Chapter 2
Ongoing Clinical Trials and the Potential Therapeutics for COVID-19 Treatment

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Hossein Abolhassani, Ghazal Bashiri, Mahdi Montazeri, Hasan Kouchakzadeh, Seyed Abbas Shojaosadati, and Seyed Ehsan Ranaei Siadat

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2.1 Introduction

It is demonstrated that Coronavirus disease 2019 (COVID-19) pathogenesis is involved with both the direct harm inflicted by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and on the other hand, excessive inflammatory and immune response from the host [1]. Taking the biology and viral pathogenesis of SARS-CoV-2, and the potential treatment mechanisms of the virus into account thoroughly in previos chapter, many therapeutics and medications have been proposed to be efficacious against the COVID-19 pandemic [1–3]. On account of the fact that there are no particular treatment options available for COVID-19, the drug repurposing approach has been taken into consideration as a promising strategy for the treatment of SARS-CoV-2 infection [4, 5]. Among them, antivirals have demonstrated satisfactory inhibitory effects against COVID-19 in vitro, in vivo, and in clinical

Hossein Abolhassani, Ghazal Bashiri, and Mahdi Montazeri contributed equally to this work.

H. Abolhassani · G. Bashiri · S. A. Shojaosadati (✉)
Biotechnology Group, Faculty of Chemical Engineering, Tarbiat Modares University, Tehran, Iran
e-mail: shoja_sa@modares.ac.ir

M. Montazeri · H. Kouchakzadeh (✉)
Protein Research Center, Shahid Beheshti University, Tehran, Iran
e-mail: h_kouchakzadeh@sbu.ac.ir

S. E. R. Siadat
Rahpouyan Fanavar Sadegh Company, Pardis Technology Park, 20th Km of Damavand Road, Tehran, Iran

conditions as well [5, 6]. On the other hand, as the severe patients are generally associated with the acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and cytokine storm, immunomodulators and anti-inflammatory drugs, as well as biological products, have been employed aiming to enhance the innate immune system and alleviate the damage caused by the deregulated inflammatory responses to manage the infection and control the symptoms leading to surviving the severe patients [7, 8]. Many therapeutic strategies and medications acting on targets of the virus or on the targets of the host have been proposed and are being developed in several clinical studies to be evaluated regarding their safety and efficacy against COVID-19 (Table 2.1) [1, 4]. The therapeutic interventions, medications, biological, and natural products alongside combination therapy approach that may have a promising role in suppressing COVID-19 is highlighted based on current evidence in this chapter./Para>

2.2 Antivirals/Anti-HIV and Antimalarials

Viruses are obligate, intracellular parasites containing either RNA or DNA that utilize host cells for their reproduction [107]. Viruses such as HIV, herpes simplex, varicella-zoster, respiratory syncytial, cytomegalovirus, HBV, HCV, or influenza virus are known to be associated with the development of a wide range of infections [108]. In the early 1950s, with research on anticancer drugs, advancements in developing antiviral chemotherapy, particularly in compounds preventing viral replication, are commenced [109]. Having expertise in the mechanisms of viral replication has assisted scientists in comprehending the viral life cycle, thereby finding potential antiviral agents for each step of replication [109]. The efficacy of antiviral agents heavily depends on their potency and therapeutic index. That is, besides their damaging effects on viruses, they should remain non-toxic to the host cells. In this regard, target sites special to viruses, without any human homolog, can aid in achieving a high therapeutic index [110]. Since the outbreak of a new infection, COVID-19, health professionals have been trying to find proper drugs for the treatment of infected patients [110].

However, repurposing available antiviral/anti-HIV and antimalarial drugs, with known safety, dosages, and pharmacokinetic properties, is recently gaining attention, given the limited time and high cost required for discovering new drugs [5, 110]. In this regard, many antivirals have been employed to test their efficiency and safety against COVID-19 (Table 2.1). As a result, several therapeutics such as remdesivir, favipiravir, arbidol as well as the combination of lopinavir and ritonavir are identified as potent agents against COVID-19 by WHO [5].

Table 2.1 Potential therapeutics with their clinical trials for the treatment of COVID-19

Therapeutic	Target	Effect	Clinical trial phase (NCT number) (https://clinicaltria ls.gov)	Refs.
Antivirals				
Remdesivir	RdRP (virus)	Inhibiting viral replication	Phase 3 (NCT04501952), Phase 3 (NCT04292899)	[9–14]
CQ/HCQ	Endosoamal pH, ACE2 (host)	Inhibiting viral entry and post entry	Phase 4 (NCT04331600), Phase 4 (NCT04382625)	[5, 15–18]
Kaletra (lopinavir/ritonavir)	3CLpro (virus)	Inhibiting protease activity in the replication cycle	Phase 4 (NCT04252885), Phase 3 (NCT04328012), Phase 3 (NCT04321174)	[19, 20]
Umifenovir (arbidol)	S protein/ACE2 interaction (virus)	Inhibiting viral entry	Phase 4 (NCT04260594)	[21–23]
Favipiravir	RdRP (virus)	Inhibiting viral replication	Phase 3 (NCT04600895), Phase2 (NCT04358549)	[24–27]
Oseltamivir (tamiflu)	Neuraminidase (virus)	Inhibiting release of viral particles from host cells	Phase 4 (NCT04255017), Phase 3 (NCT04558463)	[28, 29]
Ribavirin	Inosine monophosphate dehydrogenase, RdRP (virus)	Inhibiting viral replication	Phase 3 (NCT04392427), Phase 2 (NCT04605588)	[5, 30, 31]
Darunavir/cobicistat	3CLpro (virus)	Inhibiting protease activity in the replication cycle	Phase 3 (NCT04252274)	[32–34]
Tenofovir/emtricitabine	Nucleoside reverse transcriptase (virus)	Inhibiting viral replication	Phase 2/3 (NCT04359095), Phase 2/3 (NCT04519125)	[35, 36]
Camostat mesylate	TMPRSS2 (host)	Inhibiting viral entry and fusion	Phase 3 (NCT04608266), Phase 2/3 (NCT04608266)	[37–39]
Nafamostat mesylate	TMPRSS2 (host)	Inhibiting viral entry and fusion	Phase 2/3 (NCT04473053)	[16, 40]

Table 2.1 (continued)

Therapeutic	Target	Effect	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
APN01	S protein (virus)	Inhibiting viral entry	Phase 2 (NCT04335136)	[3, 41, 42]
Molnupiravir	RdRP (virus)	Inhibiting viral replication	Phase 2/3 (NCT04575584), Phase 2/3 (NCT04575597)	[43–45]
Sofosbuvir	RdRp (virus)	Inhibiting viral replication	Phase 2/3 (NCT04497649)	[46, 47]
Ivermectin	Nuclear transport process (virus)	Inhibiting viral replication	Phase 3 (NCT04530474), Phase 2/3 (NCT04422561)	[4, 5, 48]
Losartan	ACE2 (host)	Inhibiting viral entry	Phase 3 (NCT04606563), Phase 2 (NCT04312009)	[38, 49]
Valsartan	ACE2 (host)	Inhibiting viral entry	Phase 4 (NCT04335786)	[7, 49]
Famotidine	3CLpro (virus) (feasible)	Inhibiting protease activity in the replication cycle	Phase 3 (NCT04370262), Phase 3 (NCT04389567)	[50, 51]
Novaferon	Replication system (virus (	Inhibiting viral replication	Phase 3 (NCT04669015)	[52, 53]
Bromhexine	TMPRSS2 (host)	Inhibiting viral entry and fusion	Phase 4 (NCT04405999)	[7, 49]
Nitazoxanide	Immune interferon response (host) (feasible)	reducing cytokine storm (feasible)	Phase 4 (NCT04406246) Phase 3 (NCT04359680)	[5, 6, 54]
Nelfinavir	3CLpro (virus)	Inhibiting protease activity in the replication cycle	–	[55–57]
Auranofin	Redox enzymes, endoplasmic reticulum (ER) (host)	Inhibiting viral replication, reducing cytokine storm	–	[58–62]
Carmofur	3CLpro (virus)	Inhibiting protease activity in the replication cycle	–	[63, 64]

(continued)

Table 2.1 (continued)

Therapeutic	Target	Effect	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
Niclosamide	3CLpro (virus)	Inhibiting protease activity in the replication cycle	Phase 3 (NCT04558021), Phase 2/3 (NCT04603924)	[6, 65]
Galidesivir	RdRp (virus)	Inhibiting viral replication	Phase 1 (NCT03891420)	[38, 66, 67]
Azvudine	Reverse transcriptase (virus)	Inhibiting viral replication	Phase 3 (NCT04668235)	[38, 68]
Quercetin	S protein/ACE2 interaction (virus) (feasible)	Inhibiting viral entry and pathogenesis, reducing cytokine storm	N/A phase (NCT04377789), Phase 2 (NCT04536090)	[69]
Immunomodulators and Anti-inflammatory Drugs				
NK cells	Immune system (host)	Boosting innate and adaptive immunity	Phase 1/2 (NCT04365101), Phase 1 (NCT04280224)	[1, 7, 62]
MSCs	Immune system (host)	Immunomodulation, reducing cytokine storm, regenerating tissues	Phase 3 (NCT04371393), phase 2 (NCT04466098)	[70, 71]
type I IFNs (IFN-α, IFN-β)	IFNAR signaling (host)	Boosting immunity against viral infection and replication	Phase 3 (NCT04320238), Phase 2 (NCT04385095)	[4, 8, 49, 72–74]
CP/IVIG	S protein (virus)	Boosting immunity against viral entry and pathogenesis	Phase 3 (NCT04418518), Phase 2/3 (NCT04374526)	[75, 76]
Tocilizumab	IL–6 (host)	Reducing cytokine storm	Phase 4 (NCT04377750), Phase 3 (NCT04320615)	[38, 77]
Sarilumab	IL–6 (host)	Reducing cytokine storm	Phase 4 (NCT02735707), Phase 3 (NCT04327388)	[38, 78]

(continued)

Table 2.1 (continued)

Therapeutic	Target	Effect	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
Eculizumab	C5-activated complement (host)	Reducing cytokine storm and tissue damage induced by inflammation	Phase 2 (NCT04346797)	[79, 80]
Bevacizumab	VEGF (host)	Reducing endothelial injury and microvascular permeability induced by ARDS and ALI (feasible)	Phase 2 (NCT04275414), Phase 2 (NCT04344782)	[1, 81]
Infliximab	TNF-α (host)	Reducing cytokine storm	Phase 3 (NCT04593940), Phase 2 (NCT04425538)	[82–84]
Anakinra	IL-1 (host)	Reducing cytokine storm	Phase 3 (NCT04680949), Phase 3 (NCT04362111)	[85, 86]
Emapalumab (in combination with anakinra)	INF-γ and IL-1 (host)	Reducing cytokine storm	Phase2/3 (NCT04324021)	[87, 88]
Meplazumab	CD147 (host)	Inhibiting viral entry, reducing cytokine storm	Phase 2/3 (NCT04586153), Phase 1/2 (NCT04275245)	[89, 90]
Sirolimus	mTORC1 (host)	Inhibiting viral replication, reducing cytokine storm (feasible)	Phase 2 (NCT043416755), Phase 1/2 (NCT04482712)	[91, 92]
Baricitinib	JAK (host)	Reducing cytokine storm	Phase 3 (NCT04421027), Phase 2/3 (NCT04340232)	[3, 5]
Ruxolitinib	JAK (host)	Reducing cytokine storm	Phase 3 (NCT04377620), Phase 3 (NCT04362137)	[49, 93]

Table 2.1 (continued)

Therapeutic	Target	Effect	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
Imatinib	Tyrosine kinase (host)	Inhibiting viral entry, reducing cytokine storm (feasible)	Phase 3 (NCT04394416), Phase 3 (NCT04422678)	[62, 94]
Tofacitinib	JAK (host)	Reducing cytokine storm	Phase 2 (NCT04415151), Phase 2 (NCT04469114)	[38, 62]
Cyclosporine	IL-2 (host)	Reducing cytokine storm	Phase 4 (NCT04392531), Phase 2 (NCT04492891)	[4]
Fingolimod	Sphingosine-1-phosphate receptor (host)	Inhibiting inflammation and autoimmune reaction by sequestering T cells in lymph nodes	Phase 2 (NCT04280588/withdrawn)	[1, 95]
Thalidomide	TNF-α (host)	Reducing cytokine storm	Phase 2 (NCT04273529), Phase 2 (NCT04273581)	[1, 96]
NSAIDs	Cyclooxygenase enzymes (host)	Inhibiting the production of prostaglandins and inflammation (feasible)	Phase 3 (NCT04325633), Phase 4 (NCT04334629)	[38, 97, 98]
Low molecular weight heparins	Factor Xa (host)	Reducing coagulation	Phase 4 (NCT04584580) Phase 3 (NCT04401293)	[62, 99]
Azithromycin	S protein/ACE2 interaction (virus) (feasible)	Inhibiting viral entry and translation (feasible)	Phase 3 (NCT04381962), Phase 3 (NCT04332107)	[4, 100]
Methylprednisolone	Steroid receptors in inflammatory cells (host)	Immunosuppressing, reducing cytokine storm	Phase 4 (NCT04263402), Phase 3 (NCT04438980)	[85, 101]
Dexamethasone	Steroid receptors in inflammatory cells (host)	Immunosuppressing, reducing cytokine storm	Phase 4 (NCT04663555), phase 3 (NCT04327401)	[102, 103]

(continued)

Table 2.1 (continued)

Therapeutic	Target	Effect	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
Vitamin D	Immune system (host)	Boosting immunity, reducing cytokine storm	Phase 4 (NCT04411446), Phase 4 (NCT04552951)	[38, 104]
Vitamin C	Immune system (host)	Boosting immunity, reducing cytokine storm	Phase 3 (NCT04401150), Phase 2 (NCT04363216)	[85, 105]
Zinc	Immune system (host)	Inhibiting viral entry and pathogenesis, reducing cytokine storm	Phase 4 (NCT04621461)	[69, 106]

2.2.1 *Remdesivir*

By the arisen of the COVID-19 pandemic caused by SARS-CoV-2, remdesivir is being considered as one of the highly potential therapeutic agents for the treatment of COVID-19 [111]. The researches on developing remdesivir commenced by the cooperation between the United State Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Gilead—the U.S. Centers for Disease Control and Prevention (CDC) to provide potential anti-viral therapeutic agents against RNA-based viruses, namely, Ebola virus and the Coronaviridae family viruses [9]. This led to the compilation of a library for nucleoside analogs, small molecules with antiviral activity against infections such as HBV, HIV, and herpes viruses [112, 113].

