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Races of small molecule clinical trials for the treatment of COVID-19: An up-to-date comprehensive review

Suwen Hu[1,2,3,4,5,6] | Songwei Jiang[1,2,3,4] | Xiang Qi[1,2,3,4] | Renren Bai[1,2,3,4] | Xiang-Yang Ye Ph.D., Professor[1,2,3,4] | Tian Xie[1,2,3,4]

[1]School of Pharmacy, Hangzhou Normal University, Hangzhou, China

[2]Key Laboratory of Elemene Class Anti-Cancer Chinese Medicine of Zhejiang Province, Hangzhou Normal University, Hangzhou, China

[3]Engineering Laboratory of Development and Application of Traditional Chinese Medicine from Zhejiang Province, Hangzhou Normal University, Hangzhou, China

[4]Collaborative Innovation Center of Chinese Medicines from Zhejiang Province, Hangzhou Normal Umiversity, Hangzhou, China

[5]Hangzhou Huadong Medicine Group, Pharmaceutical Research Institute Co. Ltd., Hangzhou, China

[6]Department of Chemistry and Biochemistry Los Angeles, University of California, Los Angeles, California, USA

Correspondence
Xiang-Yang Ye, Tian Xie and Renren Bai, School of Pharmacy, Hangzhou Normal University, Hangzhou, Zhejiang 311121, China.
Email: xyye@hznu.edu.cn, xbs@hznu.edu.cn and renrenbai@hznu.edu.cn

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Abstract

The coronavirus disease-19 (COVID-19) pandemic has become a global threat since its first outbreak at the end of 2019. Several review articles have been published recently, focusing on the aspects of target biology, drug repurposing, and mechanisms of action (MOAs) for potential treatment. This review gathers all small molecules currently in active clinical trials, categorizes them into six sub-classes, and summarizes their clinical progress. The aim is to provide the researchers from both pharmaceutical industries and academic institutes with the handful information and dataset to accelerate their research programs in searching effective small molecule therapy for treatment of COVID-19.

KEYWORDS
anti-viral agent, COVID-19, small molecules

Abbreviations: 3CL^{pro}, 3C-like protease; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ALDH1, aldehyde dehydrogenase 1; Ang II, angiotensin II; AR, androgen receptor; ARDS, acute respiratory distress syndrome; AT, angiotensin II receptor type; AT1R, angiotensin receptor type I; ATF-6, activating transcription factor 6; ATP, adenosine triphosphate; BTK, Bruton's tyrosine kinase; CCL2, C-C Motif Chemokine Ligand 2; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; CD11b, cluster of differentiation molecule 11b; CD147, cluster of differentiation 147; CD16, cluster of differentiation 16; CD18, integrin beta chain-2; CD4, cluster of differentiation 4; CD62L, L-selectin; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; CRS, cytokine release syndrome; CSS, cytokine storm syndrome; CUL4-RBX1-DDB1, cullin 4- ring box proteins- DNA binding protein 1; CYP3A4, cytochrome P450 3A4; cysLT, cysteinyl leukotriene; DHODH, dihydroorotate dehydrogenase; DPP4, dipeptidyl peptidase-4; EGFR, epidermal growth factor receptor; FDA, food and drug administration; GLP-1, glucagon-like peptide-1; G-CSF, granulocyte colony-stimulating factor; HCoV-19, human coronavirus 2019; HCoV229E, human coronavirus 229E; HCoV-HKU1, human coronavirus HKU1; HCoV-NL63, human coronavirus NL63; HCoV-OC43, human coronavirus OC43; HCV, hepatitis C virus; hERG, the human Ether-à-go-go-Related Gene; HIV, human immunodeficiency viruses; HMG-CoA, β-Hydroxy β-methylglutaryl-CoA; HSV, herpes simplex virus; IL, Interleukin; IMPDH, Inosine-5′-monophosphate dehydrogenase; JAK–STAT, Janus kinase-signal transducer and activator of transcription protein; MAPK, mitogen-activated protein kinase; MAS1, mas-related G-protein coupled receptor; MasR, mas receptor; MCP1, monocyte chemoattractant protein-1; MERS-CoV, middle East respiratory syndrome-related coronavirus; MOA, mechanism of action; M^{pro}, main protease; mRNA, messenger ribonucleic acid; MRSA, methicillin-resistant Staphylococcus aureus; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; NIH, National Institutes of Health; NK-1, neurokinin-1; NLRP3, NLR family pyrin domain containing 3; NMDA, *N*-methyl-d-aspartate; NS5A, nonstructural protein 5A; NSCLC, non-small-cell lung carcinoma; NSP15, nonstructural protein 15; PGE2, prostaglandin E2; P-gp, P-glycoprotein; PI3K, phosphatidylinositol 3-kinase; PTSD, post-traumatic stress disorder; RAR, retinoic acid receptor; RAS, pulmonary renin-angiotensin system; RdRP, RNA-dependent RNA polymerase; RNA, ribonucleic acid; ROS, reactive oxygen species; S1P1, sphingosine-1-phosphate receptor 1; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe Acute Respiratory Syndrome Coronavirus 2; SGLT2, sodium/glucose cotransporter 2; SV-SMC, saphenous vein- structural maintenance of chromosomes protein; TKI, tyrosine kinase inhibitor; TLR7/9, toll-like receptor 7/9; TMPRSS2, transmembrane protease, serine 2; TNF, tumor necrosis factor; VDCC, voltage-dependent calcium channel; vRNP, viral ribonucleoprotein; WHO, world health organization; XPO1, exportin 1.

1 | INTRODUCTION

Since its first large-scale outbreak in central China in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the coronavirus disease-19 (COVID-19) pandemic globally (Sahin et al., 2020; Wang, Hu, et al., 2020), and has led to severe damage to human lives and the economy of more than 200 countries worldwide. By the time this manuscript is submitted, 143,445,675 people have been infected by this virus, and the death toll mounts up to 3,051,736 globally (World Health Organization website, n.d.). Besides SARS-CoV-2, six more coronaviruses have been characterized by now: human CoV229E (HCoV-229E, 1966), human CoV OC43 (HCoV-OC43, 1967), human CoV HKU1 (HCoV-HKU1, 2004), human CoV NL63 (HCoV-NL63, 2004), severe acute respiratory syndrome CoV (SARS-CoV, 2003), and Middle East respiratory syndrome CoV (MERS-CoV, 2013). Chronological analysis of the commence time and severity of these viruses suggests that the outbreak cycle of the coronaviruses is getting shorter and shorter, and the impact of the viruses is getting worse and worse. To treat current SARS-CoV-2 infection, and more importantly to prepare for unforeseeable new coronaviruses in the future, scientists from the globe respond quickly in attempt to identify suitable solutions such as small molecules for the potential therapy or vaccines for the prevention.

SARS-CoV-2 belongs to a class of coronaviruses featured with positive-sense, enveloped, single-stranded RNA (Zeidler & Karpinski, 2020). The spike proteins (S proteins) on the viral envelope include two subunits, S1 and S2, which are the key surface proteins that participate in the interaction between the viruses and the host cells, and eventually promote the virus to enter the host cell (Walls et al., 2020).SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors to enter the lung cells (Figure 1a). After the attachment of the virus to the host cells, the S protein of the virus interacts with protease enzymes from the host cells, enabling the virus fusing to the host cell membrane (Cascella et al., 2021). This process relies on transmembrane serine protease (TMPRSS2) activating S proteins (Hoffmann et al., 2020; Valencia, 2020). After the genomic RNA released into the cytoplasm and then translated to produce polyproteins, which is facilitated by virally encoded chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro}) (Cascella et al., 2021). Polyproteins cleavage affords non-structural proteins for the viral RNA replicase-transcriptase complex. Viral nucleocapsids are assembled with the structural proteins after the viral replication and transcription. Upon encasing viral RNA, these nucleocapsids form the new virions and are then released from the cells via exocytosis (Valencia, 2020). Clinical studies indicate that several cytokines from severe patients' tissue undergo extensive changes, which play a crucial role in the COVID-19 pathogenesis (Liu, Zhang, Huang, Yang, et al., 2020; Mehta, McAuley, et al., 2020; Wan et al., 2020). Hypercytokinemia (also known as "cytokine storm") may play as a pivotal role in life-threatening pathological processes (Figure 1b) (Xu, Shi, Li, & Zhou, 2020; Xu, Shi, Wang, et al., 2020). It has been proven that $CD4^+$ T cells are rapidly activated to secret inflammatory cytokines upon the infection with SARS-CoV-2, which further lead to $CD14^+$ $CD16^+$ monocyte activation with high interleukin expression (such as IL-1, IL-6 etc. see Figure 1b) (Zhou, Fu, et al., 2020). Thus, blocking the IL-1 or the IL-6 receptors could potentially alleviate

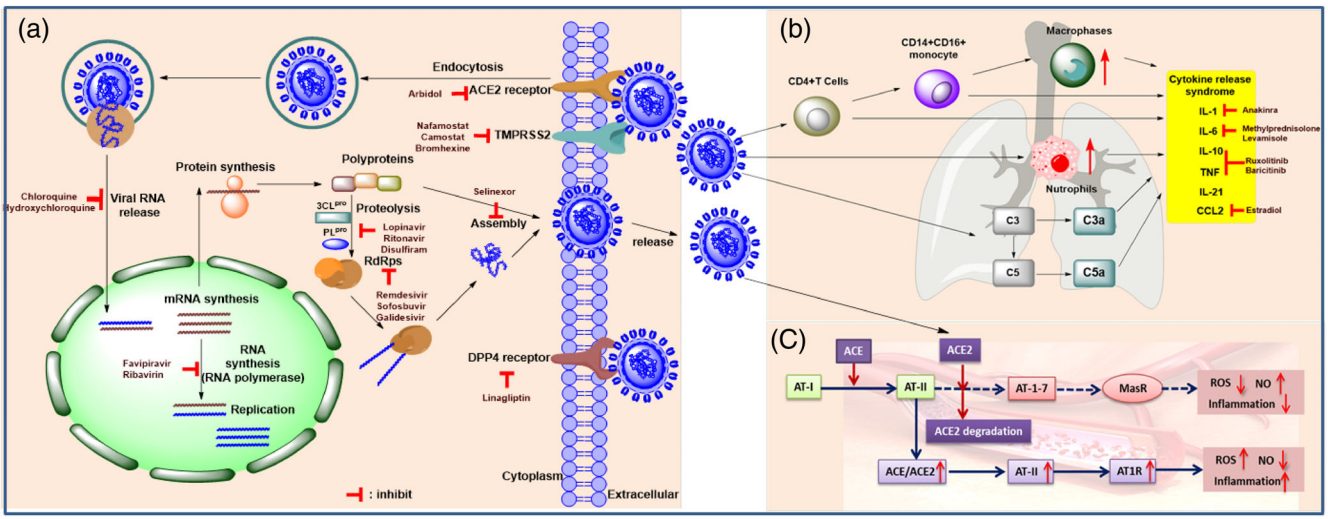


FIGURE 1 (a) Schematic illustration of the replication cycle of SARS-CoV-2 and the biological targets for the potential treatment. (b) the inhibition of excessive inflammatory response. (c) SARS-CoV-2 infects type II alveolar epithelial cells (type II AEC) via the interaction between its S proteins and the ACE2 receptor by promoting internalization and degradation of ACE2 and pulmonary ACE/ACE2 imbalance. In turn, the degradation of angiotensin II (AT II) into angiotensin 1–7 (AT-1-7) is prevented (dotted arrows), reducing anti-inflammatory signaling through the mas receptor (MasR), and promoting pro-inflammatory AT II signaling through the angiotensin receptor type I (AT1R) in vascular endothelial cells. Complex interactions involving the renin-angiotensin system, oxidative state, endothelial interaction, and immune activation lead to alveola edema, lung inflammation, microvascular thrombosis, and acute respiratory distress syndrome. Potential targets have been identified as possible pharmacotherapies for the prevention, treatment, or management of COVID-19

immunopathology caused by SARS-CoV-2. The pulmonary renin-angiotensin system (RAS) is composed by two pathways, whose balance is crucial for pulmonary homeostasis (Figure 1c). Angiotensin II (Ang II), generated by endothelial ACE, acts on angiotensin II receptor type 1 (AT1) to promote pro-inflammatory effects and vasoconstriction, whereas epithelial ACE2 cleaves Ang II into Ang (1–7), which acts on the MAS1 (MAS proto-oncogene) oncogene to exert anti-inflammatory and vasodilatory effects. The ACE-dependent Ang II formation is a vital pathophysiological mechanism in different forms of acute respiratory distress syndrome (ARDS) (South et al., 2020).

SARS-CoV-2 interacts with ACE2, triggers ACE2 degradation and the ratio of ACE/ACE2 imbalance, further drives Ang II-mediated vascular inflammation and pulmonary injury which lead to severe COVID-19 symptoms (Figure 1c) (South et al., 2020).

Global scientific communities and pharmaceutical industries have been racing for success to cope with the COVID-19 pandemic in two major approaches: vaccines for the prevention (Buchholz et al., 2004; Cheng et al., 2020) and small molecule drugs for the potential treatment (Clinical trial ID: NCT04252885, n.d.; Cava et al., 2020; Kadam & Wilson, 2017; Lu, 2020; Pant et al., 2021; Sheahan, Sims, Leist, et al., 2020; Wu et al., 2020; Zhou, Hou, et al., 2020). The vaccine approach might ultimately be the most effective solution to the current pandemic (Karpiński et al., 2021). However, the small molecule approach is also pivotally important and desperately needed. Such approach not only could treat the patients at high risk or in critical condition in the current pandemic but also could prepare for diseases caused by unforeseeable new coronaviruses in the future.

