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REVIEW

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Revisiting potential druggable targets against SARS-CoV-2 and repurposing therapeutics under preclinical study and clinical trials: A comprehensive review

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Abstract

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of the most contagious diseases in human history that has already affected millions of lives worldwide. To date, no vaccines or effective therapeutics have been discovered yet that may successfully treat COVID-19 patients or contain the transmission of the virus. Scientific communities across the globe responded rapidly and have been working relentlessly to develop drugs and vaccines, which may require considerable time. In this uncertainty, repurposing the existing antiviral drugs could be the best strategy to speed up the discovery of effective therapeutics against SARS-CoV-2. Moreover, drug repurposing may leave some vital information on druggable targets that could be capitalized in target-based drug discovery. Information on possible drug targets and the progress on therapeutic and vaccine development also needs to be updated. In this review, we revisited the druggable targets that may hold promise in the development of the anti-SARS-CoV-2 agent. Progresses on the development of potential therapeutics and vaccines that are under the preclinical studies and clinical trials have been highlighted. We anticipate that this review will provide valuable information that would help to accelerate the development of therapeutics and vaccines against SARS-CoV-2 infection.

KEYWORDS

clinical trial, COVID-19, drug repurposing, drug targets, therapeutics, vaccines

1 | INTRODUCTION

COVID-19 that was first surfaced in China has already emerged as a global pandemic with a total of 10,421,869 cases, including 508,422 deaths, as of June 30, 2020 (worldometers.info/coronavirus/). COVID-19 and the similar previous outbreaks such as SARS and Middle East Respiratory Syndrome (MERS) share common signs and symptoms, such as sore throat, persistent high fever, pneumonia with common pathologies, such as immune dysfunction, and multi-organ failure (Andersen, Rambaut, Lipkin, Holmes, & Garry, 2020; Forster, Forster, Renfrew, & Forster, 2020). Like other coronaviruses, SARS-CoV-2 possesses several structural and nonstructural proteins that are implicated in crucial cell functions (Ashour, Elkhatib, Rahman, & Elshabrawy, 2020). Of the structural proteins, spike glycoproteins facilitate the attachment of the virus to their host cells. The helicase, main protease (M^{pro}), papain-like protease (PLpro), RNA dependent RNA polymerase (RdRp) are among the nonstructural proteins that are critical for viral replication (Forster et al., 2020; Siu et al., 2008). With their significant roles in the viral life cycle, these proteins present promising pharmacological targets for developing potential therapeutics against SARS-CoV-2 infection.

Target-based drug discovery (TDD) is one of the most successful and efficient strategies to find the remedy of any disease. An estimated 70% of the first-class drugs approved by the United States Food and Drug Administration in between 1999 to 2013 were based on TDD (Croston, 2017; Eder, Sedrani, & Wiesmann, 2014). TDD is not only restricted to the discovery of small molecules as drug targets but also extends to protein biologics, genetic materials, and antibodies. The advantages of target-based strategies over phenotypic approaches include high throughput, convenient, and less expensive (Croston, 2017; Zheng, Thorne, & McKew, 2013). Molecular pharmacology, biochemistry, genomics, computational modeling, structural biology, system biology, and mutational analysis are usually employed to carry out the TDD for the complete understanding of any drug candidate and also ensuring the effective therapeutics for upcoming days (Croston, 2017).

Although research communities have responded rapidly, still there is no vaccine or effective therapeutics for COVID-19 (Harrison, 2020). Some of the existing antiviral drugs from other viral diseases, including Remdesivir, are being considered as repurposing medicine to treat COVID-19 patients, which resulted in mixed outcomes (Gautret et al., 2020; Molina et al., 2020). It is, therefore, crucial to focus on alternative rational strategies for the development of urgent therapeutics to control the ongoing pandemic. Developing new therapeutic drugs and vaccines requires a proper understanding of the disease, the immune response pattern after infection, and the pathogenesis of the virus. To accelerate this effort, we present a scoping review summarizing the potential drug targets and therapeutics under trials by critically analyzing all relevant published literature on this field. This review would provide concrete evidence concerning the drug targets, previous use of the drugs, and early findings of possible drug mechanisms. Moreover, our review would provide insightful evidence for future SARS-CoV-2 research and might support researchers to discover a potential remedy.

2 | STRUCTURE AND LIFE CYCLE OF BETACORONA VIRUS

SARS-CoV-2 is a member of the betacoronavirus genera and possesses 16 nonstructural proteins (NSP) and four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The N protein clamps the Ribonucleic acid (RNA) genome, whereas the S, E, and M proteins together shape the viral envelope, and the glycoprotein spikes render coronaviruses to form their unique crown-like appearance (Figure 1a; Anthony et al., 2017; Ashour et al., 2020). In addition to the knowledge on the structural makeup, a critical understanding of the life cycle and pathogenesis of SARS-CoV, in general, is essential to discover potential vaccines and therapeutics to prevent and treat SARS-CoV and SARS-like coronavirus (SL-CoV), including SARS-CoV-2 infections in the future. Crucial steps of SARS-CoV life cycle are, therefore, illustrated in Figure 1b and also highlighted below:

1. Receptor recognition is the first step of virus entry into the host cell that occurs by the recognition of the receptor by the spike protein of the virus. First, the receptor-binding domain (RBD) of S protein attaches with the host cell receptor, angiotensin-converting enzyme 2 (ACE2). S protein is then proteolytically cleaved by a type II transmembrane protease (TMPRSS2) resulting into two subunits called S1 and S2 where S2 is crucial for membrane fusion and virus entry (Glowacka et al., 2011; Holmes, 2003; Li, 2015; Li et al., 2006; Wan, Shang, Graham, Baric, & Li, 2020; Wong, Li, Moore, Choe, & Farzan, 2004). Splitting of the S protein by proteases is essential for the viral entry to the host cells in a pH-dependent manner (Simmons et al., 2004; Yang & Shen, 2020).
2. After uncoating, CoVs then release the RNA (5′ methylated cap and a 3′ polyadenylated tail) into the host cell cytoplasm for replication (Fehr & Perlman, 2015; Kim et al., 2020; Li, 2015).
3. Genomic RNA of CoV acts as an mRNA for translation of the replicase polyproteins 1a (pp1a) and 1ab (pp1ab) using the translation machinery of the host cell. Then the polyprotein is split into effector proteins by viral proteinases (3CLpro and PLpro), resulting in a number of NSPs including RdRp and helicase that form the replicase–transcriptase complex (Báez-Santos, St John, & Mesecar, 2015; Fehr & Perlman, 2015; Gorbalenya et al., 2020; Kim et al., 2020; Ratia et al., 2006; Sola, Almazán, Zúñiga, & Enjuanes, 2015).
4. RdRp and helicase localize to double-membrane vesicles and produce subgenomic RNA, from which other proteins such as structural proteins are produced by translation. At the same time, the full-length positive-strand RNA is synthesized as genomic RNA (Fehr & Perlman, 2015; C. J. Gordon et al., 2020; Sola et al., 2015; Kim et al., 2020).

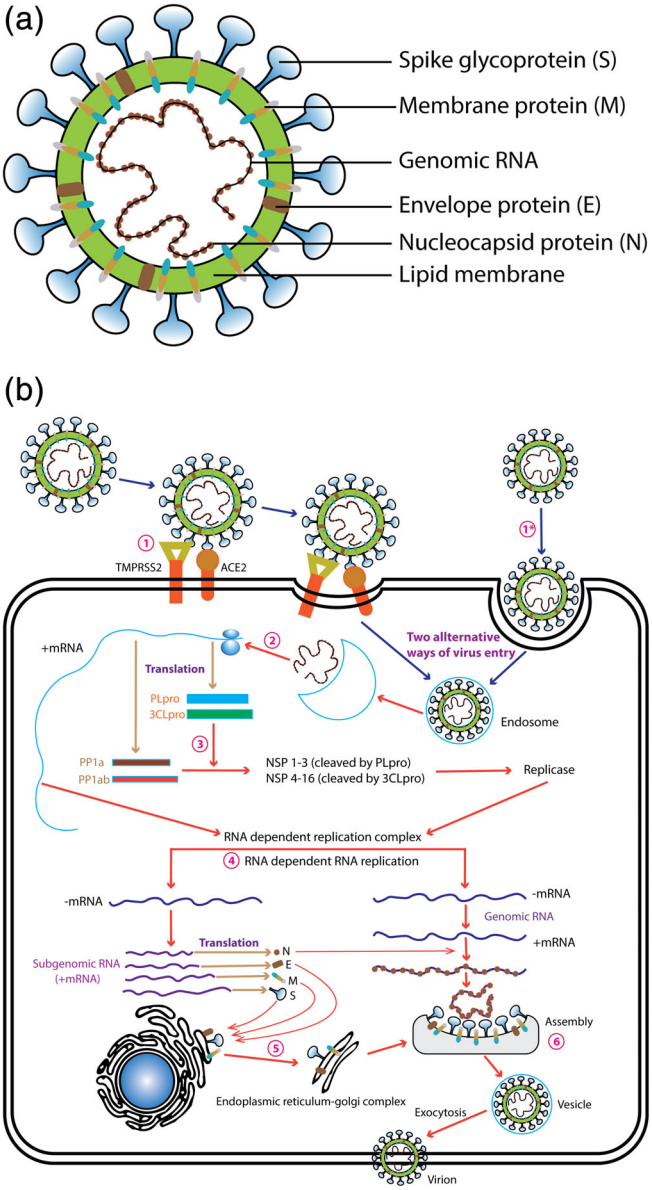

FIGURE 1 (a) A schematic diagram of the SARS-CoV-2 (modified from Du et al., 2009). S, Spike protein; E, envelope protein; single-stranded positive-sense viral RNA, and M, membrane protein are depicted. (b) A schematic diagram of the SARS-CoV-2 life cycle in a host cell (modified from Du et al., 2009). (1) Virus entry into the host cell via ACE2 or endocytosis, (2) Release of RNA from endosome, (3) Proteolytic cleavage of polyprotein, (4) synthesis of genomic and subgenomic RNA, (5) structural protein synthesis and maturation, and (6) Assembly of viral particles and mature viral particle. 3CLpro, chymotrypsin-like protease; ACE2, Angiotensin-converting enzyme 2; E, Envelope protein; M, membrane protein; N, nucleocapsid; PLpro, papain-like protease; S, Spike protein; TMPRSS2, Transmembrane protease, serine 2

5. NSP 3, 4, and 6 are responsible for anchoring the coronavirus replication and transcription complex through recruitment of intracellular Endoplasmic Reticulum (ER) membrane to form double-membrane vesicles (Fehr & Perlman, 2015; Sola et al., 2015; Stertz et al., 2007).
6. Viral nucleocapsids are assembled with genomic RNA and N protein in the cytoplasm, followed by budding into the lumen of the ERGIC (Endoplasmic Reticulum–Golgi Intermediate Compartment; Sola et al., 2015; Stertz et al., 2007).
7. The virions are then released from the cell through exocytosis (Sola et al., 2015; Stertz et al., 2007).