For nucleosides to become their active metabolites, it is requisite to undergo intracellular phosphorylation [14]. It should be noted that the development of the nucleoside monophosphate is the rate-limiting step for their intracellular activation [114]. Accordingly, nucleosides were modified to phosphoramidate, ester, and monophosphate prodrugs, enhancing both their intracellular delivery and activation [14, 112, 115–117]. With the outbreak of the Ebola virus in West Africa (2013–2016), the library of nucleoside molecules was appraised to find the most potential ones against the virus, resulting in the identification of remdesivir (formerly GS-5734), a monophosphoramidate prodrug of the 1′-cyano-substituted nucleoside analog (GS-441524) [11, 13, 118]. Even though remdesivir was a potential therapeutic agent for the treatment of the Ebola virus and its safety profile in the human population was established, it was outdone by monoclonal antibodies, namely, Zmapp (triple mono-clonal antibody cocktail), MAb114 (single monoclonal antibody), and REGN-EB3 (a cocktail of three monoclonal antibodies), in phase 3 clinical trial. Hence, remdesivir is not being utilized in this regard anymore [10, 119, 120]. However, in addition to Ebola virus, remdesivir has demonstrated wide antiviral activities against MERS-CoV, SARS-CoVs, Marburg virus, respiratory syncytial virus, HCV, and several paramyxoviruses [14, 72, 121, 122].

For remdesivir (GS-5734) to be converted into its active metabolite, it undergoes intracellular metabolic conversion [123]. Once remdesivir (GS-5734) enters cells, it is metabolized into an alanine metabolite (GS-704277), processed into the monophosphate derivative, and then it is converted into its active form of nucleoside triphosphate (NTP) [9, 13]. Owing to the fact that the resultant NTP resembles the natural nucleotide, that is, ATP, it could be misleadingly considered by the RdRp as a nucleotide for incorporation into the nascent RNA strand, thereby bringing the replication of RNA to a halt [124–127]. It should be noted that CoVs have a proof-reading ability enabling the virus to remove wrongly incorporated nucleosides [123, 124]. However, remdesivir seems to be capable of suppressing such activities due to the mechanism of its inhibitory effect and delayed RNA chain termination [128].

As it was shown in a series of recent studies on SARS-CoV-2 RdRp and MERS-CoV RdRp, the inhibition of the RNA replication cannot happen immediately after the addition of remdesivir. Rather, it occurs after three nucleotides were added into the nascent RNA [129]. Thus, remdesivir inhibits further growth of the RNA strand

by the delayed RNA chain termination phenomenon; meanwhile, the three added nucleotides might account for the protection of inhibitor (remdesivir) from excision by the viral 3'–5' exonuclease activity, which is responsible for the proofreading ability of the CoVs [12, 125].

Many clinical studies are aiming to assess the efficiency of remdesivir for SARS-CoV-2-infected patients. Remdesivir is known to be well tolerated in clinical studies and compassionate use [130–132]. However, its main adverse effects may include multiple organ-dysfunction syndromes, septic shock, acute kidney injury (AKI), and hypotension [133]. In a compassionate use of remdesivir for patients with COVID-19 infection, patients received a 10-day course of treatment with remdesivir (200 mg on day1 and 100 mg daily for 9 days). The results showed 68% (36 of 53 patients) clinical improvement in patients. However, increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension were the most common adverse events experienced by patients under treatment, particularly those patients receiving invasive ventilation. Serious adverse events were observed for 12 patients (23%), among which multiple organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension were most common in patients receiving invasive ventilation at the baseline [132].

In a randomized, double-blind, placebo-controlled, multicenter trial on patients with severe COVID-19 at 10 hospitals in Hubei, China, 237 patients randomly received either placebo or remdesivir (158 remdesivir and 79 placebo). The results showed that patients under treatment with remdesivir had faster clinical improvements compared with those receiving placebo; however, differences were not significant. 66% of patients receiving remdesivir and 64% of those receiving placebo experienced some adverse events [134].

Based on the preliminary results of the first stage of the Adaptive COVID-19 Treatment Trial (ACTT-1), in which patients with COVID-19 were randomly given either remdesivir or placebo as a control group, from among 1059 patients, 538 were assigned to remdesivir and 521 to placebo while the outcome of the study was the time to recovery. The results showed that the patients receiving remdesivir recovered in 11 days; however, recovery time for those receiving placebo was 15 days. Moreover, the Kaplan–Meier estimates of the death rate by 14 days in patients treated with remdesivir and placebo were 7.1% and 11.9%, respectively [131].

In a phase 3 SIMPLE trial, the effect of receiving remdesivir for either 5 or 10 days plus standard of care versus standard of care alone was assessed for patients with moderate COVID-19 pneumonia. The results showed that patients receiving remdesivir for 5 days were 65% more likely to have clinical improvement at day 11 compared with those receiving standard of care alone; however, no significant differences were observed between patients treated with remdesivir for 10 days and those receiving SOC alone.

In the SIMPLE-severe study on patients with SARS-CoV-2 receiving remdesivir for either 5 days or 10 days (200 mg on day 1 and 100 mg daily), from among 397 patients, 200 patients were under treatment for 5 days while 197 patients were under treatment for 10 days. For both groups, the percentage of patients with adverse events was similar (70% in the 5-day group and 74% in the 10-day group). Among all patients, 21% of patients treated for 5 days and 35% of patients treated for 10 days

experienced serious adverse events. Also, serious adverse events of Grade 3 or higher for patients receiving remdesivir for 5 days and 10 days were 30% and 43%, respectively. The most common adverse events experienced were nausea (10% in the 5-day group vs. 9% in the 10-day group), increased alanine aminotransferase (6% vs. 8%), acute respiratory failure (6% vs. 11%), and constipation (7% in both groups) while 4% of the 5-day group and 10% of the 10-day group discontinued treatment due to adverse events. The most common serious adverse events in patients receiving remdesivir for 10 days were the acute respiratory failure (9%, vs. 5%) and respiratory failure (5%, vs. 2%). It should be mentioned that for patients with severe COVID-19 independent of mechanical ventilation, no noticeable differences were observed for patients treated with remdesivir for 5 days and 10 days [130]. According to the newest information released from mortality trials, recommended by the WHO expert groups, in hospitalized patients infected with COVID-19, remdesivir had little or no effect on inpatient overall mortality, initiation of ventilation, and duration of hospital stay [135]. Nevertheless, remdesivir, as the first treatment for COVID-19 patients requiring hospitalization, was approved by the FDA after a phase 3 clinical study sponsored by Gilead Sciences (NCT04292899).

2.2.2 *Chloroquine and Hydoroxychloroquine*

Chloroquine, an amine acidotropic form of quinine, was first synthesized as an anti-malaria drug in 1934 and has been utilized for the treatment and prophylaxis of malaria for many years [15]. In 1946, hydroxychloroquine sulfate, hydroxyl analog of the chloroquine, was synthesized by introducing a hydroxyl group into CQ. Both CQ and HCQ have been utilized for the treatment of malaria, lupus, and rheumatoid arthritis for many years [16, 136]. They share similarities such as pharmacokinetics, mode of action, indications, and type of drug toxicity; however, they slightly differ in the clinical indications and toxic doses [15, 137]. Even though the utilization of both CQ and HCQ for the treatment of malaria is being limited owing to the arisen of chloroquine-resistant P. falciparum strains, they have shown broad-spectrum activities against bacterial, fungal, and viral infections such as autoimmune diseases [15, 138].

Inhibitory effects of CQ and HCQ against CoVs could be fulfilled in various ways [139, 140]. A complete review of their mechanisms of action can be found elsewhere [141]. Despite observed controversy regarding the exact mechanism of action, it was proved that the very mechanism of action, for CoVs entry, is mainly dependent on not only the type of the virus but also the type of the host cells [139, 142, 143]. Since the interaction of COVID-19 S protein with the receptor ACE2 on the host cells is a critical step for initiating the infection process, one of the feasible inhibitory effects of CQ on viral attachment could be through impairing terminal glycosylation of the ACE2 receptor, thereby impeding viral binding and its subsequent entry [18, 144]. On the other hand, another possible way of inhibition could happen through the interaction of CQ and HCQ with viral S proteins, thus preventing the binding of

S proteins on the host cell membrane receptors according to some in silico studies [145]. Moreover, as it is known, for CoVs, the endocytic pathway is one of the chief mechanisms of viral entry into host cells [139]. In this regard, on account of the weak diprotic base nature of CQ and HCQ, their accumulation in acidic organelles such as lysosomes and endosomes increases the pH of their surrounding ambient [5]. Hence, CQ and HCQ are able to prevent the attachment and subsequent entry of the virus mainly dependent on the acidic endo-lysosomal pH, by inhibiting the acidification of the lysosome in that enzymatic protease activities responsible for the cleavage of S protein and subsequent viral entry [146]. In addition, the elevation of pH caused by CQ and HCQ could impair not only the correct maturation and recognition of viral antigens by dendritic cells but also the maturation process of viral proteins completed in the ERGIC and trans-Golgi network (TGN) vesicles both of which require acidic pH [15, 141]. Furthermore, the inhibition of the autophagic process by CQ and HCQ could be involved with the effects of COVID-19 prevention. The viral assembly process occurs in the ERGIC, related directly to autophagosome biogenesis. After the use of CQ/HCQ, the autophagic process could be inhibited by the subsequent pH elevation in lysosomes leading to the SARS-COV-2 halt. Besides, the inhibition of the autophagic process might also associate with the activity suppression of the recycled materials accompanying the autophagic process accounting for the nucleation and replication process of COVID-19 [16].

Moreover, apart from its anti-viral activity, HCQ could act as an anti-inflammatory agent capable of decreasing the production of some cytokines [17, 147]. The secretion of cytokines, such as IL-1β, IL-1RA, IL-6, IL-7, IL-8, IL-2R, TNF-α, known as the cytokine storm, is associated with the disease severity [148, 149]. The possible mechanisms of CQ and HCQ are their involvement in anti-thrombotic activities, and suppressing the release of IL-6, IL-1β, and TNF-α, which are key modulators of inflammation [141, 148].

There are several clinical studies conducted to assess the efficacy of HCQ and CQ on patients infected with COVID-19 [16]. In a study, it was observed that the patients treated with CQ experienced a faster and higher rate of viral suppression compared with those patients in the control group [150]. In another study, the effects of high dosage and low dosage of the CQ on patients infected with severe COVID-19 was assessed, and the results indicated that the higher dosage of CQ should not be used for severe COVID-19 patients, since it might cause a safety hazard, particularly when used with azithromycin and oseltamivir [151]. According to the results of a study, HCQ brought a decreased mortality in critical patients infected with COVID-19 [152]. However, contradictory results were also obtained. For instance, Mahevas et al. found that HCQ could not significantly decrease the admission to ICU, death, or ARDS in COVID-19 patients with hypoxemic pneumonia [153]. According to the findings of another study, it was also demonstrated that CQ cannot prevent the SARS-CoV-2 entry into the lung cells in vitro, in that CQ targets a pathway for viral activation that is not active in the lung cells [154]. Similarly, Mallat et al. indicated that HCQ resulted in a slower viral clearance and mild to moderate disease compared to the control group in patients infected with COVID-19 [155]. On June 15, 2020, the FDA revoked the emergency use authorization for both CQ and HCQ [16] and

according to the newest information released from mortality trials, recommended by the WHO expert groups, in hospitalized patients infected with COVID-19, HCQ had little or no effect on inpatient overall mortality, initiation of ventilation, and duration of the hospital stay [135]. Nonetheless, the efficiency of CQ/HCQ as an antiviral treatment for COVID-19 is still assessing in phase 4 clinical studies in the USA (NCT04331600, NCT04382625). HCQ was proved to have 40% less toxicity in animals [156]. However, the most common side effects of both CQ and HCQ at therapeutic doses include myopathy, electrocardiographic changes, bleaching of hair, retinopathy, pruritus, headaches, and gastrointestinal symptoms [5].