Since 2020, several review articles have been published regarding the advances of coronavirus treatment in different aspects. For example, Pillaiyar et al. (2020) reviewed the small molecule inhibitors for the potential treatment of coronavirus by focusing on the drug repurposing and drug discovery stage. Zhu et al. (2021), Zeng et al. (2020) used the deep learning approach to identify 41 old drugs potentially repurposable for treatment of COVID-19. Jean et al. (2020) reviewed the treatment reality and challenges for COVID-19. Zhang & Penninger et al. (2020) reviewed the ACE2 as a potential therapeutic target for COVID-19. Ghosh et al. (2020) summarized the drug development and medicinal chemistry aspect of COVID-19 therapeutics. Naujokat et al.(2020) concisely summarized the candidate drugs against COVID-19 by discussing some of the recent clinical studies, but not in a comprehensive manner. Monpara et al. (2020) focused on COVID-19 associated complications and biological targets for potential treatment. Most recently, Alahari et al. reviewed the mechanisms of action (MOAs) for repurposing drugs in the treatment of COVID-19 (Yousefi et al., 2021). In addition to above reviews, other approaches such as drug repurposing strategy (DRS) (Sahoo et al., 2021), system biology (Jaiswal et al., 2020), and computation practices (Ojha et al., 2021) were also reviewed recently.

Focusing on the small molecule approach, this article systematically summarizes those small molecules in current clinical trials for the potential treatment of COVID-19 in a comprehensive manner. By the time this review is submitted (April 22, 2021), there are 5441 COVID-19 related clinical studies listed on the NIH Clinical Trials website (http://ClinicalTrials.gov), ranging from evaluation of small molecule pharmacotherapies, mesenchymal stem cells or T-cell-based therapies, convalescent plasma therapies, and immunoglobulins to medical devices in the treatment of COVID-19. Most of the clinical studies are in Phases II-IV stages. Drug repurposing, defined as finding new indications for existing approved drugs (Tobinick, 2009), is of particular interest in the response to the COVID-19 pandemic emergency and urgency. Historic data suggest that de novo drug development typically takes 10 to 17 years and costs 800 million USD (Tobinick, 2009). Therefore, de novo drugs approach for combating COVID-19 might not turn out to be effective and satisfactory in the current pandemic emergency. On the other hand, the drug repurposing approach has been proven to be practical and successful in several cases. This approach significantly shortens the development time and reduces the cost. Repurposing existing drugs to treat COVID-19 is biologically feasible as SARS-CoV-2 shares some similarities with other coronaviruses, such as SARS-CoV and MERS-CoV (Chen, Tian, et al., 2020), and there are many successful precedents in repurposing antivirals for new virus targets (Mercorelli et al., 2018). Indeed, most of the drugs currently in clinical trials for COVID-19 are repurposed from approved antiviral drugs.

Data mining on more than four thousand clinical trials related to COVID-19 provided us with a pretty large dataset related to small molecules approach. To better discuss them, those small molecules were categorized into six classes based on the clinical features of COVID-19 and possible MOAs. The purpose of this review is to provide the researchers from both pharmaceutical industries and academic institutes with a comprehensive summary in this field so that to save their time in drug discovery research and to accelerate the finding of effective therapy for COVID-19.

2 | TYPES OF AGENTS IN CLINICAL TRAILS

To facilitate the interity of the review, we manually sorted out the drugs currently in clinical trials by querying the drug database from the FDA. Thus, for each identified small molecular drug, we searched for clinical trials on NIH Clinical Trials website using the name of drug plus "COVID-19" and screened thoroughly the results obtained. As of April 22, 2021, there are 126 small molecule drugs in at least 777 clinical trials with various stages for the potential treatment of COVID-19. These agents are classified into six categories based on their probable MOAs (Figures 2–4): (1) blocking virus-cell membrane fusion and entry (25 agents, accounting for 20%); (2) inhibiting viral replication (29 agents, accounting for 23%); (3) addressing cytokine storm syndrome (CSS) (51 agents, accounting for 40%); (4) modulating immune system (10 agents, accounting for 8%); (5) anticoagulant therapy (7 agents, accounting for 6%); and (6) antioxidant supplement (4 agents, accounting for 3%). On the other hand, all clinical candidates are grouped into four small subclasses based on their clinical stages. Thus, there are 4 agents in Phase I, 42 agents in Phase II, 46 agents in Phase III, and 34 agents in Phase IV (Figures 2–4).

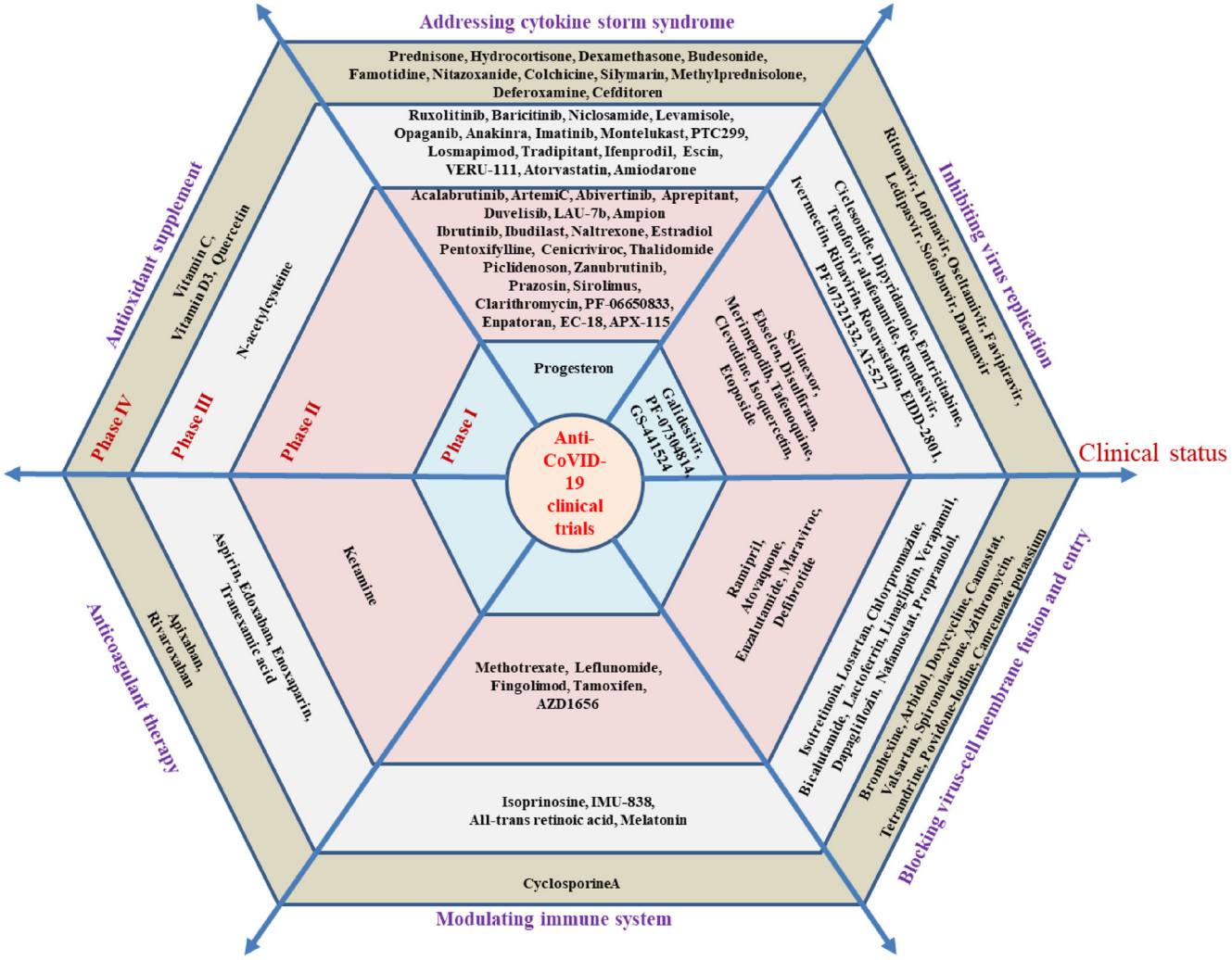


FIGURE 2 All of the small molecules in COVID-19 clinical trials as of April 22, 2021: Categorizing these trials depending upon the clinical features of COVID-19 and their probable MOAs. The hexagon contains small molecular compounds in different clinical trial stages: Phase I to phase IV from the inside to the outside

2.1 | Blocking virus-cell membrane fusion and entry

Mounting studies suggest that SARS-CoV-2 invades into the membrane of the host cells mainly through the endocytosis after the S protein binding to ACE2 on the surface of the host cells (Yang & Shen, 2020). Then the S protein with the altered configuration facilitates the viral envelope to fuse with the host cell membrane via the endosome pathway. At present, agents such as bromhexine, camostat, arbidol, linagliptin, chlorpromazine, etc. are being tested to block endocytosiswhile hydroxychloroquine and chloroquine are being investigated to block the viral genome released into the cytoplasm. However, the data from clinical trials indicate that antimalarial drug hydroxychloroquine neither helps COVID-19 patients improve the recovery or reduce their symptoms nor prevents coronavirus infection in healthy people (Self et al., 2020). Both the World Health Organization (WHO) and NIH have suspended the clinical trials related to chloroquine class of medicines. The ongoing clinical trials of potential drugs targeting to block viral entry into the host cells are summarized in Table 1.

2.2 | Inhibiting the virus replication

There are two mainly targets inhibiting virus replication: (1) the protease ($3CL^{pro}$ and PL^{pro}); and (2) the RNA-dependent RNA polymerase (RdRP). Anti-HIV agents (lopinavir or ritonavir) inhibit protease $3CL^{pro}$, thereby blocking the formation of non-structural proteins. In July 2020, the WHO announced the suspension of the lopinavir/ritonavir combination clinical trial, citing little or no effect in reducing the death rate of hospitalized COVID-19 patients in the branch trial (News press from WHO website, 2021). PF-07321332 and PF-07304814 are potent and orally active SARS-CoV 3C-like protease ($3CL^{pro}$) inhibitors currently in multiple clinical trials including Phase

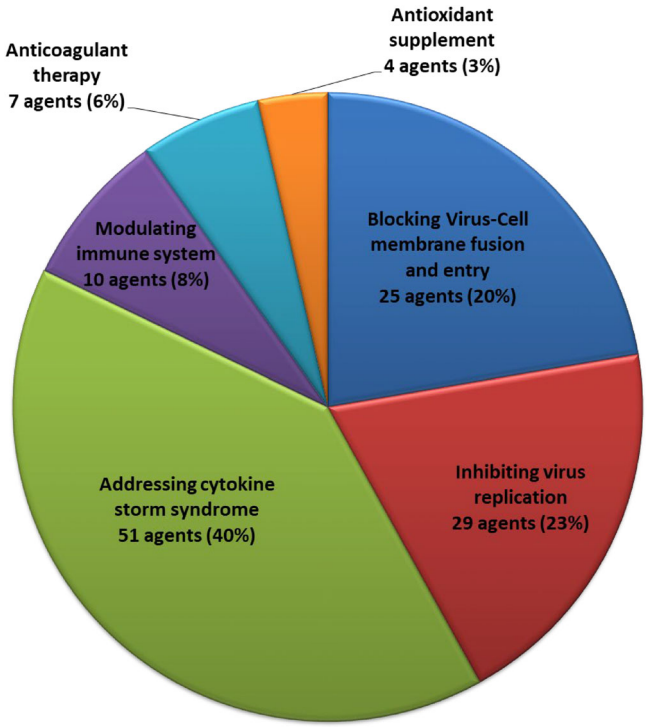


FIGURE 3 The distribution of different categories of small molecules in COVID-19 clinical trials as of April 22, 2021. Sub-classes are made based on the clinical features of COVID-19 and their possible MOAs

III (Vandyck & Deval, 2021). On the other hand, RdRP inhibitors such as remdesivir (Grein et al., 2020), sofosbuvir, and galidesivir could block the replication of the viral genome and the formation of structural proteins. Discovered by Gilead Sciences, remdesivir is the first drug to receive emergency FDA approval as sympathy medication for COVID-19 patients and is currently under various forms of approval in several countries. Especifically, molnupiravir (aka EIDD-2801 and MK-4482) induced RNA mutagenesis by the viral RNA-dependent RdRp. Molnupiravir showed an exciting experimental results in phase 2 clinical trials, and was one of the most promising small molecule anti-coronavirus drugs at present (Imran et al., 2021; Kabinger & Stiller, 2021; Malone & Campbell, 2021). In October 2021, Merck Co. submitted an Emergency Use Authorization (EUA) application to the US Food and Drug Administration (FDA) for molnupiravir based on the promising results from the Phase 3 MOVeOUT clinical trial (Press releas, Merck Company website, 2021). If approved, molnupiravir will be the first oral drug to treat COVID-19. Clinical trials for inhibiting virus replication are summarized in Table 2.

