Received: 15 May 2020 | Revised: 15 June 2020 | Accepted: 1 July 2020

DOI: 10.1002/ddr.21720

REVIEW

DDR WILEY

Designing therapeutic strategies to combat severe acute respiratory syndrome coronavirus-2 disease: COVID-19

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Abstract

A highly contagious coronavirus disease COVID-19 caused by a recently identified severe acute respiratory syndrome CoV-2 (SARS-CoV-2) initially detected in Wuhan, China has spread worldwide and become a major health crisis in the absence of specific vaccine or antiviral drugs. SARS-CoV-2 infection has resulted in overwhelming number of reported deaths. Unfortunately it is still spreading uncontrollably despite implementing stringent protective measures. Rapid development of effective therapeutic strategies for treatment and prevention of infection is crucially required. Although genomic characterization has assisted in unfolding various aspects of SARS-CoV-2 but development of specific antiviral drugs and vaccine against COVID-19 is still a worldwide challenge. Understanding the disease pathological course underlying the clinical manifestations of COVID-19 is imperative to identify the vital targets for drug development. SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) receptor to enter the host cell and primarily target type II alveolar cells. COVID-19 disease progression is associated with distressed immune functions and hyper active inflammatory system leading to development of cytokine storm which is a vital factor involved in disease advancement. The current review elucidates the disease pathology and summarizes the possible therapeutic options to battle against COVID-19 on the basis of current state of understanding about SARS-CoV-2 pathogenic pathways and knowledge gained from previous SARS and MERS-CoV epidemics. Therapeutic strategies to treat and prevent infection as well as to suppress the disease progression to reduce severity and mortality rate is discussed. Drug candidates currently under consideration and undergoing clinical trials for COVID-19 treatment are highlighted.

KEYWORDS

anti-inflammatory, antiviral, disease pathology, pharmacologic treatment, SARS-CoV-2, viral entry blockers

1 | INTRODUCTION

COVID 19 is a highly contagious respiratory tract infection caused by recently identified severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) originated from Wuhan, China (Wang et al., 2020). Unrestrained global spread of SARS-CoV-2 has resulted in 42,58,666 infected cases with ample number of reported deaths (2,94,190) across the world as on May 15, 2020 as per WHO report. Its extraordinary human to human transmission efficiency leading to irrepressibly increasing global incidents on such an alarming rate exhibited high potential for a pandemic (Chan et al., 2020; Li et al., 2020). The lack of specific antiviral medication or vaccine against SARS-CoV-2 poses

great challenge in front of drug development and healthcare workforces. Early availability of genomic characterization data has essentially facilitated in understanding various aspects of novel SARS-CoV-2 (Chan et al., 2020; Lu et al., 2020). SARS-CoV-2 is known to utilize the same entry portal as used by SARS-CoV (severe acute respiratory syndrome coronavirus), type 1 transmembrane angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell through fusion between viral and cellular membrane assisted by host cell proteases (Zhou et al., 2020a, b). Receptor binding domain is present in S1 subunit of the spike glycoprotein whereas S2 subunit contains the fusion peptide. Biochemical interactive investigations and crystal structure analysis suggest that greater binding affinity of SARS-CoV-2 spike toward ACE2 receptor as compared to SARS-CoV is accountable for enhanced infectivity (Walls et al., 2020; Wrapp et al., 2020). ACE2 receptor not only serves as the entry point for SARS-CoV-2 but has implications in pathological progression of the disease (Kuba et al., 2005). The physiological distribution and expression of ACE2 largely explains the pattern of virus propagation in target organs, susceptibility to infection and patient symptoms in COVID-19. It is interesting to note that ACE2 receptor is present more abundantly in type II alveolar epithelial cells, enterocytes of the small intestine and vascular endothelial cells (Hamming et al., 2004; Jia et al., 2005). Large abundance of ACE2 receptors in alveolar type II cells makes them more vulnerable target for SARS-CoV-2. Although primary organ of target for SARS-CoV-2 is lungs however the disease progression is associated with multi organ injury affecting the heart and kidney more severely. The most common clinical symptoms of SARS-CoV-2 infection are fever, cough, headache, sore throat, myalgia, and difficult breathing. Patients in critical condition may also develop acute respiratory distress syndrome (ARDS), respiratory failure, acute cardiac injury, coagulation abnormalities, disturbed immune system causing amplified cytokines release, and multiple organ failure resulting in death (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020). Several independent retrospective studies have assessed the risk factors associated with disease severity and stipulated older population with immune-compromised/co-morbid conditions as more vulnerable targets (Wang et al., 2020; Zhou et al., 2020a, b). A cohort study involving 1,590 polymerase chain reaction (PCR)-confirmed COVID-19 cases reported a direct association between any pre-existing pathological conditions (underlying disorder) and severity of COVID-19 with cardiovascular ailments being the most prevalent comorbidity reported in COVID-19 patients (Guan et al., 2020; Yang et al., 2020). Presence of more than one comorbidity further intensifies the risk of severe outcomes including lung injury and acute respiratory distress syndrome (ARDS) leading to death (Yang et al., 2020). Looking at the infectivity and mortality rate of SARS-CoV-2 incidents the development of novel therapeutic strategies to combat COVID-19 is essential at the moment. Scientists around the world are tirelessly occupied in finding a reliable treatment option and vaccine to fight against SARS-CoV-2. The current review elucidates the disease pathology and summarizes the possible therapeutic options to battle against COVID-19 on basis of current state of understanding about SARS-CoV-2 pathogenic pathways and knowledge gained from previous SARS (severe acute respiratory syndrome) and MERS (middle east respiratory syndrome) CoVs epidemics. Therapeutic drugs currently under consideration and undergoing clinical trials are highlighted. A three stage treatment strategy design is discussed under following heads; viral entry blockers, inhibiting the viral life cycle and methods to suppress the disease progression.

2 | DISEASE PATHOLOGY

Most of the symptoms of SARS-CoV-2 infection are nonspecific and indistinguishable from other common respiratory infections. Clinical diagnosis is largely based on epidemiological history, clinical manifestations, and some laboratory examinations (Jin et al., 2020). Fluorescence reverse transcriptase-polymerase chain reaction (RT-PCR) is used to detect the presence of genetic material of SARS-CoV-2 in sputum, throat swabs and lower respiratory tract secretions samples. Extensive laboratory test findings comprise higher leucocyte count, increased erythrocyte sedimentation rate (ESR), elevated C-reactine protein (CRP), creatinine kinase, lactate dehydrogenase, increased thrombogenic biomarkers D-dimer, and prolonged prothrombin time (Huang et al., 2020). The increased ratio of neutrophils versus lymphocytes is considered as a negative prognostic factor. Elevated levels of myocardial biomarkers- troponin level, creatine kinase (CK), creatine kinase MB isoenzyme (CK-MB), and lactate dehydrogenase indicate myocardial injury (Bonow et al., 2020). Alterations in biomarkers of multi-organ injury become prominent in later stages of disease course. Increased release of plasma pro-inflammatory cytokines (IL-1b, IL-1, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor, granulocyte-macrophage colony stimulating factor, interferon-γ-inducible protein (IP10), monocyte chemo attractant protein (MCP1), platelet derived growth factor (PDGF), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF)) is associated with disease progression causing cytokine storm syndrome resulting in ARDS and even death in more severe cases (Conti et al., 2020). Of all the inflammatory mediators serum levels of interleukin 6 (IL-6) and TNF-α are increased most prominently and reflected as biomarker of cytokine storm. Elevated serum level of IL-6 not only induces cytokine storm but also increases vascular permeability with resultant interstitial oedema. CD4-positive T cells and natural killer (NK) cells were most prominent among raised infiltrating lymphocytes causing lymphocytopenia. The data obtained from analysis of 123 hospitalized patients showed significant reduction in peripheral CD8-positive T cells 28.43% and 61.9% in mild and severe group, respectively, and the NK cells reduction was 34.31% and 47.62% in mild and severe groups, respectively (Wan et al., 2020). Ground-glass opacification with or without consolidative abnormalities is revealed as hallmark of COVID-19 infection in Chest computed tomography (CT) (Huang et al., 2020). A hyper stimulated host immune response has been suggested as the starting point of lung injury mediated by uncontrolled and augmented release of pro-inflammatory cytokines (Fu et al., 2020). Pathological pattern (Figure 1) suggests that SARS-CoV-2 infection