2.2.3 Favipiravir (Avigan)

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide, T-705, Avigan), was first discovered by Toyama Chemical Co., Ltd for antiviral activity against the influenza virus and has been approved for the treatment of Influenza in Japan since 2014 because of its proven safety and effectiveness on humans in clinical trials [5, 26, 27]. Concerning COVID-19, favipiravir was approved to be utilized on 15 February 2020, in China against SARS-CoV-2 [157]. For favipiravir to be converted to its active form, that is, favipiravir-RTP (T-705 RTP) undergoes intra-cellularly phosphoribosylation, consequently exerting its antiviral activity as a pro-drug [27]. Also, it was shown that favipiravir-RTP could be efficiently recognized as a guanosine and an adenosine analog by influenza A virus polymerase [158]. Favipiravir triphosphate, a purine nucleoside analog, is believed to directly inhibit the RdRp activity of influenza A virus polymerase [25, 158]. However, the exact mode of action and accurate molecular interaction between the nucleotide and the viral polymerase has yet to be explicated [158]. In a study conducted on the influenza A (H1N1) virus, it was demonstrated that a high rate of mutation is induced with favipiravir generating a non-viable viral phenotype, a lethal mutagenesis which is a key antiviral mechanism of T-705 [159].

Favipiravir has antiviral activity against a great variety of influenza viruses such as A (H1N1) pdm09, A (H5N1), and recently emerged A (H7N9) avian virus. Moreover, favipiravir is capable of inhibiting the influenza strains resisting current antiviral drugs and showing a synergic effect in combination with oseltamivir, thus expanding influenza treatment options [160]. It was shown that its antiviral activity performs in a dose-dependent manner while it has a short half-life of 2–5.5 h [161, 162]. In addition, the metabolism of favipiravir occurs in the liver mainly by aldehyde oxidase (AO), and partially by xanthine oxidase, thereby producing an inactive oxidative metabolite, T-705M1 that is excreted by the kidneys [162]. In a small clinical study conducted on 168 critically ill patients infected with influenza, patients received either a combination of favipiravir and oseltamivir or oseltamivir alone. The results showed that the combination therapy of favipiravir and oseltamivir results in accelerating clinical recovery [163].

Favipiravir, chloroquine, arbidol, and remdesivir are under clinical studies in china to assess their efficacy and safety against SARS-CoV-2 [157]. According to

preliminary clinical results obtained from an open-label comparative controlled study of patients infected with COVID-19, patients receiving favipiravir compared with those receiving lopinavir/ritonavir experienced not only faster viral clearance but also better chest computed tomography changes [164]. Furthermore, in an in vitro study conducted on Vero E6 cells, favipiravir inhibited SARS-CoV-2 replication with EC50 values of $61.88\,\mu M$ ($9.4\,\mu g/mL$). Nevertheless, another study reported EC50 values > $100\,\mu M$ ($15.7\,\mu g/mL$) for favipiravir [24, 165]. The need for metabolic activation in the host cells for favipiravir could explain the differences between these two studies [24]. In a randomized, controlled, open-label multicenter trial performed on 240 patients infected with COVID-19, patients randomly received arbidol or favipiravir in a 1:1 ratio. According to the results, favipiravir could not considerably improve the clinical recovery rate on day 7 in comparison to arbidol. However, favipiravir appreciably improved the latency to relief for pyrexia and cough and showed mild and manageable adverse effects, including raised serum uric acid, psychiatric symptom reactions, digestive tract reaction, and abnormal LFT [166]. In a double-blinded, placebo-controlled, randomized, phase 3 trial, favipiravir is being administered as a potential therapy for mild to moderate COVID-19 outpatients (NCT04600895).

2.2.4   Lopinavir/Ritonavir (Kaletra)

Lopinavir/ritonavir combination, available under the brand name Kaletra, and developed by Abbott Laboratories, USA, is known as an anti-retroviral drug and was approved by FDA for the treatment of patients infected with HIV in 2000 [5]. Ritonavir, a potent inhibitor of cytochrome P450 3A4, inhibits the metabolism of lopinavir and increases its bioavailability, it was shown that the co-administration of these drugs in healthy volunteers increases the area under the lopinavir plasma concentration–time curve > 100-fold [19, 167]. PLpro, a crucial factor in the protease activity and proper replication of the SARS-CoVs genome has been a target of interest in the treatment of COVID-19 patients [168]. It was demonstrated that lopinavir is a non-covalent, competitive, and potential inhibitor for inhibiting the PLpro of CoVs and subsequently blocking the virus replication [169]. The administration of lopinavir/ritonavir during the early peak viral replication phase (initial 7–10 days) has been reported to be crucial for the efficiency of drugs [170].

   In a study, it was demonstrated that after the administration of lopinavir/ritonavir, the viral load and clinical symptoms dramatically decreased [171]. In another study conducted on 36 pediatric patients (aged 0–16 years) infected with COVID-19, all patients received IFN-α by aerosolization twice a day, 14 (39%) patients received lopinavir/ritonavir syrup (twice a day), and 6 patients needed oxygen inhalation. The results indicated that all patients were cured and the hospital stay meantime was 14 days [172]. On the contrary, in a randomized controlled, open-label clinical trial conducted on 199 patients infected with severe COVID-19, no specific difference was observed in patients treated with lopinavir/ritonavir compared to those who received standard care, and gastrointestinal disturbances were more prevalent adverse events

between patients treated with lopinavir/ritonavir than patients in the control group [173].

In an open-label, randomized, phase 2 trial in adults infected with COVID-19, patients were assigned to either a 14-day triple combination of IFN-β-1b, lopinavir/ritonavir and ribavirin or a control group (lopinavir/ritonavir); results showed that triple combination therapy was superior to control group regarding decreasing the time of hospital stay and alleviating symptoms in patients with mild to moderate COVID-19 [174]. In another study, four patients infected with COVID-19 underwent treatment with lopinavir/ritonavir (lopinavir 400 mg/ritonavir 100 mg, q12 h through oral route), arbidol (0.2 g, three times in a day through oral route), and Chinese traditional medicine Shufeng Jiedu capsule (SFJDC) (2.08 g, three times in a day through oral route) while the duration of treatment was 6–15 days. According to the obtained results, from among four patients, three patients showed considerable improvement in pneumonia-associated symptoms, and for the other patients suffering from severe pneumonia, signs of improvement were observed [175]. The most common adverse effects of lopinavir/ritonavir have been reported to be diarrhea, nausea, and, vomiting (gastrointestinal adverse effects from mild to moderate). However, less common adverse effects observed in patients treated with lopinavir/ritonavir consist of an allergic reaction, asthenia, malaise, headache, myalgias, arthralgias, myocardial infarction, seizures, and lactic acidosis [20, 167, 176]. Lopinavir/ritonavir is still in phase 4 of a clinical study in China to be evaluated for COVID-19 patients (NCT04252885).

2.2.5 Umifenovir (Arbidol)

Arbidol, or umifenovir, an indole-derivative with broad-spectrum activity against both enveloped and non-enveloped viruses, was initially approved in China and Russia for the treatment of influenza A and B [177, 178]. Arbidol is believed to block the entry of influenza virus (A and B) into the host cells by increasing the stability of the hemagglutinin (HA) and hampering low pH reorganizations necessary for fusion machinery of hemagglutinin with the membrane [5, 21, 23]. Arbidol could interfere with advanced stages of the viral life cycle, in that it is capable of interacting with both viral proteins and lipids [4, 179]. Regarding its structure, the presence of amine in position 4 and the hydroxyl moiety in position 5 is crucial for its antiviral activity [39]. It is reported that 40% of the drug could be excreted unchanged after the administration while its half-life is between 17 and 21 h [22].

In a study conducted on 69 patients infected with SARS-CoV-2 in Wuhan, arbidol therapy led to not only a decrease in the mortality rate but also an improvement in the discharge rate [180]. In another study, the therapeutic efficacy of co-administration of arbidol and lopinavir/ritonavir compared to only lopinavir/ritonavir on COVID-19 patients was evaluated, and the results showed that the combination of arbidol and lopinavir/ritonavir culminates in slowing down the development of lung lesions, decreasing the feasibility of respiratory and gastrointestinal transmission toward

decreasing the viral load of COVID-19 [181]. In a clinical trial, 27 COVID-19 patients were recruited, among them, 10 of the patients received chloroquine phosphate, 11 received arbidol, and 6 received lopinavir/ritonavir; the results indicated that both CQ and arbidol decreased the hospitalization time as well as hospitalization expenses and shortened the viral shedding interval [182].

Furthermore, in a study, 200 inpatients infected with common-type COVID-19 received either arbidol hydrochloride capsules (control groups) or a combination of arbidol hydrochloride capsules and Shufeng Jiedu Capsule (SFJDC) (experiment group) for 14 days. The results demonstrated that combining traditional Chinese and western allopathic medicine not only improves recovery time but also has better clinical efficiency and safety [183]. On the contrary, in a clinical trial performed on 141 patients infected with COVID-19, 70 patients received IFN-α-2b, while 71 of them received a combination of arbidol and IFN-α-2b. The outcomes demonstrated that patients receiving co-administration of arbidol and IFN-α-2b experienced neither a decrease in their hospitalization time nor an acceleration in COVID-19 RNA clearance [184]. Likewise, an inefficiency is reported for umifenovir in non-ICU patients [185]. Despite the inconsistent results, arbidol is currently in phase 4 of a clinical trial, which has been conducted on 380 patients with pneumonia caused by SARS-CoV-2 in Ruijin Hospital, Shanghai, China (NCT04260594) [186].

2.2.6 Darunavir

Darunavir, a non-peptidic protease inhibitor (PI) approved by the FDA, is particularly used for the treatment of HIV-1 infection and is majorly utilized in combination with a low boosting dose of ritonavir [38]. Darunavir is more potent compared with other protease inhibitors due to its distinct chemical structure increasing binding affinity and reducing dissociation rate [5]. It has been proved that it is able to prevent viral maturation by inhibiting the cleavage of HIV gag and gag-pol polyproteins alongside inhibiting proteolytic activity and subsequent HIV-1 replication by suppressing dimerization of HIV-1 protease [33]. Therefore, darunavir is recognized as a protease inhibitor while cobicistat could be a supplement for enhancing both pharmacodynamics and pharmacokinetics of darunavir through inhibiting cytochrome P450 (CYP3A) [4, 187]. Darunavir is thoroughly metabolized by hepatic cytochrome P450 (CYP) 3A4 enzymes and is rapidly absorbed after oral intake; moreover, its terminal elimination half-life is 15 h [34]. In a study, it was demonstrated that administration of darunavir is accompanied by an increase in the risk of myocardial infarction in patients infected with HIV. Hence, employing darunavir as a potential therapeutic may be associated with enhancing the risk of cardiovascular diseases [188].

In an open-label trial conducted on 30 patients infected with COVID-19, patients randomly received either darunavir/cobicistat for 5 days on top of IFN-α-2b inhaling or IFN-α-2b inhaling alone. The results showed that darunavir/cobicistat therapy did not change the viral clearance rate at day 7 in comparison to the control group; furthermore, for patients receiving darunavir/cobicistat the median duration

of viral shedding from randomization was 8 days, while 7 days in the control group. However, no statistical significance was observed, and the recurrence of adverse events in both groups was similar. On the other hand, one of the patients receiving darunavir/cobicistat developed anemia (a decrease in the level of hemoglobin from 11.3 to 9.9 g/dL). Other observed adverse events were elevated transaminase levels and renal dysfunction. It should be noted that all of the adverse events were mild [189]. In a phase 3 clinical study, the efficacy and safety of darunavir and cobicistat are evaluating on COVID-19 patients in China (NCT04252274).

2.2.7 Ribavirin

Ribavirin, a guanosine analog, is an antiviral drug used for the treatment of patients infected with HCV and respiratory syncytial virus [5]. Its mechanisms of action could be divided into indirect and direct mechanisms. The direct mechanisms consist of interfering with RNA capping, polymerase inhibition, as well as lethal mutagenesis, and indirect mechanisms are comprised of inosine monophosphate dehydrogenase inhibition and immunomodulatory effects [190]. Ribavirin has established a good reputation for being utilized in emergency clinical plans against CoVs infection due to its availability and low cost. The most convincing outcomes generally have been obtained with early administration upon presentation with pneumonia and before sepsis or organ system failure [30]. Its half-life time is estimated to be 3.7 h, with an oral bioavailability of 52%, which could be because of the first-pass metabolism in the liver [31, 191]. Even though ribavirin is known as a potential therapeutic for the treatment of HCV, it is highly toxic. Hence, it is recommended to be used in combination therapy with IFNs or lopinavir/ritonavir in the Diagnosis and Treatment Guidelines of COVID-19 in China [39].

A combination of ribavirin and IFN-α-2b was utilized for the treatment of MERS-CoV infected rhesus macaques and demonstrated a decrease in viral replication, moderating the host response, and improving clinical results [192]. In addition, according to an open-label, randomized, phase 2 trial conducted on patients infected with COVID-19, triple combination therapy of patients with interferon-β-1b, lopinavir/ritonavir, as well as ribavirin was much safer and superior to the administration of only lopinavir/ritonavir regarding the decreasing symptoms, reducing the time of hospital stay, and viral shedding in patients infected with mild to moderate COVID-19 [174]. In order to compare the efficacy and safety of three antivirals, namely, ribavirin, lopinavir/ritonavir, and IFN-α-1b for the treatment of patients infected with COVID-19, three different therapeutic regimes were applied in a clinical trial, that is, ribavirin plus IFN-α1b or lopinavir/ritonavir plus IFN-α1b and or ribavirin plus lopinavir/ritonavir plus IFN-α1b. According to the obtained results, the combination of ribavirin plus lopinavir/ritonavir caused a considerable increase in gastrointestinal adverse effects [193]. A combination of ribavirin, nitazoxanide, and ivermectin for a duration of 7 days is assessed for COVID-19 treatment at Mansoura University in Egypt (NCT04392427).