3 | POTENTIAL DRUGGABLE TARGETS FOR SARS-COV-2 INFECTION

To find a potential therapy for SARS-CoV-2, a concrete understanding of potential drug targets is essential. Herein, we revisited a comprehensive list of SARS-CoV-2-directed targets (M^{pro}, PLpro, RdRp, spike protein, helicase, envelop protein) and host-directed targets (ACE2, TMPRSS2, and immune system) that might hold promise for the development of potential therapy against SARS-CoV-2 infections (Figure 2).

3.1 | SARS-CoV-2-directed targets

3.1.1 | Non-structural protein targets

Main protease (M^{pro})

Two large overlapping replicase polyproteins (pp1a and pp1ab), encoded by two linked ribosomal frameshift, are hydrolyzed by an extensive proteolytic action of viral proteases (Fehr & Perlman, 2015; Graham, Sparks, Eckerle, Sims, & Denison, 2008; Pillaiyar, Manickam, Namasivayam, Hayashi, & Jung, 2016). One of the crucial viral proteases is the M^{pro}, also known as 3C-like proteinase or NSP5, which is a homodimeric cysteine protease belonging to the coronavirus polyprotein group (Fan et al., 2004). Automatic cleavage of polyproteins leads to the generation of M^{pro}, which cleaves the large polyprotein 1ab at 11 cleavage sites to generate NSPs. The identification of cleaving sequence at most sites is Leu-Gln↓(Ser, Ala, Gly) to release NSP4–NSP16 (Pillaiyar et al., 2016; Yang et al., 2005; Zhang, Penninger, Li, Zhong, & Slutsky, 2020). M^{pro} directly mediates the maturation of NSPs, which is critical for the initiation of the SARS-CoV-2 replication cycle and could, therefore, be a potential druggable target (Zhang, Wu, & Zhang, 2020). For instance, pyridone-containing α-ketoamides inhibited the M^{pro} activity showing early promise for the development of anti-viral drugs (Zhang et al., 2020). Moreover, more than a hundred PDB structures of SARS-CoV-2 M^{pro} have already been deposited at the RCSB database (https://www.rcsb.org/) and more are being added regularly. Here, most of the structures were elucidated by Cryo-electron microscopy, NMR or X-ray crystallography, or even the high-throughput network-based inhibitor screening or direct ligand-based study (Jin et al., 2020; Vuong et al., 2020). While ligand-based inhibitors screening leads to the determination of complexed crystal structure of SARS-CoV-2 M^{pro}, this approach aids in the structure-assisted drug design and high-throughput screening for potential

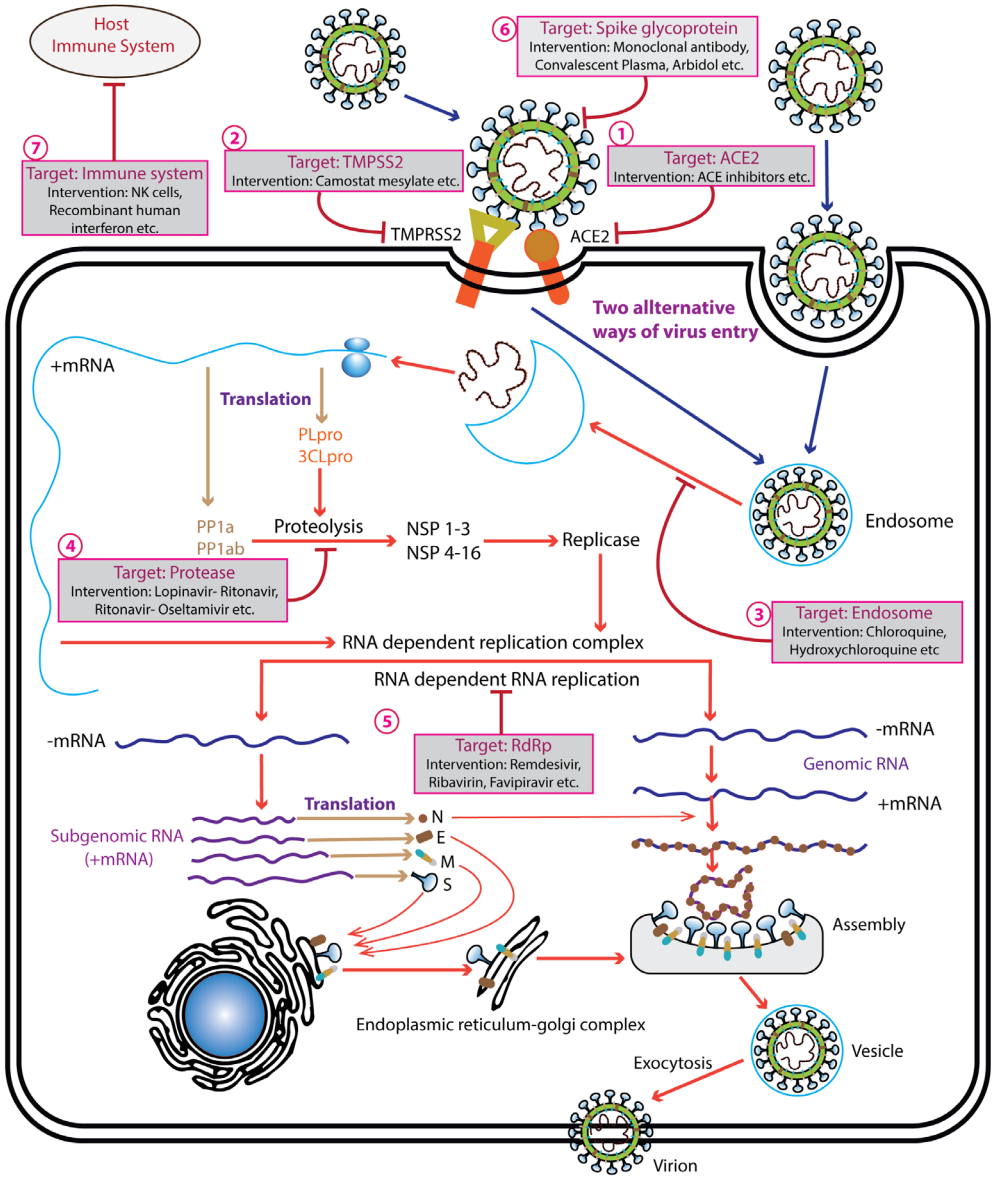

FIGURE 2 A schematic diagram indicating the potential drug targets and drugs on viral replication processes. (1) ACE2 and spike complex inhibitors: Azithromycin and Chloroquine, interrupt in ACE2 and S protein complex formation; (2) TMPRSS2 inhibitor: Camostat Mesylate blocks cleavage and activation of the S protein; (3) Targeting endosomes: chloroquine and its derivatives increase pH and inhibit viral RNA release from endosomes; (4) Targeting proteases: ASC09F, Oseltamivir, Ritonavir, Oseltamivir, Oseltamivir, Lopinavir inhibit proteases thereby inhibit viral replication; (5) Targeting RdRp: Favipiravir, Remdesivir, and Ribavirin block RdRp and cause premature termination of RNA synthesis; (6) Targeting Spike: Monoclonal antibody, Arbidol, and convalescent plasma block spike protein which results into binding interruption with ACE2; (7) Targeting host immune system: activated host immune system can block virus propagation as well as recover body from the adverse effects posed by viruses

inhibitors (Jin et al., 2020). The inhibitors targeting SARS-CoV-2 M^{pro} are virus-specific and, therefore, will not interfere with host cell proteases (Bzówka et al., 2020).

Papain like protease

Proteolytic enzymes play an essential role in viral replication, and hence could be the target of choice for the development of effective therapy against viral infections. PLpro, also termed as NSP 3, had been extensively studied for coronaviruses (Báez-Santos et al., 2015; Lei et al., 2014; Ratia et al., 2006) and the efficacy of PLpro inhibitors such as chloroquine and formoterol have been investigated recently for the treatment of COVID-19 (Rimanshee, Amit, Vishal, & Mukesh, 2020; Wu et al., 2020). PLpro cleaves the N-terminal part of the polyproteins producing mature NSP1, NSP2, and NSP3, a process that is crucial for viral replication. The cleavage specificity of PLpro corresponds to the pattern (R/K)L(R/K)GG↓X. Moreover, the enzyme acts as deubiquitinase that removes (poly) ubiquitin units from proteins tagged with them (Barretto et al., 2005; Lindner et al., 2005). The deubiquitinase activity of PLpro interferes nuclear import of interferon-regulatory factor 3 and the phosphorylation, thereby preventing the production of type-I interferons, such as IFN-α and IFN-β by the infected host cell and also helps in peptide substrate recognition (Barretto et al., 2005; Clementz et al., 2010; Devaraj et al., 2007; Frieman, Ratia, Johnston, Mesecar, & Baric, 2009; Ratia et al., 2006). Additionally, PLpro clears ubiquitin and interferon-sensitive gene 15 from host-cell proteins, a mechanism that aids coronaviruses to evade host innate immune responses. Finally, the PLpro has been reported to interfere with the nuclear factor κB pathway, which further assists SARS-CoV to counteract the innate immune response of the infected cells (Clementz et al., 2010). Therefore, pharmacological targeting of PLpro by developing PLpro inhibitors might constitute a potential therapeutic strategy that would be advantageous in not only preventing viral replication but also ensuring the normal regulation of signal networks in the infected cells.