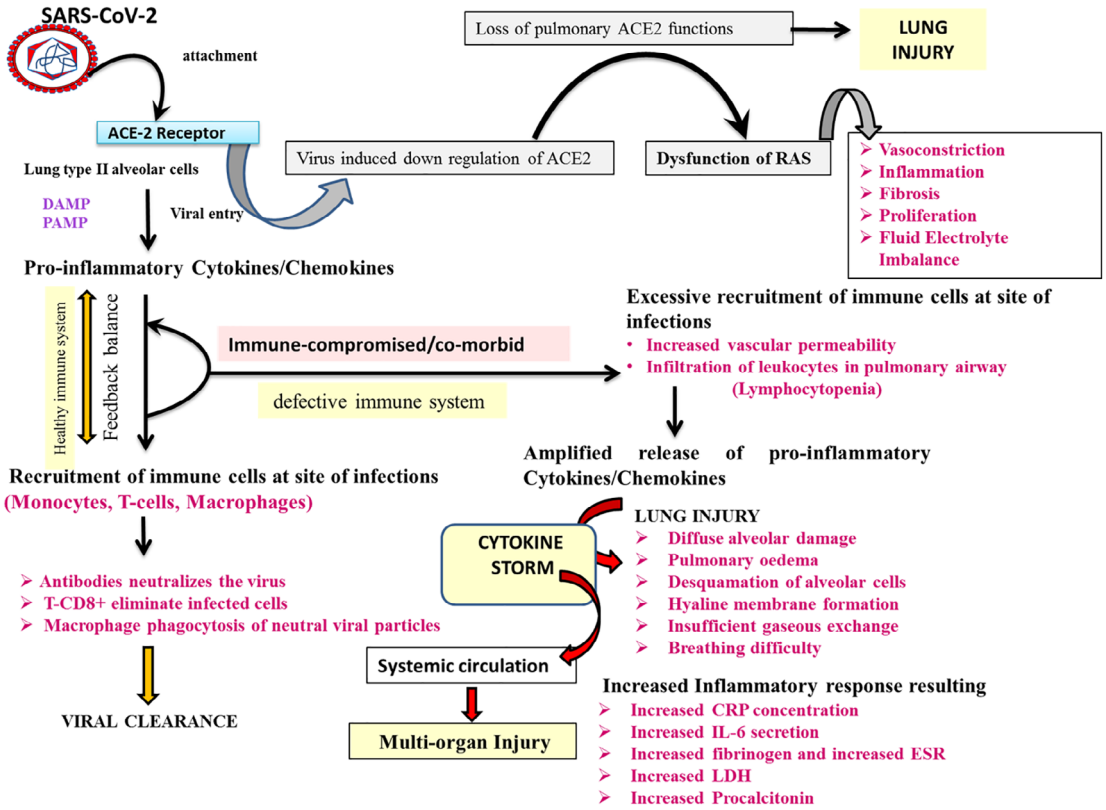

FIGURE 1 Pathological events underlying the covid-19 disease. ACE2, angiotensin converting enzyme 2; CRP, C-reactive protein; DAMP, damage-associated molecular pattern; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; LDH, lactate dehydrogenase; PAMP, pathogen-associated molecular pattern; RAS, Renin angiotensin system; SARS CoV-2, severe acute respiratory syndrome coronavirus-2

is associated with distressed immune functions and hyper active inflammation system leading to development of cytokine storm. Additionally, SARS-CoV-2 invasion induced down regulation of ACE2 receptor with subsequent altered renin angiotensin system (RAS) functions play a vital role in pathogenic progression of disease (Kuba et al., 2005). ACE2 receptor is an imperative counter regulatory element of RAS involved in catalyzing the conversion of key vasoconstrictor peptide angiotensin II to angiotensin 1–7 which on contrary has vasodilatory properties (Patel et al., 2017). Angiotensin II exerts its vasoconstrictory, pro-inflammatory, profibrotic, and oxidative effects via AT-1 type receptor. Protective effects of ACE2 in lung injury have been evaluated and well established in several animal models of ARDS (Imai et al., 2005, 2008). The virus induced down regulation of ACE-2 expression renders the enzyme unable to display anti-inflammatory, antifibrotic and protective effects in lungs and contribute to disease worsening. Down regulation of ACE2 activity in lungs is accompanied with neutrophil infiltration, increased pulmonary vascular permeability, and resultant oedema instigating the acute lung injury. Augmented release of pro-inflammatory cytokines further promotes severe lung inflammatory damage (Fu et al., 2020). Besides the diminished local protective effects in lungs, ACE2 is also not available to perform its designated role of hydrolyzing the vasoconstritory peptide angiotensin II resulting in accumulation of angiotensin II and consequent uncontrolled AT-1 type receptor activation. This impaired cascade of events results in abnormal vasoconstriction causing endothelial dysfunction, pulmonary fibrosis, hypertension, hyper coagulation, thrombosis, amplified inflammation, and thus contribute in overall enhanced disease severity. Over activation of angiotensin II causes far reaching deleterious effects in immune-compromised/co-morbid patients. Angiotensin II disturbs adaptive immune coordination and upsurges inflammatory chemokines and cytokines production with consequent ARDS (Bernstein et al., 2018). Moreover, elevated plasma level of angiotensin II is reported as an indicator of SARS-CoV-2 viral load and is directly related to disease severity. Angiotensin-1-7 is a significant active product of RAS system which mediates vasodilatory, anti-inflammatory, antifibrotic, antiatrophy and antiproliferative effects via G-protein coupled mas receptor as well as activation of AT-type 2 receptor (Patel et al., 2017). Under normal circumstances angiotensin-1-7 can be generated either by direct hydrolysis of angiotensin II or indirectly ACE2 mediated conversion of Angiotensin-I via Angiotensin-1-9 intermediate which is then cleaved by neutral endopeptidase or ACE enzyme. Angiotensin-1-7 deficiency due to loss of cellular ACE2 activity further increases the complexity of disease severity. Above observations suggest a critical role of disturbed RAS system in the signaling abnormal cellular and molecular events accountable for disease progression of COVID-19.