2.2.8 Oseltamivir (Tamiflu)

Oseltamivir (Tamiflu), a neuraminidase inhibitor (NAIs) licensed for the treatment of both influenzas A and B, was synthesized through employing two natural products from plants, namely, quinic acid, and shikimic acid [29, 194]. Oseltamivir prodrug is known as oseltamivir phosphate [28]. In the liver, oseltamivir is metabolized and converted to its active metabolite, that is, oseltamivir carboxylate [28]. It is able to prevent the release of viral particles from the host cells by binding to influenza viral neuraminidase, thereby decreasing the spread of the virus in the respiratory tract [4, 28]. Nevertheless, according to the result of a study performed on patients infected with COVID-19 in china, no positive results were obtained for patients receiving tamiflu [195]. However, the administration of oseltamivir and its combination with other drugs such as CQ, arbidol, lopinavir/ritonavir, and favipiravir are under clinical studies to evaluate their potential in the treatment of SARS-CoV-2 infection [85, 196]. In an open, prospective/retrospective, randomized controlled cohort study, the efficiency of three antiviral drugs including oseltamivir, arbidol hydrochloride, and lopinavir/ritonavir is compared for COVID-19 treatment in China (NCT04255017).

2.2.9 Ivermectin

Ivermectin, approved as both an anti-parasitic and anthelmintic agent, is a macrolide endectocide macrocyclic lactone that was originally derived from an actinomycete (*streptomyces avermitilis*) [5, 38]. Its antiviral activity was initially found by its capability in inhibiting the interaction between the nuclear transport receptor importin α/β (IMP) and integrase molecule of HIV [4, 48]. In fact, its antiviral mechanism of action involves the dissociation of the preformed IMPα/β1 heterodimer, responsible for the transport of viral proteins to the nuclear [77, 197].

   According to the result of a study conducted in Australia, ivermectin demonstrated antiviral activity against SARS-CoV-2 in clinical isolate in vitro Vero-hSLAM cells with the addition of a single dose 2 h post-infection, and it was able to reduce viral RNA around 5,000 times. Moreover, the hypothesized mechanism of action for ivermectin was observed to be likely through inhibiting IMPα/β1-mediated nuclear import of viral proteins as anticipated [198]. This drug is currently under a phase 3 clinical trial against COVID-19 in the USA, Pennsylvania, Temple University (NCT04530474).

2.2.10 Tenofovir

Tenofovir, a nucleotide analog (NA) of adenosine 5'-monophosphate, is a reverse transcriptase inhibitor with two different formulations, namely, tenofovir disoproxil

fumarate (TDF) and tenofovir alafenamide (TAF) [35]. They are commercially available prodrugs of tenofovir capable of improving their oral bioavailability and membrane permeability [35, 36]. Tenofovir alafenamide is able to selectively activate presenting preferential distribution in lymphatic tissues, and it is formulated to reduce adverse events associated with the administration of tenofovir disoproxil fumarate [199]. Both of them are vital components for the treatment of HIV and HBV [35]. Tenofovir is one of the potential nucleotide analogs under investigation for the treatment of SARS-CoV-2 [200]. A combinational administration of tenofovir/emtricitabine in addition to the use of personal protective equipment (PPE) is currently under phase 2/3 of a clinical trial for COVID-19 patients by Hospital Universitario San Ignacio, Colombia (NCT04519125).

2.2.11 Camostat Mesylate

Camostat mesylate, a serine protease inhibitor first used for the treatment of dystrophic epidermolysis, chronic pancreatitis, and oral squamous cell carcinoma, was initially manufactured by the Nichi-Iko Pharmaceutical Co., Ltd. in contribution with Ono Pharmaceutical, Japan [38, 201]. It should be noted that the S protein of human CoVs is primed by TMPRSS2, which is a serine protease [37]. In this regard, camostat mesylate may be able to inhibit the SARS-CoV-2 entry into the host cell, since it is a serine protease inhibitor blocking TMPRSS2 activity [39, 202]. In a study conducted on a pathogenic animal model of SARS-CoV-1 infection, it was observed that camostat has the potential to prevent viral spread and pathogenesis of SARS-CoV-1 [203]. Camostat mesylate is currently under phase 3 of a clinical trial for the treatment of COVID-19 patients in French (NCT04608266).

2.2.12 Nafamostat Mesylate

Nafamostat, a synthetic serine protease inhibitor that is known as an anticoagulant in nature, was first brought to the Japanese market in 1986 for the treatment of acute symptoms of pancreatitis and for applying to certain bleeding complications. This drug is capable of inhibiting different enzymatic systems such as complement, kallikrein-kinin, fibrinolytic systems, and coagulation. It has been also utilized for the prevention of liver transplantation and post-transplant syndrome [5, 38, 204]. Nafamostat is able to prevent viral entry through the host cell surface membrane. Hence, it is considered as one of the potential repurposing drugs against COVID-19 [205]. Its mechanism of action is anticipated to be through inhibiting the human protein TMPRSS2, the S protein-dependent enzyme that cleaves and thereby activates the S protein for binding to ACE2 [206, 207]. In an in vitro study, nafamostat prevented the entry of MERS-CoV, and it was demonstrated as the most potential protease inhibitor among all 1000 drugs screened [40]. This drug is currently under

phase 3 of the clinical trial on patients infected with COVID-19 by the University of Edinburgh, the UK (NCT04473053).

2.2.13   Molnupiravir

Molnupiravir, or MK-4482/EIDD-2801, pro-drug of the nucleoside analog N4-hydroxycytidine (NHC), is an RNA polymerase inhibitor that is orally available and was originally developed for the treatment of influenza [43–45]. It has shown appreciable anti-influenza activity in ferrets, mice, guinea pigs, and human airway epithelium organoids [44, 208, 209]. As a result of the collaboration between Ridgeback Biotherapeutics and Merck, molnupiravir is developing for the treatment of COVID-19 patients [43]. In a study, the effect of molnupiravir in a Syrian hamster SARS-CoV-2 infection model was investigated, and the results showed that molnupiravir considerably decreased not only infectious virus titers but also viral RNA loads in the lungs, thereby improving lung histopathology [210]. Moreover, in another in vivo study conducted on animals infected with SARS-CoV-2, molnupiravir was proved to be a potential oral drug capable of considerably decreasing the viral load in the upper respiratory tract and preventing the spread to untreated contact animals [45]. Molnupiravir administration is currently in phase 2/3 of a multicenter clinical trial by Merck Sharp & Dohme Corp (NCT04575584).

2.2.14   Sofosbuvir

Sofosbuvir, a direct-acting antiviral drug that was initially approved as an anti-HCV, could be utilized as a repurposed antiviral drug for the treatment of COVID-19 [46, 47]. Among the studies, it was predicted that sofosbuvir might be capable of binding to the SARS-CoV-2 RdRp enzyme, thereby inhibiting its activity [64, 211, 212]. In a single-center, randomized controlled trial in patients infected with moderate COVID-19, patients received either a combination therapy of sofosbuvir/daclatasvir/ribavirin or standard care. The results demonstrated that the combinational administration of these three drugs engendered recovery and lower mortality rates for patients. Nevertheless, an imbalance was observed in the baseline characteristics between the arms. Thus, larger randomized trials are needed to prove these results [213]. Additionally, according to a molecular docking study, ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir are potent drugs against COVID-19 that tightly bind to the RdRp of the SARS-CoV-2 strain, thereby preventing its function [214]. Sofosbuvir is currently under phase 2/3 of a clinical trial in Egypt by Tanta University (NCT04497649).

2.2.15 Famotidine

Famotidine, a histamine-2 receptor antagonist (H2RA), reduces the production of gastric acid [50, 51]. An in vitro study of this drug demonstrated that H2RA has anti-viral activity against HIV replication [215]. Regarding the treatment of COVID-19, according to the results obtained from in silico molecular docking, Famotidine could inhibit PLpro enzyme activity in the viral replication cycle [216]. Hence, this drug is capable of inhibiting vital enzymes in the life cycle of SARS-CoV-2 and consequently mediating the maturation of non-structural proteins [51]. In a multi-site, randomized, double-blind phase 3 clinical study, the efficiency of famotidine is evaluating for COVID-19 patients in the USA (NCT04370262).

2.2.16 Nitazoxanide

Nitazoxanide, a synthetic nitrothiazolyl-salicylamide derivative, is a broad-spectrum antiviral agent used for the treatment of a wide range of viruses, including influenza A, B, and Ebola viruses [3, 6, 54]. Nitazoxanide demonstrated in vitro antiviral activity against MERS-CoV and other CoVs; also, this drug suppresses the production of pro-inflammatory cytokines in peripheral blood mononuclear cells and IL-6 in mice [217]. Moreover, the antiviral activity of this drug could be attributed not to the virus-specific pathways, but rather to its interference with host-regulated pathways involved in viral replication [5, 217, 218]. Nitazoxanide is currently in phase 4 of clinical trials for COVID-19 treatment in Mexico by Laboratorios Liomont (NCT04406246).

2.2.17 Nelfinavir

Nelfinavir, a non-peptidic, competitive HIV protease inhibitor, is considered as one of the potential drugs against COVID-19 [55]. This drug was approved by the FDA for the treatment of HIV infection in 1997 [219]. According to the results of a study in which HIV protease inhibitors were screened to find potential drugs, CoVs, it was indicated that nelfinavir is capable of inhibiting the replication cycle of SARS-CoV-1 [56]. Similarly, in another in vitro study, it was shown that nelfinavir could inhibit 3CLpro of the virus and consequently suppressing the replication cycle of SARS-CoV-2 with EC50 and EC90 of 1.13 µM and 1.76 µM, respectively [57, 220]. According to an in silico study, based on the combinational administration of nelfinavir and cepharanthine, nelfinavir could bind the SARS-COV-2 main protease, thereby inhibiting the viral replication cycle, while cepharanthine is able to prevent viral attachment and entry into cells. Hence, their combination could be a potent multidrug for the treatment of COVID-19 [221].

2.2.18 Auranofin

Auranofin is a gold-containing triethyl phosphine that has been explored for therapeutic applications against a wide range of diseases, including cancer, neurodegenerative disorders, HIV, as well as parasitic and bacterial infections [58, 59]. According to the results of one in vitro study, auranofin inhibits the replication of SARS-COV-2 in human cells at a low micromolar concentration by reducing the viral RNA up to 95% at 48 h after infection [58]. Its mechanism of action consists of inhibiting the redox enzymes as well as induction of ER stress, thereby interfering with the protein synthesis of SARS-CoV-2 [58–61, 222].

2.2.19 Carmofur

Carmofur, an approved antineoplastic drug that was derived from 5-fluorouracil (5-FU) and was explored for the treatment of breast, gastric, bladder, and colorectal cancers, is shown to have inhibitory effects against SARS-CoV-2 [222–224]. It was demonstrated that carmofur inhibits the main protease (3CLpro) activity of the SARS-CoV-2 with an IC50 value of 1.82 µM and prevents viral replication in cells with an EC50 value of 24.30 µM [63, 64].

2.2.20 Galidesivir

Galidesivir (BCX4430, Immucillin-A), an adenosine analog as well as RdRp inhibitor that was first developed for the treatment of HCV, has shown antiviral activity against a wide variety of viruses, including togaviruses, filoviruses, arenaviruses, paramyxoviruses, orthomyxovirus bunyaviruses, CoVs, picornavirus, and flaviviruses [38, 66, 67]. This drug is currently under phase 1 of clinical trials for COVID-19 treatment in Brazil (NCT03891420).

2.2.21 Azvudine

Azvudine or 2′-deoxy-2′-β-fluoro-4′-azidocytidine (FNC) was first developed for the treatment of HIV and has antiviral activity against HBV and HCV [68, 225]. Azvudine might be able to inhibit the reverse enzyme transcriptase vital in viral transcription, thereby interfering with the replication of the CoVs [38]. This drug is currently under phase 3 of a randomized clinical trial for patients infected with COVID-19 in Brazil (NCT04668235).

2.3 Immunomodulators and Anti-inflammatory Drugs

The immune (innate and adaptive) system includes cells, molecules, and processes working together to provide the body protection against aggressive viruses, bacteria, toxins, parasites, fungi, and cancer cells [7]. However, the immune system may be weakened in individuals owing to high age or immunodeficiency disorders [1]. On the other hand, the inflammatory phase, the third phase after the mild infection and pulmonary phases, is initiated and accompanied by cytokine storm due to the excessive immune response of the host upon infection and may create complications like ARDS leading to death in many cases [148]. Considering the biology of SARS-CoV-2 and by exploring the molecular mechanisms employed by the virus regarding its interactions with host cells, the development of host immune response could be illuminated, which may lead to proposing efficient drugs for inhibiting COVID-19 [7]. The medications that have the potential to interact with the host immune system generally can fall into two main categories, the remedies with the aim of boosting the immune system and the therapeutics that intervene in the host immune response and play their role in immunomodulation or alleviating damages caused by the dysregulated inflammatory responses [1]. In this respect, many immunomodulatory therapies and anti-inflammatory drugs such as NKs, IFNs, MSCs, convalescent plasma, interleukin inhibitors, anticitokines, anticoagulants, corticosteroids, and monoclonal antibodies have been administrated to control the symptoms, modulate the immune system leading to COVID-19 treatment (Table 2.1) [1, 8, 85].

