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Hypothetical targets and plausible drugs of coronavirus infection caused by SARS-CoV-2

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Abstract

The world is confronting a dire situation due to the recent pandemic of the novel coronavirus disease (SARS-CoV-2) with the mortality rate passed over 470,000. Attaining efficient drugs evolve in parallel to the understanding of the SARS-CoV-2 pathogenesis. The current drugs in the pipeline and some plausible drugs are overviewed in this paper. Although different types of anti-viral targets are applicable for SARS-CoV-2 drug screenings, the more promising targets can be considered as 3C-like main protease (3Cl protease) and RNA polymerase. The remdesivir could be considered the closest bifunctional drug to the provisional clinical administration for SARS-CoV-2. The known molecular targets of the SARS-CoV-2 include fourteen targets, while four molecules of angiotensin-converting enzyme 2 (ACE2), cathepsin L, 3Cl protease and RNA-dependent RNA polymerase (RdRp) are suggested as more promising potential targets. Accordingly, dual-acting drugs as an encouraging solution in drug discovery are suggested. Emphasizing the potential route of SARS-CoV-2 infection and virus entry-related factors like integrins, cathepsin and ACE2 seems valuable. The potential molecular targets of each phase of the SARS-CoV-2 life cycle are discussed and highlighted in this paper. Much progress in understanding the SARS-CoV-2 and molecular details of its life cycle followed by the identification of new therapeutic targets are needed to lead us to an efficient approach in anti-SARS-CoV-2 drug discovery.

KEYWORDS
anti-virals, drug repurposing, molecular targets, novel coronavirus, proteases, SARS-CoV-2

1 | INTRODUCTION

1.1 | Life cycle of the Coronavirus

Coronaviruses (CoVs), a member of the *Coronaviridae* family, are spherical (approximate diameters of 60–140 nm), enveloped, positive-sense RNA viruses and include four genera of *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus* and *Gammacoronavirus* (Cascella, Rajnik, Cuomo, Dulebohn, & Di Napoli, 2020; Li, Luk, Lau, & Woo, 2019).

The *betacoronavirus* genome including SARS-CoV-2 comprises of the 5′-untranslated region (5′-UTR), 3′-untranslated region (3′-UTR), open reading frame (ORF) 1a/b, structural proteins and additional proteins. Sixteen non-structural proteins (nsp 1–16) are generated by a proteolytic process (mediated by 3C-like main protease [3Cl protease] and papain-like proteinase [PL proteases]) from the large replicase polyproteins (pp) (pp1a and pp1ab) encoded by the ORF1a/b. Nsps progress the organization of the replication–transcription complex and indirect escape from the host immune system (Chan et al., 2020).

Structurally, the ~30,000 nucleotide viral genomes also express four basic structural proteins of nucleocapsid (N), membrane (M), envelope (E) and spike (S), encoding from the 3′ end of the viral genome (Figure 1). The spike is a ~150 kDa homotrimer glycoprotein

conferring crown-like shape on the outer surface. The attachment of SARS-CoV-2 via the interplay of its S protein with the receptor on the host cell and angiotensin-converting enzyme is the primary stage in its life cycle which is followed by proteolytic cleavage of S protein into 2 subunits namely S1 and S2 and virus enters the cytosol (S1 mediates attachment and S2 mediates virus fusion). N protein is structurally bound to the genome of the virus and is necessary for viral RNA transcription and replication. The other critical structural protein is M protein that is involved in shaping the viral envelope. By binding to the other proteins, this protein helps to stabilize N proteins and promotes the ending of viral assembly. Finally, the E protein plays a role in the production and maturation of SARS-CoV-2.

After the viral entry, the second step is the expression of replicase proteins. Following replication and RNA synthesis (third step) and assembly (last step), virions are escaped from the cell by the aid of exocytosis (Figure 2) (Fehr & Perlman, 2015).

2 | CURRENT PLAUSIBLE DRUGS OF SARS-COV-2

2.1 | Potential drug compounds

There are three lines of drug discovery approach to develop the novel drug for SARS-CoV-2. These three approaches lead to the potential treatment options including the drug repurposing, screening molecular databases using drug design tools and screening the compound libraries in anti-viral assays. By the time demanded to randomly screen the natural or chemical compound libraries, the third option is not compatible with the rapid rate of SARS-CoV-2 transmission in the community. Therefore, drug repurposing and computational docking analysis are the two main current approaches to find potential agents for SARS-CoV-2 therapy.

The efficiency of seven anti-viral drugs (ribavirin, nafamostat, nitazoxanide, penciclovir, chloroquine (CQ) remdesivir and favipiravir) on

only a single clinical type of SARS-CoV-2 is so far evaluated in the wet laboratory. These drugs have previously exhibited an acceptable anti-viral activity on various types of RNA viruses such as SARS-CoV, MERS-CoV and Ebola virus (EBOV) (García-Serradilla, Risco, & Pacheco, 2019). The investigated potential anti-SARS-CoV-2 described in recent repurposing programmes is presented in Table 1. The cell culture investigations showed that the compounds chloroquine (CQ) and remdesivir (RDV) effectively inhibited the infection by SARS-CoV-2 with a high selectivity index at low enough micromolar concentration (Wang et al., 2020).

2.2 | Potential drug candidates in clinical trials

Remdesivir (RDV, GS-5734) is an adenosine analogue that has completed the clinical trial phase III for the purpose of viral infection control caused by the Ebola virus. The remdesivir is entered to the phase III clinical trials in Asian countries to assess the use of anti-viral drug candidate for the potential treatment of SARS-CoV-2 by Gilead Sciences. All reported potential drug candidates in clinical trials and their status are presented in Table 2. Moreover, multiple parallel attempts are in progress to develop SARS-CoV-2 vaccine. At the time of writing the article, 128 vaccine candidates are in preclinical phases and 16 candidates are in clinical phases (Table 3).

