated effectiveness against COVID-19 through their interaction with the RNA-dependent RNA polymerase of SARS-CoV-2, a pivotal enzyme in the synthesis of viral RNA.[272]

Vinegar for COVID-19 therapeutics

Vinegar is readily available, affordable, non-toxic, and has a low toxicity level in compared to other cleaning products.[273] Amruta et al[274] demonstrated that acetic acid, the primary component of vinegar, is effective at inactivating SARS-CoV-2. The median tissue culture infectious dose $TCID_{50}$ assay revealed that 15 minutes of exposure to 6% acetic acid completely and permanently inhibited viral replication. Exposing SARS-CoV-2 to a solution of 6% acetic acid led to noteworthy alterations in its morphology, characterized by distorted formations, a reduction in the quantity of viral particles, and a disrupted arrangement of the virion structure. Moreover, ELISA results demonstrated that 6% acetic acid significantly inhibited the binding of SARS-CoV-2 spike RBD to human ACE2. At 30-minute timepoint, 6% acetic acid showed the greatest inhibition.[274]

Vaccines

Vaccine represents one of the most dependable and economic measures in public health history, responsible for annually saving numerous lives. Immunization stands as the most efficient strategy for averting SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel strongly advises prompt COVID-19 vaccination for all those meeting eligibility criteria as defined by the CDC's Advisory Committee on Immunization Practices.[97] After the decipherment of the genetic sequence of SARS-CoV-2 in March 2020, the WHO proclaimed COVID-19 a pandemic, and since then, scientists and pharmaceutical corporations have been racing against time to develop vaccines.[275] As of March 4, 2022, data from the Coronavirus Vaccine Tracker database reveals that there have been 50 authorized vaccines for complete utilization. Globally, 92 vaccines are undergoing phase 3 clinical trials, 72 vaccines are in phase 2 clinical trials, 66 vaccines are in phase 1 clinical trials, and 12 vaccine candidates have been discontinued.[276] In clinical trials, there are 4 different kinds of vaccines such as mRNA, DNA, protein subunit and viral vector vaccines where mRNA vaccines: BNT-162b2 (Pfizer, BioNTech), mRNA-1273 (Moderna); DNA vaccines: INO-4800 (Inovio); viral vector vaccines: AZD-1222 Ad5-CoV (AstraZeneca; Oxford University), Ad26.COV2.S (Johnson & Johnson) and protein subunit vaccines: NVX-CoV2373 (Novavax). Among these, Pfizer-BioNTech's (BNT162b2), Moderna (mRNA-1273), and Johnson and Johnson (Ad26.COV2.S) vaccines have gained emergency usage authorization in the United States.[276] Notably, the United Kingdom took the lead in approving the mRNA vaccines produced by Pfizer-BioNTech, making this decision in December 2020.[277] In a multinational, placebo-controlled, pivotal efficacy trial of 43 548 patients, 21 720 patients received BNT162b2 (Pfizer-BioNTech's) mRNA vaccine and 21 728 patients received a placebo. The result showed that BNT162b2 was 95% effective in preventing COVID-19

patients compared to placebo control. Moderna (mRNA-1273) vaccine has a 94% efficacy, and the data has been sent to regulators around the world. The ChAdOx1 (AstraZeneca; Oxford University) vaccine showed the efficacy of up to 90% and has been approved for emergency use by the European Medicines Agency and national regulator boards of UK, Argentina, India, Mexico, and Brazil.[277] Moderna and Pfizer vaccines were safe in phase 1, 2, and 3 studies, with no serious side effects recorded. RNA vaccines are the most effective in general, followed by viral vector vaccines and inactivated virus vaccines. Inactivated vaccinations exhibit the lowest rate of adverse events, and comparisons of safety between mRNA vaccines and viral vectors remain controversial.[278,279] On November 22, 2022, the CDC released information regarding the effectiveness of the BA.4 and BA.5 mRNA vaccines in averting symptomatic infection within a two-month period after the administration of the booster dose. The bivalent booster dose added 28 to 31% protection to monovalent vaccine recipients 2 to 3 months earlier. About 43% to 56% more protection was given to those who had received a monovalent vaccine more than 8 months earlier.[280] Past research indicates that this modest rise in defense against mild illness is likely to be of a limited duration. By November 15, 2022, only 10% of those recommended the bivalent vaccine had received it.[280] As of December 2022, the BA.4 variant had ceased its circulation, and BA.5 represented less than a quarter of all SARS-CoV-2 strains. The current safety profile of COVID-19 vaccines is sufficient for widespread immunization, but continuous monitoring of vaccine safety over the long term is necessary, particularly in the context of older individuals with preexisting health conditions. The main barriers to receiving SARS-CoV-2 vaccinations predominantly include vaccine reluctance and skepticism. The majority of people are skeptical of vaccine safety, which poses a significant obstacle. In the United States, a sense of skepticism has been evident, with 50% of Americans showing willingness to receive the vaccine, 30% expressing uncertainty, and 20% outright refusing the vaccine.[281] In a separate survey targeting adult Americans, 58% indicated their intention to get vaccinated, 32% remained uncertain, and 11% had no intention of getting vaccinated.[282]