RNA dependent RNA polymerase

RdRp, also termed as NSP 12, is a pivotal enzyme of RNA viruses, including coronavirus, that catalyzes the replication of RNA from an RNA template, probably with the assistance of NSP7 and NSP8 as co-factors (Guo, Huang, Lin, & Lv, 2020; Kirchdoerfer & Ward, 2019; Subissi et al., 2014; Venkataraman, Prasad, & Selvarajan, 2018). A protein complex consisting of NSP 7, NSP 8, and NSP 12 of SARS-CoV-2 is related to that of SARS-CoV with a root-mean-square deviation value of 0.82 for 1,078 Cα atoms (Gao et al., 2020). RdRp protein of SARS-CoV-2 and SARS-CoV share 96% amino acid sequence identity and 82% sequence identity at their genomic RNA level (Morse, Lalonde, Xu, & Liu, 2020). The RdRp of SARS-CoV-2 contains a large and deep groove as an active site for the polymerization of RNA. Residues that show variations between the SARS-CoV-2 and SARS-CoV RdRps are mostly distal to this active site. This high sequence conservation and structural homogeneity of RdRp in coronaviruses suggest that nucleotide analogs developed for the SARS-CoV RdRp are likely to be effective against the SARS-CoV-2 RdRp (Morse et al., 2020). Previously published literature provides convincing evidence that RdRp could be a druggable target for the development of potent therapy against SARS-CoV-2 infection (Kandeel, Ibrahim, Fayez, & Al-Nazawi, 2020; Lung et al., 2020), which includes nucleotide analog targeting RdRp (Deval, Jin, Chuang, & Kao, 2017; Gordon et al., 2020; Stephen & Lin, 2018; Tchesnokov, Feng, Porter, & Götte, 2019). Remdesivir (GS-5734), a prodrug and adenosine analog, can be incorporated into nascent viral RNA, and subsequently inhibit the RdRp (Siegel et al., 2017). Furthermore, Remdesivir showed high considerable efficacy in controlling SARS-CoV-2 infection in a recent in vitro study (Wang et al., 2020). β-D-N4-hydroxycytidine, a ribonucleoside analog, also inhibits SARS-CoV-2 replication as evidenced by reducing viral genomic RNA (Sheahan et al., 2020).

Helicase

SARS-CoV helicase (NSP13) is one of the 16 NSPs generated after the proteolytic cleavage of two large polyproteins (pp1a and pp1ab). This helicase, being one of the components of the replicase–transcriptase complex, plays significant roles in the life cycle of SARS-CoV (Marra et al., 2003; Subissi et al., 2014), which constitutes the basis of targeting this enzyme for the development of potential antiviral agent. Helicases are motor proteins that unwind double-stranded nucleic acids into two single-strands during replication (Adedeji et al., 2014; Shum & Tanner, 2008). Moreover, NSP13 N-terminus carries 26 cysteines where 14 positions are highly conserved and assumed to possess a binuclear Zn^{2+}-binding cluster (Seybert et al., 2005). Importantly, an antiviral compound Bananin, which is an adamantane derivative, has been reported to inhibit helicase activities, thereby preventing the replication of SARS-CoV (; Tanner et al., 2003) and can also be evaluated against SARS-CoV-2.

3.1.2 | Structural protein target

Spike glycoprotein

The spike protein (S), giving a crown-like appearance to virion surface, render diverse molecular actions that usually mediates the coronavirus entry into the specific host (Belouzard, Chu, & Whittaker, 2009). The spike protein of SARS-CoV and SARS-CoV-2 shares ~76% amino acid identity; however, SARS-CoV-2 S protein binds 10 times more strongly than SARS-CoV S protein to their common host cell receptor (Du et al., 2009; Hoffmann et al., 2020; Li, 2016; Tortorici et al., 2019; Wrapp et al., 2020). Heavily glycosylated, the spike protein possesses a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail (Li, 2016). The ectodomain consists of a receptor-binding subunit (S1) and a membrane-fusion subunit (S2; Broer, Boson, Spaan, Cosset, & Corver, 2006; Li, 2016). During virus entry, the S1 subunit recognizes and interacts to host receptors, and further conformational changes in the S2 subunit assist the fusion between the viral envelope protein and the host cell membrane (Du et al., 2009; Li, 2016; Tortorici et al., 2019). S1 subunit has two major domains: the N-terminal domain (NTD) and the C-terminal domain (CTD). Depending on the coronavirus type, either CTD or NTD can function as the RBD and bind with diverse proteins and sugars (Li, 2016). Notably, SARS-CoV and MERS-CoV utilize CTD to bind their receptors (Kubo, Yamada, & Taguchi, 1994; Li et al., 2005; Ou et al., 2020; N. Wang et al., 2013). Then, the proteases found in the cellular environment cause the cleavage of S proteins, which ensures viral fusion. SARS-CoV-2 possesses a furin cleavage site between S1 and S2 subunit that permits efficient cleavage by proteases, including furin that determines viral infectivity and host range (Andersen et al., 2020; Coutard et al., 2020; Ou et al., 2020; Walls et al., 2020). The S protein of the SARS-CoV-2 contains a furin-like cleavage site, which is absent in other coronaviruses of the same clade (Coutard et al., 2020). The S protein also activates the immune response of the host cell toward coronaviruses (Dosch, Mahajan, & Collins, 2009; Walls et al., 2020). Since the S protein of coronaviruses is reported for their vital associations with initial receptor binding and other critical membrane fusion steps, they could be putative targets for blocking the infection. Prior studies revealed that peptide inhibitors to SARS-CoV-2 S protein provide promising avenues for SARS-CoV-2 treatment by blocking the S protein interaction with ACE2 and thus efficiently preclude the virus entry into human cells. Moreover, these inhibitors can be used as inhaled therapeutics, preventing the virus activation in the lungs (Ou et al., 2020; Walls et al., 2020).

Recently, Wan et al. (2020) and Tai et al. (2020) sequenced and characterized RBD of SARS-CoV-2, including its receptor-binding motif (RBM) that directly associates with ACE2. They also identified some important amino acid residues in SARS-CoV-2 RBM (especially Gln493), which facilitates the interactions with human ACE2 and reveals the high capacity of SARS-Cov-2 human infection. Moreover, other crucial amino acid residues in SARS-CoV-2 RBM, particularly Asn501, contributed SARS-CoV-2, gaining some ability for human-to-human transmission (Tai et al., 2020; Wan et al., 2020). It was also found that five important amino acids of RBD are conserved in Pangolin-CoV and SARS-CoV-2 (Zhang, Lin, et al., 2020). These findings would give valuable information for finding antigens with improved sensitivity for SARS-CoV-2 serological detection and vaccine development.

Envelope protein

E protein of coronavirus is a short polypeptide integral membrane protein that has been involved with different steps of the life cycle of the virus, such as assembly, budding, envelope formation, and pathogenesis (Masters, 2006). It has been reported that the absence or inactivation of E protein could impact either virion morphology or tropism (Khattari et al., 2006; Pervushin et al., 2009). E proteins of coronaviruses have shown cation-selective ion channel activity and thus have membrane permeabilizing property (Wilson, McKinlay, Gage, & Ewart, 2004). SARS-CoVs lacking E protein show lower viral titer, immature, and inefficient progenies (Kuo, Hurst, & Masters, 2007), thereby recommending E protein a suitable drug target to prevent viral replication and infection.

3.2 | Host cell target

3.2.1 | Angiotensin-converting enzyme 2

ACE2 is a type I membrane protein, which is expressed in the heart, lungs, kidneys, and intestine. An N-terminal peptidase domain (PD) and a C terminal Collectrin-like domain (CLD) are usually found in a full-length ACE2 (Donoghue et al., 2000; H. Zhang et al., 2001). A recent report demonstrated that the ectodomain of the SARS-CoV-2S protein interacts with the PD of ACE2 (Wrapp et al., 2020). Like SARS-CoV, the SARS-CoV-2 virus exploits the ACE2 receptor to gain entry into host cells. Human cell-derived proteases cleave SARS-CoV-2 S protein into S1 and S2, where S1 initially interacts its receptor molecule ACE2, and the other fragment, S2, further leads to the membrane fusion after the cleavage by a human cell surface serine protease (TMPRSS2) (Hoffmann et al., 2020). These findings provide valuable insights into the molecular basis for coronavirus recognition and infection. The S protein of SARS-CoV-2 is approximately 10- to 20-fold more likely to bind to human ACE2 protein the S protein of SARS-CoV (Wrapp et al., 2020). This increase in affinity might have facilitated a more favorable person-to-person transmission of the SARS-CoV-2 infection than the SARS-CoV (Hoffmann et al., 2020). ACE2 can thus act as a unique adhesion protein molecule for SARS-CoV-2 infection and be a promising drug target for the prevention of SARS-CoV-2 infection. Disrupting the interaction between spike protein and ACE2 might, therefore, be a possible way of developing a drug against SARS-CoV-2. A Phase 1 and Phase 2 clinical trial of human recombinant soluble ACE2 (hrsACE2), a 23-mer peptide fragment, was carried out recently and suggested to use for the treatment of COVID-19 (Khan et al., 2017; Zhang, Penninger, et al., 2020). SARS-CoV-2 infected Vero-E6 lines were incubated with hrsACE2 and found that hrsACE2 can preclude the early entrance of SARS-CoV-2 infections in host cells perhaps by binding with RBD of S protein (Monteil et al., 2020).