3 | TREATMENT STRATEGIES

Unfortunately the SARS-CoV-2 infection is spreading in uncontrolled way despite implementing stringent protective measures. It is essential to understand and exploit various host and viral factors for developing prophylactic and therapeutic approaches to combat COVID-19. Various therapeutic strategies and candidate drugs to combat COVID-19 are presented in Table 1.

3.1 | Viral entry blockers

Strategies to interfere with viral and host protein interactions to block viral invasion in host cell represent effective approach for preventing viral infection and propagation at an early stage. There are two ways by which SARS-CoV-2 can gain cell entry, either via receptor mediated endocytosis or via host-viral membrane fusion. In both ways spike glycoprotein is the point of attachment of SARS-CoV-2 to the target membrane bound angiotensin-converting enzyme 2 (ACE2) receptor. Presence of receptor binding domain in viral spike protein put forward glycoprotein spike as major target for development of anti SARS-CoV-2 drugs. Chemical structures of putative SARS-CoV-2 entry blockers is presented in Figure 2.

3.1.1 | Griffithsin

It is a carbohydrate-binding, red algae-derived protein having broad spectrum antiviral activity. It potentially binds the surface oligosaccharides of viral glycoprotein and does not allow spike interactions with target receptor (O'Keefe et al., 2010). By disrupting the initial viral-host interface interactions griffithsin avert viral intracellular passage and constitute a pre-exposure prophylactic opportunity against SARS-CoV-2.

3.1.2 | Host cellular proteases inhibitors

A cellular surface complex embracing an ACE2 receptor and assisting protease TMPRSS2 operates as a portal for SARS-CoV-2 cell entry (Hoffmann et al., 2020a). Spike protein encompasses two functional units S1 and S2 subunits responsible for attachment with host receptor and membrane fusion, respectively. Furin dependent S1/S2 cleavage uncover the fusion domain followed by TMPRSS2 mediated spike protein activation leading to conformational changes in spike protein which is a crucial phenomenon for membranes fusion and successful entry of SARS-CoV-2 (Coutard et al., 2020; Hoffmann et al., 2020). Inhibition of cellular proteases associated with cleavage and activation of viral spike comprises an efficient tool for opposing the viral invasion.

Furin convertase inhibitors

Acquisition of a polybasic cleavage region specifically processed by an endoprotease furin plays a dynamic role in SARS-CoV-2 viral spike slicing and host cell penetration (Walls et al., 2020). Furin convertase inhibitors by obstructing the S1/S2 cleavage fundamental for membrane fusion can greatly alter the pathogenicity of SARS-CoV-2 and prevent furin facilitated viral entry into target cells.

TMPRSS2 inhibitors

TMPRSS2 serine protease is critical for post-cleavage activation of spike protein and preparing for the viral and cellular membrane fusion. It is reported that camostat mesylate, a clinically approved serine protease TMPRSS2 inhibitor potentially reduces viral penetration in host cell (Hoffmann et al., 2020). Nafamostat mesylate an amino guanidine derivative is another approved TMPRSS2 serine protease inhibitor previously studied as MERS-CoV inhibitor is also reported to display SARS-CoV-2 inhibitory activities (Hoffmann et al., 2020; Yamamoto et al., 2016).

3.1.3 | Receptor mediated endocytosis inhibition

Obstructing the receptor-mediated endocytosis is a captivating way to block the SARS-CoV-2 cell penetration and intracellular assemblage of viral particles.

Clathrin mediated endocytosis inhibitors

Clathrin mediated endocytosis is regulated through AP 2 associated protein kinase 1 (AAK1) as well as cyclin G associated kinases (CGK). Baricitinib an FDA approved antirheumatic drug is reported to inhibit AAK1 and CG kinases both and disrupt endocytosis facilitated viral trafficking across the membrane (Richardson et al., 2020). Baricitinib is currently under clinical trials to assess its efficacy and safety in COVID-19 patients. Chlorpromazine, a well-known antipsychotic medication is also known to interfere with clathrin coated vesicle assembly and unveiled antiviral activity against SARS and MERS-CoVs in vitro (Inoue et al., 2007; de Wilde et al., 2014). Thus chlorpromazine is also anticipated to serve as anti-SARS-CoV-2 agent.

Endosomal acidifier inhibitors

A popular antimalarial drug chloroquine increases the endosomal pH and makes the environment more alkaline which is unsuitable for host-viral membrane fusion thus suspend the viral genome release and replication (Savarino et al., 2003). Chloroquine and derivatives are also reported to interfere with ACE-2 receptor glycosylation pattern and impairs its interaction with viral spike protein thus hamper viral cell access (Savarino et al., 2006).

Umifenovir

Umifenovir, an indole derivative popularly known as arbidol is a broad spectrum antiviral compound (Pécheur et al., 2016). Arbidol exerts viral entry inhibitory properties by disturbing the membrane fluidity leading to conformational rearrangements and making the lipid bilayer less disposed to fusion (Teissier et al., 2011). Arbidol is

TABLE 1 Treatment strategies and candidate drugs for the treatment of COVID-19

Compound	Class	Treatment strategies	Mechanism of action	References
Griffithsin	Red algae derived protein	Spike glycoprotein inhibition	It binds surface oligosaccharides of viral glycoproteins and thereby blocks virus–host cell binding	O'Keefe et al. (2010)
Furin convertase inhibitors	Protease inhibitor	Non-endosomal viral entry inhibition	Inhibit furin dependent S1/S2 cleavage	Walls et al. (2020)
Camostat mesylate	Serine protease inhibitor	Non-endosomal viral entry inhibition	Inhibit host serine protease TMPRSS2 mediated activation of viral spike protein	Hoffmann et al. (2020)
Nafamostat mesylate	Serine protease inhibitor	Non-endosomal viral entry inhibition	Inhibit host serine protease TMPRSS2 mediated activation of viral spike protein	Hoffmann et al. (2020)
Baricitinib	JAK inhibitor	Receptor mediated endocytosis inhibition Suppress disease progression	Bind AP 2 associated protein kinase 1 (AAK1) Inhibit cyclin G associated kinase (CGK) Inhibition of janus kinase-STAT pathway	Richardson et al. (2020)
Chlorpromazine	Antipsychotic	Receptor mediated endocytosis inhibition	Interfere with clathrin coated vesicle assembly	de Wilde et al. (2014) and Inoue et al. (2007)
Umifenovir	Antiviral	Inhibit host cell-viral membrane fusion	Disturb the membrane fluidity leading to conformational rearrangements and makes the lipid bilayer less unsuitable for fusion	Teissier et al. (2011)
Chloroquine	Antimalarial	Prevent viral entry Arrest disease progression	Interfere with ACE2 receptor glycosylation Endosomal acidification inhibition Anti-inflammation immunomodulation	Savarino et al. (2006) Savarino et al. (2003)
Teicoplanin	Glycopeptide antibiotic	Cathepsin protease inhibition	Blocks cathepsin protease mediated cleavage of spike protein in late endosomes	Zhou et al. (2016)
Lopinavir	Antiviral	Viral protease (3CL pro) inhibition	Inhibits proteolysis of viral polyproteins and interrupt viral replication cycle	Chu et al. (2004)
Ritonavir	Antiviral	Viral protease (3CL pro) inhibition	Inhibits proteolysis of viral polyproteins and interrupt viral replication cycle	Chu et al. (2004)
Disulfiram	Irreversible acetaldehyde dehydrogenase inhibitor	Viral protease (PL2pro) inhibition	Inhibits proteolysis of viral polyproteins and interrupt viral replication cycle	Lin et al. (2018)
Aloe emodin	Plant-derived phenolic compound	Viral protease (3CL pro) inhibition	Inhibits proteolysis of viral polyproteins and interrupt viral replication cycle	Lin et al. (2005)
Hesperetin	Plant-derived phenolic compound	Viral protease (3CL pro) inhibition	Inhibits proteolysis of viral polyproteins and interrupt viral replication cycle	Lin et al. (2005)
Remdesvir	Antiviral	RNA dependent RNA polymerase inhibition	Premature chain termination and viral protein synthesis inhibition	Tchesnokov et al. (2019)
Favipiravir	Antiviral	RNA dependent RNA polymerase inhibition	Incorporates into the nascent viral RNA and blocks viral replication and transcription process	Furuta et al. (2013)