3 | MOLECULAR TARGETS OF SARS-COV-2 DRUG DISCOVERY

3.1 | Host attachment and entry

3.1.1 | Modification of host cell serine protease

Despite the possibility of surface alteration of RNA viruses, blocking the cell surface viral receptor, thereby inhibiting the virus entry, can be a proper option in designing the approach of drug discovery.
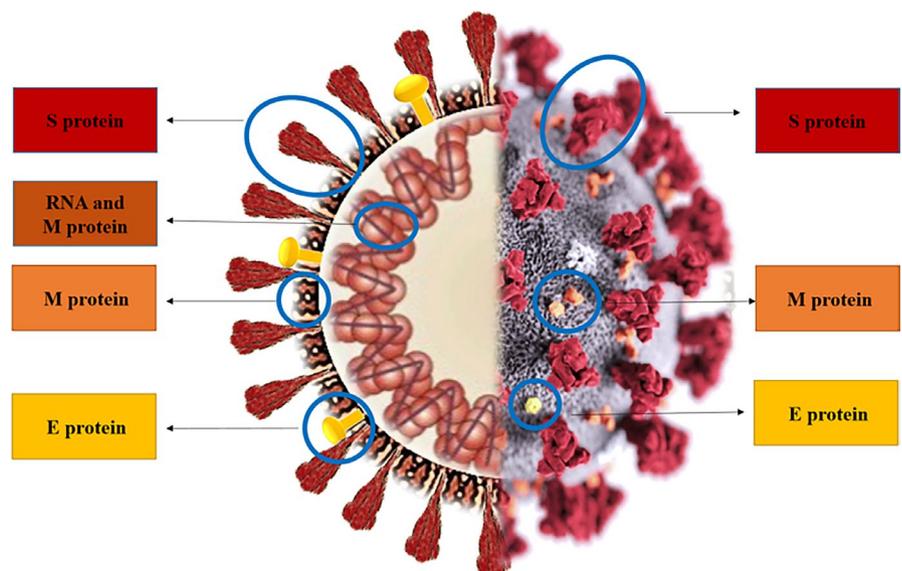

FIGURE 1 The schematic diagram (original in this paper) of the SARS-CoV-2 surface proteins
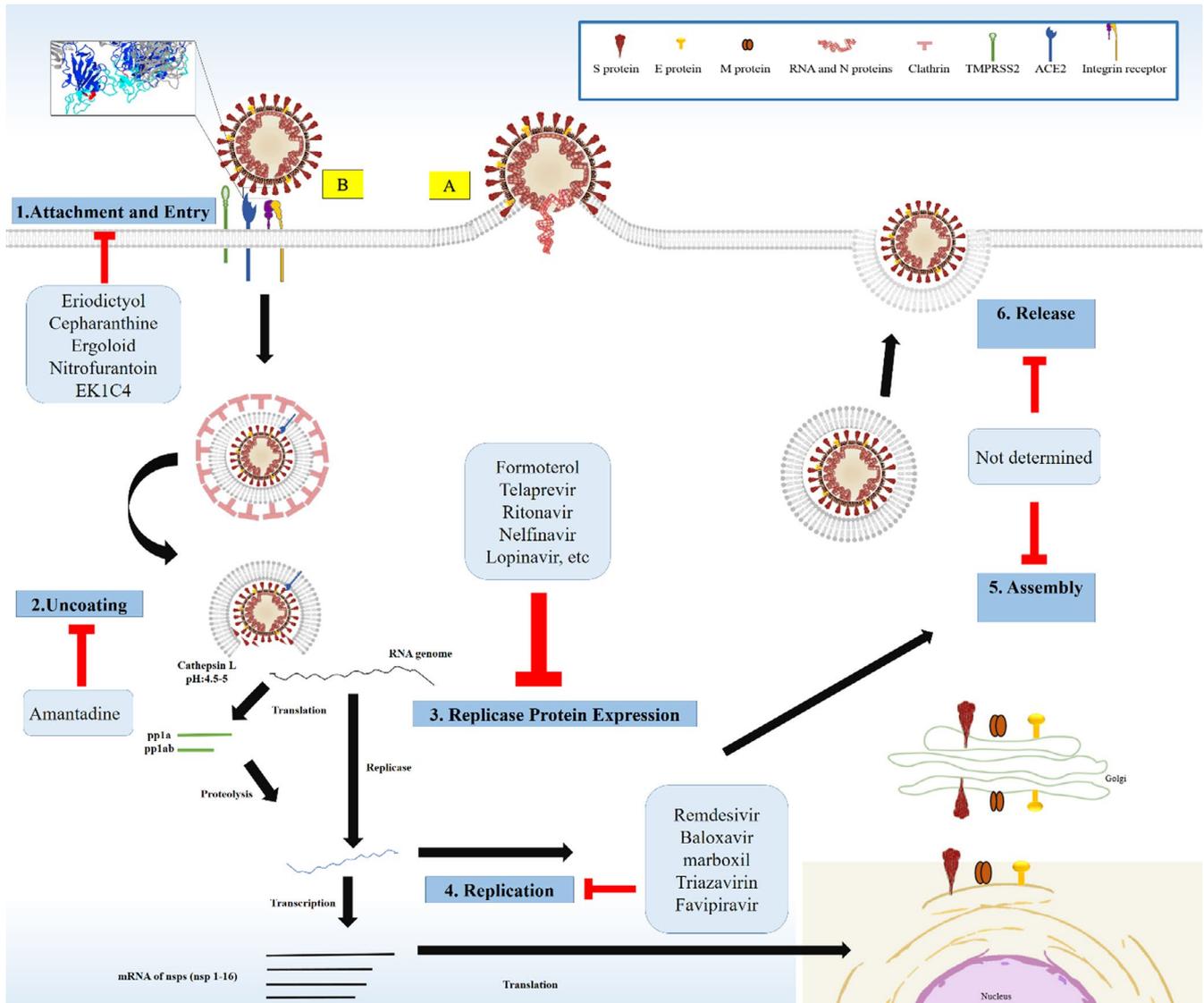
FIGURE 2 Cell cycle of SARS-CoV-2 in the host cells. The virus goes into the target cells via direct membrane fusion (a) or a clathrin-mediated endosomal pathway (b). Binding of the surface unit of the S protein (S1) to angiotensin-converting enzyme 2 (ACE2) facilitates the viral attachment. Viral fusion is primed by TMPRSS2, and the active spike protein of SARS-CoV-2 acquires an RGD motif (in itsS1 domain) known to bind integrins. The attachment to integrin may play an auxiliary role in ACE2 binding, like simplifying endocytosis by signalling through the integrin. RGD is not found in other coronaviruses. The viral RNA is unveiled by the effect of endosomal cathepsins at low pH. Following, the replicase gene of the viral genome is translated into large polyproteins which are cleaved by the proteases to yield 16 non-structural proteins (nsps). In consequence of replication, transcription and translation, assembly of nucleocapsids with RNA and N proteins is occurred in the cytoplasm, followed by budding into golgi intermediate compartment. Then, the enveloped virus is exocytosed. Plausible drugs inhibiting each step of the cycle are indicated in light blue boxes