2.3 | Addressing CSS

CSS refers to a group of related medical conditions in which the immune system releases excess of inflammatory signals (interferons,

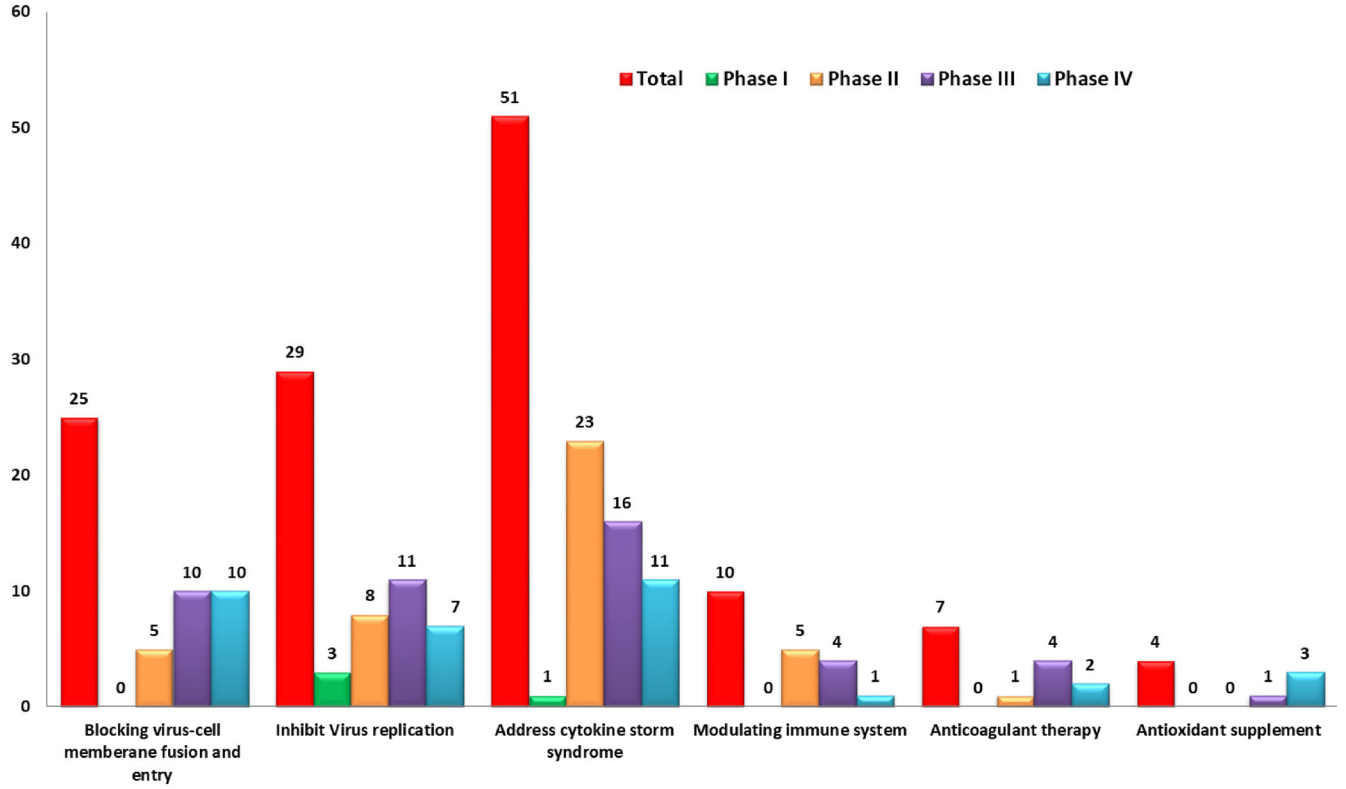
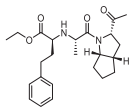
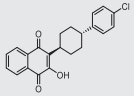
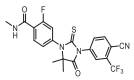
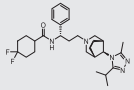
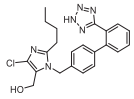
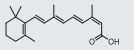


FIGURE 4 Mechanisms of action of agents in phase I-IV

TABLE 1 Blocking virus-cell membrane fusion and entry

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Ramipril 	ACE inhibitor	Type 2 diabetes, vascular disease, hypertension, metabolic syndrome X, peripheral arterial disease, kidney transplant	ACE inhibitor	NCT04366050 (Phase 2)	Phase 2/NCT04366050/ enrolling by invitation/ May Huaier Granule 11, 2020–May 2021	(Amat-Santos et al., 2020)
Atovaquone 	Mitochondrial cytochrome bc1 complex inhibitor, antimalarial agent	HIV infections, malaria, plasmodium falciparum malaria, rabies	Elevating endosomal pH and interfere with ACE2 glycosylation	NCT04339426 (Phase 2) NCT04456153 (Phase 2)	Phase 2/NCT04456153/ completed/July 22, 2020–January 31, 2021	(Clinical trial ID: NCT04456153, n.d.; Farag et al., 2020; Sachdeva et al., 2020)
Enzalutamide 	Androgen receptor (AR) antagonist	Prostate cancer	Blocking TMPRSS2	NCT04456049 (Phase 2) NCT04475601 (Phase 2)	Phase 2/NCT04475601/ recruiting/July 15, 2020–July 8, 2021	(Cattrini et al., 2020)
Maraviroc 	CCR5 antagonist	HIV infection, endothelial dysfunction,	Inhibiting s-protein mediated cell fusion and SARS-CoV-2 multiplication	NCT04441385 (Phase 2) NCT04475991 (Phase 2) NCT04710199 (Phase 2) NCT04435522 (Phase 1)	Phase 2/NCT04441385/ recruiting/June 26, 2020–November 30, 2020	(Koenig et al., 2020; Risner et al., 2020; Shamsi et al., 2020)
Losartan 	AT II receptor antagonist	Hypertension, kidney disease, proteinuria, emphysema, colitis, etc.	ACE2 blocker preventing virus entry into the host cells	Approximately 8 clinical trials, some of the examples are: NCT04335123 (Phase 1) NCT04447235 (Phase 2) NCT04428268 (Phase 2) NCT04643691 (Phase 2) NCT04311177 (Phase 2) NCT04312009 (Phase 2) NCT04606563 (Phase 3) NCT04343001 (Phase 3)	Phase3/NCT04606563/ recruiting/October 9, 2020–June 30, 2021	(Gurwitz, 2020; Messerli et al., 2020)
Isotretinoin (13-cis-retinoic acid) 	Anti-apoptosis	Severe acne	Down-regulates ACE2 receptors, combination with all-trans retinoic acid may enhances neutralizing antibodies in COVID-19 infected Patients	Approximately 9 clinical trials, some of the examples are: NCT04353180 (Phase 3) NCT04396067 (Phase 2) NCT04577378 (Phase 2) NCT04389580 (Phase 2) NCT04578236 (Phase 2) NCT04361422 (Phase 3) NCT04382950 (Phase 1)	Phase 3/NCT04353180/not yet recruiting/October 2020–June 2021	(Hamouda Elgarhy, 2020)

(Continues)

TABLE 1 (Continued)

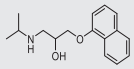
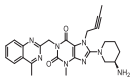
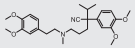
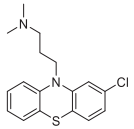
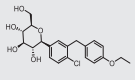
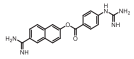
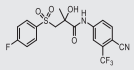
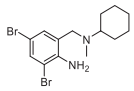
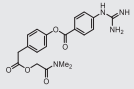
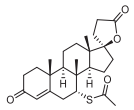
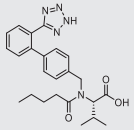
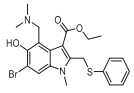
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Lactoferrin (protein)	Anti-microbial, anti-inflammatory, and immunomodulatory	Anti-gram-negative, anti-gram-positive bacteria, fungi and viruses	Inhibiting the union of ACE2 with SARS-CoV-2 spike protein, blocking the heparan sulfate proteoglycan receptor	NCT04526821 (Phase 2) NCT04421534 (Phase 3) NCT04412395 (Phase 3) NCT04427865 (Phase 3) NCT04847791(not applicable) NCT04475120 (Phase 3) NCT04713735 (not applicable)	Phase 3/NCT04475120/completed/April 15, 2020–July 2, 2020	(Chang et al., 2020; Hu et al., 2021)
Propranolol 	Non-selective β_1/β_2-blocker	Hyperalgesia, social anxiety disorder, migraine headache, cigarette smoking, asthma, etc.	Blocking entry of SARS-COV-2 through downregulation of the ACE2 receptor and CD147	NCT04467086 (Phase 3)	Phase 3/NCT04467086/not yet recruiting/December 2020–April 2021	(Vasanthakumar, 2020)
Linagliptin 	DPP-4 inhibitor	Diabetes mellitus, type 2	Inhibiting DPP4, blocking DPP4 inteacting with spike protein of the MERS-Co-V	NCT04371978 (Phase 3)	Phase 3/NCT04371978/recruiting/October 1, 2020–June 30, 2021	(Solerte et al., 2020)
Verapamil 	Calcium channel blocker and P-gp inhibitor, CYP3A4 inhibitor	Heart arrhythmias, high blood pressure and angina research	A slow-channel calcium-blocking agent. Blocking ion channels to inhibit coronavirus entry.	NCT04351763 (Phase 3)	Phase 3/NCT04351763/recruiting/April 27, 2020–March 2, 2021	(Clinical trial ID: NCT04351763, n.d.)
Chlorpromazine 	Antagonist of dopamine D_2, 5-HT_{2A}, potassium channel and sodium channel.	Psychotic disorders such as schizophrenia. Glioblastoma multiforme	K^+/Na^+ channel inhibitor, inhibits clathrin-mediated endocytosis,	NCT04366739 (Phase 3) NCT04354805 (Phase 3)	Phase 3/NCT04366739/not yet recruiting/April 29, 2020–August 30, 2020	(Plaze et al., 2020)
Dapagliflozin 	Competitive SGLT2 inhibitor	Diabetes mellitus (DM)	Reducing the viral load and preventing the lowering of cytosolic pH	NCT04350593 (Phase 3)	Phase 3/NCT04350593/active, not recruiting/April 22, 2020–April 2021	(Cure & Cumhur Cure, 2020)
Nafamostat 	Serine protease inhibitor,	Acute kidney injury	TMPRSS2 inhibitor	NCT04390594 (Phase 3) NCT04352400 (Phase 3) NCT04418128 (Phase 3)	Phase 3/NCT04390594/recruiting/August 13, 2020–February 12, 2021	(Fernandez-Fernandez et al., 2020)

TABLE 1 (Continued)

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Bicalutamide 	Non-steroidal AR antagonist	Prostate cancer, neoplasms, prostate,	Blocking TMPRSS2	NCT04509999 (Phase 3) NCT04652765 (Phase 1)	Phase 3/NCT04509999/ recruiting/October 26, 2020–September 2022	(Cattrini et al., 2020)
Bromhexine 	Clearing mucus from respiratory tract, antioxidant	Chronic bronchitis, asthma and other causes of phlegm not easy to cough out	TMPRSS2 inhibitor	NCT04340349 (Early Phase1) NCT04424134 (Phase 3) NCT04355026 (Phase 4) NCT04273763 (not applicable)	Phase 4/NCT04355026/ recruiting/April 10, 2020–June 30, 2020	(Habtemariam et al., 2020; Maggio & Corsini, 2020)
Camostat 	Serine protease inhibitor,	Corona virus infection, COVID-19, coagulopathy cardiovascular complication COVID-19	TMPRSS2 inhibitor	Approximately 19clinical trials, some of the examples are: NCT04353284 (Phase 2) NCT04524663 (Phase 2) NCT04583592 (Phase 2) NCT04608266 (Phase 3) NCT04455815 (Phase 3) NCT04657497 (Phase 3) NCT04530617 (Phase 2)	Phase 4/NCT04338906/ withdrawn (lack of public funding)/June 1, 2020–December 2021	(Huang et al., 2020)
Spironolactone 	AR antagonist	Heart failure, cardiomyopathy, alcoholic, alcoholism, osteoarthritis, Hypoglycemia, healthy	Inhibiting the androgen-dependent expression of TMPRSS2	NCT04643691 (Phase 2) NCT04424134 (Phase 3) NCT04826822 (Phase 3) NCT04345887 (Phase 4)	Phase 4/NCT04345887/not yet recruiting/April 21, 2020–July 21, 2020	(Cadegiani et al., 2020; Liaudet & Szabo, 2020)
Valsartan (diovan) 	AT II receptor antagonist	Hypertension stage 2 systolic hypertension	ACE2 inhibitor, inhibition of TMPRSS2	NCT04335786 (Phase 4)	Phase 4/NCT04335786/ recruiting/April 17, 2020–December 2020	(Vitiello et al., 2020)
Arbidol (umifenovir) 	Antiviral agent	Influenza	Inhibition of ACE2/S protein interaction, blocking membrane fusion	NCT04350684 (Phase 4) NCT04260594 (Phase 4) NCT04476719 (Phase 1)	Phase 4/NCT04350684/ enrolling by invitation/ April 15, 2020–April 22, 2020	(Clinical trial ID: NCT04260594, n.d.; Clinical trial ID: NCT04252885, n.d.; Huang et al., 2020)

(Continues)

TABLE 1 (Continued)

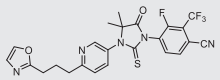
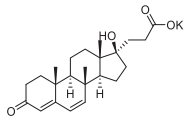
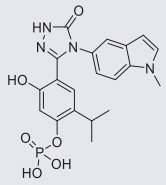
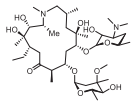
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Proxalutamide (GT0918) 	Androgen receptor (AR) antagonist	COVID-19, Prostate cancer	ACE2 and TMPRSS2 levels in lung and cardiac cells are reduced by ant androgens	NCT04853134 (Phase 3) NCT04728802 (Phase 3) NCT04853927 (Phase 3) NCT05009732 (Phase 3) NCT04870606 (Phase 3) NCT04446429 (not applicable)	Phase 3/NCT04728802/ completed/January 28, 2021–April 15, 2021	(McCoy et al., 2021)
Canrenoate potassium 	Competitive mineralocorticoid receptor (aldosterone receptor) antagonist	Brain-dead organ donors, Cirrhosis, COVID-19 pneumonia	Pleiotropic effects with favorable renin–angiotensin–aldosterone system (RAAS) and ACE2 expression, reduction in transmembrane serine protease 2 (TMPRSS2) activity and antiandrogenic action	NCT04977960 (Phase 2) NCT04912011 (Phase 4)	Phase 4/NCT04912011/ recruiting/June 3, 2021–August 31, 2021	(Kotfis & Lechowicz, 2021:)
Defibrotide 	Thrombotic microangiopathies, Kawasaki disease, Sickle cell disease	Coagulopathy	Mediated by the p38 MAPK pathway, which is upregulated as a result of the binding of SARSCoV2 on ACE2 receptors on the surface of endothelial cells and, in turn, activates the transcription of the proinflammatory cytokines.	NCT04335201 (Phase 2) NCT04652115 (Phase 2) NCT04530604 (Ohase 1) NCT04348383 (Phase 2)	Phase 2/NCT04335201/ recruiting/April 6, 2020–June 20, 2021	(Macciò et al., 2020)
Azithromycin 	Inhibit translation via interacting with 50S subunit of the bacterial ribosome	Acute bacterial, community-acquired pneumonia, uncomplicated skin infections, et al	Inhibiting viral invasion via interact with spike protein/CD147 interaction or blocking CD147 expression	Approximately 52 clinical trials, some of the examples are: NCT04334382 (Phase 3) NCT04371406 (Phase 3) NCT04359316 (Phase 4) NCT04339816 (Phase 3) NCT04332107 (Phase 3) NCT04621461 (Phase 4) NCT03871491 (Phase 3)	Phase 4/NCT04621461/ completed/November 2020–February 8, 2021	(Damle et al., 2020; Ulrich & Pillat, 2020)

TABLE 1 (Continued)