2.3.1 Natural Killer Cells

The higher mortality rate of elderly patients compared to other generation individuals infected with COVID-19 could be explained by the weakening of the immune system with age and considered somehow as aging-associated diseases in chronic disease states [77, 101, 226]. NK cells as practical components of the innate immune system are against viral infections. NK cells are able to rapidly release granzymes and perforins inducing cell lysis. In addition, they are crucial sources of interferon-gamma (IFN-γ) capable of mobilizing antigen-presenting cells (APCs) and activating antiviral immunity [7]. Hence, the injection of NK cells into elder and fragile patients' bodies could be efficacious in SARS-CoV-2 clearance with no severe side effects [1, 77]. Chen et al. indicated that macrophages and NK cells have a crucial function in the clearance of SARS-CoV-1 [227]. The safety and efficacy of CYNK-001, an immunotherapy containing NK cells derived from human placental CD34 + cells on moderate COVID-19 patients, are currently assessing in a phase 2/3 clinical study at multicenters in the USA (NCT04365101).

2.3.2 Mesenchymal Stem Cells

In severe patients, SARS-CoV-2 infection may generate a threatening cytokine storm in the lungs. MSCs, as a safe and well-tolerated therapeutic option, can be used to benefit through their immunomodulatory, antimicrobial, antiapoptotic, and regenerative effects [70]. The anti-inflammatory activity of MSCs has been associated with decreasing pro-inflammatory cytokines and producing paracrine factors leading to regenerative medicine in pulmonary epithelial cells [1]. MSCs are able to regulate the function of both innate and adaptive immune systems through either passive or active cell–cell interaction, secretion of trophic factors, or activation of regulatory T cells [2, 70]. Clinically, the employing of intravenous transplantation of MSCs for severe SARS-CoV-2 patients has been reported to be safe and effective [71, 228, 229]. It has been reported that MSC therapy for COVID-19 patients exerts no adverse effects on the patients [230, 231]. The efficacy and safety of the MSC remestemcel-L administration are evaluating on COVID-19 patients with ARDS in phase 3 multicenter clinical study in the USA (NCT04371393).

2.3.3 Interferons

IFNs are soluble endogenous signaling proteins with high antiviral activity secreted by cells including cells with hematopoietic origin upon viral or bacterial infection. The interferon-stimulating genes (ISG) generally associated with immunomodulation, signaling, and inflammation are activated by the INF fixation on interferon α/β receptor (IFNAR), the receptors found at most cells plasma membrane [4, 232]. IFNs have been utilized as a therapeutic option against autoimmune disorders, different cancers, and viral infections including hepatitis B and C [1, 232]. IFNs play significant roles in enhancing the immune system by restricting the spread of infectious viral, adjusting innate immunity responses, and activation of adaptive immune responses [7, 233, 234]. Hence, employing recombinant human interferons (rhIFNs) has been considered as a potential treatment method against COVID-19 while SARS-CoV-2 has shown sensitivity to some human type I IFNs like IFN-α and IFN-β [94, 235, 236]. However, the adverse reactions of fever, myalgias, headaches, leukopenia, lymphopenia, and autoimmune hepatitis may be associated with the administration of IFNs [72].

2.3.3.1 Interferon-α

IFN-α is a cytokine secreted by the immune cells in the body capable of eliciting a practical host-mediated immune cell response for various cancer treatments and inhibition of replication of viruses like SARS-CoVs, HIV, and HCV while SARS-CoV-2 has shown significantly high sensitivity to IFN-α [8, 72, 237]. IFN-α has

been exploited as a favorable antiviral activity due to low toxicity and its crucial roles in the inhibition of the virus replication at the early stage of infection, moderating the symptoms of the acute phase of the disease, shortening the disease duration leading to the survival of severe patient [8]. To enhance the stability of IFN-α and prolong its half-life from 4.6 to 22–60 h, Pegylated IFN-α-2b has been utilized providing a situation in which the lower dosing could be injected frequently [72]. In a retrospective multicenter cohort clinical trial, 242 of 446 COVID-19 patients received IFN-α-2b as a treatment in Hubei, China. It was observed that early administration (≤5 days after admission) of IFN-α-2b was responsible for the reduced in-hospital mortality while peculiarly, late administration of IFN-α-2b was involved with increased mortality [238]. In a phase 3 clinical study, the efficiency of rhIFN-α-1b in preventing COVID-19 is currently assessing on a large number of patients at Taihe Hospital Shiyan, Hubei, China (NCT04320238).

2.3.3.2   Interferon-β

IFN-β is a signaling cytokine that has a broad range of applications against viral infections like HCV and HBV. It is able to activate cytoplasmic enzymes stimulating them to prevent viral replication [38, 74]. IFN-β with the ability of maintaining endothelial barrier activity, pro-inflammatory response, and defensive function in the lungs has demonstrated the highest potency among the IFNs in prophylactic protection and antiviral potential post-infection effects [74, 234, 239]. IFN-β-1 has demonstrated efficacy against SARS-CoV-1 [240]. Consequently, on account of the high similarity of SARS-CoV-1 with SARS-CoV-2, IFN-β-1 has been introduced as a potential therapeutic in COVID-19 treatment [241]. Despite inhibiting the production of IFN-β and obstructing the innate immune system response by SARS-CoV-2, the virus has shown sensitivity to the antiviral activity of externally administrated type I IFNs [236].

In a phase 2 clinical study (NCT04385095), safety and efficacy of inhaled nebulized IFN-β-1-a (SNG001) were assessed for the treatment of patients admitted to hospital with COVID-19, and it was demonstrated that in comparison with patients who received placebo, treated patients with SNG001 had a greater chance of treatment with more rapid recovery [73]. Likewise, IFN-β-1-b has indicated potency in inhibiting SARS-CoV-1, MERS-CoV, and SARS-CoV-2 infections [241]. Also, a combination therapy of IFN-β-1-b, lopinavir/ritonavir, and ribavirin was evaluated on COVID-19 patients admitted to hospital in a phase 2 clinical study (NCT04276688) and demonstrated a high potential in alleviating symptoms and reducing the disease duration and hospital stay in patients with mild to moderate SARS-CoV-2 infection [174].

2.3.4   Convalescent Plasma or Intravenous Immunoglobulin

The pooled plasma or hyperimmune immunoglobulins derived from recovered patients of a disease, termed convalescent plasma (CP) has been widely employed to treat many infectious diseases such as MERS-CoV, SARS-CoV-1, Ebola, and SARS-CoV-2 with favorable outcomes through passive immunity delivery and replacement therapy for antibody deficiencies [38, 242, 243]. On account of the fact that CP or intravenous immunoglobulin (IVIG) possesses neutralizing antibodies to SARS-CoV-2, which could be exploited as a potential therapy to directly neutralize the virus, modulate the inflammatory response, and control the overactive immune system (i.e., cytokine storm) [75, 76, 243]. In the hope of minimizing morbidity and mortality, all these benefits of CP are expected to be attained if used in early administration and non-critically hospitalized patients [8, 76].

Improvement in the clinical status of small sample sizes of critically ill patients was reported in some studies by the administration of CP with low serious adverse reactions [243–247]. Despite the risks involved with CP and IVIG administration for COVID-19 patients, including transfusion-associated lung injury and circulatory overload, allergic/anaphylactic reactions and less common risks like transmission of infections and red blood cell alloimmunization [41], very low adverse events have been reported in a safety study of CP for 20,000 hospitalized patients implying that CP is safe in hospitalized patients with COVID-19 [246]. In a phase 3 clinical trial, CP has been employed for treating hospitalized COVID-19 patients in New York, the USA (NCT04418518).

2.3.5   Anticitokines, Immunosuppressants, and JAK Inhibitors

Since COVID-19 is associated with a significant increase in the level of serum cytokines, that is, the cytokine storm, repurposing of available anticytokines with proven safety has come to the fore [248, 249]. In this regard, considering the role of the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway in Angiotensin II type 1 receptor, the receptor that is expressed on peripheral tissues and immune cells as cytokine receptors with the role of the renin-angiotensin system (RAS) signal transduction, targeting of this pathway in hospitalized patients by employing JAK and Adaptor-associated kinase (AAK) inhibitors like sirolimus, baricitinib, ruxolitinib, imatinib, cyclosporine, and tofacitinib capable of inhibiting type I/II cytokine receptors could not only reduce the clinical symptoms in organs like lung, kidney, and heart but also inhibit the cytokine storm in ARDS condition associated with severe SARS-CoV-2 infection [3, 250, 251].

2.3.5.1 Sirolimus

Sirolimus, known as rapamycin (trademark name: Rapamune), is a natural product isolated from the bacterium *Streptomyces hygroscopicus in* Easter Island. Sirolimus was initially isolated as an antifungal agent with potential anticandida activity [92, 252]. Nevertheless, its antitumor/antiproliferative and immunosuppressive properties were proved by further studies [252]. Also, sirolimus is capable of weakening the immune system, surprisingly strengthening T cells activity in the course of pathogenic invasions, delaying age-related illnesses in humans, and having an inhibitory effect on the mammalian target of rapamycin complex 1 (mTORC1) receptor [91].

On account of the fact that mTORC1 has a pivotal role in the viral replication of different viruses, including orthohantavirus and CoVs, sirolimus could be a potential therapeutic agent for repurposing against COVID-19 [85, 91, 253]. According to the results obtained from an in vitro study, sirolimus affected PI3K/AKT/mTOR pathway, thereby inhibiting MERS-CoV activity [254]. Moreover, an in silico study showed that sirolimus could be a potential drug for the treatment of patients infected with COVID-19 using a network-based drug repurposing model [253]. This drug is currently in phase 2 of a clinical trial for patients infected with COVID-19 performing in the USA by the University of Cincinnati (NCT04341675).

2.3.5.2 Baricitinib

Baricitinib under the brand name olumiant, an inhibitor of cytokine-release approved in 2018 for the treatment of rheumatoid arthritis, is a potential JAK inhibitor that selectively inhibits the JAK1 and 2, consequently reducing inflammation in patients infected with COVID-19 [3, 255–257]. Moreover, baricitinib is capable of inhibiting AAK1 and Cyclin G-associated kinase (GAK) [3]. Both AAK1 and GAK are important regulators of endocytosis. Hence, targeting AAK1 and GAK makes baricitinib also a potential candidate for not only inhibiting the viral entry but also interfering with the virus assembly [258]. The effectiveness and safety of baricitinib have been shown through conclusive results such as lower fatality rate and higher discharge rate obtained from clinical studies conducted on COVID-19 patients receiving baricitinib [256, 259]. This drug is undergoing phase 3 of a clinical study performing on 1400 COVID-19 patients in the USA (NCT04421027).

2.3.5.3 Ruxolitinib

Ruxolitinib, also known as INC424 or INCB18424, is a potent inhibitor of JAK1 and 2 that was approved by the FDA against myelofibrosis, polycythemia vera, and acute graft-versus-host disease [38, 93, 260, 261]. Its main mechanism of action includes interfering with the JAK-STAT, one of the chief regulator cell signaling pathways, through interacting with JAK and preventing the activation of STAT,

thereby reducing the elevated levels of cytokines [93, 257]. Given these points, ruxolitinib could be considered as one of the potent drugs against a wide range of diseases, including COVID-19. According to studies conducted on COVID-19 patients receiving ruxolitinib, obtained results demonstrated that this drug successfully reduced both the inflammatory blood cytokine levels such as IL-6 and the acute phase protein ferritin; moreover, the administration of ruxolitinib brought about rapid respiratory and cardiac improvement, significant chest computed tomography (CT) improvement, faster recovery from lymphopenia, clinical stabilization, as well as favorable side-effect profile [262, 263]. Ruxolitinib is under phase 3, randomized, double-blind, placebo-controlled, multicenter clinical study on patients infected with COVID-19 in the USA (NCT04377620).

2.3.5.4 Fingolimod

Fingolimod, known as FTY720, is an orally administered compound acting as the modulator of sphingosine-1-phosphate (S1P) receptors and was chemically derived from an immunosuppressive metabolite (myriocin) isolated from a fungus (*Isaria sinclairii)* [38, 264, 265]. In fact, fingolimod could play a role as a potent functional antagonist of S1P1 receptors on T cells subsequently sequestering lymphocytes in lymph nodes [1]. This drug has shown conclusive results in the treatment of multiple sclerosis (MS) on account of its capability to reduce the inflammatory damages and effect on the central nervous system (CNS) [95, 266]. Based on pathological findings, besides ventilator support, immune modulators such as fingolimod should be taken into consideration, in that, their combination might prevent the progression of ARDS [196].

2.3.5.5 Thalidomide

Thalidomide, which is an antiangiogenic, anti-inflammatory, as well as anti-fibrotic agent, was initially synthesized by the CIBA pharmaceutical company in 1954 and used as a sedative, antiemetic, and tranquilizer for morning sickness [267]. Thalidomide has inhibitory effects on TNF-α synthesis and is used for the treatment of multiple inflammatory diseases, including Behçets' disease and Crohn's disease [77, 96]. Even though the exact mechanism of action for the anti-inflammatory effects of thalidomide has yet to be found, researchers have attributed its anti-inflammatory effects to its ability for accelerating the degradation of messenger RNA in blood cells, thereby reducing the blood serum level of TNF-α, which is a cytokine involved in systemic inflammation and cytokine storm [268, 269]. Due to its properties, clinical studies are conducting to assess the immunomodulatory effects of thalidomide on reducing lung damage caused by SARS-CoV-2 [77]. Thalidomide is under phase 2 of a randomized, multicenter, placebo-controlled, double-blind clinical trial on 100 patients infected with COVID-19 performing by Wenzhou Medical University in China (NCT04273529).