3.2.2 | Transmembrane serine protease 2

Although the ACE2 is available in the vascular endothelial cells of all organs, the lungs are more susceptible to SARS-CoV infection (Hamming et al., 2004). This phenomenon strengthens the possibility of other factors associated with the actual pathogenesis of SARS-CoV-2. One such factor which accounts for the viral entry into host cells is TMPRSS2, a well-known human alveolar and airway protease (Shulla et al., 2011). TMPRSS11a, a TMPRSS2 related protein, has been found to cleave SARS-CoV S protein and to moderately accelerate viral infections (Kam et al., 2009). TMPRSS2 probably facilitates viral pathogenesis and transmission in two ways: First, TMPRSS2 might activate SARS-CoV S protein for virus–cell and cell–cell fusion. Second, TMPRSS2 might protect viral recognition by different neutralizing antibodies of the host (Glowacka et al., 2011). Evidence suggests that the entry of SARS-CoV-2 into host cells requires both ACE2 and TMPRSS2 (Hoffmann et al., 2020), thereby suggesting that TMPRSS2 might be a potential drug target. Matsuyama et al. (2020) showed that a TMPRSS2-expressing in VeroE6 cell line is highly susceptible to SARS-CoV-2 infection displaying the critical role of TMPRSS2 in the pathogenesis of this viral disease. Previously, Bromhexine hydrochloride, an FDA approved component in mucolytic cough suppressants, showed specific inhibition on TMPRSS2 with no adverse effect in prostate cancer patients and reduction of the progression of metastasis (Lucas et al., 2014). Bromhexine hydrochloride might be repurposed as a TMPRSS2 inhibitor for preventing SARS-CoV-2 infection as well (Hoffmann et al., 2020).

3.2.3 | Targets on the immune system

Cytokine storm

SARS-CoV-2 causes imbalanced and exuberant immune responses termed as cytokine release syndrome or cytokine storm, which triggers lung impairment and reduces the survival of the infected patients (Pedersen & Ho, 2020; Tisoncik et al., 2012). The inflammatory cytokines are usually produced by different macrophages, which are associated with cytokine storm (Luo et al., 2020; Pedersen & Ho, 2020). SARS-CoV-2 significantly increases levels of proinflammatory cytokines such as IL-6, IL-10, and TNFα in infected patients (Channappanavar et al., 2016; Diao et al., 2020; Nikolich-Zugich et al., 2020). Furthermore, SARS-CoV-2 induced activation of a cluster of differentiation four positive ($CD4^+$) T cells stimulate the generation of T helper cells and secrete interleukin (IL)-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF triggers monocytes to further release of IL-6 and other factors, resulting in the generation of a cytokine storm. This cytokine storm results in acute respiratory distress syndrome, multiple organ failure, and even death (Chen, Zhang, et al., 2020a; Zhou et al., 2020). Targeted immunomodulation to decrease cytokine storm might be a feasible option to reduce pulmonary inflammation and mortality. Since only antiviral candidates may not be enough to combat such cytokine storm or complications in the respiratory tract, identifying effective targets for immune therapeutics along with antiviral agents could be a potential strategy. Preliminary results from a study suggest that Hydroxychloroquine might have anti-cytokine storm properties (Yao et al., 2020). Additionally, Lenziluman has been reported to be

protective against cytokine storm and neurotoxicity in mouse models. Furthermore, Lenzilumab, an anti-GM-CSF monoclonal antibody, can be considered as a viable therapeutic option as COVID-19 patients (Sterner et al., 2019).

Activation of natural killer cell

The innate immune response itself, without the association of $CD8^+$ T cells and antibodies, is capable of controlling SARS-CoV (Frieman, Heise, & Baric, 2008). NK cells are the part of innate lymphocyte subsets that mediate anti-tumor and antiviral responses, and therefore have the potential for clinical use (Abel, Yang, Thakar, & Malarkannan, 2018). Previous studies showed that NK cells showed significant roles in mitigating of SARS-CoV (Chen et al., 2010; National Research Project for SARS (NSPS), 2004). Recent epidemiological studies showed that SARS-CoV-2 infection in children is less frequent and lethal compared to that of adults, which might be due to the increased lymphocyte count, especially NK cells and trained immunity in children (Cristiani et al., 2020). Therefore, the approaches focused on valorizing the innate antiviral immune responses are a possible way to find a remedy against SARS-CoV-2. Arabinoxylan treatment resulted in the upregulation of NK cells against neuroblastoma in vitro and in vivo studies (Pérez-Martínez et al., 2015). Arabinoxylan, therefore, possesses potentiality for the treatment of COVID-19 patients; however, clinical trials are needed to determine its effectivity.

Activation of autophagy

Autophagy is a natural mechanism of a cell which ensures the maintenance of cellular homeostasis by lysosomal catabolic action, leading the degradation and recycling of intracellular endogenous (macromolecules, abnormal proteins, and damaged organelles) and exogenous (viruses and bacteria) particles (Galluzzi et al., 2017; Levine & Klionsky, 2004). Some viruses have developed strategies to escape autophagic degradation and use host autophagy machinery for their self-replication (Dong, Dong, & Levine, 2013). The significance of the autophagy process and its therapeutic development for SARS-CoV, MERS-CoV, and SARS-CoV-2 are reviewed by (Yang & Shen, 2020). A recent study showed that MERS-CoV halts the fusion of autophagosomes and lysosomes, whereas inhibitors like S-phase kinase-associated protein 2 induced autophagy, which leads to the reduction of the replication of MERS-CoV (Gassen et al., 2019). Thus, it seems that a considerable relationship exists between the autophagy machinery and coronavirus infections; therefore, these relationships need to be elucidated in SARS-CoV-2 to understand disease prognosis and also to enhance autophagocytosis as a possible treatment corridor.

4 | POTENTIAL THERAPEUTICS

Many potential therapeutics are currently in different stages of clinical trials, to find out an effective treatment for COVID-19, including drugs that have already proven effective for other viral diseases such as human immunodeficiency virus (HIV) and malaria. Drug repurposing could be a rational strategy to develop urgent therapeutics. More than one drug and treatment strategy might prove its worth, and different strategies might work effectively at different infection stages and risk groups. The big challenge will be conducting clinical trials on an urgent basis, determining the effectiveness of different drugs alone or in combination. However, the scientists should take caution to avoid mistakes that occurred during the West African Ebola epidemic, in which haphazard experiments flourished and randomized clinical trials were framed up so late, resulting in little patients in the trial. Besides, developing new drugs or testing procedures may take several years to develop. That is why the World Health Organization (WHO) and other organizations are emphasizing the repurposing therapeutic candidates that have already been approved for other diseases. Researchers are studying antiviral drugs that have performed well in animal studies against SARS-CoV and MERS-CoV as well to determine their effectivity against SARS-CoV-2. Here, we reviewed some of the potential therapeutics and antivirals, which are under preclinical study and clinical trials. This review would help researchers to get quick and collective information regarding potential drugs.

4.1 | Drugs targeting viral entry

As virus entry is a crucial step for the pathogenesis of the COVID-19, we provide a comprehensive list of repurposed drugs/chemicals that have been reported to block viral entry via different mechanisms (Table 1). Monotherapy or combined therapy of these drugs are in preclinical, Phase 1, Phase 2, or Phase 3 clinical trials. Hoffmann et al. (2020) showed that Camostat mesylate interferes with TMPRSS2-mediated viral entry, thus reduces the severity of the COVID-19 disease. Similarly, Arbidol, an antiviral that inhibits the hemagglutinin of the influenza virus and blocks the entry into the cell, is recommended to use against influenza viruses and arboviruses (Kadam & Wilson, 2017; Wang et al., 2004). An open, prospective/retrospective, randomized controlled cohort study is underway at Tongji Hospital, China, to study the safety and efficacy of Arbidol Hydrochloride and Arbidol Hydrochloride combined with interferon atomization in humans (Table 1). In this study, the interventional subjects will be given a standard supportive therapy with Arbidol Hydrochloride (0.2 g, three times a day) or Arbidol Hydrochloride combined with Interferon (PegIFN-α-2b) atomization (45 g) (NCT04254874). Trials with Arbidol Hydrochloride, along with other drugs, are also undergoing at Ruijin Hospital, China, and Tongji Hospital, China (NCT04260594, NCT04255017). Moreover, a recent study has demonstrated that a fusion protein made of rhACE2 and an Fc (Fragment crystalization) region of the human immunoglobulin IgG1 shows high-affinity binding to the receptor-binding domain of SARS-CoV-2 and potently neutralized SARS-CoV-2 in vitro, which provides a basis for further drug development (Lei et al., 2020; Monteil et al., 2020). This fusion protein can be considered for further studies in animals and