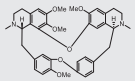
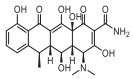
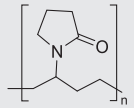
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Tetrandrine 	Voltage-gated Ca^{2+} current (ICa) and Ca^{2+} -activated K^+ current inhibitor	Corona virus disease 2019, COVID-19	Inhibiting voltage-gated Ca^{2+} current (ICa) and Ca^{2+}-activated K^+ current.	NCT04308317 (Phase 4)	Phase 4/NCT04308317/ enrolling by invitation/ March 5, 2020–March 1, 2021	(Clinical trial ID: NCT04308317, n.d.; Heister & Poston, 2020)
Doxycycline 	Broad-spectrum metalloproteinase (MMP) inhibitor	Anal chlamydia infection, rosacea, overactive bladder, HIV infections, sinusitis, acne vulgaris	Inhibition of the E2 envelope glycoprotein involved in virus entry	Approximately 10 clinical trials, some of the examples are: NCT04591600 (Phase 2) NCT04523831 (Phase 3) NCT04371952 (Phase 3) NCT04370782 (Phase 4) NCT04407130 (Phase 2) NCT04551755 (Phase 2) NCT04584567 (Phase 3)	Phase 4/NCT04370782/ completed/28, 2020–September 30, 2020	(Francini et al., 2020; Maurya, 2020)
Povidone-iodine  X I_2 n:x=10:1	Antibacterial agent (MRSA and MSSA strains)	External uses-infection; cesarean section, vaginal surgeries, arrhythmia	Interacting with surface proteins of enveloped viruses, destabilize membrane fatty acids, inducing cell apoptosis	Approximately 12clinical trials, some of the examples are: NCT04410159 (Phase 2) NCT04549376 (Phase 2) NCT04510402 (Phase 2) NCT04371965 (Phase 2) NCT04872686 (Phase 3) NCT04344236 (Phase 2) NCT04603794 (Phase 4)	Phase 4/NCT04603794/ recruiting/October 1, 2020–November 2020	(Pattanshetty et al., 2021)

TABLE 2 Inhibiting virus replication

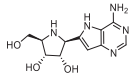
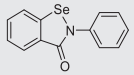
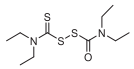
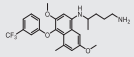
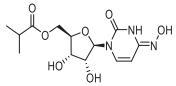
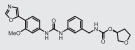
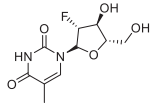
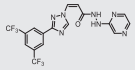
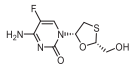
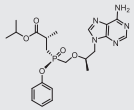
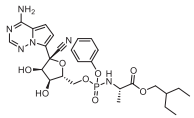
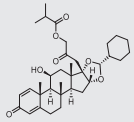
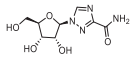
Drug	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
Galidesivir 	Viral RNA-dependent RNA polymerase (RdRP) inhibitor	Not yet approved	Inhibiting RNA dependent RNA polymerase	NCT03891420 (Phase 1)	Phase 1/NCT03891420/recruiting/April 9, 2020–May 31, 2021	(Elfiky, 2020; Silva Arouche et al., 2020)
Ebselen (PZ-51, SPI-1005, CCG-39161,) 	Potent voltage-dependent calcium channel (VDCC) blocker	Not yet approved	Inhibiting main protease via binding to M^{pro} from forming selenosulfide	NCT04484025 (Phase 2) NCT04483973 (Phase 2)	Phase 2/NCT04484025/not yet recruiting/May 2021–June 2022	(Haritha et al., 2020; Ma et al., 2020)
Disulfiram (tetraethylthiuram disulfide; TETD) 	Aldehyde-dehydrogenase (ALDH1) inhibitor	Cocaine addictive, chronic alcoholism	Blocking the M^{pro} protease, inhibiting cytokine release induced by NF-kB and NLRP inflammasome	NCT04485130 (Phase 2) NCT04594343 (Phase 2)	Phase 2/NCT04594343/recruiting/November 20, 2020 –July 20, 2021	(Ma et al., 2020; Wang et al., 2003)
Tafenoquine 	Anti-malarial prophylactic agent.	Not yet approved	Inhibiting virus infection via down regulating M^{pro} activity	NCT04533347 (Phase 2)	Phase 2/NCT04533347/recruiting/February 19, 2021–June 8, 2021	(Chen, Yang, et al., 2020; Dow et al., 2020)
EIDD-2801 (Molnupiravir, MK-4482) 	Virus RNA mutation	Antivirus, not yet approved	Induced RNA mutagenesis by the viral RNA-dependent RNA polymerase (RdRp)	NCT04405739 (Phase 2) NCT04392219 (Phase 1) NCT04575584 (Phase 3) NCT04405570 (Phase 2)	Phase 3/NCT04575584/active, not recruiting/October 5, 2020–August 10, 2021	(Sheahan, Sims, Zhou, et al., 2020; PubChem, National Library of Medicine, n.d.; Kabinger & Stiller, 2021)
Merimepodib(MMPD, VX-497) 	Noncompetitive inosine monophosphate dehydrogenase (IMPDH) inhibitor	Not yet approved	Inhibiting Zika viral RNA replication	NCT04410354 (Phase 2)	Phase 2/NCT04410354/terminated (Failure to meet primary endpoint)/June 16, 2020–December 1, 2020	(X. Tong et al., 2018)
Clevudine (L-FMAU) 	Nucleoside analog of the unnatural L-configuration, non-competitive inhibitor that is not incorporated into the viral DNA but rather binds to the polymerase.	Chronic hepatitis B	Inhibition of viral RNA synthesis	NCT04891302 (Phase 2) NCT04347915 (Phase 2)	Phase 2/NCT04347915/recruiting/April 15, 2020–January 30, 2021	(Hui & Lau, 2005; Jang et al., 2011)
Selinexor		Multiple myeloma				(Uddin et al., 2020)

TABLE 2 (Continued)

Drug	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
	Selective nuclear transport (SINE) inhibitor		Interference nuclear export of vRNPs, viral mRNAs mediated by XPO1, blocking late-stage viral assembly processes	NCT04349098(Phase 2) NCT04355676(Phase 2)	Phase 2/NCT04349098/completed/April 17, 2020–October 5, 2020	
Emtricitabine 	Nucleoside reverse transcriptase inhibitor (NRTI).	HIV infection, PrEP adherence monitoring, healthy, hepatitis B	Reverse transcriptase inhibitor	NCT04712357 (not applicable) NCT04519125 (Phase 2) NCT04334928 (Phase 3) NCT04405271 (Phase 3)	Phase 3/NCT04405271/recruiting/July 31, 2020–April 1, 2021	(Ayerdi et al., 2020)
Tenofovir alafenamide 	HIV-1 nucleotide reverse transcriptase inhibitor	HIV infections, hepatitis B.	Reverse transcriptase inhibitor	NCT04519125 (Phase NCT04334928 (Phase 3) NCT04405271 (Phase 3)	Phase 3/NCT04405271/not yet recruiting/July 31, 2020–November 15, 2020	(Duan et al., 2020)
Remdesivir 	Nucleoside analog with effective antiviral activity	Not yet approved	Viral RNA-dependent RNA polymerase (RdRP) inhibitor, reducing viral multiplication	Approximately 33 clinical trials, some of the examples are: NCT04539262 (Phase 2) NCT04610541 (Phase 3) NCT04501952 (Phase 3) NCT04292730 (Phase 3) NCT04560231 (Phase 1) NCT04672564 (Phase 3) NCT04480333 (Phase 1)	Phase3/NCT04292899/completed/March 6, 2020–April 9, 2020	(Coomes & Haghbayan, 2020; Wang, Cao, et al., 2020)
Ciclesonide 	Glucocorticoid receptor inhibitor	Obstructive airway diseases. Asthma, Allergic Rhinitis, Perennial	Inhibiting the replication of SARS-CoV-2 genomic RNA via targeting viral endonuclease NSP15	NCT04330586 (Phase 2) NCT04435795 (Phase 3) NCT04377711 (Phase 3) NCT04381364 (Phase 2) NCT04356495 (Phase 3)	Phase 3/NCT04377711/completed/June 8, 2020–January 5, 2021	(Kimura et al., 2020)
Ribavirin 	Nucleoside inhibitor	HIV infections, hepatitis C	RNA-dependent RNA polymerase inhibitor	Approximately 8 clinical trials, some of the examples are: NCT04828564(Phase 3) NCT04563208 (Phase 2) NCT04494399 (Phase 2) NCT04460443 (Phase 3) NCT04356677 (Phase 1) NCT04392427 (Phase 3)	Phase 3/NCT04392427/not yet recruiting/October 2020–May 2022	(S. Tong et al., 2020; Khalili et al., 2020)

(Continues)

TABLE 2 (Continued)

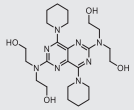
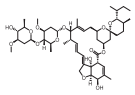
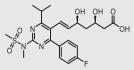
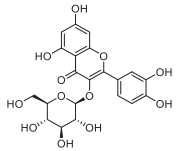
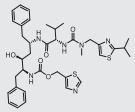
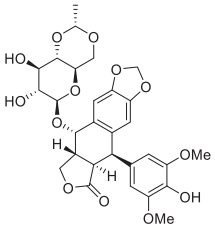
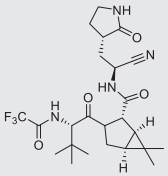
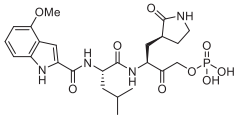
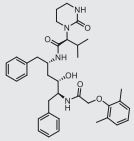
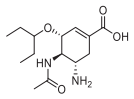
Drug	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
Dipyridamole 	Phosphodiesterase inhibitor	Cirrhosis, hypertension, status; splenectomy, venous thrombosis, brain ischemia, transient ischemic attack, arteriosclerosis,	Suppressing HCoV-19 replication	NCT04391179 (Phase 2) NCT04424901 (Phase 2) NCT04410328 (Phase 3)	Phase 3/NCT04410328/recruiting/October 21, 2020–March 15, 2021	(Liu, Li, Liu, Chen, & Luo, 2020; Liu, Zheng, Huang, Shan, & Huang, 2020; Ma & Wang, 2021)
Ivermectin 	Anti-parasite agent, impα/β_1-mediated nuclear import inhibitor	Healthy, rosacea, lymphatic filariasis, loiasis	Blocking α/β1-mediated nuclear import	Approximately 56 clinical trials, some of the examples are: NCT04529525 (Phase 3) NCT04381884 (Phase 2) NCT04523831 (Phase 3) NCT04391127 (Phase 3) NCT04602507 (Phase 2) NCT04422561 (Phase 3) NCT04530474 (Phase 3)	Phase 3/NCT04523831/completed/June 1, 2020–August 22, 2020	(Heidary & Gharebaghi, 2020; Sharun et al., 2020)
Rosuvastatin 	HMG-CoA reductase enzyme inhibitor, cholesterol level inhibitor, block hERG current	Dyslipidemias, non-ST-elevation acute coronary syndromes, cardiovascular disease, myocardial infarction, hypercholesterolemia	Targeting COVID-19 virus M^{pro}	NCT04472611 (Phase 3)	Phase 3/NCT04362137/not yet recruiting/August 1, 2020–August 1, 2021	(Farag et al., 2020)
Isoquercetin (Quercetin 3-glucoside, IQC-950AN) 	Regulates the expression of nitric oxide synthase 2 (NO2) via modulating the nuclear factor-κB (NF-κB) transcription regulation system	Cardiovascular disease, chronic kidney disease, Covid19	M^{pro} inhibitor	NCT04536090 (Phase 2) NCT04733651 (Phase 2) NCT04622865 (Phase 2)	Phase 2/NCT04622865/recruiting/November 10, 2020–June 2021	(Saeedi-Boroujeni & Mahmoudian-Sani, 2021)
Ritonavir 	HIV type 1aspartate protease inhibitor	HIV infection	Inhibit the coronaviral $3CL^{pro}$ protease	Approximately 24 clinical trials, some of the examples are: NCT04403100 (Phase 3) NCT04321174 (Phase 3) NCT04291729 (Phase 4) NCT04345276 (Phase 4) NCT04261270 (Phase 3) NCT04386876 (Phase 1) NCT04466241 (Phase 2)	Phase 4/NCT04291729/completed/February 17, 2020–March 19, 2020	(Cao et al., 2020; Chu et al., 2004; Li & De Clercq, 2020; Ma et al., 2021; Sheahan, Sims, Leist, et al., 2020; Zhang, Lin, et al., 2020)

TABLE 2 (Continued)

Drug	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
Etoposide (VP-16; VP-16-213) 	Topoisomerase II inhibitor	Adult acute lymphocytic leukemia, NK + T Cell lymphoma, mantle cell lymphoma, small cell lung cancer	SARS-3CL protease inhibitor	NCT04356690 (Phase 2)	Phase 2/NCT04356690/Active, not recruiting/April 22, 2020–December 2021	(Rashid et al., 2022)
PF-07321332 	SARS-CoV 3C-like protease (3CLPRO) inhibitor	COVID-19	$3CL^{pro}$ inhibitor	NCT04960202 (Phase 3) NCT04962230 (Phase 1) NCT05005312 (Phase 1) NCT04909853 (Phase 1) NCT04962022 (Phase 1) NCT05032950 (Phase 1) NCT04756531 (Phase 1) NCT05011513 (Phase 3)	Phase 3/NCT04960202/recruiting/July 13, 2021–October 16, 2021	(Vandyck & Deval, 2021)
PF-07304814 	Potent 3CLpro protease (Mpro) inhibitor	Viral disease	$3CL^{pro}$ proteaseinhibitor	NCT04535167 (Phase 1) NCT04627532 (Phase 1)	Phase 1/NCT04627532/completed/November 13, 2020–December 17, 2020	(Boras, 2021; Vandyck & Deval, 2021)
Lopinavir 	HIV type 1 aspartate protease inhibitor	HIV infection	Inhibit the viral proteases: $3CL^{pro}$ or PI^{pro}, increasing t1/2 via inhibiting cytochrome P450 when combined with lopinavir	Approximately 18 clinical trials, some of the examples are: NCT04403100 (Phase 3) NCT04307693 (Phase 2) NCT04321174 (Phase 3) NCT04455958 (Phase 2) NCT04255017 (Phase 4) NCT04330690 (Phase 2) NCT04386876 (Phase 1)	Phase 4/NCT04255017/recruiting/February 1, 2020–June 1, 2020	(Cao et al., 2020; Chu et al., 2004; Li & De Clercq, 2020; Ma et al., 2021; Sheahan, Sims, Leist, et al., 2020; Zhang, Lin, et al., 2020)
Oseltamivir 	Virus neuraminidase enzyme inhibitor	Influenza A and B viruses	Virus-release blockers	NCT04303299 (Phase 3) NCT04558463 (Phase 3) NCT04516915 (Phase 3) NCT04255017 (Phase 4) NCT02735707 (Phase 4) NCT04338698 (Phase 3)	Phase 4/NCT04255017/recruiting/February 1, 2020–June 1, 2020	(Akram et al., 2020; Clinical trial ID: NCT04255017, n.d.; Whitley, 2007)