2.3.6 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs have been widely utilized for controlling acute and chronic inflammatory circumstances [270]. Generally, NSAIDs act by curbing prostaglandin synthases 1 and 2, known as cyclooxygenase enzymes (COX-1 and COX-2) that are responsible for producing prostaglandins (PGs) and provoking pain and fever [271–273]. NSAIDs have been employed to reduce fever and muscle pain caused by COVID-19. However, there is a heated controversy as to whether these drugs are safe [270]. On account of the fact that most studies postulating not protective effects of NSAIDs have been majorly in vitro or on animals rather than on humans [272], further studies are needed to determine the role of NSAIDs in the context of SARS-CoV-2 infection.

2.3.6.1 Naproxen

Naproxen a member of NSAIDs is a propionic acid derivative, which is administered orally and rectally, has been widely used against rheumatic diseases and non-rheumatic circumstances [97, 98]. It was demonstrated by Zheng et al. that naproxen is capable of exerting antiviral activity against influenza A and B viruses, in that this drug obstructs the nuclear export of the viral nucleoproteins, hampering influenza replication [274]. Additionally, in another study conducted on COVID-19 patients receiving ibuprofen and naproxen, conclusive results such as diminishing the probability of hospitalization and requiring mechanical ventilation were obtained [275]. Currently, the efficacy of naproxen on hospitalized COVID-19 patients is assessing through phase 3 of a randomized clinical study performing by Hôpitaux de Paris (NCT04325633).

2.3.6.2 Ibuprofen

Ibuprofen is NSAID with analgesic, antipyretic, and anti-inflammatory properties, which was first introduced in the UK in 1969 and has been used against symptoms of acute pain, inflammation, fever, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout, and Bartter's syndromes [38, 276, 277]. Its mechanisms of action consist of reducing the activity of COX enzyme, thereby inhibiting the production of prostaglandins [278]. Regarding the effectiveness of ibuprofen against COVID-19 infection, there are quite a few contradictory suggestions made by studies. For example, whether ibuprofen could facilitate the cleavage of the ACE2 receptor on host cells, thereby interfering with the viral entry, or whether ibuprofen may decrease the excess inflammation or cytokine release in COVID-19 infection has been discussing. However, due to a lack of substantiated evidence, these claims are just possible protective effects of ibuprofen against CoV infection [279, 280]. Moreover, even though it is hypothesized that ibuprofen might increase the severity of COVID-19 infection, according to one study performed on 430 patients infected with COVID-19,

ibuprofen was not associated with worse clinical outcomes, compared with parac-etamol or no antipyretic. Nevertheless, further clinical studies are required to confirm their results [281]. This drug is currently under phase 4 of a clinical study conducting on 230 participants infected with COVID-19 by King's College London in the UK (NCT04334629).

2.3.6.3 Paracetamol

Paracetamol (acetaminophen), which was initially synthesized through its precursor, that is, phenacetin in 1878, has been used to relieve acute and chronic pain world-wide [282, 283]. This drug is currently the most prevalent analgesic in the world and possesses weak inhibitory effects on the synthesis of prostaglandins [283, 284]. According to suggested warnings regarding the administration of ibuprofen for COVID-19 patients, paracetamol was recommended as a safer option. Although paracetamol has been reported to have no or insignificant anti-inflammatory and antiplatelet activity, this drug has been constantly used for the control of COVID-19 [285, 286]. Nonetheless, paracetamol might cause glutathione (GSH) depletion, which might result in developing severe COVID-19, particularly in more vulnerable groups. Therefore, clinical studies are needed to investigate the efficacy and adverse effects of this drug on patients infected with COVID-19 [286].

2.3.7   Corticosteroids

Corticosteroids have been proposed to be utilized for the suppression of lung inflam-mation in SARS-CoV-1 and MERS-CoV owing to their anti-inflammatory effects and the potential in reducing mortality [72, 287]. Prognosis improvement and clin-ical recovery promotion have been reported in a systematic review of corticosteroid therapy for severe COVID-19 patients [288]. Nevertheless, the efficacy and safety of the administration of corticosteroids like methylprednisolone, dexamethasone, and budesonide for the management of SARS-CoV-2 infection are still controver-sial [200, 287, 289]. The administration of corticosteroids in the management of COVID-19 may bring the risk of damages like prolonged mechanical ventilation, delayed viral clearance, and avascular necrosis. Thus, it demonstrates the need for a high consideration in corticosteroid administration for COVID-19 patients while also requiring more clinical data [289].

2.3.7.1 Methylprednisolone

Whether methylprednisolone could be a potential drug for the suppression of unwanted immune reactions is questionable [1]. However, it is believed by many medical researchers that methylprednisolone could improve the deregulation of the

host immune response and increase the blood pressure where is low due to the cytokine storm [85]. Wu et al. reported that the risk of mortality was decreased by the administration of methylprednisolone for severe patients with ARDS. In fact, 23 of 50 (46%) patients who received methylprednisolone died while the mortality rate in patients with no methylprednisolone treatment was higher (61.8% (21 of 34 patients)) [101]. The routine use of corticosteroids including methylprednisolone is opposed by the Infectious Diseases Society of American. On the other hand, they do recommend the administration of corticosteroids for the patients with developed ARDS in order to set the cytokine storm in the context of a clinical trial [290]. The efficacy of different hormone doses of methylprednisolone is evaluating on severe COVID-19 patients in a phase 4 clinical study in Hubei, China (NCT04263402).

2.3.7.2 Dexamethasone

Dexamethasone is on the list of essential medicine of the WHO, which is available worldwide at low cost [291]. It is published that early treatment of ARDS with dexamethasone could reduce the ventilator days and mortality in patients generally with established moderate-to-severe ARDS [102]. A lower 28-day mortality was reported by employing dexamethasone treatment at a dose of 6 mg once daily for up to 10 days in hospitalized patients with COVID-19 who were receiving respiratory support (NCT04381936) [291]. In a phase 3 clinical study (NCT04327401), administration of intravenous dexamethasone plus standard care, compared with standard care alone for the COVID-19 patients with moderate or severe ARDS, showed promising results and caused a significant increase in the number of days alive and free of mechanical ventilation over 28 days [103]. In a phase 4 clinical trial in Brno, Czechia, the effect of two different doses of dexamethasone is assessing on COVID-19 patients with ARDS (NCT04663555).

2.3.8 Antibiotics

2.3.8.1 Azithromycin

Azithromycin, a broad-spectrum antibiotic, is an orally administered acid-stable antibacterial drug that is structurally related to erythromycin with analogous antimicrobial activity [38, 292, 293]. This drug is known for its antimicrobial activity against some gram-negative organisms, especially Haemophilus influenza that is associated with respiratory tract infections [293]. Besides its antibacterial activity, azithromycin has shown a wide variety of antiviral and immunomodulatory activities. Hence, this drug could be a potent candidate in suppressing viral infections, particularly COVID-19 [294]. Further, regarding SARS-CoV-2, it was shown that azithromycin inhibits the viral entry into the host cells by interacting with SARS-CoV-2 S protein and ACE2 [4, 100]. Also, it should be noted that, in the context

of COVID-19, the combination of HCQ and azithromycin has been associated with serious adverse events, including a higher risk of cardiac toxicity and arrhythmias [294]. However, in one randomized-controlled clinical trial, results showed that treatment with a combination of azithromycin and HCQ was associated with a reduction in mortality of COVID-19 patients, and while administered alone, azithromycin did not show a higher risk of adverse events compared with the administration of the combination of HCQ and azithromycin or HCQ alone [295]. Azithromycin versus usual care is under phase 3 of a multicenter open-label clinical trial in ambulatory care of COVID19 by the collaboration of Pfizer in the UK (NCT04381962).

2.3.8.2 Teicoplanin

Teicoplanin is a glycopeptide antibiotic that besides its antibacterial activities against gram-positive bacteria, including staphylococci, streptococci, and enterococci, has shown conclusive results against the Ebola virus, influenza virus, flavivirus, HCV, HIV, and CoVs such as MERS-CoV and SARS-CoV-1 [62, 296]. As for CoVs, including SARS CoV-2, teicoplanin is capable of preventing the replication of the virus-cell cycle by inhibiting the viral RNA release. This could happen simply because teicoplanin inhibits the low pH cleavage of viral S protein by cathepsin L in the endosome [4]. Moreover, the concentration of teicoplanin needed in vitro for inhibiting 50% of SARS-CoV-2 viruses (IC50) was 1.66 μM, which was far lower than the IC50 reached in human blood (8.78 μM for a daily dose of 400 mg) [297, 298]. Nonetheless, these results are required to be confirmed by further clinical studies.

2.3.8.3 Tetracyclines

Tetracyclines (doxycycline, tetracyclines, minocycline) are polyketide antibiotics that have a broadspectrum antimicrobial activity [4, 299]. Tetracycline's mechanism of action, that is, blocking protein synthesis in *staphylococcus aureus* cells and inhibiting cell growth in a bacteriostatic manner was first delineated in 1953; further studies showed that these drugs act through binding to bacterial ribosomes [300]. Studies on the skin showed that tetracyclines are also capable of reducing the levels of inflammatory cytokines [301]. Thus, due to their anti-inflammatory effects, tetracyclines could be considered for the treatment of COVID-19 patients. Another possible mechanism of action of tetracyclines against COVID-19 is related to its chelating activity. In better words, tetracyclines are capable of chelating zinc from host matrix metalloproteinases (MMPs), thereby limiting viral replication, and this happens because CoVs bind to the host MMPs for viral survival [302–304]. Doxycycline is under phase 3 of a multicenter, randomized, clinical study performed on 330 COVID-19 patients receiving either doxycycline or placebo conducting by Nantes University Hospital in France (NCT04371952).

2.3.9 Low Molecular Weight Heparins as Anticoagulants

Owing to the fact that coagulopathy has been one of the major causes of morbidity and mortality in COVID-19 patients, anticoagulation therapy has been considered as one of the potential ways of combating COVID-19 [305]. In this regard, heparins are clinically approved anti-coagulants, and low molecular weight heparins (LMWHs), derived from unfractionated heparins either by chemical or by enzymatic depolymerization, are glycosaminoglycans that have been utilized in the prophylaxis of post-surgical venous thromboembolism as well as non-surgical patients with acute pathology and reduced mobility [77, 99, 306]. Due to the fact that unfractionated heparins and LMWHs have inhibitory effects on proteases, including factor Xa, thrombin, furin, and cathepsin-L, it has been hypothesized that LMWH and unfractionated heparin could be considered as potential drugs for not only targeting protease cleavage but also the viral entry of SARS-CoV-2 [307]. Nevertheless, these suggestions need to be confirmed by in vitro and clinical studies. According to a retrospective clinical study, from among 42 patients with COVID-19, 21 underwent LMWH treatment, and 21 were assigned to the control group during hospitalization. Results showed that LMWH treatment not only caused improvement in the coagulation dysfunction of patients but also exerts anti-inflammatory effects through reducing IL-6 and increasing lymphocyte percent [308]. Another retrospective study was performed to assess the safety of intermediate-dose regimens of one LWMH, that is, enoxaparin in COVID-19 patients with pneumonia, especially in older patients. Their results proposed that the use of an intermediate dose of LWMH seems to be safe and possible for COVID-19 patients, but further clinical studies are needed to substantiate these suggestions [305]. LMWH is currently under phase 4 of a randomized clinical trial performing by Ain Shams University of Egypt (NCT04584580). Moreover, another phase 3 ongoing clinical trial, in the USA, is performing to compare the effects of full dose administration of enoxaparin vs. prophylactic or intermediate dose of enoxaparin in high-risk COVID-19 patients (NCT04401293).

2.3.10 Adjunctive Supplements and Vitamins

2.3.10.1 Vitamin D

Vitamin D, a crucial group of fat-soluble secosteroids, is generally known for its functions in the maintenance of bone health and calcium-phosphorus metabolism [309]. A wide range of antioxidant, immunomodulatory, anti-inflammatory, and antifibrotic functions have been recently attributed to vitamin D. It has been considered to be able to inhibit cytokine storm in SARS-CoV-2 infection and decrease the expression levels of pro-inflammatory type 1 cytokines like IL-12, IL-16, IL-8, TNF-α, IFN-γ while increasing regulatory T cells and type 2 cytokines including IL-4, IL-5, IL-10

[69, 104, 309]. The elderly patients and individuals with common variable immun-odeficiency and bronchiectasis who are recognized with vitamin D deficiency are reported to be at a high risk of viral respiratory tract infections, acute lung injury, and particularly COVID-19 infection [104, 310]. On the contrary, no relationship between vitamin D concentration and the severity of COVID-19 in hospitalized patients was reported by Hernández et al. [311]. However, considering the several beneficial functions of vitamin D and its effects on immune cell proliferation and activity, pulmonary ACE2 expression, and priming effects against the viral replication, it has been proposed to employ high-dose vitamin D as a safe adjuvant therapeutic intervention to reduce the risk of COVID-19 severity and mortality [38, 104, 309]. Nevertheless, further studies are still needed to validate this association between vitamin D and COVID-19. Two clinical trials are currently in phase 4 to evaluate the efficiency of high doses of cholecalciferol (vitamin D3) on morbidity and mortality of COVID-19 patients in Spain and Argentina (NCT04552951, NCT04411446).