Remarks and Future Directions

In the current situation, rapid transmission of SARS-CoV-2 across multiple nations has been related to severe sickness, posing a grave threat to public health. Officially documented effective therapy for the treatment and prophylaxis of COVID-19 patients does not exist at this time, despite the existence of numerous controversies based on extensive studies. The long-term goal is to conduct more clinical trials in order to determine the most effective, safe, affordable, and tolerant therapies, antiviral medicines, and vaccines for COVID-19 infection. Finally, in order to put an end to the COVID-19 epidemic, the development of widely available functional vaccinations is critical. There is a need for different types of medications or vaccines for diverse populations, such as infants and children, pregnant women, and immunocompromised people, because the bulk of vaccines under development are aimed at the healthy population, that is, adults aged 18 to 55. A safe regulatory framework must also be established for these vaccines to be used for different populations other than adults. The emergence of new variants of COVID-19 has made it a far more dangerous virus. In order to halt the mutation and prevent the emergence of variants that can entirely escape the immune surveillance system, rapid herd immunity by vaccination is required. However, in terms of regaining faith in "life returning to normal," it is hardly possible to effectively immunize the vast majority of the world's population within a short period of time. Therefore, accelerated attention for the development of innovative COVID-19 therapies must be required in order to eliminate the pandemic.

Limitations of the Study

Urgent clinical and therapeutic measures are imperative to effectively combat the swift proliferation of SARS-CoV-2 infection and human-to-human transmission. Unfortunately, most current SARS-CoV-2 treatments primarily revolve around supportive care, and the development of targeted antiviral medications continues to present a significant challenge in the clinical realm. In order to identify successful pharmacological therapies, one of the difficulties to overcome is the dearth of evaluation methods and acceptable animal models utilized for assessing drug activity in laboratories around the world.[283] In particular, no one has ever explained why human coronavirus (HCoV) illnesses can't be reproduced in nonhuman primate (NHP) models, which makes the results less useful and less reliable in real life. Suitable models established under stringent laboratory settings and with improved technology are likewise problematic. Limited alternative treatments that have been administered to COVID-19 patients lack substantial in vivo evidence demonstrating their benefits, and analyses that consolidate various treatments have not succeeded in identifying effective therapeutic choices. In particular, the present experimental CoV research platforms are not sufficient to facilitate the development of new antiviral drugs. Furthermore, CoV replication frequently generates offspring viruses with a variety of genomic variants. Recombination across viral genomes is also common, and gene-level modifications can lead to treatment resistance if the mutations modify the agents' target domains. Moreover, a crucial approach in devising treatment protocols involves combining established medications with proven safety records and wide-ranging antiviral capabilities. While certain of these drugs have displayed anti-coronavirus effects in laboratory settings, their suitability in terms of pharmacokinetics, pharmacodynamics, and potential side effects might not align with in vivo demands. Additionally, viral and patient-related factors could present challenges in the clinical exploration of COVID-19.[284] Finally, one of the current review's shortcomings is its dependence on previously published findings.

Conclusion

The emergence, rapid spread over countries and severity of SARS-CoV-2 led the mankind into hapless which unveiled our lack of research initiatives against viral pandemic. Since the emergence, researchers have tried to develop effective drugs and vaccines against SARS-CoV-2. Among these options, both mRNA vaccines and viral vector vaccines have demonstrated significant efficacy in preventing disease progression, leading to their approval for emergency usage in numerous countries. The volume and severity of the COVID-19 pandemic, as well as the absence of specialized treatments for COVID-19, necessitated the off-label study of repurposed approved medications in order to seize the morbidity, mortality and spread of this new disease. Despite the attention put in this strategy, it has produced a limited success in preventing the spread of COVID-19. These failures highlighted the need for new, more specialized drugs. Although the authorized antivirals have saved millions of lives in the past few decades, the current challenge is to find effective and well-tolerated drugs for treating COVID-19 and limiting the spread of SARS-CoV-2. Numerous antiviral medications, including remdesivir, favipiravir, paxlovid, molnupiravir, lopinavir/ritonavir (LPV/RTV) in combination with ribavirin, as well as combinations like azithromycin plus hydroxychloroquine, nitazoxanide plus azithromycin and hydroxychloroquine, tocilizumab, bamlanivimab, and etesevimab, have the potential to ameliorate respiratory symptoms. As a result, they can lead to a reduction in the duration of viral shedding and hospitalization period. But using antivirals like oseltamivir, umifenovir, disulfiram, teicoplanin and ivermectin hasn't helped much. Patients with COVID-19 may also be benefited from intravenous immunoglobulin therapy, convalescent plasma therapy, corticosteroid therapy, cell-based therapy, and other therapies like nanobodies, vitamins, natural compounds and vinegar. Overall, this research would be useful as an updated compendium of drugs being investigated and repurposed for the treatment and prevention of SARS-CoV-2 infection. Importantly, the stated mechanisms of action of these drugs may serve as a crucial benchmark for future studies examining different COVID-19 therapy strategies and treatments.

Author Contributions

Conceptualization: MEM, MH, MMH. Writing – original draft: MEM, MH, FA, MMH. Writing – review & editing: MEM, MH, FA, MMH.

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