(Continues)

TABLE 2 (Continued)

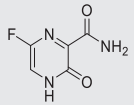
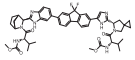
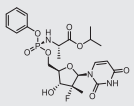
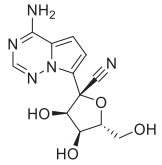
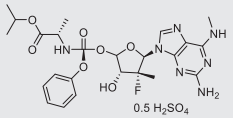
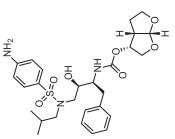
Drug	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
Favipiravir 	Viral RNA polymerase inhibitor	Influenza	RNA dependent RNA polymerase inhibitor, reducing virus replication	Approximately 38 clinical trials, some of the examples are: NCT04402203 (Phase 3) NCT04464408 (Phase 3) NCT04359615 (Phase 4) NCT04303299 (Phase 3) NCT04529499 (Phase 3) NCT04349241 (Phase 3) NCT04600999 (Phase 3) NCT04613271 (Phase 3)	Phase 4/NCT04359615/not yet recruiting/April 20, 2020–May 3, 2020	(Coomes & Haghbayan, 2020; Wang, Cao, et al., 2020)
Ledipasvir 	Inhibitor of the hepatitis C virus NS5A	Hepatitis C, hepatocellular carcinoma	RdRP inhibitor	NCT04498936 (Phase 4) NCT04530422 (Phase 3)	Phase 4/NCT04498936/sofosbuvir/ledipasvir and nitazoxanide for treatment of COVID-19	(Mevada et al., 2020; Sayad et al., 2020)
Sofosbuvir 	HCV RNA replication inhibitor	Hepatitis C, liver cirrhosis	RdRP inhibitor	Approximately 8 clinical trials, some of the examples are: NCT04530422 (Phase 3) NCT04498936 (Phase 4) NCT04497649 (Phase 3) NCT04532931 (Phase 2) NCT04535869 (Phase 3) NCT04561063 (Phase 2) NCT04460443 (Phase 3)	Phase 4/NCT04498936/completed/July 15, 2020–October 30, 2020	(Ju et al., 2020; Elfiky, 2020; Sayad et al., 2020)
GS-441524 	Inhibits feline infectious peritonitis virus (FIPV), parent nucleoside of remdesivir	COVID-19	Interferes with the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp)	NCT04859244 (Phase 1)	Phase 1/NCT04859244/completed/April 26, 2021–May 1, 2021	(Yan & Muller, 2020)
AT-527 (R07496998) 	HCV viral replication inhibitor	HCV Infection	Inhibit the RdRp for RNA synthesis	NCT04889040 (Phase 3) NCT04709835 (Phase 2) NCT04396106 (Phase 2) NCT04877769 (Phase 1)	Phase 3/NCT04889040/recruiting/May 17, 2021–August 3, 2021	(Good et al., 2021)

TABLE 2 (Continued)

Drug	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
Darunavir 	HIV protease inhibitor	HIV infections, healthy	Protease inhibitor	NCT04252274 (Phase 3) NCT04435587 (Phase 4) NCT04303299 (Phase 3)	Phase 4/NCT04435587/recruiting/July 13, 2020–June 2021	(Kutlu & Metin, 2020; Papic et al., 2020)

interleukins, tumor necrosis factors (TNF), chemokines, and several other mediators), resulting in a clinical presentation of unremitting high fever, hyperferritinemia, hepatosplenomegaly, cytopaenia, lymphadenopathy and central nervous system abnormalities, and, if untreated, could lead to the organ failure and even the death (Fajgenbaum & June, 2020; Gao et al., 2021). Abundant studies have revealed that majority of COVID-19 patients are often have higher levels of inflammatory mediators in blood. Those inflammatory mediators include cytokines and chemokines such as interleukin (IL)-1 IL-6, IL-7, IL-10, IL-21, TNF, and monocyte chemoattractant protein-1 (MCP1, also known as CCL2) etc. (Chen, Wu, et al., 2020; Gorbalenya et al., 2020; Hojyo et al., 2020; Tay et al., 2020). Therefore, COVID-19 could be featured as a cytokine release syndrome (CRS) and the fatality could be caused by the high mortality cytokine storm. In fact, the approach on addressing the CSS for the potential treatment of COVID-19 is currently investigated in clinics. For example, physicians apply medicines such as corticosteroids (prednisone, methylprednisolone, and hydrocortisone), interleukin inhibitors (anakinra, levamisole, and colchicine), and JAK–STAT inhibitors (ruxolitinib and baricitinib) to patients to see whether these medicines could alleviate the symptoms of COVID-19. Studies suggest that suppressing the release of cytokine could probably improve the clinical outcomes (L. Lu et al., 2020). However, the adverse consequences were also observed in patients when corticosteroid therapy was applied during COVID-19 infection. Thereby, it is important to strictly control the time and dosage of glucocorticoids administration in the disease prognosis (Sanders et al., 2020). Glucocorticoids are mainly used in severe patients with CSS (Ye et al., 2020). The WHO currently does not recommend the routine use of corticosteroids in COVID-19 patients, due to the potential delay in viral clearance. Hence, corticosteroids should be given to patient with certain symptoms such as severe acute respiratory distress syndrome or refractory septic shock (Mehta, Mazer-Amirshahi, et al., 2020). Agents in clinical trials for potential inhibiting cytokine storm in COVID-19 are summarized in Table 3.

2.4 | Modulating immune system

Special cells (such as white blood cells B- and T-lymphocytes), organs (such as bone marrow, spleen, and thymus), and chemicals (antibodies) mainly compose the immune system (Sompayrac, 2019). The well-working immune system produces antibodies to kill pathogens and protects the body against viruses and diseases. The immune system in human body plays a fundamental role in maintaining health (Chowdhury et al., 2020). After invasion into the human body, SARS-CoV-2 will encounters a robust innate immune response when it moves to the respiratory tract (Rokni et al., 2020; Tang et al., 2005). The immune system plays a critical role in the body's defenses against SARS-CoV-2 infection. Immune system modulation prevents tissue damage resulting from an excessive response. Under some circumstances, drugs modulating immune system could be an efficient strategy for fighting against COVID-19. Agents such as cyclosporine A, isoprinosine, all-trans retinoic acid are in clinical trials aiming to

suppress the virus infection through modulation of the immune system (Table 4).

2.5 | Anticoagulant therapy

SARS-CoV-2 can invade cells lining blood vessels and cause a series of consequences related to cardiovascular diseases and thrombosis. More specifically, the virus invasion could induce endothelial dysfunction which further leads to pulmonary thrombi (Carfora et al., 2021; Poissy et al., 2020). Applying anticoagulant therapy in COVID 19 patients has scientific support and is in line with the COVID-19 global pandemic emergency. Agents such as rivaroxaban and apixaban are in ongoing clinical trials to combat COVID-19 associated hypercoagulation (Figure 2 and Table 5). The efficacy and effectiveness of using anticoagulant therapy for COVID-19 await clinical data.

2.6 | Antioxidant supplement

Antioxidant agents help prevent free radicals or reactive oxygen species (ROS) from harming healthy cells in human body. The effects of antioxidants on heart disease, cancer, and arthritis have been widely studied. As a powerful antioxidant, vitamin-C might protect the human body against SARS-CoV-2 infection through its important role in enhancing human body immunity (Carr & Maggini, 2017). A high-dose vitamin C in coping with the oxidative stress in COVID-19 patients is currently being studied (Colunga Biancatelli et al., 2020; Hunt et al., 1994). In addition, vitamin D supplementation might lower the odds of developing respiratory infections according to the data from observational studies (Table 6) (Martineau et al., 2017; McCartney & Byrne, 2020)

3 | AGENTS IN THE DRUG DEVELOPMENT PHASES OF THE PIPELINE

Approved drugs or clinical candidates in COVID-19 clinical trials are arranged and analyzed based on their highest stage of clinical trial. A summary of the drug name, structure, class, original mechanism, FDA-approved indication(s), possible mechanism for COVID-19 treatment, the highest anti-COVID-19 phase (clinical trial ID) etc. are presented in this section (Figure 4 and Tables 1–6).

3.1 | Phase I/II clinical candidates

The primary goal of Phase I study is to assess the safety, the tolerability, the pharmacokinetic parameters, and the pharmacodynamics effects of a drug candidate in healthy volunteers. At the end of this phase, the optimum dose and formulation will be determined. The information obtained could be used for subsequent phases. There are four agents in Phase I clinical trials (Figure 4). PF-07304814 is an inhibitor of $3CL^{pro}$ currently in several clinical stages including Phase I. Galidesivir and GS-441524, RdRP inhibitors, are being tested in Phase I for potential blocking viral replication. Progesterone, a steroid hormone, aims to address the CSS. No small molecule in other categories is currently in phase I trials. It takes a long time to develop a new drug from scratch, so researchers focus their main efforts on drug repurposing.

A phase II trial is designed to obtain the therapeutic effects and side effects of the drug candidate in patients with the disease. In contrast to only two trials in phase I, there are significantly more trials in phase II. The drugs for phase II trials are all FDA-approved drugs for indications other than COVID-19. In fact, there are 42 agents in approximately 85 phase II trials (Figure 4).

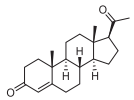
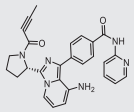
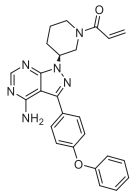
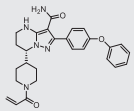
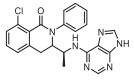
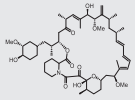
There are 5 small molecules in phase II trials aiming to block virus-cell membrane fusion and entry, 8 small molecules inhibiting the viral replication, 23 small molecules addressing cytokine storm, 5 small molecules modulating the immune system, and 1 small molecule used as anticoagulant therapy. There is no small molecule phase II trial using antioxidant supplement.

Of the drugs blocking virus-cell membrane fusion and entry, there are three agents (ramipril and atovaquone and defibrotide) targeting ACE, one agent (enzalutamide) acting as androgen receptor (AR) antagonist aiming to block TMPRSS2, the other agent (maraviroc) acting as CCR5 antagonist inhibiting cell fusion. Of the drugs targeting viral replication, there were four M^{pro} protease inhibitors (ebselen, disulfiram, tafenoquine and isoquercetin. Ebselen and disulfiram are nonspecific promiscuous SARS-CoV-2 main protease inhibitors), one $3CL^{pro}$ inhibitor (etoposide), two agents (, merimepodib and clevudine) targeting RNA, one agent (selinexor) inhibiting virus assembly processes. Of the drugs addressing CSS, there were three Bruton's tyrosine kinase (BTK) inhibitors (zanubrutinib, acalabrutinib, and ibrutinib), one phosphatidylinositol 3-kinase (PI3K) inhibitor (duvelisib), one mTOR inhibitor (sirolimus), one agent (enpatoran) blocking the activation of Toll-like receptor 7 (TLR7) and TLR8, 8 agents (artemiC, abivertinib, estradiol, pentoxifylline, aprepitant, prazosin, PF-06650833 and ampion) mediating the release of inflammatory cytokines, 9 agents (ibudilast, LAU-7b, naltrexone, piclidenoson, clarithromycin, thalidomide, EC-18, APX-115 and cenicriviroc) are anti-inflammatory drugs. Of the drugs modulating the innate immune system, there are four agents: methotrexate, leflunomide, fingolimod, and tamoxifen. There is only one agent (ketamine) used for symptomatic control.