2.3.10.2 Vitamin C

Vitamin C (ascorbic acid) as an essential micronutrient and a potent antioxidant agent could play significant roles in neutralizing free radicals, preventing cellular damage, and associating with immune health [105]. Vitamin C has been reported to be effective against viruses like influenza viruses and reducing the duration and severity of upper respiratory infections [69, 85]. Many studies have demonstrated that vitamin C could involve with the development and maturation of T lymphocytes and NKs in the immune defense. Generally, it accumulates in phagocytic cells like neutrophils and can contribute to enhancing chemotaxis, phagocytosis, inhibition of reactive oxygen species (ROS) generation, preventing the neutrophils accumulation in the lung, and modulation of cytokine production network in the host inflammation response. Hence, employing vitamin C appears to be effective in preventing and treating respiratory and systemic infections [85, 105, 312]. The high dosage administration of vitamin C, a safe supportive treatment with no major side effects, has been considered as a potential treatment for reducing the cytokine storm and recovering COVID-19 patients [38, 85, 313, 314]. Currently, in a phase 3 clinical trial, the effect of high-dose intravenous vitamin C is evaluated on the mortality or persistent organ dysfunction of COVID-19 patients in Canada (NCT04401150).

2.3.10.3 Zinc

Zinc, as a micronutrient food supplement, has anti-inflammatory and antioxidant activities with an evident function in immunity on account of its roles as a cofactor, signaling molecule, and a structural element [69, 315]. Zinc deficiency has been reported to be responsible for the up-regulation of TNF-α, IFN-γ, JAK signaling in the lungs, cytokine production, and induction of apoptosis in lung epithelial cells [316]. Zinc could play its role in preventing viral pathogenesis through inhibiting viral

entry, fusion, and replication alongside attenuating the risk of hyper-inflammation, preserving natural tissue barriers while protecting cells and tissues from oxidative damage and dysfunction [69, 106, 315]. The administration of zinc as a potential well-tolerated supplementary therapeutic against COVID-19 has been considered in several studies owing to its possible anti-inflammatory, antioxidant, immunomodulatory, and direct antiviral effects [69]. The efficacy of zinc in higher risk COVID-19 outpatients is currently assessing in a phase 4 clinical placebo-controlled trial in the USA (NCT04621461).

2.3.11 Miscellaneous Therapies

2.3.11.1 Nitric Oxide

Nitric oxide (NO) is an important cellular signaling molecule that is produced by nitric oxide synthase (NOS) by converting arginine and oxygen into citrulline and nitric oxide [317–319]. NOS exists in a wide range of cells such as neurons, macrophages, airway epithelial cells, and vascular endothelial cells, and mediate neurotransmission, smooth muscle contraction, and mucin secretions [2]. It was demonstrated that NO possesses broadspectrum antiviral activity against ectromelia virus, vaccinia virus, herpes simplex type 1 viruses, CoVs, and influenza A and B viruses [319–321]. Besides, different inflammatory stimuli like cytokines can bring about high and sustained production of NO by inducible nitric oxide synthase (iNOS). Furthermore, iNOS causes anti-inflammatory or pro-inflammatory responses, cytotoxicity, or cytoprotection [319]. Concerning SARS-CoV-2, inhalation of nitric oxide is being evaluated for use against COVID-19, because inhaled NO has a chief role in pulmonary and cardiovascular physiology [322]. Inhaled nitric oxide gas is under phase 2 of a randomized clinical trial performing on 470 COVID-19 patients by Massachusetts General Hospital (NCT04312243).

2.3.11.2 Statins

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) with anti-inflammatory and immunomodulatory, anti-thrombotic, and antioxidant activities. Therefore, they could be considered as repurposing drugs for restoring viral infection-induced endothelial dysfunction, decreasing the severity of the lung injury and mortality rate caused by SARS-CoV-2, and maintaining the homeostasis of the patients [5, 323]. Moreover, it was postulated that stains might decrease the fatality rate caused by MERS-CoV [324]. Nevertheless, studies on animal models infected with SARS and MERS infections proposed that the administration of statins that suppress the myeloid differentiation primary response protein (MYD88) signaling might worsen the disease condition [5, 325]. It should be noted that since statins have a potency for drug–drug interaction with some protease inhibitor drugs,

their co-administration is contraindicated [326]. Additionally, myopathy and severe rhabdomyolysis are two major side effects of statins, and less prevalent adverse effects include peripheral neuropathy, hepatotoxicity, impaired myocardial contractility, and autoimmune diseases [327]. Phase 2 of a randomized clinical study is currently conducting on COVID-19 patients to assess the efficacy of atorvastatin as an adjunctive treatment by Mount Auburn hospital in the USA (NCT04380402).

2.3.11.3   Losartan

Losartan, an angiotensin-receptor antagonist without agonist properties, is a selectively and orally available ACE2 inhibitor that plays a role by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin 2 through inhibiting the binding of it to the angiotensin II type 1 receptor [38, 328]. Thus, it is considered as a repurposing drug against COVID-19 infection. While orally administered, roughly 14% of the losartan is converted to its metabolite, E 3174, which is 10-to-40-fold more active compared with its original compound, with an estimated terminal half-life from 6 to 9 h [328]. Losartan is currently under phase 3 of a multicenter clinical trial for assessing its protective effect against COVID-19 (NCT04606563).

2.4   Recombinant Proteins and Monoclonal Antibodies

Three phases of infection have been proposed for COVID-19, the first one is mild infection requiring only symptomatic treatment. The pulmonary phase is the second phase necessitating mostly antiviral treatment where recombinant proteins like APN01, meplazumab and novaferon could play a vital role by inhibiting the viral entry and replication. The third phase of the SARS-CoV-2 infection is the inflammatory response phase mainly experienced by severe COVID-19 patients. The third phase is generally associated with complications and immune-inflammatory response accompanied by abundant macrophages, neutrophils, lymphocytes, immune mediators, and pro-inflammatory cytokines. IL-1, IL-6, and TNF-α are the most prominent pro-inflammatory cytokines in the body [62, 148].

IL-1 binds to the IL-1 receptor to modulate its function leading to the production of other pro-inflammatory cytokines. IL-6, another key pro-inflammatory cytokine, binds to the IL-6 receptor expressed on monocytes, neutrophils, macrophages, and other leukocytes and interact with membrane-bound gp130 to activate its downstream JAK signal. The excessive IL-6 signaling may cause a faster decline of lung elasticity, more severe bronchoalveolar inflammation, and organ damages. The need for mechanical ventilation has been recently reported to be strongly connected to the elevated IL-6 [1, 148, 329]. In this regard, the administration of monoclonal antibodies (mAbs) and recombinant proteins could be highly effective. Several mAbs and proteins such as tocilizumab, sarilumab, bevacizumab, and anakinra

have been utilized to reduce hyper inflammation and the risk of ARDS and organ dysfunction (Table 2.1) [38, 330].

2.4.1 APN01

APN01, a recombinant human ACE2 (rhACE2) that was originally developed by Apeiron Biologics, is currently utilized for the treatment of patients infected with COVID-19 [38, 41]. APN01, which is a soluble recombinant ACE2, may prevent SARS-CoV-2 entry, as it imitates the innate human enzyme ACE2 on the surface of the host cells employed by the virus for entering the cells [3, 42]. By so doing, the S protein of the virus binds not to the ACE2 on the host cell, but rather to the soluble ACE2, (APN01), thereby preventing viral infection and increasing the viral load [77]. In the meantime, APN01 decreases damaging inflammatory reactions in the lungs and reduces lung injuries [3, 331]. It was demonstrated that the administration of APN01 as a therapeutic could decrease the level of Angiotensin II, thus preventing the ACE enzyme from accessing its substrate. This mechanism has the potential to inhibit further activations of the ACE2 angiotensin receptor [77, 332]. In a study, it was demonstrated that APN01 can reduce SARS-CoV-2 recovery from Vero cells by a factor of 1,000–5,000 in a dose-dependent manner [333]. APN01 is currently under phase 2 in a randomized, double-blind clinical trial for COVID-19 therapy, which is performing in a multicenter in Austria, Denmark, Germany, Russian Federation, and the UK by Apeiron Biologics (NCT04335136).

2.4.2 Novaferon

Novaferon (Nova) is a novel recombinant IFN-α like protein with 176 amino acids. Novaferon has exhibited anticancer and antiviral activities. In China, this drug has been approved for the treatment of chronic HBV. Li et al. in 2014, by studying the antitumor effects of novaferon and comparing it with recombinant humanized IFN-α-2b (rhIFN-α-2b), demonstrated that novaferon has stronger antitumor effects than rhIFN-α-2b [334, 335]. Novafen is able to block the virus replication in COVID-19-infected cells and also prevent the virus from entering healthy cells.

Zhang et al. reported a significantly higher clearance rate of SARS-CoV-2 employing novafron alone or by its combination with lopinavir/ritonavir compared with lopinavir/ritonavir alone [52, 53, 336]. Novaferon is currently under Phase 3 of randomized, double-blind clinical trials for hospitalized COVID-19 patients' treatment (NCT04669015).

2.4.3   Tocilizumab

Tocilizumab or atlizumab is a recombinant humanized monoclonal antibody (rhmAb) against IL-6 under the trade name Actemra [337]. It has FDA approval for the treatment of rheumatoid and polyarticular juvenile idiopathic arthritis and systematic juvenile idiopathic. Tocilizumab plays its role through the membrane and soluble IL-6 receptor blockade and inhibiting the cytokine release syndrome process (CRS) [38]. Actemra is able to restrain the cytokine storm induced by SARS-CoV-2 [330]. Several studies have shown that a single dose of 400 ml administration of tocilizumab could render benefits through better breathing, faster fever reduction while it is also capable of reducing the inflammation response, vasopressor support, and mortality rate in COVID-19 [8, 77, 338]. Nevertheless, some side effects regarding the administration of tocilizumab have been reported including increased upper respiratory infections, hypertension, hematological effects, gastrointestinal perforation and hepatotoxicity [77]. For the management of the severe SARS-CoV-2 infection, tocilizumab has been employed in phase 4 and 3 clinical trials (NCT04377750, NCT04320615).

2.4.4   Sarilumab

Sarilumab, developed by Regeneron Pharmaceuticals and Sanofi, is another immunomodulatory drug. In May 2017, the FDA approved Sarilumab for the treatment of rheumatoid arthritis under the Kevzara brand name. Sarilumab has the potential to suppress the growth of some xenograft prostate and lung tumors either as a single drug or in combination with other therapeutics [339, 340]. Sarilumab, like tocilizumab, is an IL-6 rhmAb that could suppress COVID-19-associated overactive inflammatory immune responses and cytokine storm. The most common side effects of this drug include cough or sore throat, thrombocytopenia, blocked or runny nose, urinary and respiratory tract infections, neutropenia, hypercholesterolemia, mild hepatotoxicity, and cold sores [78, 341]. In a randomized, embedded, multifactorial, adaptive platform trial for community-acquired pneumonia (REMAP-CAP), a clinical phase 4 study, the efficiency of a range of interventions including sarilumab has been evaluating on ICU admitted COVID-19 patients (NCT02735707).

2.4.5   Eculizumab

Eculizumab has the FDA approval for the treatment of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH) diseases [342]. One of the most effective methods for preventing tissue damage is to suppress the production of excessive inflammation responses and cytokines caused by SARS CoV-2. Eculizumab with the brand name of soliris as a rhmAb against the complement

protein C5 could inhibit the cleavage of C5 into C5a and C5b [343]. Consequently, it is able to prevent the terminal complement complex C5b-9 and subsequently the membrane attack complex formation, production of reactive oxygen species, and initiation of releasing cytokine storm. In addition, it could inhibit the formation of the C5a, responsible for the development of acute lung injury [80]. Despite the benefits of eculizumab, it may exhibit some side effects such as bradycardia, atrioventricular block, and hypertension in some patients [79]. Eculizumab is currently under phase 2 clinical trial against COVID-19 in France (NCT04346797).

2.4.6 Bevacizumab

Bevacizumab (under brand name avastin) is a humanized monoclonal antivascular endothelial growth factor (anti-VEGF) antibody that has been approved for the treatment of several cancers such as breast, brain, and renal cancers by the FDA. Studies have shown that upon ARDS the amount of VEGF produced by epithelial and inflammatory cells increases in patients. The increase in VEGF causes vascular permeability and pulmonary edema [1, 344, 345]. Bevacizumab with a specific ability in binding to VEGF and subsequent inhibition of its linking to VEGF receptor on the surface of endothelial cells could be a potential therapeutic for the treatment of ARDS and ALI caused by COVID-19 [81, 346]. However, the administration of bevacizumab is associated with an increased risk of cardiovascular events in some cases [347]. In multiple cohort randomized controlled trials, bevacizumab is under phase 2 for COVID-19 treatment at Hôpitaux de Paris in France (NCT04344782).