Binding of the viral spike (S) glycoproteins to cellular receptor ACE2 and priming the S protein by transmembrane serine protease 2 (TMPRSS2) are both the essential factors for cell entry of coronaviruses. TMPRSS2 mediates the entry by two distinct mechanisms. One mechanism is the cleavage and activation of the spike glycoproteins of coronaviruses (like HCoV-229E and HCoV-EMC) which facilitates the virus-cell membrane entry. Conformational flexibility of S protein which is needed for fusion will be created by proteolytic cleavages (Bosch, van der Zee, de Haan, & Rottier, 2003) catalysed by TMPRSS2 as the most relevant cellular proteases in this process. Another mechanism is the proteolytic cleavage of angiotensin-converting enzyme 2

(ACE2) by TMPRSS2, which might activate the coronavirus spike glycoprotein. Proteolytic cleavages of S protein happen only after ACE2 cleavage results in SARS-CoV-2-cell membrane fusion and cathepsin L-independent cell entry. SARS-CoV-2 RNA is then released into the cytoplasm, and viral replication is efficiently processed (Table 4).

3.1.2 | Angiotensin-converting enzyme 2 (ACE2)

A type I membrane zinc metalloprotease named angiotensin-converting enzyme 2 (ACE2) is mainly expressed in arterial cells and lung alveolar

TABLE 1 Potential repurposing candidates with effectiveness on SARS-CoV-2

Drug candidate	Target	Anti-viral mechanism of action	References
Remdesivir	RNA polymerase	An adenine analogue that participates into nascent viral RNA chains and causes in pre-mature termination	Wang et al. (2020)
Baloxavir marboxil	RNA polymerase	Cap-dependent endonuclease inhibitor	Harrison (2020)
Triazavirin	RNA polymerase	A guanosine nucleotide analogue that inhibits RNA synthesis	Loginova et al. (2011)
Favipiravir (Avigan)	RNA polymerase	Inhibits RNA-dependent RNA polymerase (RdRp)	Wang et al. (2020)
Ribavirin	RNA polymerase	Inhibits viral RNA synthesis and mRNA capping	Khalili, Zhu, Mak, Yan, and Zhu (2020)
Penciclovir	RNA polymerase	Inhibits RNA-dependent RNA polymerase (RdRp)	Wang et al. (2020)
Acyclovir fleximer analogue	RNA polymerase	Inhibits RNA-dependent RNA polymerase (RdRp)	Li and De Clercq (2020)
Galidesivir	RNA polymerase	Inhibits viral RNA polymerase function by terminating non-obligate RNA chain	Li and De Clercq (2020)
Ritonavir	Protease	Inhibits 3CLpro	Stower (2020)
ASC09F	Protease	A combination drug containing ASC09 (HIV protease inhibitor) + ritonavir/ Oseltamivir	Li and De Clercq (2020)
Camostat	Protease	Serine protease inhibitor with activity against the host TMPRSS2 protease	Li and De Clercq (2020)
Danoprevir	Protease	A potent HCV protease (NS3/4A) inhibitor	Shah, Modi, and Sagar (2020)
Nelfinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Xu et al. (2020)
Colistin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Valrubicin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Icatibant	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Bepotastine	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Epirubicin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Epoprostenol	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Vapreotide	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Rupintrivir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Liu and Wang (2020)
Lopinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Stower (2020)
Ebselen	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Jin et al. (2020)
Cinanserin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Zhang and Liu (2020)
Flavonoids	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Zhang and Liu (2020)
Beclabuvir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Talluri (2020)
Saquinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Talluri (2020)
α-ketoamide	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Zhang, Lin, et al. (2020))
Hesperidin	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Adem, Eyupoglu, Sarfraz, Rasul, and Ali (2020)
Angiotensin II human acetate	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Contini (2020)
GHRP-2	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Contini (2020)
Indinavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Contini (2020)
Cobicistat	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Contini (2020)
Atazanavir	Protease	Inhibits chymotrypsin-like protease (3CLpro)	Contini (2020)
Mycophenolic acid	Protease	Inhibits papain-like protease (PLpro)	Elfiky and Ibrahim (2020)
Grazoprevir	Protease	Inhibits papain-like protease (PLpro)	Elfiky and Ibrahim (2020)
Formoterol	Protease	Inhibits papain-like protease (PLpro)	Arya, Das, Prashar, and Kumar (2020)

(Continues)

TABLE 1 (Continued)