(Continues)

TABLE 1 (Continued)

Compound	Class	Treatment strategies	Mechanism of action	References
Ribavirin	Antiviral	RNA dependent RNA polymerase inhibition	Inhibits viral RNA synthesis and mRNA capping. Reduction of the intracellular GTP pool	Wray et al. (1985)
Saracatinib	Dual kinase inhibitor (Src/abl family of kinases inhibitor)	Inhibit viral replication	Selective inhibition of Src-family of tyrosine kinases (SFK) signaling and prevent viral replication	Shin et al. (2018)
Resveratrol	Phytogenic polyphenol	Inhibit virion assembly	Reduces expression level of nucleocapsid protein (N) and prevent virion assembly	Lin et al. (2017)
Oseltamivir	Antiviral	Inhibit new viral particles exocytosis	Inhibits neuroamidase enzyme (NA) and prevent exocytosis	Schirmer and Holodniy (2009)
Tocilizumab	Humanized monoclonal antibody	Interleukin (IL)-6 inhibition	Prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors	Xu et al. (2020)
Siltuximab	Recombinant monoclonal antibody	Interleukin (IL)-6 inhibition	Prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors	Raimondo et al. (2017)
Sarilumab	Human monoclonal antibody	Interleukin (IL)-6 inhibition	Prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors	Gritti et al. (2020)
Anakinra	Interleukin-1 receptor antagonist	Interleukin (IL)-1 inhibition	Inhibits the proinflammatory cytokines interleukin (IL)-1α and (IL)-1β and prevent hyper-inflammation	Goldbach-Mansky (2009)
Adalimumab	Monoclonal antibody	Tumor necrosis factor (TNF) α inhibition	Inhibits tumor necrosis factor (TNF) α and prevent TNF dependent cytokine cascade and tissue damage	Huang et al. (2020)
Recombinant human soluble ACE2 (rhACE2)	RAS modifier	ACE2 enhancement Restore renin angiotensin system balance	Neutralizes the spike glycoprotein Competitively inhibit SARS-CoV-2 interactions with host cell receptor	Imai et al. (2005) and Lei et al. (2020)
Losartan	Angiotensin AT1 receptor blocker	Restore renin angiotensin system balance	Block angiotensin II mediated tissue damaging effects exerted by activation of AT1 receptor	Fu et al. (2020)
AVE0091	Non peptide selective mas receptor agonist	Restore renin angiotensin system balance	Increase tissue protective effects mediated by mas receptor activation	da Silveira et al. (2010)

also reported to prevent viral entry by inhibiting clathrin dependent trafficking. (Blaising et al., 2013). Arbidol represents a privileged molecule instigating early intervention with viral-host cell membrane fusion as well as stimulate immunogenic response and weaken pathogenic progression (Glushkov & Gus' kova, 1999; Teissier et al., 2011). In a recent study umifenovir (400 mg, thrice a day) significantly reduced viral load and mortality rate in COVID patients (Cao et al., 2020). Arbidol administration along with standard lopinavir/ritonavir therapy greatly improved clinical symptoms compared to the control group receiving only lopinavir/ritonavir and proved a bonus drug (Deng et al., 2020). Several clinical studies are aiming to comprehend its potential against SARS-CoV-2 induced pneumonia.

3.2 | Inhibition of viral replication

Targeting various integral elements of viral life cycle is a promising approach to attenuate viral pathogenicity and further spread in the host cell. Figure 3 is a representation of key steps involved in SARS-CoV-2 life cycle (Fehr & Perlman 2015). After entering the host cell viral genetic material is exposed intracellularly. Single strand positive