3.2 | Phase III clinical candidates

Phase III clinical trials are the studies in the efficacy confirmatory stage. Its goal is to further verify the therapeutic effectiveness and the safety of a drug candidate on patients with specific indications, and to assess the overall risk–benefit relationships. The results from this stage trial will ultimately provide substantial ground for the new drug registration applications. In this stage of the trial, a larger array of trials and more patients will be required and assessed than those tirals in phase II

TABLE 3 Addressing the cytokine storm syndrome

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Progesteron 	Steroid hormone regulating menstrual cycle	Suicidal ideation, infertility, hormone replacement, concussion	Inhibiting pro-inflammatory cytokines IL-1β and IL 12	NCT04365127 (Phase 1)	Phase1/NCT04365127/completed/April 27, 2020–August 20, 2020	(Mauvais-Jarvis et al., 2020)
Acalabrutinib 	BTK inhibitor	Not yet approved	BTK inhibitor, decreased inflammatory cell infiltration and proinflammatory cytokines	NCT04380688(Phase 2) NCT04346199(Phase 2) NCT04497948(Phase 1) NCT04564040(Phase 1)	Phase 2/NCT04346199/completed/June 12, 2020–November 17, 2020	(Roschewski et al., 2020)
Ibrutinib 	Irreversible BTK inhibitor	Lymphocytic, waldenstrom macroglobulinemia, mantle-cell, B-cell, etc.	BTK inhibitor, decreasing inflammatory cell infiltration and proinflammatory cytokines	NCT04375397 (Phase 2) NCT04665115 (Phase 2) NCT04439006 (Phase 2)	Phase 2/NCT04439006/recruiting/July 22, 2020–December 31, 2021	(Treon et al., 2020)
Zanubrutinib 	Selective BTK inhibitor	Not approved yet	BTK inhibitor, decreased inflammatory cell infiltration and proinflammatory cytokines	NCT04382586 (Phase 2)	Phase 2/NCT04382586/active, not recruiting/July 6, 2020–February 2, 2021	(Chong et al., 2020)
Duvelisib 	Selectivite p100δ inhibitor	Not approved yet	Inhibiting phosphatidylinositol 3-kinase(PI3K) which plays acrucial role in eliciting immune response.	NCT04372602 (Phase 2) NCT04487886 (Phase 2)	Phase 2/NCT04372602/recruiting/October 12, 2020–November 30, 2021	(Clinical trial ID: NCT04487886, n.d.)
Sirolimus (rapamycin) 	mTOR inhibitor	Kidney transplantation, blue rubber bleb nevus syndrome, venous malformation, kidney transplantation, uterine fibroids	Alleviating cytokine strom and T-cell senescence, preventing severe COVID-19 progression	Approximately 7 clinical trials, some of the examples are: NCT04461340 (Phase 2) NCT04371640 (Phase 1) NCT04341675 (Phase 2) NCT04409327 (Phase 2)	Phase 2/NCT04341675/recruiting/April 24, 2020–July 2020	(Omarjee et al., 2020)

(Continues)

TABLE 3 (Continued)

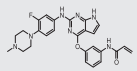
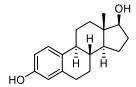
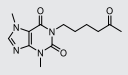
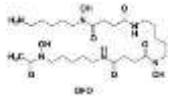
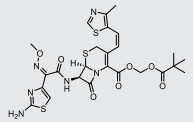
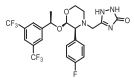
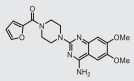
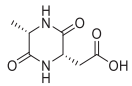
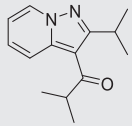
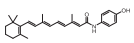
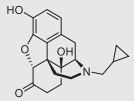
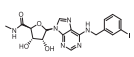
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
ArtemiC (artemisinin, curcumin, frankincense and vitamin C)	Anti-inflammation	Not currently approved	Diminishing activity of TNF-α and IL-6 levels	NCT04382040 (Phase 2)	Phase 2/NCT04382040/completed/May 8, 2020–November 2020/MGC pharmaceuticals d.o.o)	(Clinical trial ID: NCT04382040, n.d.)
Abivertinib 	Tyrosine kinase inhibitor (TKI), BTK Inhibitor, third-generation EGFR tyrosine kinase inhibitor	Not yet approved	Inhibition of vital pro-inflammatory cytokine production, such as IL-6, IL-1β and TNF-α	NCT04528667 (Phase 2) NCT04440007 (Phase 2)	Phase 2/NCT04528667/recruiting/September 2020–May 2021	(Clinical trial ID: NCT04440007, n.d.; Sorrento Therapeutics Inc, News Release, 2020)
Estradiol 	Enhancing expression of interleukin 6 via the estrogen receptor β (ERβ) pathway	Menorrhagia, vaginal atrophy, healthy, suicidal ideation	Anti-inflammatory and immunomodulatory, blocking the proinflammatory cytokines production, such as IL-6, IL-1β, TNF-α and chemokine CCL2	NCT04359329 (Phase 2)	Phase 2/NCT04359329/recruiting/April 20, 2020–November 15, 2020	(Mauvais-Jarvis et al., 2020)
Pentoxifylline 	Competitive nonselective phosphodiesterase inhibitor	Type 2 diabetes, chronic renal failure, severe alcoholic hepatitis, lupus nephritis, irritable bowel syndrome, diabetic kidney disease et al.	Anti-inflammatory, blocking the proinflammatory cytokines production, such as IL-6, IL-1, TNF-α, C-reactive protein and other immunoregulators.	NCT04433988 (Phase 2) NCT04570254 (not applicable)	Phase 2/NCT04433988/not yet recruiting/December 13, 2020–December 30, 2021	(Assimakopoulos et al., 2020; González-Pacheco et al., 2020)
Deferoxamine 	Iron chelator	Iron overload, diabetic foot ulcer, acute ischemic stroke, Beta-Thalassemia,	Inhibiting IL-6 synthesis through decreasing NF-kB.	NCT04333550 (Phase 2) NCT04361032 (Phase 3) NCT04389801 (Phase 4)	Phase 4/NCT04389801/Not yet recruiting/May 15, 2020–September 30, 2020	(Clinical trial ID: NCT04389801, n.d.; Dalamaga et al., 2020)
Cefditoren (Pivoxil, ME 1207) 	New-third generation cephalosporin antibiotic, broad spectrum of activity against Gram-positive and gram-negative bacteria	Rhinosinusitis, COVID-19 pneumonia, urinary tract infections	Decrease IL-6 level and other pro-inflammatory cytokines	NCT04709172 (Phase 4)	Phase 4/NCT04709172/recruiting/January 14, 2021–April 5, 2021	(Clinical trial ID: NCT04709172, n.d.)

TABLE 3 (Continued)

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/ start–(estimated)end dates	References
Aprepitant (cinvanti) 	Neurokinin 1 receptor antagonist	Postoperative nausea and vomiting, healthy volunteers, emesis, breast cancer, leukemia	Anti-inflammatory, blocking inflammatory cytokines release mediated by the binding of substance P to NK1 receptors	NCT04470622 (Phase 2)	Phase 2/NCT04470622/ recruiting/July 20, 2020–June 2021/ Heron Therapeutics	(Clinical trial ID: NCT04470622, n.d.; Mehboob et al., 2020)
Prazosin 	Selective alpha 1-adrenergic blocking agent.	PTSD, panic disorder, hypertension and anxiety and anxiety	α-1 adrenergic receptor antagonist, prevent cytokine storm	NCT04365257 (Phase 2)	Phase 2/NCT04365257/ recruiting/May 13, 2020–June 30, 2021	(Konig et al., 2020)
Ampion (DA-DKP, aspartyl-alanyl diketopiperazine) 	Modulating inflammatory immune response via molecular pathways related to T lymphocyte energy deficiency	Inflammation associated with osteoarthritis	Anti-inflammatory, blocking the proinflammatory cytokines production in T-cells	NCT04456452 (Phase 1) NCT04839965 (Phase 2) NCT04606784(Phase 1)	Phase2/NCT04839965/ recruiting/April 2021–October 2021	(Clinical trial ID: NCT04414618, n.d.)
Ibudilast 	Nonselective phosphodiesterase inhibitor	Asthma, multiple sclerosis	Anti-inflammatory	NCT04429555 (Phase 2)	Phase 2/NCT04429555/ recruiting/November 2020–June 30, 2021	(Clinical trial ID: NCT04429555, n.d.)
LAU-7b (fenretinide [4-HPR]) 	Retinoic acid receptors (RAR) inhibitor	Not approved yet	Anti-inflammatory and antiviral activities	NCT04417257 (Phase 2)	Phase 2/NCT04417257/ recruiting/June 29, 2020–May 15, 2021	(Orienti et al., 2020)
Naltrexone 	Blockade of opioid receptors, κ-opioid receptor antagonist	Alcoholism, opioid use, obesity	Interrupt the inflammation	NCT04365985 (Phase 2) NCT04756128 (Phase 2) NCT04604678 (Phase 2) NCT04604704 (Phase 2) NCT04708327 (Phase 2)	Phase 2/NCT04365985/ recruiting/April 29, 2020–May 2021	(Choubey et al., 2020)
Piclidenoson 	Adenosine A3 receptor agonist	Not approved yet	Anti-inflammatory	NCT04333472 (Phase 2)	Phase 2/NCT04333472/ recruiting/January 6, 2021–March 6, 2022	(David & Shweta, 2020)

(Continues)

TABLE 3 (Continued)

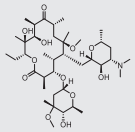
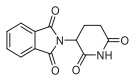
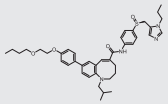
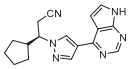
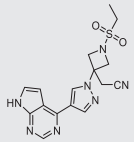
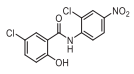
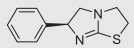
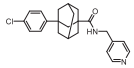
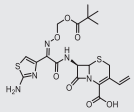
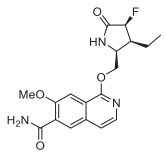
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Clarithromycin 	Macrolide antibiotic and a CYP3A4 inhibitor	Antibiotics-bacterial infection, nontuberculous mycobacteria, mycobacterium avium complex, crohn's disease, ulcer, peptic ulcer, periodontitis	Anti-inflammatory nature and enhance the immunity	NCT04398004 (Phase 2) NCT04622891 (not applicable)	Phase 2/NCT04398004/completed/May 6, 2020–November 30, 2020	(Chalichem et al., 2020; Millán-Oñate et al., 2020)
Thalidomide 	Cereblon (CRBN) inhibitor, sedative, part of the cullin-4 E3 ubiquitin ligase complex CUL4-RBX1-DDB1	Mantle cell lymphoma, NSCLC, congestive heart failure, multiple myeloma, gastric cancer	Anti-inflammatory and anti-fibrosis	NCT04273581 (Phase 2) NCT04273529 (Phase 2)	Phase 2/NCT04273581/ot yet recruiting/February 18, 2020–April 30, 2020	(Khalil et al., 2020)
Cenicriviroc 	Dual CCR2/CCR5 antagonist	Not yet approved	Anti-inflammatory and immunomodulatory effects	NCT04500418 (Phase 2)	Phase 2/NCT04500418/recruiting/August 25, 2020–September 30, 2021	(Okamoto et al., 2020)
Ruxolitinib 	Selective JAK1/2 inhibitor	Thalassemia major, splenomegaly	Inhibit the downstream IFNg pathway targeting JAK kinase receptor	Approximately 19 clinical trials, some of the examples are: NCT04414098 (Phase 2) NCT04477993 (Phase 3) NCT04581954 (Phase 2) NCT04362137 (Phase 3) NCT04348071 (Phase 3) NCT04377620 (Phase 3) NCT04338958 (Phase 2)	Phase 3/NCT04362137/completed/May 2, 2020–October 17, 2020	(Goker Bagca & Biray Avci, 2020; Neubauer et al., 2020)
Baricitinib 	JAK1 and JAK2 inhibitor	Rheumatoid arthritis	JAK–STAT signal blocking	Approximately 11 clinical trials, some of the examples are: NCT04358614 (Phase 3) NCT04320277 (Phase 3) NCT04340232 (Phase 3) NCT04373044 (Phase 2) NCT04421027 (Phase 3) NCT04346147 (Phase 2) NCT04832880 (Phase 3)	Phase 3/NCT04421027/recruiting/June 12, 2020–May 19, 2021	(Cantini et al., 2020; Favalli et al., 2020)

TABLE 3 (Continued)

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/ start–(estimated)end dates	References
Niclosamide 	Anti-parasitic drug, STAT3 inhibitor, DNA replication inhibitor	Not yet approved	Blocking signaling pathways including mTORC1, IL-6-JAK1-STAT3 signaling	Approximately 13 clinical trials, some of the examples are: NCT04558021 (Phase 3) NCT04399356 (Phase 2) NCT04542434 (Phase 2) NCT04372082 (Phase 3) NCT04603924 (Phase 3) NCT04436458 (Phase 2) NCT04524052 (Phase 1)	Phase 3/NCT04558021/ recruiting/October 8, 2020–January 30, 2021	(Pindiprolu & Pindiprolu, 2020; Xu, Shi, Wang, et al., 2020)
Levamisole 	Anthelmintic and immunomodulator	Broad-spectrum insect repellent	Down regulating the level of IL-6 and TNF-α	NCT04360122 (Phase 3) NCT04383717 (Phase 3) NCT04331470 (Phase 3)	Phase 3/NCT04331470/ recruiting/April 4, 2020–April 20, 2020	(Uyaroğlu et al., 2020)
Opaganib 	Selective, competitive sphingosine kinase 2 (SK2) inhibitor	Not yet approved	Down regulating the level of IL-6 and TNF-α, inhibiting viral replication	NCT04414618 (Phase 2) NCT04467840 (Phase 3) NCT04502069 (Phase 2)	Phase 3/NCT04467840/ recruiting/August 21, 2020–June 2021	(Kurd et al., 2020)
Anakinra 	Interleukin-1 receptor (IL-1) antagonist	Rheumatoid arthritis, knee injuries	Interleukin-1 (IL-1) blockage	Approximately 17 clinical trials, some of the examples are: NCT04826588 (Phase 3) NCT04364009 (Phase 3) NCT04443881 (Phase 3) NCT04603742 (Phase 2) NCT04357366 (Phase 2) NCT04339712 (Phase 2) NCT04412291 (Phase 2)	Phase 3/NCT04443881/ recruiting/May 8, 2020–December 2020	(Gallelli et al., 2020)
PF-06650833 	Interleukin-1 receptor associated kinase 4 (IRAK4) inhibitor	Rheumatoid arthritis, lupus, lymphomas	Inhibition of interleukin-1 receptor associated kinase 4 (IRAK4) in ameliorating the proinflammatory state and improving outcomes in severe COVID-19.	NCT04933799 (Phase 2)	Phase 2/NCT04933799/ recruiting/June 22, 2021–March 6, 2022	(Clinical trial ID: NCT04933799, n.d.)