Drug candidate	Target	Anti-viral mechanism of action	References
Telaprevir	Protease	Inhibits papain-like protease (PLpro)	Elfiky and Ibrahim (2020)
Diarylheptanoids	Protease	Inhibits papain-like protease (PLpro)	Zhang and Liu (2020)
Darunavir/cobicistat alone or with lopinavir/ritonavir	Protease	An HIV-1 protease and cytochrome P450 (CYP)3A enzyme inhibitor	Zhai et al. (2020)
Ikarugamycin	ACE2	ACE2 inhibitors that block the site of viral spike protein interaction	Yang, Li, Bai, and Hou (2020)
Molsidomine	ACE2	Decrease the expression of ACE2	Yang et al. (2020)
Eriodictyol	ACE2	Binding potency to viral S protein at its host receptor or to the S protein–human ACE2 interface	Smith and Smith (2020)
Nitrofurantoin	ACE2	Binding potency to viral S protein at its host receptor or to the S protein–human ACE2 interface	Smith and Smith (2020)
Cepharanthine	ACE2	Binding potency to viral S protein at its host receptor or to the S protein–human ACE2 interface	Smith and Smith (2020)
Baricitinib	Kinase	Janus-associated kinase (JAK) inhibitor which is an important regulator of clathrin-mediated endocytosis.	Richardson et al. (2020)
Ruxolitinib	Kinase	Janus-associated kinase (JAK) inhibitor blocking ACE2-mediated endocytosis	Stebbing et al. (2020)
Nitazoxanide	Interferon response	Induces the host innate immune response to produce interferons	Wang et al. (2020)
Nafamostat	Spike glycoprotein	Inhibits the membrane fusion	Wang et al. (2020)
Teicoplanin	Cathepsin L	Antibiotic inhibiting the low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes	Zhang, Ma, et al. (2020))
Ciclesonide	Endoribonuclease	A corticosteroid that inhibits replication via inhibition of viral nsp15	Matsuyama et al. (2020)
Camrelizumab	Programmed cell death 1 (PD-1)	A humanized monoclonal antibody (mAb) targeting PD-1	AminJafari and Ghasemi (2020)
Emtricitabine	Reverse transcriptase	Non-nucleoside reverse transcriptase inhibitor	Harrison (2020)
Tenofovir	Reverse transcriptase	Nucleotide reverse transcriptase inhibitor	Harrison (2020)
Azvudine	Reverse transcriptase	Experimental reverse transcriptase inhibitor drug against HIV-1/AIDS	Harrison (2020)
Methylprednisolone	Nuclear receptors	Synthetic corticosteroid that binds to nuclear receptors to dampen proinflammatory cytokines	Harrison (2020)
IFN alpha-1b	Immunomodulation	Bind to cellular surfaces' receptors and initiate the JAK-STAT signalling cascades	Harrison (2020)
Interferon alfa-2a	Immunomodulation	Interferon alfa-2b is a recombinant cytokine with anti-viral properties	Li and De Clercq (2020)
Tocilizumab	IL-6 receptor	Immunosuppressive anti-IL-6 receptor mAb	Harrison (2020)
Amantadine	Viroporin E	Inhibits the uncounting stage	Aranda Abreu et al. (2020)
Thalidomide	ND	Regulating immunity, inhibiting the inflammatory cytokine surge	Dastan et al. (2020)
Umifenovir (Arbidol)	ND	Membrane fusion inhibitor targeting the viral entry	Li and De Clercq (2020)
Chloroquine/hydroxychloroquine	ND	1. Elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes 2. Inhibit the entry through changing the glycosylation of ACE2 receptor and spike protein	Touret and de Lamballerie (2020)
Fingolimod	ND	Sphingosine-1-phosphate receptor regulator	Rosa and Santos (2020)
Dipyridamole	ND	Adenosine deaminase and phosphodiesterase inhibitor	Aly (2020)

Abbreviation: ND, not determined.

TABLE 2 Potential drug candidates for SARS-CoV-2 in clinical trials and their status in June 2020 based on clinicaltrials.gov database

ClinicalTrials.gov Identifier	Intervention	Mechanism of action	Status (Phase)
NCT04343092	Ivermectin (IVM)	Inhibiting the importin (IMP) α/β receptor	I
NCT04321096	Camostat Mesilate	Protease inhibition	II
NCT04324996	Biological: NK cells, IL15-NK cells,NKG2D CAR-NK cells,ACE2 CAR-NK cells, …	Secreting The super IL15 superagonist and GM-CSF neutralizing single-chain variable fragment (scFv)	II
NCT04276688	Lopinavir/ritonavir; Ribavirin; Interferon Beta-1B	Inhibition of protease and viral mRNA synthesis	II
NCT04280588	Fingolimod	Modulation of Sphingosine 1-phosphate receptor	II
NCT04273529	Thalidomide	Inhibition of Inflammatory cells and cytokines	II
NCT04288102	Biological: Mesenchymal stem cells	Possessing a comprehensive immunomodulatory function	II
NCT04317092	Tocilizumab	IL-6-mediated signalling inhibition	II
NCT04321993	Lopinavir/ritonavir; Hydroxychloroquine sulphate; Baricitinib (janus kinase inhibitor); Sarilumab (anti-IL-6 receptor)	Protease and janus kinase inhibition, anti-IL-6 receptor	II
NCT04313023	PUL-042 Inhalation Solution	Reducing the severity of SARS-CoV-2	II
NCT04275245	Meplazumab	Host cell expressed CD147 antibody Inhibition of the S protein binding to the cell	II
NCT04279197	Acetylcysteine	Mucolytic agent	II
NCT04311177	Losartan	Angiotensin II receptor blocker	II
NCT04292899	Remdesivir	RNA polymerase inhibition	III
NCT04325633	Naproxen	Prostaglandin G/H synthase inhibition	III
NCT04304313	Sildenafil citrate	cGMP-specific phosphodiesterase type 5 (PDE5) inhibition	III
NCT04320615	Tocilizumab (TCZ)	IL-6-mediated signalling inhibition	III
NCT04315896	Hydroxychloroquine	Accumulation and raising the pH of the vacuole	III
NCT04317040	CD24Fc	Regulation of immune responses	III
NCT04261270	ASC09F + Oseltamivir; Ritonavir + Oseltamivir; Oseltamivir	Protease inhibition; neuraminidase inhibition	III
NCT04321616	Hydroxychloroquine; Remdesivir	Accumulation and raising the pH of the vacuole; RNA polymerase inhibition	III
NCT04315298	Sarilumab	IL-6-mediated signalling inhibition	III
NCT04324021	Emapalumab	Neutralizing the interferon-gamma	III
NCT04252274	Darunavir and cobicistat	Protease inhibition- cytochrome P450 3A (CYP3A) isoforms inhibition	III
NCT04308317	Tetrandrine	Not described	IV
NCT04286503	Carrimycin	Macrolide antibiotic	IV
NCT04254874	Arbidol Hydrochloride combined with Interferon atomization	Dual-acting direct anti-viral/host-targeting	IV
NCT04263402	Methylprednisolone	Corticosteroid	IV
NCT04252885	Umifenovir (Arbidol)	Dual-acting direct anti-viral/host-targeting	IV
NCT04255017	Umifenovir (Arbidol); Oseltamivir; Lopinavir/ritonavir	Dual-acting direct anti-viral/host-targeting Neuraminidase inhibition; protease inhibition	IV
NCT04291729	Drug: Ganovo (Danoprevir) + ritonavir ± Interferon nebulization	Protease inhibition	IV

epithelial cells. ACE2 hydrolyses the angiotensin I to produce angiotensin (1–9) (Donoghue et al., 2000). The enzyme is known for its implication as the virus receptor of SARS-CoV (Kuba et al., 2005) which was proved as the cellular receptor of SARS-CoV-2 by Zhou et al (Zhou et al., 2020). Blocking the entrance of SARS-CoV-2 through the intervention of ACE2 seems to be a possible target for anti-viral drug discovery.