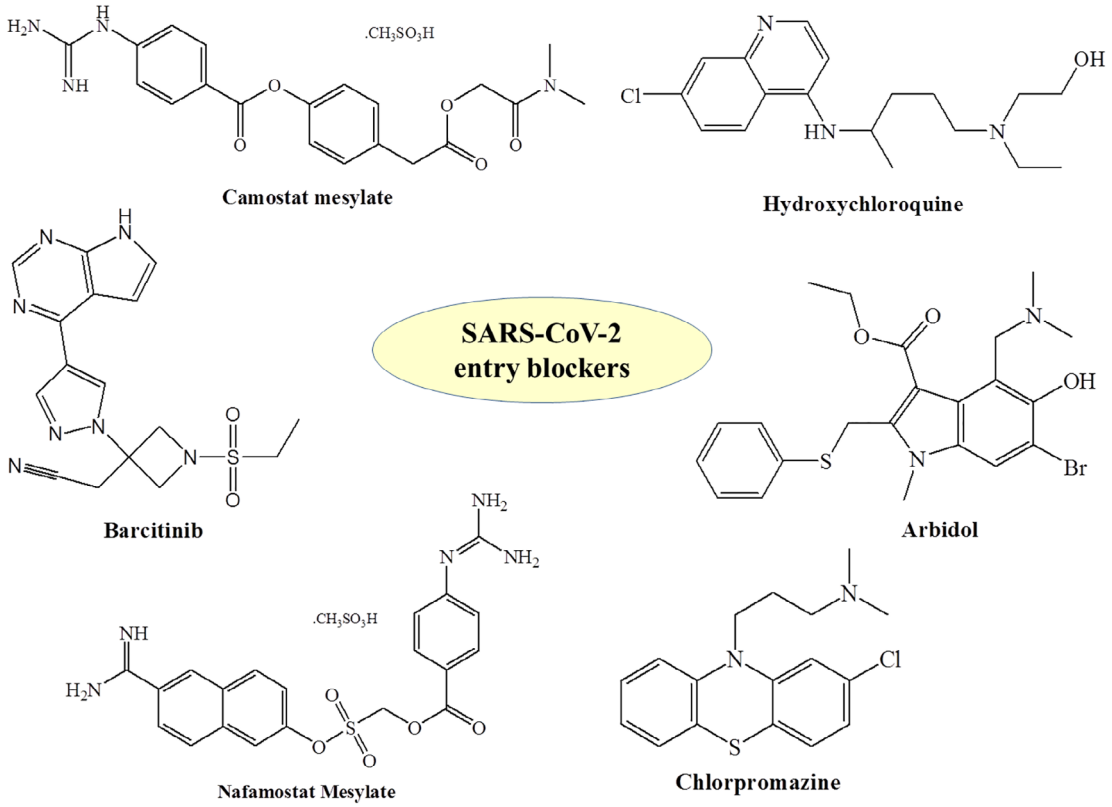

FIGURE 2 Chemical structures of putative SARS-CoV-2 entry blockers

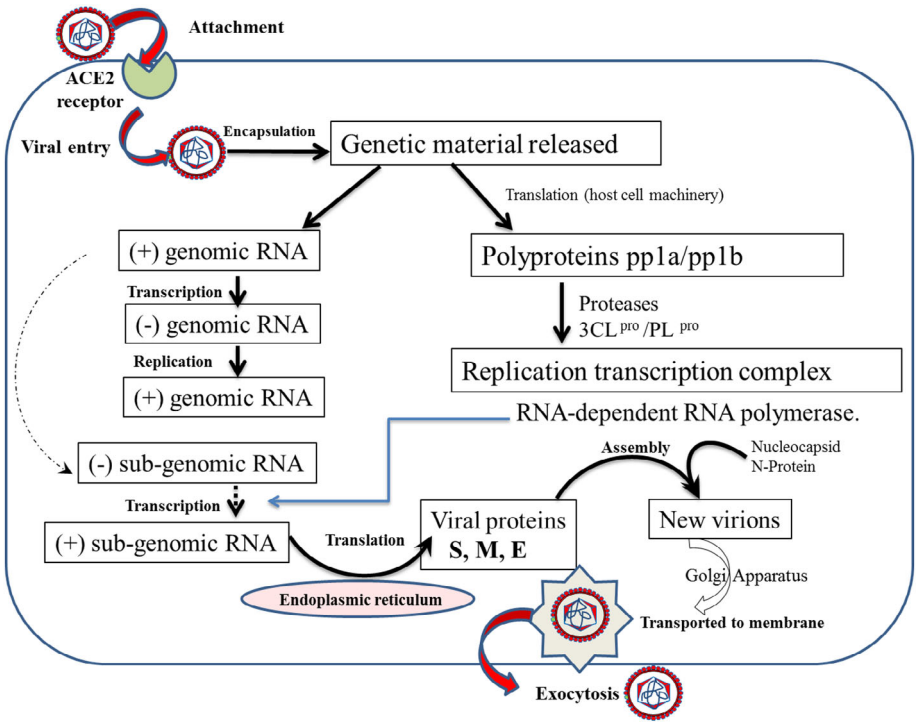

FIGURE 3 Key events involved in SARS-CoV-2 viral life cycle

sense viral RNA is capable of exploiting the host cell machinery ribosomes for translating polyproteins pp1a/pp1b which upon proteolysis generates several nonstructural proteins coalescing to form replication transcription complex including RNA dependent RNA polymerase. Hydrolysis of polyproteins pp1a/pp1b is conducted by cysteine proteases, namely the 3 chymotrypsin-like protease (3CLpro) and the

secondary papain-like protease 2 (PL2pro). Various candidate drugs which intrusively obstruct the crucial replication and transcription of SARS-CoV-2 to halt viral propagation are presented in Figure 4.

3.2.1 | Protease inhibitors

Lopinavir an FDA approved treatment for antihuman immunodeficiency virus (HIV) inhibits proteases dependent proteolysis of viral polyproteins (3CL Pro) and hinders the replication and synthesis of viral RNA. Concomitant administration of ritonavir is associated with enhanced plasma concentration, half-life and antiviral efficiency of lopinavir (Sham et al., 1998) A combination therapy of lopinavir–ritonavir sold under the brand name Kaletra™ along with ribavirin displayed synergistic effects and noteworthy reduction in viral load in SARS-CoV patients (Chu et al., 2004). Adding interferon INF in above mentioned combination further improved clinical outcomes in MERS infected cases (Kim et al., 2016). The results obtained in MERS and SARS-CoVs cases are encouraging and advocate consideration of these agents against COVID-19. Several clinical studies are underway to assess the efficacy of lopinavir/ritonavir along with other antivirals in SARS-CoV-2 patients. However, the initial results obtained from a randomized trial with 199 COVID-19 patients LPV/r 400/100 mg twice daily did not show significant reduction in viral loads and statistically insignificant difference between treatment group and standard supportive care (Cao et al., 2020). Administering arbidol along with LPV-r is associated with delayed disease progression and improved clinical outcomes compared with LPV/r mono therapy (Deng et al., 2020). However, the later study did not include critical patients requiring invasive/noninvasive oxygen support. These findings advice early intervention and combining one or more drugs (arbidol) might offer better clinical outcomes. Disulfiram, bis(diethylthiocarbamoyl) disulfide first FDA approved medication for chronic alcoholism revealed irreversible inhibitory effects on papain-like protease 2 in SARS as well as MERS in vitro (Lin et al., 2018) advocating its probable role in reducing SARS-CoV-2 infection. Cathepsin-L is another imperative host cell protease accessible for S-protein priming. Selective inhibitors of human cathepsin L (SID 26681509, teicoplanin) can substantially block the release of single stranded RNA viral genome in cytoplasm and arrest viral replication at a very beginning stage. Teicoplanin a glycopeptide antibiotic is reported to inhibit cathepsin L driven cleavage of spike protein at low pH in late endosomes with proven efficacy against MERS, SARS-CoVs (Zhou et al., 2016). Teicoplanin successfully inhibited SARS-CoV-2 at micro molar concentrations (IC50 of 1.66 μM) in vitro (Baron et al., 2020). Advanced investigations are recommended to further assess its antiviral effectiveness as future anti-COVID-19 drug. Two phenolic compounds aloe emodin and hesperetin are also reported to suppress proteolytic processing of replicase polypeptides in SARS-CoV by inhibiting 3C-like protease in a dose dependent manner and halts viral propagation (Lin et al., 2005).