(Continues)

TABLE 3 (Continued)

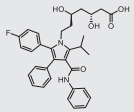
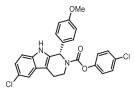
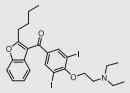
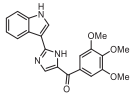
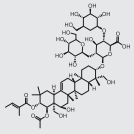
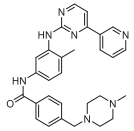
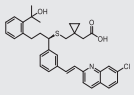
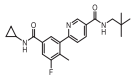
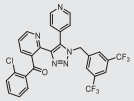
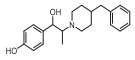
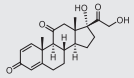
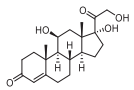
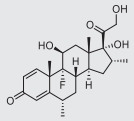
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Atorvastatin 	HMG-CoA reductase inhibitor	Stable angina, acute coronary syndrome, hepatocellular carcinoma, cardiovascular disease, ischemia et al.	lower levels of inflammatory cytokines	NCT04466241 (Phase 2) NCT04380402 (Phase 2) NCT04486508 (Phase 3)	Phase 3/NCT04486508/active, not recruiting/July 30, 2020–April 4, 2021	(Ghati et al., 2020; Li, 2020; Tan et al. 2020)
PTC299 	Dihydroorotate dehydrogenase (DHODH) inhibitor	Not yet approved	Blocking the proinflammatory cytokines production such as IL-6, IL-17, IL-17F	NCT04439071 (Phase 3)	Phase 3/NCT04439071/recruiting/July 9, 2020–January 30, 2021	(Luban et al., 2021)
Amiodarone 	ATP-sensitive potassium channel inhibitor	Atrial fibrillation, atrial fibrillation, new oonset atrial fibrillation, paroxysmal atrial fibrillation, ventricular Tachycardia et al.		NCT04351763 (Phase 3)	Phase 3/NCT04351763/recruiting/April 27, 2020–March 2, 2021	(Sanchis-Gomar et al., 2020)
VERU-111 	Orally bioavailable α and β tubulin inhibitor	Metastatic castration resistant prostate cancer	Anti-inflammatory action against the key cytokines involved in the cytokine storm	NCT04388826 (Phase 2) NCT04842747 (Phase 3)	Phase 3/NCT04842747/not yet recruiting/April 30, 2021–January 5, 2022	(Clinical trial ID: NCT04388826, n.d.)
Escin 	Vasoprotective anti-inflammatory, anti-nociceptive and anti-edematous agent.	Chronic venous insufficiency	Vasoprotective anti-inflammatory	NCT04322344 (Phase 2)	Phase 3/NCT04322344/recruiting/March 23, 2020–June 30, 2020	(Clinical trial ID: NCT04322344, n.d.; Gallelli et al., 2020)
Imatinib 	Tyrosine kinases inhibitor	Breast cancer, gastrointestinal stromal tumors, chronic myeloid leukemia	Tyrosine kinase inhibitors in the regulation of inflammation	NCT04794088 (Phase 2) NCT04422678 (Phase 3) NCT04394416 (Phase 3) NCT04357613 (Phase 2) NCT04346147 (Phase 2)	Phase 3/NCT04394416/recruiting/June 2, 2020–June 1, 2022	(Sisk et al., 2018)
Montelukast 	Cysteinyl leukotriene receptor 1 (Cysltr1) antagonist	Asthma and liver injury, reduce cardiac damage	Anti-inflammatory, reducing production of cytokine	NCT04714515 (Phase 3) NCT04389411 (Phase 3) NCT04695704 (Phase 3) NCT04718285 (Phase 2)	Phase 3/NCT04714515/completed/February 20, 2020–March 30, 2020	(Bozek & Winterstein, 2020; Fidan & Aydoğdu, 2020)

TABLE 3 (Continued)

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
Losmapimod 	p38 MAPK inhibitor	Not yet approved	Reduce the acute exaggerated pro-inflammatory responses	NCT04511819 (Phase 3)	Phase 3/NCT04511819/active, not recruiting/August 28, 2020–June 2021	(Clinical trial ID: NCT04511819, n.d.)
Tradipitant 	Neurokinin-1 (NK-1) antagonist	Eczema, pruritus, gastroparesis, chronic pruritus, and atopic dermatitis	NK-1 antagonist involved in neuroinflammatory processes	NCT04326426 (Phase 3)	Phase 3/NCT04326426/enrolling by invitation/April 13, 2020–August 1, 2020	(Clinical trial ID: NCT04326426, n.d.)
Ifenprodil (NP-120) 	Noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist	Posttraumatic stress disorders	NDMA receptor-type subunit 2B antagonist and the subunit receptor mainly expressed on T cells and neutrophils	NCT04382924 (Phase 3)	Phase 3/NCT04382924/active, not recruiting/August 5, 2020–January 2022	(Clinical trial ID: NCT04382924, n.d.)
Prednisone 	Synthetic corticosteroid agent, upregulating natriuretic peptide receptor type A	Comparative study, immunosuppressive agents, inflammatory bowel disease, multiple sclerosis	Agonist of glucocorticosteroid, blocking inflammatory and immune responses.	NCT04534478 (Phase 4) NCT04344288 (Phase 2)	Phase 4/NCT04534478//not yet recruiting/September 7, 2020–May 2, 2021	(Herman et al., 2020)
Hydrocortisone 	Human endogenous metabolite, steroid hormone or glucocorticoid secreted by the adrenal cortex	Coronary artery disease, healthy, septic shock, asthma	Agonist of glucocorticosteroid, blocking inflammatory and immune responses.	NCT04348305 (Phase 3) NCT02735707 (Phase 4) NCT02517489 (Phase 3) NCT04599959 (not applicable) NCT04563676 (not applicable)	Phase 4/NCT02735707/recruiting/April 11, 2016–December 2021	(Copin et al., 2020; Petersen et al., 2020)
Dexamethasone 	Glucocorticoid receptor agonist	Cervical radiculopathy, cancer, inflammatory response, hip fracture, pain	Agonist of glucocorticosteroid, reducing CD11b, CD18, and CD62L	Approximately 31 clinical trials, some of the examples are: NCT04834375 (Phase 4) NCT04603729 (Phase 3) NCT04499313 (Phase 3) NCT04325061 (Phase 4) NCT04325061 (Phase 4) NCT04347980 (Phase 3) NCT04563494 (Phase 4) NCT03170882 (Phase 2)	Phase 4/NCT04834375/recruiting/March 19, 2021–March 19, 2022	(Horby et al., 2021)

(Continues)

TABLE 3 (Continued)

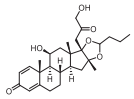
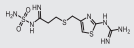
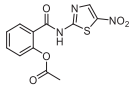
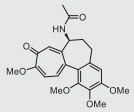
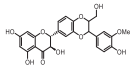
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/ start–(estimated)end dates	References
Budesonide 	Orally active glucocorticoid receptor agonist	Asthma	Glucocorticoid receptor agonist, Suppress the immune reaction locally in the respiratory system.	NCT04331470 (Phase 3) NCT04374474 (Phase 4) NCT04361474 (Phase 3)	Phase 4/NCT04374474/ active, not recruiting/ May 18, 2020–November 24, 2020	(De León-Rendón et al., 2020)
Famotidine 	Competitive histamine H2-receptor antagonist	Peptic ulcer, HIV infections, aspirin, dyspepsia, stomach ulcer, heartburn	Anti-inflammatory action	NCT04836806 (Phase 4) NCT04504240 (Phase 3) NCT04545008 (Phase 1) NCT04565392 (Phase 4) NCT04724720 (Phase 2) NCT04370262 (Phase 3) NCT04389567 (not applicable)	Phase 4/NCT04565392/ not yet recruiting/May 1, 2021–November 1, 2021	(Ennis & Tiligada, 2021)
Nitazoxanide 	Antiprotozoal agent	Irritable bowel syndrome, hepatitis C, diabetes mellitus type 2	Control excessive inflammatory immune responses	Approximately 24 clinical trials, some of the examples are: NCT04406246 (Phase 4) NCT04552483 (Phase 2) NCT04498936 (Phase 4) NCT04463264 (Phase 3) NCT04486313 (Phase 3) NCT04532931 (Phase 2) NCT04563208 (Phase 2)	Phase 4/NCT04498936/ completed/July 15, 2020–October 30, 2020	(Kelleni, 2020; Mahmoud et al., 2020; Pepperrell et al., 2020)
Colchicine 	Tubulin inhibitor and microtubule disrupting agent	Myocardial infarction, intercritical gout	Anti-inflammatory effects, an inhibitor of NLRP3 inflammasomes and mitigating interleukin activation.	Approximately 27 clinical trials, some of the examples are: NCT04818489 (Phase 4) NCT04392141 (Phase 2) NCT04416334 (Phase 3) NCT04472611 (Phase 3) NCT04322565 (Phase 2) NCT04724629 (Phase 3) NCT04492358 (Phase 3)	Phase 4/NCT04818489/ recruiting/March 25, 2021–May 25, 2021	(Deftereos et al., 2020; Nasiripour & Zamani, 2020)
Silymarin 	p38 MAPK pathway inhibitor	Non-alcoholic fatty liver disease, metastatic colorectal cancer, hepatitis	Anti-inflammatory and anti-oxidant effects	NCT04394208 (Phase 3) NCT04816682 (Phase 4)	Phase 4/NCT04816682/ recruiting/March 17, 2021–June 30, 2021	(Clinical trial ID: NCT04394208, n.d.)
Methylprednisolone						

TABLE 3 (Continued)

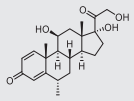
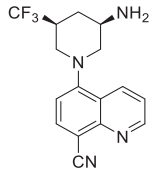
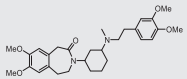
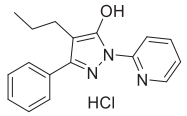
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated)end dates	References
	Synthetic corticosteroid, anti-inflammatory and immunomodulating properties	COPD, purpura, schoenlein-henoch, postoperative pain, drug interaction potentiation, et al.	Anti-inflammatory, decreasing level of IL-6, ACE2 activation	Approximately 15 clinical trials, some of the examples are: NCT04499313 (Phase 3) NCT04485429 (Phase 3) NCT04603729 (Phase 3) NCT04826588 (Phase 3) NCT03708718 (Phase 2) NCT04780581 (Phase 4) NCT04765371 (Phase 3)	Phase 4/NCT04780581/recruiting/February 1, 2021–December 1, 2021	(Edalatifard et al., 2020; Liu, Zheng, Huang, Shan, & Huang, 2020)
Enpatoran (M5049) 	Dual TLR7/8 inhibitor	Systemic lupus erythematosus, Coronavirus Disease 2019	Blocks the activation of toll-like receptor (TLR) 7 and TLR8, reduction in the inflammatory response	NCT04448756 (Phase 2)	Phase 2/NCT04448756/Active, not recruiting/June 26, 2020–August 22, 2021	(Clinical trial ID: NCT04448756, n.d.)
EC-18 	Anti-inflammation	Stomatitis, chemotherapy-Induced neutropenia, febrile neutropenia	Anti-inflammatory, prevention of COVID-19 infection to severe pneumonea or ARDS	NCT04500132 (Phase 2) NCT04569227 (Phase 2)	Phase 2/NCT04569227/recruiting/September 29, 2020–September 2021	(Clinical trial ID: NCT04569227, n.d.)
APX-115 (Ewha-18,278) 	pan NADPH oxidase (Nox) inhibitor	Healthy, diabetic nephropathies	NADPH-dependent generation of superoxide and secondary reactive oxygen species (ROS). ROS are often generated during virus infection, thus promoting apoptosis, lung injury, and inflammation/allergy.	NCT04880109 (Phase 2)	Phase 2/NCT04880109/not yet recruiting/May 10, 2021–February 2022	(Clinical trial ID: NCT04880109, n.d.)

TABLE 4 Modulating immune system

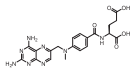
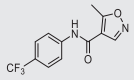
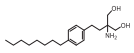
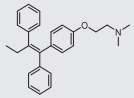
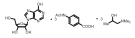
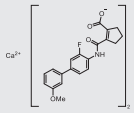
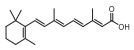
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/ status/start–(estimated) end dates	References
Methotrexate 	Enzyme dihydrofolate reductase inhibitor, an immunosuppressant and antineoplastic agent	Rheumatoid arthritis, ophthalmopathy, thyroid-associated, psoriatic arthritis	Immunomodulatory agent, preventing excessive immunereaction	NCT04352465 (Phase 2) NCT04610567 (Phase 2)	Phase 2/NCT04610567/ recruiting/October 27, 2020–March 15, 2021	(Abuo-Rahma et al., 2020)
Leflunomide 	Dihydroorotate dehydrogenase inhibitor	Rheumatoid arthritis, psoriatic arthritis, immunoglobulin G4 related sclerosing disease, juvenile idiopathic arthritis	Immunomodulatory agent, preventing excessive immunereaction	NCT04532372 (Phase 2) NCT04361214 (Phase 1)	Phase 2/NCT04532372/ recruiting/January 7, 2021–September 18, 2022	(Abuo-Rahma et al., 2020)
Fingolimod 	Sphingosine 1-phosphate (S1P) antagonist, pak1 activator, a immunosuppressant	Multiple sclerosis, relapsing–remitting	Immune modulator, S1P1 receptors antagonist	NCT04280588 (Phase 2)	Phase 2/NCT04280588/ withdrawn (no participants enrolled)/ February 22, 2020–July 1, 2020	(Barzegar et al., 2020; Pelletier & Hafler, 2012)
Tamoxifen 	Selective estrogen receptor modulator (SERM), Hsp90 activator	Breast cancer, infertility, menorrhagia, endometrium	Modulation of NK cells activity and reduce viral replication, through reducing PGE2 production	NCT04389580 (Phase 2) NCT04568096 (Phase 2)	Phase 2/NCT04568096/ not yet recruiting/ November 2020–December 2020	(Almosawey et al., 2020; Hamouda Elgarhy, 2020)
Isoprinosine 	Immunostimulant	Immunostimulant	Immunostimulant	NCT04360122 (Phase 3) NCT04383717 (Phase 3)	Phase 3/NCT04360122/ not yet recruiting/May 20, 2020–November 1, 2020	(Clinical trial ID: NCT04360122, n.d.; Kumar et al., 2020)
IMU-838 (vidofludimus calcium) 	Immunomodulatory agent, DHODH inhibitor, inhibiting IL-17 secreting	Not yet approved	Selective immunomodulatory effect against highly activated immune cells	NCT04516915 (Phase 2) NCT04379271 (Phase 3)	Phase 3/NCT04379271/ recruiting/June 11, 2020–September 2020	(Clinical trial ID: NCT04379271, n.d.; Immunic Therapeutics website)
All-trans retinoic acid 	Neutrophil elastase inhibitor, RAR nuclear receptor agonist	Acute promyelocytic leukemia	Enhance neutralizing antibodies	NCT04396067 (Phase 2) NCT04568096 (Phase 2) NCT04730895 (Phase 2) NCT04578236 (Phase 2) NCT04353180 (Phase 3)	Phase 3/NCT04353180/ not yet recruiting/April 2021–June 2021	(Clinical trial ID: NCT04396067, n.d.)