TABLE 1 Therapeutics targeting viral entry

Target	Specific effect/ target molecule	Intervention(s)	Status of SARS-CoV-2 trial	Sponsor/collaborators	NCT number
TMPRSS2	Sialic receptors	DAS181	Not applicable	Renmin Hospital of Wuhan University, Ansun Biopharma, Inc.	NCT04324489
	Serine protease inhibitor	Camostat Mesilate	Phase 1, phase 2	University of Aarhus	NCT04321096
Endosome	Endosomal acidification	Chloroquine diphosphate	Phase 2	FundaÃ§Ã£o de Medicina Tropical Dr. Heitor Vieira Dourado, Marcus VinÃcius GuimarÃ£es de Lacerda, Mayla Gabriela Silva Borba, Wuelton Marcelo Monteiro, Gisely Cardoso de Melo, Fernando Fonseca de Almeida e Val, Felipe Gomes Naveca, Maria Paula Gomes MourÃ£o, Ludmila AbrahÃ£o Hajjar, Jorge Souza MendonÃ§a	NCT04323527
	Endosomal acidification	Chloroquine or Hydroxychloroquine	Not applicable	University of Oxford	NCT04303507
	Endosomal acidification	Colchicine	Phase 2, Phase 3	Lucio Manenti, Azienda Ospedaliero-Universitaria di Parma, Montreal Heart Institute, DACIMA Software	NCT04322565, NCT04322682
	Lysosome	†1 Bromhexine hydrochloride tablets †2 Arbidol hydrochloride †3 Recombinant human interferon Î ± 2b spray	Not applicable	Second Affiliated Hospital of Wenzhou Medical University, WanBangDe Pharmaceutical Group Co., Ltd.	NCT04273763
	Lysosome	Hydroxychloroquine	Early Phase 1, Phase 2, Phase 3	National Institute of Respiratory Diseases, Mexico, Sanofi; Columbia University; National Institute of Respiratory Diseases, Mexico, Sanofi; University of Minnesota; Rambam Health Care Campus, Rabin Medical Center; Shanghai Public Health Clinical Center	NCT04315896, NCT04318444, NCT04318015, NCT04308668, NCT04323631, NCT04261517
	Lysosome	Hydroxychloroquine sulfate	Phase 4	University Hospital, Akershus	NCT04316377
	Lysosome	Thalidomide	Phase 2	First Affiliated Hospital of Wenzhou Medical University, Second Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital	NCT04273581
Spike glycoprotein	Spike glycoprotein	†1 N-acetylcysteine + Fuzheng Huayu tablet †2 N-acetylcysteine + placebo	Phase 2	ShuGuang Hospital, Hubei Hospital of Traditional Chinese Medicine, Jingmen No.1 Peopleâ€™s Hospital, Tongji Hospital	NCT04279197
	Spike glycoprotein	Nitric oxide	Phase 2	Massachusetts General Hospital, Xijing Hospital, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico	NCT04305457, NCT04306393, NCT04312243
	Spike glycoprotein	Nitric oxide 0.5%/nitrogen 99.5% gas for Inhalation	Phase 2	University of British Columbia, Mallinckrodt	NCT03331445
	Spike glycoprotein	†1 Abidol hydrochloride †2 Abidol hydrochloride combined with interferon atomization	Phase 4	Tongji Hospital	NCT04254874

TABLE 1 (Continued)

Target	Specific effect/ target molecule	Intervention(s)	Status of SARS-CoV-2 trial	Sponsor/collaborators	NCT number
	Spike glycoprotein	Anti- SARS-CoV-2 plasma	Phase 2, Phase 3	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Mayo Clinic; Foundation IRCCS San Matteo Hospital, OSPEDALE CARLO POMA ASST MANTOVA, OSPEDALE MAGGIORE LODI, OSPEDALE ASST CREMONA; Wuhan Union Hospital, China; Peking Union Medical College Hospital, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology	NCT04323800,
	Spike glycoprotein	Arbidol	Phase 4	Jieming QU, Ruijin Hospital	NCT04260594
	CD147	Meplazumab	Phase 1, Phase 2	Tang-Du Hospital	NCT04275245
	Spike glycoprotein	Baricitinib	Phase 3	Hospital of Prato	NCT04320277
	Spike glycoprotein	Human amniotic fluid	Early Phase 1	University of Utah	NCT04319731

Note: †1, †2, and †3 are different arms of parallel intervention.

humans to see its effectiveness. Moreover, S protein-specific monoclonal antibodies can be generated to neutralize the spike protein, which may lead to the inhibition of viral entry. Recently, Tian et al. (2020) identified a monoclonal antibody, CR3022, which binds with the RBD of the spike protein of SARS-CoV-2 in vitro. CR3022, therefore, might be a potential drug candidate against SARS-CoV-2 infection. Despite the role of ACE2 in viral entry, targeting interruption of ACE2 may not be the best strategy to prevent SARS-CoV-2 (Guo et al., 2020) because ACE2 also maintains blood pressure. So, the entry inhibition strategy must be pathogen-specific rather than host-specific. Further studies should be carried out to discover potential entry inhibitors that block that viral entry without disturbing the maintenance of the blood pressure. Some other potential therapeutics that block the virus entry into target cells are summarized in Tables 1 and 2.

4.2 | Targeting the virus replication cycle

The replication cycle of coronavirus or the virus-infected host cells possesses several virus-specific processes or protein molecules that could be targeted for effective antiviral drug design. An effective antiviral agent might halt the viral progression in the infected cell without being allergic or toxic to surrounding noninfected cells (Zhu, Meng, Wang, & Wang, 2015).

4.2.1 | Targeting viral RNA release

We have already discussed above the role of endosomal/lysosomal acidification and the role of their acidic pH-dependent proteases in the virus life cycle (Yang & Shen, 2020). The inhibition of this pathway might be a potential therapeutic strategy. Several therapeutics such as Chloroquine (CQ), a well-studied lysosomotropic antimalarial drug, and its derivatives hydroxychloroquine and colchicine would be an option for blocking this target. CQ effectively blocks viral progression by raising endosomal pH needed for membrane fusion between the host cell and viral candidates and releasing RNA from endosomes (Savarino, Boelaert, Cassone, Majori, & Cauda, 2003). Although CQ and hydroxychloroquine were found to be effective against SARS-CoV-2 (Gautret et al., 2020; Wang et al., 2020), several recent evidence claimed some unprecedented effects. A recent study reported that hydroxychloroquine (either alone or in combination with azithromycin) showed no positive outcome in patients with COVID-19 (Magagnoli et al., 2020), instead was linked with increased overall mortality (27.8% in hydroxychloroquine and 22.1% in hydroxychloroquine plus azithromycin versus 11.4% in the control group). A multinational, observational, real-world study of patients with COVID-19 also claimed that hydroxychloroquine or chloroquine showed no evidence of benefit, rather it was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19 (Mehra, Desai, Ruschitzka, & Patel, 2020). Moreover, a

TABLE 2 Therapeutics working on multiple targets

Target	Specific effect/target molecule(s)	Intervention(s)	Status of SARS-CoV-2 trial	Sponsor/collaborators	NCT number
Combined intervention	3CLpro, interferon receptor (IFNAR)	†1 Lopinavir/ritonavir †2 Ribavirin †3 Interferon Beta-1B	Phase 2	The University of Hong Kong, Hospital Authority, Hong Kong	NCT04276688
	3CLpro, interferon receptor (IFNAR)	†1 Xiyanping injection †2 Lopinavir/ritonavir, alpha-interferon nebulization	Not applicable	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	NCT04275388
	ACE2 and spike binding complex, Endosomal acidification	†1 Azithromycin †2 Chloroquine	Phase 3	Population Health Research Institute	NCT04324463
	ACE2 and spike binding complex, Endosomal acidification	†1 Azithromycin †2 Hydroxychloroquine	Phase 4	Chronic Obstructive Pulmonary Disease Trial Network, Denmark	NCT04322396
	ACE2 and spike binding complex, Endosomal acidification	†1 Hydroxychloroquine + azithromycin †2 Hydroxychloroquine	Phase 3	Hospital Israelita Albert Einstein, EMS, Hospital do Coracao, Hospital Sirio-Libanes, Brazilian Research In Intensive Care Network; Hospital do Coracao, Hospital Israelita Albert Einstein, Hospital Sirio-Libanes, Brazilian Research In Intensive Care Network, EMS	NCT04321278, NCT04322123
	Endosomal acidification, RdRp	†1 Hydroxychloroquine †2 Remdesivir	Phase 2, Phase 3	Oslo University Hospital	NCT04321616
	Spike glycoprotein, 3CLpro	†1 Carrimycin †2 lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate	Phase 4	Beijing YouAn Hospital, Shenyang Tonglian Group Co., Ltd., Institute of Medicine and Biotechnology, Chinese Academy of Medical Sciences, Huangshi Central Hospital, Shenyang Pharmaceutical University, First Affiliated Hospital of Chongqing Medical University, The Second Affiliated Hospital of Harbin Medical University, No. 2 People's Hospital of Fuyang City, First Affiliated Hospital Bengbu Medical College, Renmin Hospital of Wuhan University, The Sixth People's Hospital of Shenyang, Nanyang Central Hospital	NCT04286503
	Spike glycoprotein, 3CLpro	†1 Abidol hydrochloride †2 Oseltamivir †3 Lopinavir/ritonavir	Phase 4	Tongji Hospital	NCT04255017

Note: †1, †2, and †3 are different arms of parallel intervention.

recent systematic review found no difference between the hydroxychloroquine treated group and an untreated group of COVID-19 patients (Sarma et al., 2020). WHO had recently postponed further clinical trials on hydroxychloroquine due to unexpected results in previous trials, however, this repurposed drug has been allowed for re-evaluation. All of this evidence points to the significance of waiting for the final results of ongoing prospective, randomized, controlled studies before considering these drugs as a therapeutic option for COVID-19.

4.2.2 | Protease inhibitors

Proteases have a crucial role in many signaling pathways and represent promising drug targets fora wide range of diseases, including viral diseases. A few protease blockers are currently under Phase 1, Phase 2, or Phase 3 clinical trials as potential drugs for treating COVID-19 (Tables 1 and 2). ASC09/Ritonavir, Lopinavir/Ritonavir, ASC09F + Oseltamivir, and Ritonavir + Oseltamivir are some protease inhibitor drug candidates that inhibit 3CLpro and prevent subsequent progression of replication (Table 1). For example, monotherapy or combination of Lopinavir and Ritonavir has been studied against MERS-CoV both in vitro and in an animal model and found to be effective (Chan et al., 2015; de Wilde et al., 2014). Studies showed that the combination of Lopinavir and Ritonavir with Ribavirin and Interferon alfa (IFN-α) resulted in the survival of MERS-patients through viral clearance (Kim, Won, Kee, Jung, & Jang, 2016). Some investigators are operating randomized, open-label trials to evaluate and compare the efficacy and safety of Lopinavir and Ritonavir for COVID-19 patients (Table 3). A recent case report claimed that a 54-year-old patient administered with lopinavir/ritonavir showed a significant reduction of viral loads with no or little coronavirus titers (Lim et al., 2020). A recent clinical trial (ChiCTR2000029308), however, showed that lopinavir–ritonavir treatment caused no benefit to hospitalized patients with severe COVID-19 compared to standard care (Cao et al., 2020). Treatment with lopinavir–ritonavir was not associated with time to clinical improvement, mortality at 28 days, detectable viral RNA, and gastrointestinal adverse events compared with the standard-care group (Cao et al., 2020). These contradictory yet promising findings highlight the importance of conducting clinical trials before using a drug as a therapeutic candidate.