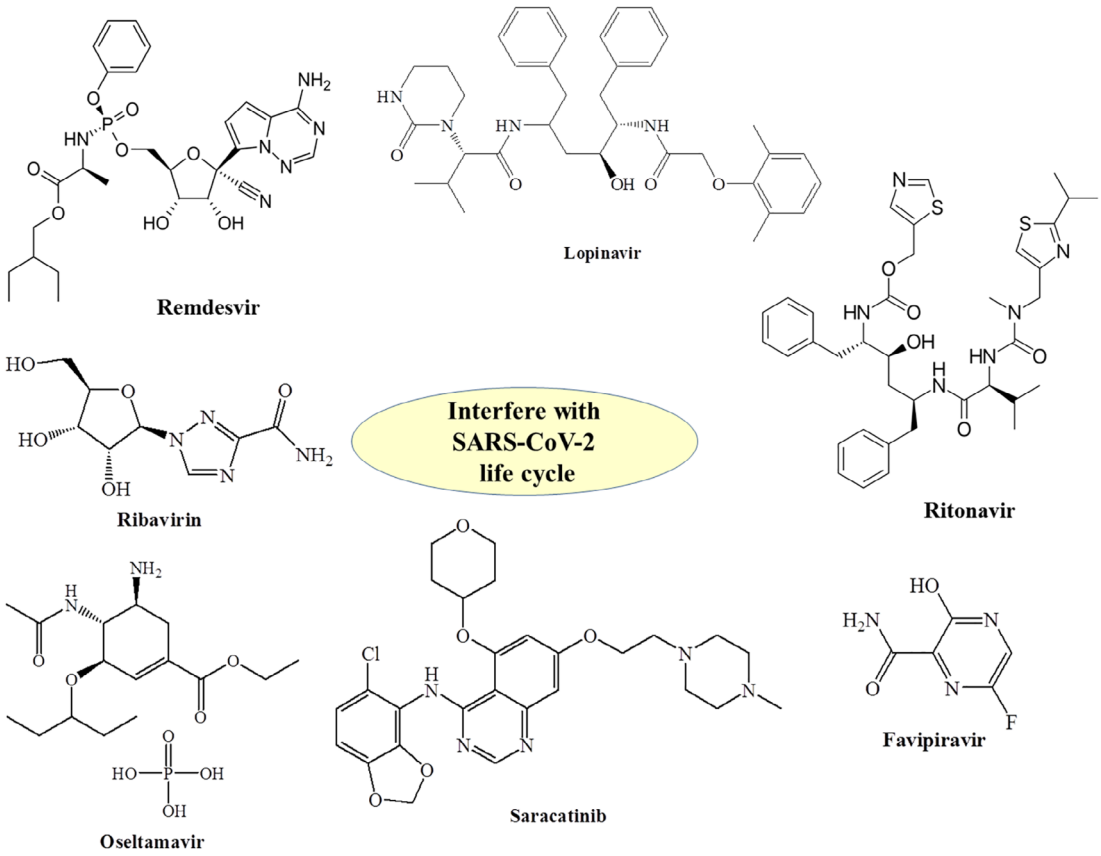

FIGURE 4 Candidate drugs interfering with SARS-CoV-2 replication cycle

3.2.2 | RNA dependent RNA polymerase inhibitors

RNA dependent RNA polymerase is a crucial enzyme involved in viral replication cycle inhibition of which reduces the viral ability to replicate in host cell and prevent further viral spread and infection.

Remdesvir

Remdesvir a monophosphoramidate prodrug of adenosine analog restrict the RNA dependent RNA polymerase functions by premature chain termination and consequent viral protein synthesis inhibition (Tchesnokov et al., 2019). Originally developed to combat ebola virus remdesvir also displayed antiviral effects against wide range of RNA viruses including SARS, MERS, filovirus and pneumoviruses etc. (Sheahan et al., 2017). Recently remdesvir revealed inhibitory effects (EC90 of 1.76 μM) against SARS-CoV-2 in an in vitro cell culture study (Wang et al., 2020). Encouraging results obtained from first COVID-19 patient in U.S. treated with remdesvir further augmented interest in remdesvir as a hopeful candidate to treat COVID-19 (Holshue et al., 2020). In a cohort study involving 53 patients from US, Europe and Japan of whom 34 patients required intensive care (4 on extracorporeal membrane oxygen support and 30 patients received mechanical ventilation) improved clinical symptoms were observed in 68% (36 of 53) cases. However mortality rate was higher among patients receiving invasive ventilation 18% (6 out of 34) as compared to those who were not 5% (1 out of 19) (Grein et al., 2020). Currently several clinical studies are undergoing to evaluate its safety and therapeutic efficacy in COVID-19 patients.

Favipiravir

Favipiravir, chemically a pyrazine carboxamide derivative (Avigan, an approved anti-influenza treatment) is a prodrug and gets converted to its active metabolite intracellularly (Furuta et al., 2017). Triphosphorylated form of favipiravir (favipiravir ribofuranosyl-5′-triphosphate) is a selective inhibitor of RNA dependent RNA polymerase and disrupt viral replication process. Being a guanosine analog it is mistakenly incorporated into the nascent viral RNA and block the integration of required nucleotide for viral replication and transcription process. It displays antiviral effects against broad spectrum of RNA viruses such as arena virus, ebola virus, alpha virus, flavi virus, lassa virus, bunya virus, and filo virus (Furuta et al., 2013, 2017). In a preliminary data obtained from 80 patient's clinical study favipiravir displayed superior clinical effects and less adverse reactions as compared to (LPV/ RTV) treatment and reported reduced viral clearance time with favipiravir (Cai et al., 2020). Another randomized clinical trial (ChiCTR200030254) including 240 COVID-19 patients reported higher efficacy of favipiravir in terms of clinical recovery rate (71.43%) as compared to umifenovir (55.86%) (Chen et al., 2020). Currently favipiravir is undergoing various trials alone (NCT04336904) and in combination with humanized monoclonal antibody tocilizumab targeting IL-6 receptor to assess their potential use in COVID-19 treatment (NCT04310228). Other clinical trials assessing combination therapy (favipiravir in combination with chloroquine phosphate and oseltamivir, NCT04303299) for COVID-19 management are running in China.

Ribavirin

Chemically 1-(β-D-Ribofuranosyl)-1H-1,2,4-triazole-3-carboxamide, also known as tribavirin is a marketed broad spectrum antiviral drug. Its active metabolite hampers viral RNA synthesis and mRNA capping. The antiviral effect of ribavirin is presumed to operate via reduction of the intracellular GTP pool and increased faulty incorporation of the nucleoside analogue into the nascent viral RNA. Ribavirin further limits viral protein synthesis by direct inverse effects on viral polymerases (Wray et al., 1985). The dual therapy comprising ribavirin with IFN-α showed significant antiviral effect on MERS-CoV (Omrani et al., 2014). Synergistic effects of adding ribavirin along with protease inhibitors and IFN-α in SARS and MERS-CoVs inhibition have already been discussed earlier in this review (Chu et al., 2004; Kim et al., 2016). Although no convincing clinical benefit of using ribavirin alone in 2019-nCoV is observed yet. Currently several studies are undergoing to determine its role in COVID-19 treatment.

3.2.3 | Kinase inhibitors

Saracatinib an investigational drug (AZD0530) developed by Astrazeneca is reported to efficiently inhibit viral RNA replication in dengue virus in vitro (de Wispelaere et al., 2013). The underlying mechanism of action implicates selective inhibition of Src-family of tyrosine kinases (SFK) signaling and preventing viral replication. Saracatinib is reported to disrupt MERS-CoV replication process in vitro with EC_{50} around 3 μM in huh-cells (Shin et al., 2018). Synergistic effects were observed against MERS CoV when gemcitabine, a deoxycytidine based chemotherapeutic agent was used along with saracatinib (Shin et al., 2018). Extracellular signal-regulated kinases (ERK)/mitogen-activated protein kinases (MAPK) also epitomize attractive targets for designing treatment course against SARS-CoV-2. Trametinib an FDA approved, selective, reversible allosteric MEK1/2 inhibitor and selumetinib (MEK1/2 inhibitor, ERK1/2 inhibitor) both demonstrated prominent MERS inhibitory activities in vitro (Kindrachuk et al., 2015). Considering these observations kinase inhibitors represent a viable opportunity for exploring SARS-CoV-2 treatment alternatives.