TABLE 4 (Continued)

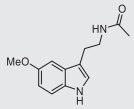
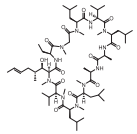
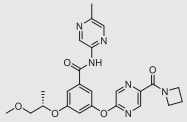
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/ status/start–(estimated) end dates	References
Melatonin 	Selective ATF-6 inhibitor	Parkinson's disease, infertility, immediate dental implant, immediate dental implant, postoperative pain, anxiety, acute ischemic stroke	Modulate the immune response and neuroinflammation	Approximately 8 clinical trials, some of the examples are: NCT04474483 (Phase 2) NCT04470297 (Phase 2) NCT04568863 (Phase 2) NCT04353128 (Phase 3) NCT04409522 (not applicable) NCT04531748 (Phase 2) NCT04530539 (not applicable)	Phase 3/NCT04353128/ recruiting/April 20, 2020–October 2020	(Bahrampour Juybari et al., 2020)
Cyclosporinea (Synonyms: cyclosporine; Ciclosporin) 	Immunosuppressant, inhibiting CD11a/ CD18 adhesion	End-stage renal disease, renal function and chronic allograft vasculopathy, kidney transplantation, etc	Immunomodulatory agent acting on T cells	NCT04540926 (Phase 2) NCT04412785 (Phase 1) NCT04492891 (Phase 2) NCT04392531 (Phase 4) NCT04451239 (not applicable)	Phase 4/NCT04392531/ recruiting/April 16, 2020–March 2021	(Rudnicka et al., 2020; Tian et al., 2020)
AZD1656 	Glucokinase activator	Type II diabetes	Activate the migration of T regulatory cells to sites of inflammation	NCT04516759 (Phase 2)	Phase 2/NCT04516759/ completed/August 18, 2020–April 25, 2021	(Clinical trial ID: NCT04516759, n.d.)

TABLE 5 Anticoagulant therapy

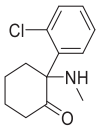
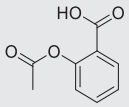
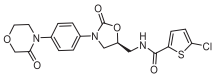
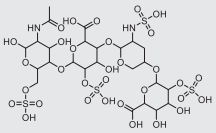
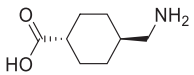
Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
Ketamine 	Antagonist of *N*-methyl D-aspartate receptor	Anesthesia, pain relief, sedation, and memory loss	Anesthesia, pain relief	NCT04365985 (Phase 2)	Phase 2/NCT04365985/recruiting/April 29, 2020–May 2021	(Suri & Sindwani, 2020)
Aspirin 	Non-selective and irreversible COX-1 and COX-2 inhibitor	Common cold, healthy, acute coronary syndrome, et al.	Interfering with normal platelet aggregation, COX-1 inhibitor	NCT04365309 (Phase 3) NCT04363840 (Phase 2) NCT04343001 (Phase 3) NCT04410328 (Phase 3) NCT04324463 (Phase 3) NCT04808895 (Phase 3)	Phase 3/NCT04410328/recruiting/October 21, 2020–March 15, 2021	(Clinical trial ID: NCT04365309, n.d.; Bianconi et al., 2020)
Rivaroxaban 	Selective and direct Factor Xa (FXa) inhibitor	Atherosclerosis, mitral valve stenosis|atrial fibrillation	Adequate antithrombotic therapy	NCT04504032 (Phase 2) NCT04508023 (Phase 3) NCT0441604 (Phase 3) NCT04324463 (Phase 3)	Phase 3/NCT04324463/recruiting/April 21, 2020–December 31, 2020	(Di Tano et al., 2020)
Enoxaparin 	Anticoagulant medication	Pulmonary embolism (PE), deep vein thrombosis (DVT)	Adequate antithrombotic therapy	Approximately 8 clinical trials, some of the examples are: NCT04427098 (Phase 2) NCT04366960 (Phase 3) NCT04400799 (Phase 3) NCT04540926 (Phase 2) NCT04492254 (Phase 3) NCT04408235 (Phase 3) NCT04640181 (Phase 2)	Phase 3/NCT04400799/recruiting/June 15, 2020–March 14, 2021	(Drago et al., 2020)
Tranexamic acid 	Antifibrinolytic agent, blocking lysine-binding sites of plasmin and elastase-derived plasminogen fragments	Prevent blood loss in surgical procedure	Antifibrinolytic agent, that competitively inhibits activation of plasminogen to plasmin, an enzyme that degrades fibrin clots.	NCT04338126 (Phase 2) NCT04550338 (Phase 3) NCT04338074 (Phase 2)	Phase 3/NCT04550338/not yet recruiting/December 1, 2020–December 31, 2022	(Ogawa & Asakura, 2020)

TABLE 5 (Continued)

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/ status/start–(estimated) end dates	References
Edoxaban	FXa inhibitor	Atrial fibrillation (AF), venous thrombosis| neoplasms| anticoagulant, ischemic stroke, blood coagulation disorder, coronary artery disease	Anticoagulant activity of direct FXa inhibitors	NCT04516941 (Phase 3) NCT04542408 (Phase 3)	Phase 3/NCT04542408/ recruiting/November 12, 2020–May 31, 2021	(Al-Horani, 2020)
Apixaban	FXa inhibitor	Deep vein thrombosis| pulmonary embolism, diabetes, venous thromboembolism, etc.	Anticoagulant properties	NCT04512079 (Phase 4)	Phase 4/NCT04512079/ recruiting/September 8, 2020–March 2021	(Al-Horani, 2020)

or phase I. There are 46 agents in approximately 294 trials in total (Figure 4). Among them, 10 agents aim at blocking virus-cell membrane fusion and entry, 11 small molecules inhibit viral replication, 16 small molecules address CSS, four small molecules modulate the innate immune system, four small molecules are used as anticoagulant therapy, and one small molecule is from the category of antioxidant supplement.

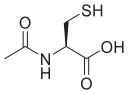
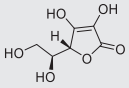
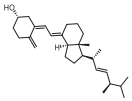
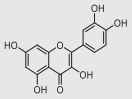
Of the drugs blocking virus-cell membrane fusion and entry, there are four agents (losartan, isotretinoin, lactoferrin, and propranolol) interacting with ACE2, one agent (linagliptin) inhibiting DPP4, two compounds (verapamil, chlorpromazine) targeting on ion channel, one agent (dapagliflozin) reducing the viral load, and two agents (nafamostat and bicalutamide) blocking TMPRSS2. Of the drugs targeting virus replication, there are two reverse transcriptase inhibitors (emtricitabine and tenofovir alafenamide), five RNA-targeting agents (remdesivir, ciclesonide, EIDD-2801, AT-527 and ribavirin), one phosphodiesterase inhibitor (dipyridamole), one Impα/β1-mediated nuclear import inhibitor (ivermectin), one M^{pro} inhibitor (rosuvastatin) and one $3CL^{pro}$ inhibitor (PF-07321332). In the category of the drugs addressing CSS, there are three JAK inhibitors (ruxolitinib, baricitinib, and niclosamide), five interleukin modulators (levamisole, opaganib, anakinra, atorvastatin, and PTC299), two modulators targeting inflammatory cytokines release (amiodarone, and VERU-111), one inflammatory inhibitor (escin), one tyrosine kinase inhibitor (imatinib), one cysteinyl leukotriene (cysLT) receptor antagonist (montelukast), one p38 MAPK pathway inhibitors (losmapimod), one neurokinin-1 (NK-1) antagonist (tradipitant), and one N-methyl-d-aspartate (NMDA) receptor antagonist (ifenprodil). There are four agents (isoprinosine, IMU-838, all-trans retinoic acid, and melatonin) modulating the innate immune system and four agents (aspirin, enoxaparin, tranexamic acid, and edoxaban) used as anticoagulant therapy. There is only one agent (N-acetylcysteine) belonging to antioxidant supplement sub-class. Dipyridamole does not inhibit the SARS-CoV-2 main protease. Its antiviral activity might involve other mechanisms (Ma & Wang, 2021).

3.3 | Phase IV clinical candidates

Phase IV clinical trial is conducted by the applicant after the new drug has already been approved by FDA. The main objective in this phase is to assess the long-term benefits and risks of using the drug in general population groups or in special population groups. In category, there are 34 agents in approximately 386 trials (Figure 4). Among them, 10 agents aim at blocking virus-cell membrane fusion and entry, 7 small molecules inhibit viral replication, 11 small molecules address CSS, 1 small molecule modulates immune system. In addition, there are currently 2 agents used as anticoagulant therapy and 3 agents identified as antioxidant supplements.

Of those drugs blocking virus-cell membrane fusion and entry, three agents are TMPRSS2 inhibitors (bromhexine, camostat, and spironolactone), three agents (valsartan, arbidol and canrenoate potassium) interact with ACE2, one agent (azithromycin) interfers with S protein/CD147 interaction, one agent (tetrandrine) inhibits voltage-gated Ca^{2+} current (ICa) and Ca^{2+}-activated K^{+} current, one agent

TABLE 6 Antioxidant supplement

Drug name and structure	Original mechanism	FDA-approved indication(s)	Possible mechanism for anti-COVID-19	Clinical trials ID (stage)	The highest anti-COVID-19 phase/ID/status/start–(estimated) end dates	References
N-acetylcysteine 	ROS inhibitor, mucolytic agent reducing thickness of mucus,	Gastric mucosal lesion, polycystic ovary syndrome, etc.	Antioxidant precursor to glutathione (γ-glutamylcysteinylglycine), mucolytic agent	NCT04374461 (Phase 2) NCT04792021 (Phase 3) NCT04545008 (Phase 1) NCT04458298 (Phase 2) NCT04419025 (Phase 2) NCT04703036 (Phase 1) NCT04755972 (not applicable)	Phase 3/NCT04792021/recruiting/March 9, 2021–June 2021	(Andreou et al., 2020; Poe & Corn, 2020)
Vitamin C (ascorbic acid) 	Effective reducing agent and donor antioxidant	Scurvy, upper respiratory tract infections, reduces the risk of lung cancer.	Upregulating phagocytes and lymphocytes activity, modulating immune system	Approximately 24 clinical trials, some of the examples are: NCT04401150 (Phase 3) NCT04468139 (Phase 4) NCT04363216 (Phase 2) NCT04264533 (Phase 2) NCT02735707 (Phase 4) NCT04780061 (Phase 3) NCT04828538 (not applicable)	Phase 4/NCT02735707/recruiting/11, 2016–December 2021	(Baladia et al., 2020)
Vitamin D3 (Cholecalciferol) 	Inducing cell differentiation and preventing the proliferation of cancer cells	Epilepsy, healthy, vitamin D deficiency, osteoporosis	Protect respiratory infections	Approximately 14 clinical trials, some of the examples are: NCT04344041 (Phase 3) NCT04536298 (Phase 3) NCT04411446 (Phase 4) NCT04482673 (Phase 4) NCT04407286 (Phase 1) NCT04386850 (Phase 3) NCT04395768 (Phase 2)	Phase 4/NCT04482673/recruiting/July 31, 2020–December 31, 2021	(Weir et al., 2020)
Quercetin 	Stimulator of recombinant SIRT1, PI3K inhibitor	Menopause related conditions, mountain sickness, flushing	Prophylactic, antioxidant	NCT04853199 (early Phase 1) NCT04578158 (Phase 2) NCT04468139 (Phase 4) NCT04536090 (Phase 2) NCT04377789 (not applicable)	Phase 4/NCT04468139/recruiting/June 20, 2020–July 20, 2020	(Diniz et al., 2020)

(doxycycline) inhibits the E2 envelope glycoprotein involved in virus entry, and one binder of surface proteins of enveloped viruses (povidone-iodine). Of those drugs targeting virus replication, two agents (ritonavir and lopinavir) inhibit the coronaviral $3CL^{pro}$ protease, one compound (oseltamivir) blocks virus-release, three agents (favipiravir, ledipasvir, and sofosbuvir) target RdRp, and 1 agent (darunavir) inhibits HIV protease. Of those drugs addressing CSS, there are four glucocorticosteroid agonists (prednisone, hydrocortisone, dexamethasone, and budesonide), one competitive histamine H2-receptor antagonist (famotidine), 1 antiprotozoal agent (nitazoxanide), four interleukin modulators (colchicine, methylprednisolone, deferoxamine and cefditoren), one mTOR inhibitor (sirolimus), and one p38 MAPK pathway inhibitor (silymarin). In addition, there is 1 immunosuppressive drug (cyclosporine A) which could modulate the immune system. Apixaban and rivaroxaban belong to anticoagulant therapy. vitamin C, vitamin D3, and quercetin are used as antioxidant supplements.

4 | CONCLUSIONS AND OUTLOOK

At present, several COVID-19 vaccines have been approved for clinical use in many countries worldwide. The vaccine approach aims at the preventive management, which will increase antibody level against the virus and reduce the probability for viral infection in a certain extend. However, the vaccine approach is not suitable for those people already infected with the virus. As SARS-CoV-2 continues to worsen global health conditions and economic situations, the number of people infected with this virus continues climbing. Therefore, seeking effective medicines to treat COVID-19 is urgently needed. This review gathers all small molecules currently in active clinical trials, categorizes them into six sub-classes, and analyzes possible therapeutical treatments and their underlying mechanisms against COVID-19. Among all of the clinical trials, the antioxidant supplement sub-class accounts for the smallest percentile, while addressing CSS sub-class accounts for the largest percentile. Blocking virus-cell membrane fusion/entry and inhibiting virus replication are two sub-classes next to addressing CSS sub-class, and together these two sub-classes account for 42% of all clinical agents. The agents from the above two sub-classes are all belonged to repurposing drugs. Some preliminary results from the studies using repurposing antiviral drugs in clinic have demonstrated the efficacy in blocking virus-cell membrane fusion and entry or inhibiting virus replication. In addition, given the hyper-inflammatory response mediated by addressing CSS agents or modulating immune system agents are expected to work in preventing body deterioration. Finally, Anticoagulant therapy and antioxidant supplement are also playing important roles in combating COVID-19. However, their effectiveness, safety/side-effects remain to be watched. In summary, repurposing antiviral and anticancer drugs for treatment of COVID-19 show promising. The races of small molecules for the treatment of COVID-19 are intense, and is likely to show some promise in the future.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Suwen Hu https://orcid.org/0000-0002-3991-645X
Songwei Jiang https://orcid.org/0000-0003-2698-7125
Xiang Qi https://orcid.org/0000-0002-6408-2696
Renren Bai https://orcid.org/0000-0002-3511-5794
Xiang-Yang Ye https://orcid.org/0000-0003-3739-0930
Tian Xie https://orcid.org/0000-0001-7066-1443

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