3.1.3 | Integrins

Recently, Sigrist et al suggested that SARS-CoV-2 may also bind to integrins on the host cells, through a conserved motif (RGD) containing Arg-Gly-Asp in receptor-binding domain of S protein that is absent in

TABLE 3 Vaccine candidates for SARS-CoV-2 in clinical trials and their current status in June 2020 based on clinicaltrials.gov, ISRCTN registry and Chinese clinical trial registry database

Identifier	Interventions	Mechanism of action	Status (Phase)
NCT04400838	ChAdOx1	Non-replicating viral vector	III
NCT04379336	Bacille Calmette–Guérin (BCG)	Enhancing non-specific immune responses through Bacillus Calmette-Guérin vaccination	III
NCT04412538	Inactivated SARS-CoV-2	Inactivated	II
NCT04276896	LV-SMENP-DC	Lentiviral vector system (NHP/TYF) expressing viral proteins and immune modulatory genes to modify dendritic cells (DCs) and to activate T cells	II
NCT04383574	Inactivated SARS-CoV-2	Inactivated	II
NCT04436471	Adeno-based	Non-replicating viral vector	II
ChiCTR2000031781	Adenovirus Type 5 Vector	Non-replicating viral vector	II
ChiCTR2000031809	Inactivated SARS-CoV-2	Inactivated	I/II
ChiCTR2000032459	Inactivated SARS-CoV-2	Inactivated	I/II
NCT04368988	Recombinant Spike Protein	SARS-CoV-2 Recombinant Spike Protein Nanoparticle vaccine (SARS-CoV-2 rS) with or without MATRIX-M™ Adjuvant	I/II
ISRCTN17072692	LNP-nCoVsaRNA	Self-amplifying ribonucleic acid (saRNA) vaccine encoding the S glycoprotein of SARS-CoV-2	I
NCT04368728	3 LNP-mRNAs	Not mentioned	I
NCT04405076	mRNA-1273	Novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, spike (S) protein	II
NCT04313127	Ad5-nCoV	Adenovirus type 5 vector that expresses S protein	I
NCT04336410	NO-4800	DNA plasmid encoding S protein delivered by electroporation	I
NCT04299724	Pathogen-specific aAPC	APCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	I

other coronaviruses (Sigrist, Bridge, & Le Mercier, 2020). The conformational changes due to ACE2 binding expose the RGD containing region. Different viruses like Ebola virus (Schornberg et al., 2009), human papillomavirus (Yoon, Kim, Park, & Cheong, 2001), HIV-1 (Monini et al., 2012) and EBV (Tugizov, Berline, & Palefsky, 2003) use integrins for cell attachment or entry. Treatment of multiple sclerosis/Crohn's diseases using the natalizumab antibody ($\alpha 4\beta 1/\beta 7$ integrin inhibitor) and the treatment of acute coronary syndrome with the small molecule tirofiban ($\alpha IIb\beta 3$ blocker) are examples of approved drugs based on the integrin inhibition, highlighting the impact of integrin in treatment of various diseases (Ley, Rivera-Nieves, Sandborn, & Shattil, 2016). These studies confirm that the inhibition of integrin may prevent the occurrence of some coronaviruses in host cells and can be considered a prolific target for anti-viral drug discovery.

3.1.4 | Host tyrosine kinase receptor

The growth factor receptors of receptor tyrosine kinases (RTKs) are autophosphorylated after ligand binding being involved in mediating cell-to-cell communication and controlling a vast range of complicated biological processes like cell growth, motility and differentiation (Lemmon & Schlessinger, 2010). The sequel of ligand binding is conformational changes of RTKs enabling its autophosphorylation and

therefore activation of a wide variety of downstream cellular signalling pathways. RTKs also play a critical role in signalling pathways, such as the Ras/mitogen-activated protein kinase (MAPK), PI3K/Akt and JAK/STAT pathways. The particular RTK blockers, known as AG879 and tyrphostin A9 (A9), are also reported as strong anti-viral activity against the influenza A virus (Kumar, Liang, Parslow, & Liang, 2011). It was shown that the approved blockers can impair the infection of major HCV variants in in vitro and in vivo models (Jilg & Chung, 2012). The tyrosine kinase inhibitor such as genistein can also block the replication of arenavirus, herpes simplex virus type 1 (HSV-1) and HIV-1 (Vela, Bowick, Herzog, & Aronson, 2008). Dong et al introduced an RTK inhibitor named (A9) as a competent blocker of transmissible gastroenteritis virus (TGEV) infection belong to *Alphacoronavirus* genera as a successor model for CoV in cell-based assays (Dong et al., 2020). The inhibitors of RTK suppress the viral replication through different mechanisms like interferon signalling, Raf/MEK/Erk pathway and the p38 signalling pathway. These achievements represent the RTKs as a probable host-centred approach to treat the SARS-CoV-2.

3.1.5 | Viral spike protein

The trimeric S glycoprotein responsible for the coronaviruses crown-like appearance mediates attachment to the host receptor

TABLE 4 Principle molecular targets of SARS-CoV-2 for drug discovery or design

Viral cycle	Molecular targets	Potential anti-viral drugs
Host attachment and entry	Host cell serine protease receptor	Eriodictyol, Cepharanthine, Ergoloid, Nitrofurantoin
	Host tyrosine kinase receptor	ND
	ACE2[*]	ND
	Integrins	ND
	Spike protein[*]	EK1C4
Uncoating	Ion channel proteins	Amantadine
Replicase Protein Expression	Papain-like proteinase (PLpro)	Mycophenolic acid, Grazoprevir, Formoterol, Telaprevir, Diarylheptanoids, etc
	3C-like main protease (3CLpro)[*]	Ritonavir, Nelfinavir, Lopinavir, Ebselen, Cinanserin, Ketoamide, Atazanavir,
Replication of viral genome	RNA-dependent RNA polymerase (RdRp)[*]	Remdesivir, Baloxavir marboxil, Triazavirin, Favipiravir (Avigan), Ribavirin, Penciclovir, Acyclovir fleximer analogue, Galidesivir
	Helicase	ND
	The peptidyl/ prolyl isomerases (PPIases)	ND
	Nucleoside analogues	Remdesivir, Favipiravir, ribavirin, 5-fluorouracil
Viral protein assembly	Envelope protein (protein E)	ND
Cell release of the virus	ORF7a	ND

Abbreviation: ND, not determined.

*Indicates the sofar principle targets.