3.2.4 | Preventing virion assembly

Resveratrol a phytogenic polyphenol modulates various crucial genes expressions and conspicuously interferes with viral protein synthesis in a wide range of viruses including herpes simplex, influenza virus, epstein barr virus, respiratory cyntial, HIV-1, and cytomegalo virus thus making it a broad acting antiviral (Campagna & Rivas, 2010). Resveratrol is reported to potently inhibit MERS-CoV and increase cellular survival in in vitro analysis (Lin et al., 2017). Resveratrol prominently reduces the expression level of an essential structural

nucleocapsid protein thus interfere with virion assembly and prevent further viral propagation. Its well established antioxidant and anti-inflammatory properties further supplement antiviral effects exerted by resveratrol. Antiviral potential of resveratrol rationalize further assessment of its role in SARS-CoV-2 induced COVID-19 disease.

3.2.5 | Neuroamidase inhibitors

Oseltamivir sold under name tamiflu is a prophylactic and treatment method of choice for acute and uncomplicated influenza infection. It competitively inhibits neuroamidase enzyme (NA) on the viral surface and disable exocytosis of newly formed virions out of infected cells (Schirmer & Holodniy, 2009). Neuroamidase enzyme is responsible for the cleavage of sialic acids glycoconjugates operating as link between host cell surface and budding virions (Schirmer & Holodniy, 2009). Thus inhibition of NA activity is expected to block the viral propagation cycle and prevent further spread of infection. Oseltamivir is currently being studied for its prospective use in COVID-19 patients.

3.3 | Suppressing the disease progression

Pathogenesis of SARS-CoV-2 infection is primarily associated with distressed immune functions and hyper active inflammatory system affecting multiple organ functioning. Various drugs capable of regulating particular inflammatory pathway and arresting the disease progression to reduce disease severity are discussed under this section.

3.3.1 | Chloroquine/hydroxycholoroquine

Chloroquine, an aminoquinoline derivative widely used as antimalarial, antirheumatic, and autoimmune medication is currently the most used medicine for treatment of COVID-19 patients. Interference with ACE2 receptor glycosylation and altered endosomal environment mediated impaired viral entry is claimed as mode of antiviral action displayed by chloroquine (CQ) and hydroxychloroquine (HCQ) (Savarino et al., 2003, 2006). Besides its direct antiviral effect choloroquine through its anti-inflammatory and immunomodulatory properties might contribute in therapeutic management of COVID-19 patients and halt pathogenic progression of SARS-CoV-2 infection (Vincent et al., 2005). Chloroquine (CQ) and hydroxychloroquine (HCQ) can regulate immune system and reduce the cytokine storm by controlling release of pro-inflammatory chemo/cytokines and prevent ARDS. Thus chloroquine can efficiently combat SARS-CoV-2 infection at both entry and post entry level. Previous studies have witnessed the antiviral activities of CQ and HCQ against a diverse range of viral infections (Keyaerts et al., 2004; Vincent et al., 2005; Yan et al., 2013). Chloroquine is reported to selectively inhibit SARS-CoV-2 at micro molar concentration (EC50 = 1.13 μM; CC50 > 100 μM, SI > 88.50) in vitro (Wang et al., 2020). Hydroxy analog of chloroquine is considered better antiviral agent with lower toxicity and better tolerance (Liu et al., 2020). In subsequent clinical studies chloroquine phosphate is reported to be notably efficacious in alleviating SARS-CoV-2 associated pneumonia with no severe adverse effects (Gao et al., 2020). Concomitant use of azithromycin is reported to boost the antiviral effects of HCQ (Gautret et al., 2020). However, a special caution should be taken while treating patients with cardiovascular diseases due to high risk of serious cardiac adverse effects associated with concomitant and prolonged use of azithromycin and chloroquine. Further clinical trials results are awaited to ensure the efficacy and safety of HCQ in prevention and treatment of COVID-19 infected people.

3.3.2 | Interleukin (IL)-6 inhibitors

Elevated levels of interleukin-6 are believed to be the culprit responsible for disturbed and overstimulated inflammatory response and consequential cytokine storm in COVID-19 patients. Tocilizumab a humanized monoclonal antibody is a well-recognized immunosuppressant for treatment of various autoimmune ailments. Tocilizumab can effectively bind membrane bound as well as soluble form IL-6 receptor both and slowdown the IL-6 enabled cytokine storm (Sakkas, 2016). Scientific evidences are available documenting the efficacy of tocilizumab in treating cytokine storm syndrome (Le et al., 2018). Based on its capability to diminish the evil effects associated with abnormally augmented IL-6 levels the use of humanized monoclonal antibodies targeting IL-6 receptor is hypothesized to suppress the intensified inflammatory reactions and prevent disease worsening. Preliminary data obtained from 20 severely ill COVID patients treated with tocilizumab supports significant effectiveness and safety of interleukin-6 inhibitors (Xu et al., 2020). Other approved interleukin-6 antibodies siltuximab and sarilumab having similar spectrum of activity are also under consideration to neutralize over stimulated inflammatory condition in severe COVID-19 cases (Raimondo et al., 2017; Gritti et al., 2020). Clinical trials are ongoing to evaluate the effectiveness and safety profile of these drugs in treating COVID-19 patients.

3.3.3 | Interleukin (IL)-1 antagonists

Raised levels of IL-1β a pro-inflammatory cytokine and its natural antagonist detected in the blood and alveolar lavage sample of COVID-19 patients is correlated with hyper-inflammatory response and linked complications (Huang et al., 2020). Under normal circumstances IL-1β is released from nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammosome as a defensive tool in response to any danger signal. Aberrant elevation in IL-1β is associated with exuberant systemic inflammatory reaction fundamental to ARDS. It is hypothesized that antagonism of IL-1 receptor might prove advantageous in controlling hyper inflammation and linked complications. Anakinra, a recombinant human protein is an FDA approved IL-1

antagonist used for the treatment of rheumatoid arthritis and various auto-inflammatory conditions including cytokine storm syndrome (Goldbach-Mansky, 2009). Large therapeutic window and good safety profile further rationalizes the consideration of anakinra as a reasonable approach to combat COVID-19. Anakinra is currently under clinical assessment in combination with tocilizumab to understand the effect of parallel blockade of both interleukin-1 and interleukin-6 pathways. Canakinumab, (IL-1β inhibitor) and rilonacept (IL-1α/IL-1β inhibitor) (Dubois et al., 2011) might also prove helpful to reduce hyper-inflammation linked COVID-19 disease advancement. Currently, anakinra is being trialed in a randomized placebo-controlled study in children and adults with COVID-19 associated cytokine storm syndrome in China (NCT02780583).