4.2.3 | Replication blocker

RdRp is a vital enzyme of the viral replication machinery; hence, RdRp blockers could be effective antiviral therapy against SARS-CoV-2 infection. Depending on their mechanism of action, RdRp inhibitors are of two types, that is, (a) nucleoside and nucleotide structural analogs which mimic the structure of the natural nucleoside triphosphate substrates and could interact competitively in the active site of RdRp polymerase and (b) non-nucleoside inhibitors are allosteric inhibitors which interact in a noncompetitive fashion for the substrates (Brown, 2009; Velkov et al., 2014). Favipiravir (T-705) is a broad-spectrum prodrug that is metabolized into an active ribofuranosyl triphosphate derivative that selectively inhibits the viral RdRp polymerase activity (Velkov et al., 2014). Favipiravir was shown to inhibit the replication of the respiratory syncytial virus and also been proven effective against influenza in Japan (Delang, Abdelnabi, & Neyts, 2018; Furuta, Komeno, & Nakamura, 2017), which indicates that it might be effective against SARS-CoV-2. A multicenter, randomized, and controlled clinical trial study with 150 participants is underway with Favipiravir combined with Tocilizumab for the treatment of COVID-19 at Peking University First Hospital (Table 3). Recently, a prospective, randomized, controlled, open-label multicenter trial (ChiCTR2000030254) involving adult COVID-19 patients treated with Favipiravir versus Arbidol showed that Favipiravir increased clinical recovery rate, improved the latency to relief for pyrexia and cough along with mild and manageable adverse effects (Chen, Xiong, Bao, & Shi, 2020). Furthermore, Cai et al. (2020) studied the effects of Favipiravir versus Lopinavir/ritonavir for the treatment of COVID-19. There were two arms (Favipiravir + Interferon-α versus Lopinavir/ritonavir) in this open-label control study. The 45 patients registered in the control arm (Lopinavir/ritonavir) and the 35 patients in the Favipiravir arm (Favipiravir + Interferon-α) where all baseline characteristics were compared between the two arms. The Favipiravir arm showed significant improvement in chest imaging, associated with faster viral clearance with lower adverse events compared with the control arm (Cai et al., 2020). Remdesivir, an adenosine nucleoside analog prodrug and developed by Gilead Sciences (Foster City, CA) against the Ebola virus, incorporates into nascent viral RNA chains resulting in the premature termination of RNA synthesis (Wang, Cao, et al., 2020). Monotherapy and combination therapy of Remdesivir with CQ or Interferon-beta (IFN-β) halted SARS-CoV-2 replication and treated patients were clinically recuperated (Sheahan et al., 2020; Wang, Zhang, et al., 2020). A Phase 3 randomized, double-blind, placebo-controlled, multicenter study of Remdesivir in hospitalized adult patients with severe COVID-19 is completed (NCT04257656). The primary endpoint of the trial concluded that patients with COVID-19 receiving Remdesivir showed a faster time to clinical improvement (numerically, not statistically significant) compared to the patients receiving the placebo group (Wang, Cao, et al., 2020). Moreover, a double-blind, randomized, placebo-controlled clinical trial (NCT04280705) evidenced that intravenous Remdesivir was efficacious compared to placebo in reducing the time to recovery with lower respiratory tract infection (Beigel et al., 2020). Recently, the FDA approved the emergency use of Remdesivir as an experimental drug. On the other hand, Ribavirin, a synthetic purine nucleoside derivative could interfere in the guanosine triphosphate formation, hinders capping of viral mRNA, and thus inhibits viral RNA-dependent RNA polymerase activity (Khalili, Zhu, Mak, Yan, & Zhu, 2020). It could be used as a broad-spectrum antiviral therapeutic agent that has already been reported against a wide range of DNA and RNA viruses such as paramyxovirus, Influenza A and B, Hepatitis C, respiratory syncytial virus, parainfluenza, and HIV (Elfiky, 2020; Khalili et al., 2020; Tam, Lau, & Hong, 2001; Tan et al., 2004). Several phases of clinical trials are undergoing to study the efficacy of Remdesivir and Ribavirin

TABLE 3 Therapeutics intervening viral replication process

Target	Specific effect/ target molecule	Intervention(s)	Status of SARS-CoV-2 trial	Sponsor/collaborators	NCT number
Protease	3CLpro	†1 ASC09/ritonavir †2 lopinavir/ritonavir	Not applicable	First Affiliated Hospital of Zhejiang University, Ascletis Pharmaceuticals Co., Ltd.	NCT04261907
	3CLpro	†1 ASC09F + Oseltamivir †2 Ritonavir + Oseltamivir †3 Oseltamivir	Phase 3	Tongji Hospital	NCT04261270
	3CLpro	Darunavir and Cobicistat	Phase 3	Shanghai Public Health Clinical Center	NCT04252274
	3CLpro	Ganovo + ritonavir ± interferon nebulization	Phase 4	The Ninth Hospital of Nanchang, Ascletis Pharmaceuticals Co., Ltd.	NCT04291729
	3CLpro	Lopinavir/ritonavir	Phase 3	Darrell Tan, St. Michael's Hospital, Toronto; Jiangxi Qingfeng Pharmaceutical Co. Ltd.	NCT04321174, NCT04295551
	3CLpro	†1 Lopinavir/ritonavir †2 Hydroxychloroquine sulfate	Phase 2	Asan Medical Center	NCT04307693
	3CLpro	†1 Lopinavir/ritonavir †2 Hydroxychloroquine sulfate †3 Baricitinib (Janus kinase inhibitor) †4 Sarilumab (anti-IL-6 receptor)	Phase 2	Lisa Barrett, Nova Scotia Health Authority, Dalhousie University	NCT04321993
RdRp	RdRp	†1 Favipiravir combined with Tocilizumab †2 Favipiravir †3 Tocilizumab	Not applicable	Peking University First Hospital	NCT04310228
	RdRp	Remdesivir	Phase 3	Gilead Sciences; U.S. Army Medical Research and Development Command; Institut National de la SantÃ© Et de la Recherche MÃ©dicale, France; Capital Medical University, Chinese Academy of Medical Sciences; Capital Medical University; Gilead Sciences; National Institute of Allergy and Infectious Diseases (NIAID)	NCT04323761, NCT04302766, NCT04315948, NCT04252664, NCT04257656, NCT04292899, NCT04292730, NCT04280705
	RdRp	Ribavirin	Not applicable	Jiangsu Famous Medical Technology Co., Ltd.	NCT04306497
	RdRp	Galidesivir (BCX4430)	Phase 1	BioCryst Pharmaceuticals, National Institute of Allergy and Infectious Diseases (NIAID)	NCT03891420
	RdRp	Triazavirin	Phase 3	Health Commission of Heilongjiang province	ChiCTR2000030001

Note: †1, †2, †3, and †4 are different arms of parallel intervention.

for the treatment of SARS-CoV-2 as alone or in combination with other drugs (Table 3; Khalili et al., 2020).

4.3 | Drugs targeting the inflammatory responses and cytokine storm

Inflammation is an obvious outcome of SARS-CoV-2; however, no effective therapeutics targeting the inflammatory responses for SARS-CoV-2 has been approved to date. Fu, Cheng, and Wu (2020) reviewed the potential mechanism of Fc receptor (FcR) blockers such as intravenous immunoglobulin, anti-Fc specific antibodies, small molecules, and so on, which might be a therapeutic tool for reducing SARS-CoV-2 induced pulmonary inflammation. Moreover, anti-inflammatory drugs or corticosteroids might also effectively alleviate early proinflammatory response to reduce SARS-CoV-2-induced inflammatory responses by blocking FcR activation. Besides, the administration of intravenous immunoglobulin against FcR could be effective for an urgent remedy against pulmonary inflammation associated with severe lung injury as it can effectively block FcR activation. These approaches may also be applied with corticosteroids or systemic anti-inflammatory drugs (Shang, Zhao, Hu, Du, & Cao, 2020), which needs further clinical trials to study the effectiveness against SARS-CoV-2 infection (Russell, Millar, & Baillie, 2020).

Another potential option for reducing inflammation is Siltuximab, a chimeric monoclonal antibody (mAb) that binds to and halts the effect of IL-6 (Sarosiek, Shah, & Munshi, 2016; Chen et al., 2020). Recently, a study in COVID-19 patients showed that intravenous administration of Siltuximab improved clinical conditions of 33% patients, stabilized or demonstrated no clinically relevant changes in 43% of patients, whereas condition deteriorated in 24% patients (Gritti et al., 2020). These results exhibit the potential role of Siltuximab in treating patients with SARS-CoV-2 infection (Gritti et al., 2020). Furthermore, an observational case–control study with 50 COVID-19 patients with serious respiratory complications is ongoing in Italy to determine the effectivity of Siltuximab (NCT04322188). Another group of researchers (di Giambenedetto et al., 2020) used Tocilizumab, a humanized anti-human interleukin-6 receptor antibody of the IgG1 subclass, for thwarting or treating the cytokine storm in three patients of COVID-19 and found promising results such as reduction of fever, C-reactive proteins and quick relief of respiratory symptoms. A clinical trial is undergoing to test whether an anti-IL6 treatment can be effective in reducing the SARS-CoV-2-induced cytokine storm and improving lung function (NCT04315480). Some other therapeutics which have anti-inflammatory and immunomodulation property are summarized in Table 4.