(Ou et al., 2020). Despite the over 72% spike protein sequence similarity with SARS-CoV, a peculiar furin-like cleavage site at the S1/S2 position in the S protein sequence of the SARS-CoV-2 was identified, missing in the other SARS-like CoVs (Coutard et al., 2020). Following the host cell binding, cell penetration is facilitated by S protein priming using the cellular protease. Considering the S protein cleavage by furin-like protease in the host cell, blocking S protein attachment or furin-like cleavage sites are promising targets in drug discovery. Recently, Xia et al introduced a lipopeptide named EK1C4 that effectively block the SARS-CoV-2 infection in in vitro experiments with IC50 of 36.5 nM (Xia et al., 2020) by blockage of membrane fusion mediated by S proteins. The

presence of three vaccine candidates in clinical phases accentuates the importance of this protein in the process of drug development (Thanh et al., 2020).

3.2 | Inhibition of genome uncoating

The cessation of the capsid disintegration by viral or host enzymes/proteins is a drug target explored against the influenza virus, rhinoviruses, hepatitis A, poliovirus and enteroviruses (Yamauchi & Greber, 2016). In accordance with this approach, rimantadine inhibits the capsid disintegration by blocking the ion channel in the influenza virus (Balgi et al., 2013). The herbal medicine of Japan called Maoto has also shown inhibitory activity on influenza virus A (PR8) presumed by inhibition of genome release (Masui et al., 2017).

The only effort on blockage of uncoating step in the SARS-CoV-2 life cycle as a drug discovery target is reported by Aranda Abreu et al. They proposed an in situ models of amantadine as a drug to relieve the effects of SARS-CoV-2 by blocking the viroporin E (a proton channel) and inhibiting the viral uncoating (Aranda Abreu, Hernández Aguilar, Herrera Covarrubias, & Rojas Durán, 2020). The S protein-based vaccines can also induce antibodies that block the genome uncoating besides the blockage of viral receptor (Chen et al., 2020). Furthermore, it is still not determined whether the uncoating of SARS-CoV-2 can occur in both acidic and neutral conditions similar to avian coronavirus (IBV) or its uncoating can be suppressed by the neutralization of the acidic condition of endosomes and its subsequent fusion.

3.3 | Inhibition of replicase protein expression

Following the uncoating step, the replicase gene of the viral genome encodes two processed polyproteins (pp) named pp1a and pp1ab (Chan et al., 2020). Then, viral proteinases perform post-translational modification on the polyproteins yielding proteins that mediate the formation of viral replication complexes. The protease activities of all coronaviruses include both papain-like proteinase (PLpro) and coronavirus 3C-like protease which are encoded within the replicase polyproteins and mediate cleavage events. Due to their unrivalled and essential function in processing the viral polyprotein, these enzymes are appropriate targets for SARS-CoV-2 drug development.

3.3.1 | Protease

Papain-like proteinase (PLpro)

PLprotease or nsp3 releases proteins involved in both replication of coronavirus and infection processes. In addition to the LXGG motif found in-between nsp1/2, nsp 2/3 and nsp 3/4, it has two other proteolytic activities, removal of ubiquitin (Ub) and ubiquitin-like protein ISG15 (interferon induced gene 15) from cellular proteins.

Some studies have highlighted the importance of inhibiting these proteases in other coronaviruses. Ratia et al introduced a compound, GRL0617, with an EC50 of 15 μM that inhibits the replication of SARS-CoV in Vero E6 cells (Ratia et al., 2008). PLpro inhibitors of MERS-CoV (Kilianski, Mielech, Deng, & Baker, 2013), HEV (Saraswat, Chaudhary, & Sehgal, 2020), etc have also been reported. Another PLpro inhibitor named disulfiram has been identified to block the function of this enzyme in MERS and SARS in in vitro, but clinical approval of its effectiveness is lacking (Li & De Clercq, 2020). The inhibition of PLpro can be assumed as a promising target in coronavirus drug discovery.

3C-like main protease (3CLpro)
3CLprotease (also called the major protease (Mpro) or nsp5 directly mediates the polyprotein processing and maturation of viral non-structural proteins (nsps), which is the indispensable part of the viral life cycle. Initiation of viral RNA synthesis and switching translation to RNA replication are other functions of this protein. 3CLpro is among the most attractive target for anti-coronavirus drug development. Based on a recent computational drug repositioning research, five drugs, namely eravacycline, valrubicin, carfilzomib, lopinavir and elbasvir, have speculated to exhibit blocking activities on 3Cl pro of SARS-CoV-2 (Wang, 2020). According to another computational prediction, bortezomib, flurazepam, ponatinib, sorafenib and dasatinib are five other potent potential inhibitors of 3Cl pro for SARS-CoV-2 (Nguyen, Gao, Chen, Wang, & Wei, 2020).

Due to the similar active-site architecture of the 3Cl protease in coronaviruses and enteroviruses, Zhang et al designed peptidomimetic α-ketoamides as proper 3Cl protease inhibitors to attain the broad-spectrum anti-viral drugs. They introduced a compound (11r) expecting to exhibit excellent anti-viral activity against SARS-CoV-2 (Li & De Clercq, 2020; Zhang, Lin, et al., 2020).

3.4 | Replication of the CoV-19 genome

3.4.1 | RNA-dependent RNA polymerase (RdRp)

Genome multiplication is critical in the life cycle of the virus and can be an attractive target for the intervention in the infection progress. RNA-dependent RNA polymerase (RdRp) (nsp12) or RNA replicase is the most principal protein in the coronavirus replication/transcription complex (Gao et al., 2020).

The anti-viral agents of remdesivir, favipiravir and penciclovir can block the RNA-dependent RNA polymerase (RdRp) of many RNA viruses, specially the influenza virus. Wang et al. determined the efficiency of these agents on infected Vero E6 cells with SARS-CoV-2 (Li & De Clercq, 2020; Wang et al., 2020; Zhang, Lin, et al., 2020). The high concentrations of penciclovir (EC50 = 95.96 μM) and favipiravir (EC50 = 61.88 μM) were needed to decrease the viral infection, while remdesivir (EC50 = 0.77 μM) prevented the virus multiplication even at low concentrations.