2.4.7 Infliximab

Infliximab is a chimeric monoclonal anti-tumor necrosis factor (anti-TNF) alpha antibody (IgG1), which could inhibit TNF from binding to its receptors by targeting it [82, 84]. TNF is a cytokine that releases in the acute phase of inflammation and binds to its receptors (TNFRI and TNFRII) in all cells except erythrocytes. Several signaling pathways including transcription factor activation (nuclear factor-κB), proteases (caspases), and protein kinases (MAP kinase, c-Jun N-terminal kinase) are activated by connecting TNF to its receptor leading to the activation of the target cells for immune and inflammatory responses by the release of apoptotic pathway initiation and several cytokines. TNF also plays role in the activation of lymphocytes (B, T) and macrophages, production of proinflammatory cytokines such as IL-1, IL-6, and expression of adhesion molecules (ICAM-1, E-selectin) [83]. Studies have shown that TNF could induce cytokine cascade in rheumatoid arthritis and promote pathogenesis in SARS-CoV-2 [348]. Infliximab has been approved in the USA since

1988 as a drug for the treatment of some autoimmune inflammatory diseases. Infliximab could be a proper option to reduce inflammation, cytokine storm, and subsequent organ failure due to COVID-19 [82, 84, 349]. Some reactions may occur upon infliximab Infusion, which could be prevented by employing antihistamines, acetaminophen, and corticosteroids as pre-medications [83]. Infliximab is currently under phase 3 of clinical trials for severe COVID-19 patients in multi centers of the USA (NCT04593940).

2.4.8   Anakinra

Anakinra under the brand name of kinert is a modified recombinant human IL-1 receptor antagonist with a short half-life of about 3–4 h and a proper safety profile that is approved for use in rheumatoid arthritis and neonatal-onset multisystem inflammatory treatment [85, 86]. IL-1 receptors induce the innate immune response and are associated with excessive inflammation response of the host [350]. It has been hypothesized that anakinra could assist in neutralizing the SARS-CoV-2-related hyperinflammatory state, one of the main causes of ARDS in COVID-19 patients [86, 351]. Anakinra was administered for severe COVID-19 patients in a cohort study and it was observed that it can reduce both the need for invasive mechanical ventilation and mortality without serious side effects [86]. As an anti-proinflammatory cytokine drug, it has been employed in several clinical studies against COVID-19 with encouraging results and it is currently under phase 3 in multi centers of Greece (NCT04680949).

2.4.9   Emapalumab

Emapalumab is a humanized monoclonal anti-IFN-γ antibody, which is known as gamifant brand name. FDA approved Emapalumab for the treatment of hemophagocytic lymphohistiocytosis (HLH) (an illness caused by an overactive immune system) [87, 148, 352, 353]. Emapalumab could prevent the binding of IFN-γ to its cell surface receptors subsequently inhibiting the activation of inflammatory signals and cytokine release syndrome caused by SARS-COV-2 [88, 148]. In order to minimize the rate of inflammation, and the needing mechanical ventilation emapalumab was utilized in combination with anakinra in a phase 2/3 multicenter randomized clinical trial against COVID-19 (NCT04324021). Immunosuppression is reported as one of the side effects of utilizing emapalumab in some patients. Thus, patients with weak immune systems should take this drug with caution [87].

2.4.10 Meplazumab

The main entry route of the virus is to bind host cells through ACE2 receptors at the surface of the host cells. SARS-CoV-2 can also enter the host cells through the cluster of differentiation 147 (CD147). In fact, CD147 can act as a receptor for the SARS-CoV-2 spike protein [89, 354]. Moreover, CD147 could function as a mediator in the inflammatory response as a receptor for cyclophilin A (CyPA), the activator of the intracellular antiviral response, and a potent chemotactic factor for inflammatory leukocytes [90, 355]. Meplazumab is a humanized monoclonal anti-CD147 antibody (IgG2) that inhibits SARS-CoV-2 from entering the cell by blocking the expression of CD147 and reducing the infection caused by the virus. Meplazumab also plays a critical role in reducing the cytokine storm caused by COVID-19 by suppressing cyclophilin A from linking to CD147 [356, 357]. In a phase 2/3 multicenter clinical study, the safety and efficacy of meplazumab are assessing for hospitalized COVID-19 patients (NCT04586153).

2.5 Bioactive Natural Compounds and Herbal Medicines

Natural compounds as highly safe and available products have exhibited promising biological and pharmacological activities including anticancer, antiviral, antimicrobial, anti-inflammatory, and antioxidant properties. Medicinal plant-based natural compounds and traditional herbal medicines have demonstrated antiviral properties against several viruses like the influenza virus, HBV, HCV, SARS-CoV-1, and MERS-CoV. The intervention in both the viral life cycle and host response is attributed to the antiviral functions of natural compounds [358, 359]. Due to the high similarity between SARS-CoV-2 and SARS-CoV-1 in respect to genomics, epidemiologic, and pathogenesis, some herbal and natural medicines are used for the treatment of SARS-CoV-1 could be employed for inhibiting SARS-CoV-2 as well [85]. In this regard, natural compounds and herbal medicines such as theaflavin, cepharanthine, lectins, silvestrol, tryptanthrin, hirsutenoone, tanshinones I-VII, celastrol, pristimererin, iguesterin, tingenone have indicated the potential to prevent SARS-CoV-2 infection through inhibiting RdRp, ACE2, PLpro, or 3CLpro [94, 358, 359].

On the other hand, curcumin and piperine, quercetin, emodin, and scutellarein have been reported to be able to associate with the inhibition of COVID-19 while rendering their anti-inflammatory activities [358]. Particularly, extracted food supplements from plants like curcumin, piperine, and quercetin have the potential to interfere in cellular entry and replication of SARS-CoV-2 and play their roles by immune-boosting, antioxidant and anti-inflammatory functions and by repairing the tissue damages induced by COVID-19. The immunomodulatory and anticytokine effects are also proposed for these agents. Furthermore, these drugs are highly potent to be employed as adjuvants to enhance the bioavailability of other drugs

by rendering their multidrug resistance (MDR) effect [69, 360–362]. The nanoen-capsulation of quercetin, curcumin/piperine has been practiced and developed due to their hydrophobicity and utilized for the treatment of cancer cells with the capability of suppressing MDR [363, 364]. Likewise, despite the uncertainty of the precise mechanism of many natural compounds, Traditional Chinese Medicines (TCMs) like *Glycyrrhiza uralensis, Saposhnikoviae divaricata, Astragalus membranaceus, Rhizoma Atractylodis Macrocephalae* have been reported to be effective in inhibiting COVID-19 and its subsequent lung inflammation or acute lung injury [85, 94].

2.6 Combination Therapy Approach for COVID-19

Numerous drugs have been reported to be effective against SARS-CoV-2 infection employing the drug repurposing approach that targets viral entry, fusion, replication, and translation alongside regulating immunity and inflammatory response attenuating [234, 365]. In this respect, antivirals, immunomodulators, and anti-inflammatory drugs possessing different mechanisms of action could be exploited in combination to simultaneously inhibit viral functions while providing support and symptomatic treatment for SARS-CoV-2 patients. Besides, the treatment of the severe COVID-19 patients, most at the risk of dying due to the cytokine storm should be practiced with utmost importance by the combination therapy while considering drug–drug interactions and side effects [234, 366]. Some promising combinational administrations of drugs for COVID-19 therapy are presented in Table 2.2.

2.7 Perspectives and Conclusion

SARS-CoV-2 infection is associated with both direct damages induced by the virus and host inflammatory and immune response. In this regard, many antivirals have been administered to inhibit the virus while immunomodulators and anti-inflammatory drugs, as well as biological and natural compounds, have been utilized to either enhance the innate immune system or manage the deregulated inflammatory responses and control the symptoms leading to quick recovery of patients and reducing mortality. Accordingly, combination therapy could be more effective against SARS-CoV-2 infection in the case being utilized timely by taking drug-drug interactions into account. In many clinical trials, combinational administration of antivirals, immunomodulators, and anti-inflammatory drugs has been proposed considering different targets to inhibit the infection.

Alternatively, nanotechnology as a promising strategy could be applied to the COVID-19 treatment principle. Highly biocompatible natural-based vehicles such as proteins and polysaccharides are highly potent to be employed to encapsulate the potential COVID-19 therapeutics and deliver them in an efficient way by enhancing the stability and bioavailability of drugs like favipiravir alongside reducing their

Table 2.2 Potential combination therapy undergoing clinical trials for the treatment of COVID-19

Therapeutics	Targets	Proposed effects	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
Remdesivir (antiviral) + baricitinib (immunomodulator)	RdRP + JAK	Inhibiting viral replication + reducing cytokine storm	Phase 3 (NCT04401579)	[1, 7, 367]
Remdesivir (antiviral) + tocilizumab (immunomodulator)	RdRP + IL-6	Inhibiting viral replication + Reducing cytokine storm	Phase 3 (NCT04409262), phase 3 (NCT04678739)	[1, 65, 365]
Remdesivir (antiviral) + IFN-β (immunomodulator)	RdRP + IFNAR signaling	Inhibiting viral replication + boosting immunity against viral infection	Phase 3 (NCT04492475), phase 2 (NCT04647695)	[1, 7]
Lopinavir/ritonavir (antiviral) + ribavirin (antiviral) + IFN-β-1b (immunomodulator)	3CLpro + RdRP + IFNAR signaling	Inhibiting viral replication + boosting immunity against viral infection	Phase 2 (NCT04276688)	[174, 366]
Favipiravir (antiviral) + tocilizumab (immunomodulator)	RdRp + IL-6	Inhibiting viral replication + Reducing cytokine storm	N/A phase (NCT04310228)	[365, 366, 368]
HCQ (antiviral) + azithromycin (immunomodulator)	Endosoamal pH + S protein/ACE2 interaction (feasible)	Inhibiting viral entry and post entry	Phase 3 (NCT04321278), Phase 3 (NCT04347512/withdrawn)	[365, 369]
HCQ (antiviral) + nitazoxanide (antiviral/immunomodulator)	Endosoamal pH, ACE2 + Immune interferon response (feasible)	Inhibiting viral entry + reducing cytokine storm (feasible)	Phase 2/3 (NCT04361318)	[94, 365]
HCQ (antiviral) + ribavirin (antiviral) + nitazoxanide (antiviral/immunomodulator)	Endosoamal pH, ACE2 + RdRP + Immune interferon response (feasible)	Inhibiting viral entry + inhibiting viral replication + reducing cytokine storm (feasible)	Phase 2 (NCT04605588)	[6, 62]

(continued)

Table 2.2 (continued)

Therapeutics	Targets	Proposed effects	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
HCQ (antiviral) + azithromycin (immunomodulator) + tocilizumab (immunomodulator)	Endosoamal pH + S protein/ACE2 interaction (feasible) + IL-6	Inhibiting viral entry and post entry + reducing cytokine storm	Phase 2 (NCT04332094)	[4, 7, 100]
HCQ (antiviral) + azithromycin (immunomodulator) + lopinavir/ritonavir (antiviral)	Endosoamal pH + S protein/ACE2 interaction (feasible) + 3CLpro	Inhibiting viral entry and post entry + inhibiting viral replication	Phase 2 (NCT04459702)	[4, 65, 100]
Ivermectin (antiviral) + nitazoxanide (antiviral/immunomodulator)	Nuclear transport process + immune interferon response	Inhibiting viral replication + reducing cytokine storm (feasible)	Phase 2/3 (NCT04360356)	[5, 365]
HCQ (antiviral) + favipiravir (antiviral)	Endosoamal pH, ACE2 + RdRP	Inhibiting viral entry + inhibiting viral replication	Phase 3 (NCT04411433), N/A phase (NCT04392973)	[7, 170, 365]
Ribavirin (antiviral) + ivermectin (antiviral) + nitazoxanide (antiviral/immunomodulator)	RdRP + nuclear transport process + immune interferon response	Inhibiting viral replication + reducing cytokine storm (feasible)	Phase 3 (NCT04392427)	[5, 7, 94]
Danoprevir (antiviral) + ritonavir (antiviral)	Protease	Inhibiting protease activity in the replication cycle	Phase 4 (NCT04345276)	[38, 370]
CP (immunomodulator) + MSC (immunomodulator)	S protein + immune system	Boosting immunity against viral entry and pathogenesis + regenerating tissues and reducing cytokine storm	N/A phase (NCT04492501)	[1, 371]
Tocilizumab (immunomodulator) + anakinra (immunomodulator)	IL-6 + IL-1	Reducing cytokine storm	Phase 3 (NCT04330638)	[7, 65]

(continued)

Table 2.2 (continued)

Therapeutics	Targets	Proposed effects	Clinical trial phase (NCT number) (https://clinicaltrials.gov)	Refs.
Quercetin (antiviral) + bromelain (immunomodulator) + zinc (immunomodulator) + vitamin C (immunomodulator)	S protein/ACE2 interaction + immune system	Inhibiting viral entry and pathogenesis + boosting immunity and reducing cytokine storm	Phase 4 (NCT04468139)	[69, 372]

side effects. Besides, by utilizing the targeted delivery, the nanoparticle-based therapeutics could be triggered toward susceptible alveolar cells prone to be infected by SARS-CoV-2 to either protect them against COVID-19 or provide them with inhibitory drugs. It is worth noting that the nanoparticle-based vaccines have already been taken into consideration for the control of the COVID-19 pandemic and prevent its higher outbreak.

As we obtain more information about the potency of the drug formulations against COVID-19 with respect to their mechanism of action particularly in severe patients, we will be better equipped to optimize therapeutic strategies.

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Conflict of interest

The authors declare no conflict of interests.

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