5 | POTENTIAL VACCINES AND THEIR DEVELOPMENT

A vaccine is an ultimate hope to prevent and reduce the spread of COVID-19. A vaccine can be either prophylactic, which prevents future infection or therapeutic, which is used to treat diseases such as cancer or infectious diseases (Frazer, 2014; Guo et al., 2013). The whole pathogen (either killed or live-attenuated), or parts of the pathogen, such as nucleic acid, proteins, or peptides, can be used as vaccines (Haque, Shah, Paul, & Barua, 2020; Shah & Md Kawsar, 2015). Whole virus vaccines have been widely studied and showed protection against the influenza virus (Fiore, Bridges, & Cox, 2009), the human papillomavirus, and the chickenpox virus (Liesegang, 2009); whereas, subunit and peptide-based vaccines have shown immunity in vitro (Khan, Hossain, Rakib-Uz-Zaman, & Morshed, 2014) and animal studies (Islam, Clemens, & Qadri, 2018). There were efforts to develop vaccines against SARS-CoV and MERS-CoV, which were tested in animal models (Gao et al., 2003; Kim et al., 2014). However, there is no benign and operational vaccine available against SARS-CoV until now. Development of vaccines against SARS-CoV after the SARS outbreak in 2002–2004 was attempted (Greenough et al., 2005; Roberts et al., 2006; Tripp et al., 2005); however, the efforts did not result in finding any effective vaccines until now. During MERS prevalence, it was believed that SARS-CoV would provide a foundation and a template for developing vaccines against MERS-CoV infection (Jiang, Lu, & Du, 2013). However, only one MERS-CoV DNA vaccine has so far completed a Phase 1 clinical trial (Yong, Ong, Yeap, Ho, & Tan, 2019). Several more viral vectored-MERS-CoV vaccines are in progress (Yong et al., 2019) which were reviewed by Zumla, Chan, Azhar, Hui, and Yuen (2016).

A suitable vaccine of SARS-CoV-2 can prevent the spread of the current pandemic COVID-19 and can save millions of lives and billions of money. Currently, different research groups around the world are working with more than 100 candidate vaccines against SARS-CoV-2 based on (1) inactivated or weakened whole virus, (2) nucleic acid, (3) viral vector, and (4) protein subunit or virus-like particles (Figure 3), which are in the preclinical evaluation for SARS-CoV-2 (Amanat & Krammer, 2020; Chen, Xiong, Bao, & Shi, 2020). As of May 2020, some vaccines are under different phases of clinical trials (Table 5). Five of those vaccines are in Phase 1 clinical trials, six are in Phase 2 trials and one vaccine candidate is in Phase 3 clinical trials (Table 5). Those candidate vaccines are DNA based (2), inactivated virus (2), modified antigen-presenting cell (APC) (3), nonreplicating virus (2), and protein subunit based (1) (Table 5). The nonreplicating virus-based vaccine, namely ChAdOx1 nCoV-19, developed by the Consortium of the Jenner Institute, Oxford Biomedica, University of Oxford, which is under phase three clinical trial is considered as the most promising vaccine candidate so far. ChAdOx1 construct contains S protein that can elicit an immune response in the body, which might prevent subsequent infection of SARS-CoV-2 (Lane, 2020). The Phase 1 trial initiated in April where 1,000 plus immunizations have been accomplished and follow-up is currently continuing. Now commencing Phase 2 and Phase 3 trials to assess how well the vaccine provokes immune responses in older adults, and to examine whether it can render protection in the wider population (http://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials). Another vaccine is the

TABLE 4 Therapeutic agents with anti-inflammatory and immunomodulatory actions

Target	Specific effect/target molecule	Intervention(s)	Status of SARS-CoV-2 trial	Sponsor/collaborators	NCT number
Immune system	Immunomodulatory	Mesenchymal stem cell (MSC)	Phase 1, Phase 2	Beijing 302 Hospital, Innovative Precision Medicine Group (IPM), Hangzhou, China., Wuhan Huoshenshan Hospital, Wuhan, China, Tianjin Haihe Hospital, VCANBIO CELL & GENE ENGINEERING CORP., LTD, China, Shenzhen Third People's Hospital, Fifth Affiliated Hospital, Sun Yat-Sen University	NCT04252118, NCT04288102 NCT04299152
	Immunomodulatory	NestCellÂ®	Phase 1	Azidus Brasil, Cellavita Pesquisa CientÃfica Ltda, Hospital Vera Cruz	NCT04315987
	Immunomodulatory	UC-MSCs	Phase 2	ZhiYong Peng, Tuohua Biological Technology Co. Ltd, Zhongnan Hospital; Wuhan Union Hospital, China, Wuhan Hamilton Biotechnology Co., Ltd, China.	NCT04269525, NCT04273646
	Immunomodulatory	WJ-MSCs	Phase 1	Stem Cells Arabia	NCT04313322
Immune system	Angiotensin II receptor	Losartan	Phase 2	University of Minnesota	NCT04312009, NCT04311177
	Cytokine	Dexamethasone	Phase 4	Dr. Negrin University Hospital, Li Ka Shing Knowledge Institute	NCT04325061
	Cytokine	Methylprednisolone	Phase 2, Phase 3, Phase 4	Beijing Chao Yang Hospital; Tongji Hospital; Peking Union Medical College Hospital, Zhongda Hospital, Zhongnan Hospital, Renmin Hospital of Wuhan University; University of Trieste	NCT04273321, NCT04263402, NCT04244591, NCT04323592
	Cytokine	MSCs-derived exosomes	Phase 1	Ruijin Hospital, Shanghai Public Health Clinical Center, Wuhan Jinyintan Hospital, Wuhan, China, Cellular Biomedicine Group Ltd.	NCT04276987
	Eicosanoids and nuclear factor-kappa B (NF-kB)	Escin	Phase 2, Phase 3	University of Catanzaro, Azienda Ospedaliera Pugliese Ciaccio, Azienda Ospedaliera Policlinico "Mater Domini"	NCT04322344
	Infected human cells	NK cells, IL15-NK cells, NKG2D CAR-NK cells, ACE2 CAR-NK cells,NKG2D-ACE2 CAR-NK cells	Phase 1, Phase 2	Chongqing Public Health Medical Center, Chongqing Sidemu Biotechnology Technology Co., Ltd., Xinxiang medical university, First Affiliated Hospital of Xinjiang Medical University	NCT04324996, NCT04280224
	Injured cell components	CD24Fc	Phase 3	OncoImmune, Inc.	NCT04317040
	Interferon gamma (IFNy)	Emapalumab	Phase 2, Phase 3	Swedish Orphan Biovitrum	NCT04324021
	Interferon receptor (IFNAR)	†1 Recombinant human interferon Alpha-1b †2 thymosin alpha 1	Phase 3	Shanghai Jiao Tong University School of Medicine	NCT04320238
	Interferon receptor (IFNAR)	Recombinant human interferon Î ± 1Î²2	Early Phase 1	Tongji Hospital	NCT04293887
	Interleukin-1 type 1 receptor	Anakinra	Phase 2, Phase 3	Swedish Orphan Biovitrum	NCT04324021
	Interleukin-1 type 1 receptor	†1 RoActemra iv †2 RoActemra sc †3 Kevzara sc	Phase 2	Marius Henriksen, Lars Erik Kristensen, Frederiksberg University Hospital	NCT04322773
	Interleukin-1 type 1 receptor	Sarilumab	Phase 2, Phase 3	Assistance Publique - HÃ´pitaux de Paris; Regeneron Pharmaceuticals, Sanofi	NCT04324073, NCT04315298

TABLE 4 (Continued)

Target	Specific effect/target molecule	Intervention(s)	Status of SARS-CoV-2 trial	Sponsor/collaborators	NCT number
	Interleukin-6 receptor	Tocilizumab	Phase 2, Phase 3	UniversitÃ Politecnica delle Marche, Azienda Ospedaliera Ospedali Riuniti Marche Nord; Hoffmann-La Roche, National Cancer Institute, Naples; Tongji Hospital, Hubei Xinhua Hospital, Wuhan No.1 Hospital, Wuhan central hospital	NCT04315480,
	Interleukin-6, TNFα	Aviptadil	Phase 2	NeuroRx, Inc., Relief Therapeutics Holding SA	NCT04311697
	Programmed cell death protein 1	†1 Programmed death-1 (PD-1) blocking antibody +standard treatment †2 Thymosin + standard treatment	Phase 2	Southeast University, China	NCT04268537
	Prostaglandins	Naproxen	Phase 3	Assistance Publique - HÃ´pitaux de Paris	NCT04325633
	Sphingosine 1-phosphate (S1P) receptor	Fingolimod	Phase 2	First Affiliated Hospital of Fujian Medical University	NCT04280588
	Toll-like receptor (TLR)	PUL-042 Inhalation Solution	Phase 2	Pulmotect, Inc.	NCT04313023, NCT04312997

Note: †1, †2, and †3 are different arms of parallel intervention.

mRNA-1273 vaccine, a synthetic strand of mRNA, which translates the prefusion-stabilized viral spike protein. The mRNAs, after intramuscular injection, are predicted to generate antiviral responses toward the spike protein of SARS-CoV-2. Furthermore, the synthesis of the lipid nanoparticle-encapsulated mRNA vaccine does not require the virus-like conventional vaccines; therefore, these are harmless and ready to be tested (NCT04283461). However, no vaccine has completed any clinical trial yet, and no vaccines are available to prevent SARS-CoV-2 infection (Amanat & Krammer, 2020; Chen, Zhang, et al., 2020b).