After cell entry, remdesivir is metabolized into nucleoside triphosphate analogue via competing for ATP. Its incorporation by RdRp inhibits viral replication through pre-mature termination of RNA synthesis. Importantly, remdesivir inhibits the viral replication in RNA viruses including positive and negative senses like NiV, EBOV, SARS, MERS, HCoV-OC43, HCoV-229E and SARS-CoV-2 in both in vitro and in vivo studies. Although delayed chain termination is a possible mechanism of remdesivir against EBOV with negative senses RNA, the action mechanism remains to be fully explicated (Gordon, Tchesnokov, Feng, Porter, & Götte, 2020; Tchesnokov, Feng, Porter, & Götte, 2019). Sheahan et al. recently introduced a ribonucleoside analogue, β-D-N^4-hydroxycytidine, with broad-spectrum anti-viral activity against SARS-CoV-2 and other coronaviruses with mutations in RdRp conferring increased resistance to remdesivir, indicating the risk of SARS-CoV-2 becoming clinically drug resistant (Sheahan et al., 2020).

3.4.2 | Helicase

Helicase (nsp13) is a critical protein with several functions required for virus replication containing two main domains; N-terminal metal binding domain (MBD) and a conserved helicase domain at the C-terminus (Hel). This enzyme unfolds the firm secondary structures of the genome in positive-sense RNA viruses to increase the yield of its translation (Adedeji, Marchand, et al., 2012). Despite the essential function of helicase in virus multiplication, limited potential suppressors of nsp13 have been reported so far (Adedeji, Singh, et al., 2012; Shum & Tanner, 2008).

A 1,2,4-triazole derivative, SSYA10-001, has shown an inhibitory effect on both helicases of SARS- and MERS-CoVs with 25 and 7 μM of the EC50 values, respectively (Adedeji et al., 2014). In another research, Yu et al concluded that myricetin and scutellarein can suppress the helicase of SARS-CoV (Yu et al., 2012). The potent inhibition of SARS coronavirus replication and the helicase activity with EC50 of less than 10 μM is also reported by the Adamantane-derived Bananins (Tanner et al., 2005).

3.4.3 | The peptidyl/prolyl isomerases (PPIases)

The 18-kDa cytosolic cyclophilin A is a necessary cellular molecule needed for replication of RNA viruses including HIV (Luban, Bossolt, Franke, Kalpana, & Goff, 1993), HCV (Watashi et al., 2005), influenza A (Liu et al., 2012) and also coronavirus. Cyclophilins (Cyps), belonging to the family of peptidyl-prolyl isomerases (PPIases), conducts the rate-limiting cis/trans isomerization step of proline-preceding peptide bonds during the protein folding. The PPIase activity is blocked by cyclosporin A and its different analogues which are non-immunosuppressive agents (de Wilde, Pham, Posthuma, & Snijder, 2018) such as alisporivir (ALV; or Debio-025) (Landrieu et al., 2010), SCY-635 (Hopkins et al., 2010) andNIM811 (Ciechomska et al., 2005).

There are various reports indicating the effect of Cyps (Pfefferle et al., 2011; de Wilde et al., 2011) and its derivatives (Carbajo-Lozoya

et al., 2014; de Wilde et al., 2017) on different genera of coronaviruses mainly MERS-CoV, HCoV-229E, HCoV-NL63 and SARS-CoV in cell culture which might be applicable on SARS-CoV-2 as well.

3.4.4 | Nucleoside analogue inhibitors

Nucleoside analogues (dNTPs or rNTPs without 3′-OH group resulting in chain termination) are extensively applied for the hepatitis C virus (HCV), hepatitis B virus (HBV), HIV-1 and HSV therapy. Compared to the other RNA viruses, the proofreading activity of RdRp by the capability of 3′ to 5′ exoribonuclease (nsp14) leads up to 20-fold enhancement in the accuracy of replication. Thus, the enzyme of coronavirus is rather resistant to many nucleoside analogues including favipiravir (guanine analogue), ribavirin (guanosine analogue) and 5-fluorouracil (pyrimidine analogue) (Harrison, 2020).

Remdesivir, (adenosine analogue) as a potent phosphoramidate prodrug, is effective against filoviruses, pneumoviruses and paramyxoviruses with two suggested mechanisms of action (Lo et al., 2017). One is being as nucleoside analogue and the second is acting on viral RdRp. Accordingly, Peters et al evaluated the efficiency of some nucleoside analogues suggesting that compound 2 with EC50 < 10 μM was promising against HCoV-NL63 (Peters et al., 2015). The combinations of nucleotide analogues can mitigate the resistance mediated by mutations in the viral RdRp, perhaps by additive or synergistic interactions effect (Pruijssers & Denison, 2019). Despite the proofreading activity, identifying nucleoside analogue inhibitors hold promise for the treatment of SARS-CoV-2.

3.5 | Viral protein assembly

Capsid proteins have a pivotal function in the assembly of the virus, and interfering with the structure or function of these key proteins can be a solid anti-viral strategy. Coronaviruses are distinct from other coated viruses in that they are assembled in the endoplasmic reticulum and golgi intermediate compartment (ERGIC) as the intracellular membranes and transported out of the cell by exocytosis (Schoeman & Fielding, 2019). Envelope proteins (E) are clearly important in assembly of coronaviruses, but their exact mechanistic role(s) is still not yet fully described (Schoeman & Fielding, 2019). The major part of E protein is localized in intracellular trafficking and participates in coronavirus assembly, although it is expressed inside the infected cell in large quantities. The envelope protein (E) of coronaviruses (HCoV-229E, Mouse hepatitis virus (MHV), IBV) mediates the assembly of virus and generates some cation-selective ion channels that their function is not clear (Wilson, Mckinlay, Gage, & Ewart, 2004). The involvement of E protein in pivotal stages of the viral life cycle makes SARS-CoV-2 lacking E protein, a promising vaccine candidate. Pharmacological blockage of its assembly with acylguanidine and cinnamoylguanidine reduced the SARS-CoV and MHV viral titre by 76 and 88% at a concentration of 10 μM, respectively (Gage, Ewart, Wilson, Best, & Premkumar, 2007).

M protein is the other main structural proteins of SAR-CoV-2 determining the shape of the virus envelope. This protein also confirms the nucleocapsid stability, promotes viral assembly and encapsulates the viral genome. Qin et al. designed siRNAs that degrade M mRNA and block the expression of M protein in SARS-associated coronavirus, proposing an approach for researches towards developing the new therapeutic agents for CoV infection (Qin, Zhao, Cao, & Qi, 2007).