3.3.4 | Janus kinase (JAK) inhibitors

Exuberant cytokines/chemokines release play central role in respiratory failure. Janus kinases are cytoplasmic signaling tyrosine kinases which orchestrate the immune system and regulate interferon's signaling. Inhibiting the JAK-signal transducer and activator of transcription (STAT) pathway will attenuate pro-inflammatory cytokines secretion (Rane & Reddy, 2000). Baricitinib an oral JAK inhibitor notably improved the clinical symptoms and pulmonary functional parameters in COVID-19 patients (Cantini et al., 2020). Baricitinib is also known to have an inhibitory effect on adaptor-associated kinase 1 and disrupt receptor-mediated SARS-CoV-2 endocytosis (Richardson et al., 2020). However broad immunosuppressive effects of baricitinib and possible interference with production and functions of interferons (IFNs) point toward limitation of janus kinase inhibitors for anti-COVID drug design.

3.3.5 | Tumor necrosis factor (TNF) α inhibitors

Tumor necrosis factor-α a key player in immune activation and inflammation principally released from activated macrophages is found elevated in critically ill COVID-19 patients (Huang et al., 2020). Strategies to cut down TNF-α signaling to limit the further inflammation and tissue damage would certainly prove beneficial in modifying the COVID-19 disease course. Clinical trial (ChiCTR2000030089) is underway to assess efficacy of adalimumab, a potential TNF-α inhibitor in severely ill COVID patients.

3.3.6 | Renin angiotensin system (RAS) modifiers

SARS-CoV-2 invasion induced down regulation of ACE2 receptor resulting in disturbed RAS system with subsequent unsolicited accumulation of angiotensin II is a key etiological player in SARS-CoV-2 induced COVID-19 disease advancement. Employing the methods to restore the RAS balance represent a viable approach to resist the progression of COVID-19 disease.

Recombinant human soluble ACE2 (rhACE2)

Exogenous supply of recombinant human ACE2 might neutralize the spike glycoprotein and through competitive inhibition prevent SARS-CoV-2 interactions with host cell receptor. Restoration of ACE2 through use of rhACE2 will recuperate tissue protective, anti-inflammatory, antiproliferative effects of ACE2 (Imai et al., 2005, 2008). Revival of ACE2 will also aid in systemic balance of renin-angiotensin-system functioning and resist undesired over accumulation and hyperactivity of vasoconstrictor peptide angiotensin II. ACE2 enable essential catabolism of angiotensin II for generating vasodilatory peptide angiotensin-1-7 which exhibits anti-inflammatory, antiproliferative, anti-inflammatory, antifibrotic and antioxidant properties for tissue protection. in vitro studies have demonstrated rhACE2 mediated SARS-CoV-2 inhibitory effects (Lei et al., 2020). APN01, a recombinant form of ACE2 developed by APEIRON biologics is currently under evaluation in China (NCT04287686) to assess its potential benefit in treating SARS-CoV-2 induced pneumonia.

Angiotensin AT1 receptor blocker

AT1 receptor antagonists would certainly inhibit irregular vasoconstriction and intensified inflammation caused by persistent activation of AT1 receptor due to overaccumulated angiotensin II in the absence of cellular ACE2 activity. Angiotensin II disturbs adaptive immune coordination and increases inflammatory chemokines and cytokines production with consequent ARDS (Fu et al., 2020). Moreover unavailability of AT1 receptor for binding also directs angiotensin II toward AT2 type receptor. Angiotensin II exerts tissue protective effects through AT2 type receptor activation. Further activation of G-protein coupled mas receptor by selective non-peptide agonist (AVE0091) would help revamp the vasodilatory, anti-inflammatory, antifibrosis, antiatrophy and antiproliferative effects mediated by angiotensin-1-7 (da Silveira et al., 2010). Taking together above facts it is hypothesized that restoring the disturbed renin angiotensin system would surely help in reducing the severity of symptoms in COVID-19 patients.

4 | CONCLUSIONS

SARS-CoV-2 can cause a severe, highly contagious disease primarily affecting the respiratory system with subsequent maladjusted immune functions and overactive inflammatory system instigating multiple organ failure. Genetic sequence analysis of SARS-CoV-2 has revealed significant resemblance with bat CoV and human SARS-CoV although the intermediate host is unknown yet. Angiotensin-converting enzyme 2 (ACE2) receptor is recognized as entry point for SARS-CoV-2. The current understanding of pathogenesis and proliferation of SARS-CoV-2 infection is extrapolated from the existing information about SARS-CoV. Uncontrolled spread of SARS-CoV-2 despite rigorous preventive measures has put health care system under great pressure for rapid accessibility of suitable prophylactic and treatment method to cope with this lethal virus. Considering its exceptionally

higher infectivity the development of effective vaccine to control its spread and prevent the recurrence is vital need of the hour. Unfortunately, there is no specific antiviral treatment or vaccine currently available for SARS-CoV-2 infection.

In current scenario an alternative approach is to explore the promising and viable targets for drug discovery and assess the efficacy and safety of already existing approved and investigational drugs for treatment of COVID-19. Pharmacological approach to prevent viral invasion and propagation at early stages comprises various drugs such as cellular proteases inhibitors camostat mesylate, nafamostat mesylate, furin inhibitors, AP2 associated protein kinase 1 inhibitors, and endosomal entry inhibitors. Various drug candidates interfering with fundamental steps of viral replication (Lopinavir/ritonavir, teicoplanin, remdesvir, favipiravir, arbidol, ribavirin, saracatinib, oseltamivir) capable of blocking further spread of infection and reduce the severe outcomes are undergoing clinical trials to evaluate their efficacy and safety as mono or combination therapy to treat COVID-19 patients. Remdesvir an RNA dependent RNA polymerase inhibitor has demonstrated the most promising effects against SARS-CoV-2 so far. Besides targeting the primary stages of viral infection the emphasis toward reducing the disease severity and related mortality is required. The disease progression indicates the immunogenic inflammatory nature of disease. Exuberant cytokines/chemokines release play central role in respiratory failure. Further involvement of disturbed renin angiotensin system causes multifarious complications in disease advancement. The disease progression is more reckless in presence of comorbidities. Targeting the irregular inflammatory response and over activated RAS seems more beneficial in cases with severe symptoms or underlying comorbidities. Hydroxychloroquine proficiently block viral invasion along with regulating specific inflammatory pathways involved in disease progression and reduce disease severity and mortality rate. Inhibition of diverse malefactors (IL-1, IL-6, TNF- α) perceived to deteriorate the illness are associated with improved clinical profile in COVID-19 cases. Renovating the RAS balance (rhACE2, AT-1 receptor blockers, mas receptor agonists) definitely represent a worthwhile approach to counterattack the COVID-19 disease progression. Current review recapitulates the various characteristics of disease pathology and feasible targets to deal with the early and late stages of infection. Hence, clinical assessment of previously known drugs and revisiting the experiences from previous SARS-CoV and MERS-CoV epidemic challenges provide a rapid, cost-effective approach to manage the current crisis for the time being and offers opportunities to better comprehend the structural and molecular requirements for selective and effective anti-SARS-CoV-2 drug design.

FUNDING INFORMATION

This piece of work did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Rohilla S. Designing therapeutic strategies to combat severe acute respiratory syndrome coronavirus-2 disease: COVID-19. *Drug Dev Res*. 2020;1–15. https://doi.org/10.1002/ddr.21720