6 | PASSIVE AND MONOCLONAL ANTIBODY THERAPY

In the passive antibody therapy approach, the antibodies from the blood plasma or serum (convalescent plasma or sera) of people who have recuperated from SARS-CoV-2 infection are used to enhance the immunity of newly infected patients and those at risk of the disease, such as frontline caregivers or essential service providers. These serum antibodies can bind to and neutralize SARS-CoV-2 (Casadevall & Pirofski, 2020). The precise timing of collecting blood from the recovered patient is crucial to boost the immunity of the patients (Casadevall & Pirofski, 2020). Such approaches of using convalescent sera or plasma were used effectively in the past during mumps and measles epidemics (Casadevall & Pirofski, 2020). This approach has already been applied in China, where five SARS-CoV-2 infected, severely ill patients with acute respiratory distress syndrome were treated with convalescent plasma transfusion from five different recovered patients (Chen, Zhang, et al., 2020a; Teixeira da Silva, 2020). This initiative showed promising results and improved the clinical condition of the treated patients (Shen et al., 2020). However, the limited number of participants in this study precludes a definitive statement about the potential effectiveness of administering convalescent plasma. It emphasizes the need for an evaluation in clinical trials with a larger sample size and proper randomized study design (Shen et al., 2020). Recently, convalescent plasma therapy has started to treat 245 COVID-19 patients (Casadevall & Pirofski, 2020); this study will focus on the feasibility and effectiveness of plasma therapy.

Another possible treatment option is monoclonal antibody therapy. Bevacizumab, a humanized monoclonal antibody, blocks vascular endothelial growth factor (VEGF) to halt the angiogenesis in cancer patients (Ellis, 2006). A Phase 3 randomized, double-blind, placebo-controlled, multicenter study of Remdesivir in hospitalized adult patients with severe COVID-19 has been completed (NCT04257656). A multicenter randomized controlled clinical trial is undergoing at Qilu Hospital of Shandong University to check the safety and efficacy of bevacizumab in severe or critical patients with COVID-19 (NCT04305106). COVID-19 patients encounter severe hypoxia, which can upregulate VEGF. Bevacizumab might reduce the VEGF level and reduce the severity of the disease (Wang, Cai, et al., 2004).

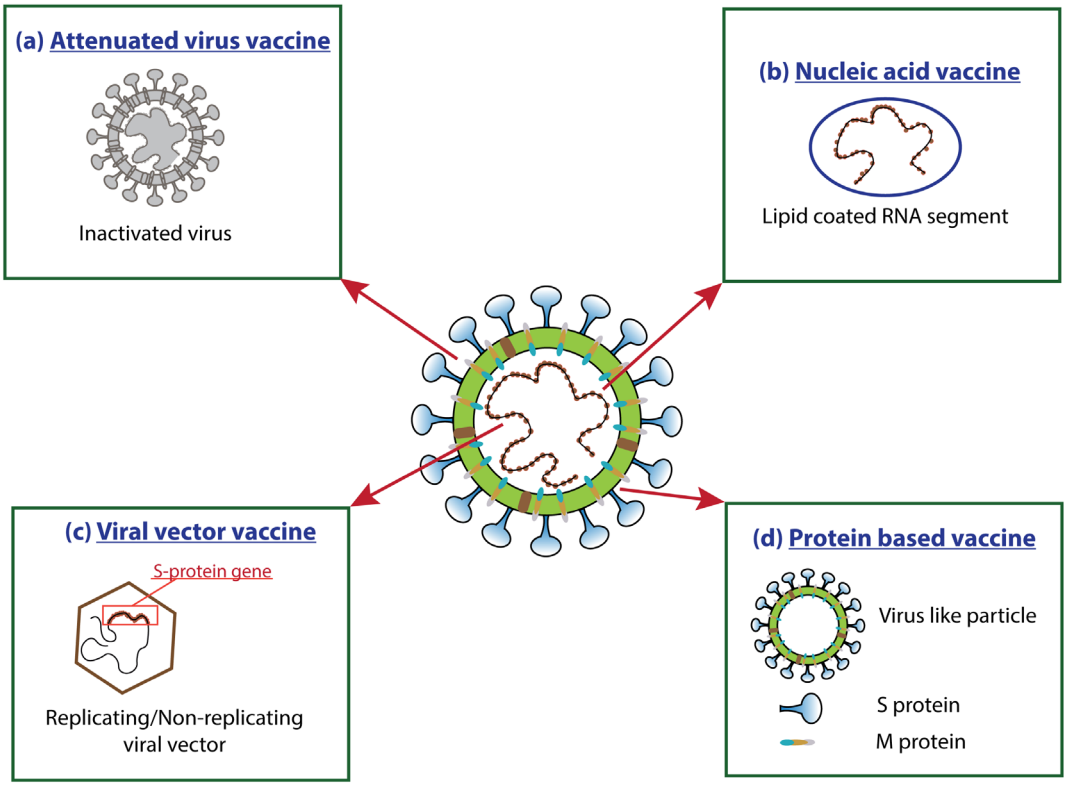

FIGURE 3 Possible strategies for vaccine design and development. (a) Attenuated Virus Vaccine: Attenuation of the virus by chemicals, such as formaldehyde, or heat; (b) Nucleic acid vaccine: Contains the genetic material only; (c) Viral vector vaccine: A genetically modified virus that can generate SARS-CoV-2 proteins in the body; (d) Protein-based vaccine: protein shells or fragments of proteins that imitate the virus's outer coat

7 | CONCLUSION AND FUTURE PERSPECTIVES

As COVID-19 spreads rapidly, the shortest and fastest approaches such as drug repurposing could be of the right choice that needs to be employed to discover potential therapeutics. Currently, some repurposed drugs have shown therapeutic promise, and thus Favipiravir, for instance, has already received temporary approval for use in COVID-19 patients. Other compounds with antiviral potential, for example, β-d-N^4-hydroxycytidine showing inhibitory effects against Chikungunya Virus, also need to be evaluated against SARS-CoV-2. However, recent hype on hydroxychloroquine or chloroquine, for example, as COVID-19 therapy should be handled carefully, as some studies claimed unprecedented side-effects posed by these anti-malarial drugs (Mehra et al., 2020). Simultaneously, the path to vaccine development also needs to be minimized for long-term protection, of course addressing all the possible side-effects. As viruses are prone to frequent mutation, vaccines based on a single target might not work for a longer time. Recently, in silico studies identified several protein subunits as vaccine candidates, combining them into a single vaccine or multiple epitope vaccines might give better results against SARS-CoV-2.

In this review, we revisited the current knowledge on the potential drug targets of therapeutic promise against SARS-CoV-2 infection and highlighted the application of the drug repurposing approach. The possible therapeutic options that are currently under clinical and preclinical studies have been discussed. We also compiled the current clinical trials mostly based on repurposing the therapeutic agents formerly designed for other indications that have been rapidly started during the early phase of the pandemic and are currently undergoing. Although far from practical application, significant progress has been made in vaccine development. Overall, this current effort leaves some valuable information on prospective druggable targets and current options of possible therapeutic as well as preventive strategies, providing a comprehensive and systematic guideline for those who are dedicated to COVID-19 research.

Beyond the approaches that have been addressed in this review, the strategies aimed at priming the host immune responses are of great potential as individuals with a compromised immune system are particularly vulnerable to COVID-19. Moreover, along with viral-specific therapeutics, immunomodulatory and anti-inflammatory agents acting against nonspecific inflammatory responses also need to be focused. The lessons learned from this emerging pandemic can help us prepare in advance for any possible future epidemics. As we live in the era of big data, systematic and multidisciplinary approaches need to be employed to find drug targets and repurposing drugs for instant drug discovery.

TABLE 5 Potential vaccine candidates for SARS-CoV-2 that are under different stages of clinical trials

Technology	Vaccine	Status of trial	Sponsor/collaborators	NCT number
D NA-based vaccine	INO-4800	Phase 1	Inovio Pharmaceuticals	NCT04336410
	bacTRL-Spike	Phase 2	Symvivo Corporation, University of British Columbia, Dalhousie University	NCT04334980
Inactivated virus	CoronaVac (SARS-CoV-2 inactivated vaccine)	Phase 1/2	Sinovac Biotech Co.	NCT04352608, NCT04383574
	V-SARS	Phase 1/2	Immunitor LLC	NCT04380532
Modified APC	LV-SMENP-DC	Phase 1/2	Shenzhen Geno-Immune Medical Institute	NCT04276896
	AV-COVID-19	Phase 1/2	Aivita Biomedical, Inc.	NCT04386252
	Covid-19/aAPC vaccine	Phase 1	Shenzhen Geno-Immune Medical Institute	NCT04299724
Nonreplicating viral vector	AZD1222 (ChAdOx1 nCoV-19)	Phase 1/2/3	Consortium of the Jenner Institute, Oxford Biomedica, University of Oxford	NCT04324606, EudraCT 2020–001072-15, EudraCT 2020–001228-32
	Ad5-nCoV	Phase 1/2	CanSino Biologics Inc., Institute of Biotechnology and so on	NCT04313127, NCT04341389, NCT04398147, ChiCTR2000031781, ChiCTR2000030906
Protein subunit	NVX-CoV2373 (SARS-CoV-2 rS)	Phase 1	Novavax	NCT04368988
	SCB-2019	Phase 1	Clover Biopharmaceuticals	NCT04405908
RNA-based vaccine	BNT162	Phase 1/2	Biontech RNA Pharmaceuticals GmbH, Pfizer	NCT04380701, NCT04368728, EudraCT 2020-001038-36
	mRNA-1273	Phase 1	Moderna, NIAID	NCT04283461
Repurposed vaccine	Bacille Calmette-Guerin (BCG) vaccine	Phase 3/4	University Medical Center Utrecht, Radboud University and so on	NCT04328441, NCT04350931, NCT04362124, NCT04379336, NCT04347876, NCT04327206, NCT04369794, NCT04373291, NCT04384549, NCT04348370, NCT04384614, NCT04387409
	Measles-mumps-rubella (MMR) vaccine	Phase 3	Kasr El Aini Hospital	NCT04357028

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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