The inhibition of viral assemble is investigated for different types of viruses including moloney murine leukaemia virus (Mo-MLV) (McNally, Wahlin, & Canto-Soler, 2010), classical swine fever virus (CSFV) (Zhou, Liu, & Chen, 2008), HIV-2 (Wu et al., 1995), HIV-1 (Li et al., 2009), dengue virus type 2 (DENV2) (Qin et al., 2005), HBV (Seo et al., 2019) and influenza A (Liu et al., 2014). However, no approved drug candidate or in clinical trial disparting the SARS-CoV-2 assembly is reported so far.

3.6 | Cell release of the virus

Prevention of the release of the viruses from host cells as the last phase of the viral cycle is an attractive strategy to minimize the dissemination of the virus mainly in pandemics to limit the released viral load in the society. Drugs like zanamivir, oseltamivir, laninamivir octanoate and peramivir inhibit this step by targeting viral neuraminidase to block the release of the Influenza virus (De Clercq & Li, 2016). Bone marrow matrix antigen 2 (BST-2), also known as tetherin or CD 317, was found as the factor causing a defect in virion release of HIV-1 mutants without the vpu accessory gene (Van Damme et al., 2008).

One of the coronavirus virulence factors is ORF7a that inhibits the bone marrow matrix antigen 2 (BST-2) (Taylor et al., 2015) related to its escape from the innate immune system by host mRNA degradation and interferon production inhibition. BST-2 is constitutively expressed in plasma cells, mature B cells and type I interferon-producing cells that can hinder the liberation of biosynthesized coronavirus from hosts. The evidence implied that ORF7a can be speculated as a potential target for anti-viral drug discovery of SARS-CoV-2.

4 | CONCLUDING REMARKS

In the preceding 20 years, two novel coronaviruses have been emerged mainly causing the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) responsible for the epidemics in 2002 and 2012, respectively (World Health Organization, 2003, 2013). Since the pandemic spread of novel coronavirus (SARS-CoV-2) and the rapidly increasing number of patients by minutes (473,061 deaths at the time of writing this article by 24 June 2020, unfortunately), the focus has been on the assessments to recruit the existing antiviral compounds which must be complemented by the new drug discovery programmes in the future. Nevertheless, the current urgent demand is being addressed by the clinical trials of 31 drugs

to approve the effectiveness of the existing anti-viral drugs on SARS-CoV-2.

The potential molecular targets in anti-SARS-CoV-2 drug discovery are surveyed in this paper that can be employed in HTS programmes for systematic drug discovery for SARS-CoV-2 infection. Negligible knowledge is still available on the biology of SARS-CoV-2 specially, viral protein synthesis and assembly and most of what we know have been for the last 7 months. Due to the high virus transmission and the global spread of coronavirus, the foremost controversial issue is the mitigation of its pathogenicity using the existing anti-viral compounds. Therefore, in silico or practical screening of molecular targets is being conducted on structural information obtained from all major variants of the virus. Although the ongoing clinical trials are evaluating the potential treatments of more than 31 drugs, there are currently no specifically certified drugs or vaccines for SARS-CoV-2.and the single drug in the frontline may/may not potentially be recognized effective after the completion of the clinical trials. In addition to the above approach, the detailed study of the viral life cycle can lead to assigning some even more effective drug targets. In this direction, some drug targets based on bioinformatics analysis and relative similarities of this new virus with other members of its family like host cell receptors, spike glycoproteins, papain-like and 3C-like protease, RdRp have been documented so far. However, an approximately half of the potent drug candidates and nearly one-third of the drugs registered on the www.clinicaltrials.gov webpage solely inhibit proteases affecting the replicase protein expression step in the viral life cycle.

While full-length S proteins of SARS-CoV-2 and SARS-CoV have up to 76% similarities in amino acid sequences, the N-terminal domain that binds to the receptor shows only 53.5% of homology reflecting its potential to bind different sugars. Therefore, emphasizing on other virus entry-related factors like cathepsin seems valuable for SARS-CoV-2 drug discovery. In fact, host proteases cathepsin L and TMPRSS2 prepare the SARS-CoV-2 S protein for cell entry (Walls et al., 2020). Considering the results of repurposing strategies and clinical tests until now, remdesivir seems a promising dual-acting drug (inhibiting viral RNA polymerases and 3C-like main protease). Studies conducted so far suggest the drug might cause some minor side effects including nausea, liver damage and cardiopulmonary failure. Beyond the ongoing studies of remdesivir, now researchers are hoping to explore whether the remdesivir can be combined with other anti-viral drugs for making a more effective SARS-CoV-2 combating cocktail. Six clinical trials are currently underway to specify testing remdesivir with other medicines, according to Informa Pharma Intelligence. Nevertheless, HIV protease inhibitors (ritonavir/lopinavir/ASC09), favipiravir and chloroquine need further investigations.

5 | FUTURE DIRECTIONS

As we proceed with the current molecular docking studies and presuming the effectiveness of the existing anti-viral compounds, the de novo drug discovery will join to evaluate the modulation of the new molecular targets of SARS-CoV-2 in bioassay platforms which were discussed above. To accelerate the long, costly and rigorous process of drug discovery, high-throughput methods and high-content screening methods can be employed. However, by the immediate global need for drugs to control the SARS-CoV-2 infection drug search is currently pursued by the repurposing approach. Accordingly, the critical viral life cycle steps like entry, genome and protein synthesis reflect the multiple drug target groups not limited to 3cl pro and RdRp that can be addressed by the conventional de novo strategy of drug discovery. Assembly and release inhibitors are less considered steps in SARS-CoV-2 life cycle for its drug discovery. While most of the drug cases for SARS-CoV-2 are registered for the control purpose rather than prophylaxis; S protein, integrins and ACE2 targets are of value for drug repurposing or discovery programmes to hinder the viral entry and fusion process. Considering the fact that the primary goal of all viruses is to deliver and replicate their genome to the competent host cells, blocking angiotensin-converting enzyme 2 (ACE2), cathepsin L, 3Cl protease and RdRp are suggested to be promising targets for anti-SARS-CoV-2 drug discovery.

CONFLICT OF INTEREST

No conflict of interest is declared on the data collected and interpreted in this paper.

ETHICAL APPROVAL

The authors declare that no ethical was needed for the current non-experimental paper.

DATA AVAILABILITY STATEMENT

The paper is a review and does not have original experimental data to make them available.

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