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Recent advances in potential drug therapies combating COVID-19 and related coronaviruses-A perspective

Shivraj Hariram Nile [a], Arti Nile [b], Shivkumar Jalde [c], Guoyin Kai [a,*]

[a] Laboratory of Medicinal Plant Biotechnology, College of Pharmacy, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, China
[b] Department of Stem Cell and Regenerative Biotechnology, Konkuk University, Seoul, 05029, South Korea
[c] Department of Medicinal Chemistry, Jungwon University, Goesan, 28420, South Korea

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ABSTRACT

Coronaviruses (CoVs) are a large family of viruses responsible for the severe pathophysiological effects on human health. The most severe outbreak includes Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS-CoV) and Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 poses major challenges to clinical management because no specific FDA-approved therapy yet to be available. Thus, the existing therapies are being used for the treatment of COVID-19, which are under clinical trials and compassionate use, based on *in vitro* and *in silico* studies. In this review, we summarize the potential therapies utilizing small molecules, bioactive compounds, nucleoside and nucleotide analogs, peptides, antibodies, natural products, and synthetic compounds targeting the complex molecular signaling network involved in COVID-19. In this review > 230 natural and chemically synthesized drug therapies are described with their recent advances in research and development being done in terms of their chemical, structural and functional properties. This review focuses on possible targets for viral cells, viral proteins, viral replication, and different molecular pathways for the discovery of novel viral- and host-based therapeutic targets against SARS-CoV-2.

1. Introduction

Coronaviruses (CoVs) are enveloped viruses having non-segmented, positive sense single-stranded RNA genome rather than DNA, belonging to the family *Coronaviridae* and contain the largest genomic RNA among any viruses broadly distributed in humans and other mammals (Pillaiyar et al., 2020; Zumla et al., 2016). CoVs are named from crown-like spikes protruding from their outer surface and grouped in four main sub-groups, mainly alpha, beta, gamma, and delta (Sheahan et al., 2020a, 2020b, 2020b). CoVs were first identified in the mid-1960s, seven of which infect human beings. These are MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS), NL63 (alpha coronavirus), 229E (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), and severe acute respiratory syndrome-related coronavirus (SARS-CoV-2, novel coronavirus responsible for COVID-19). People around the world commonly get infected by human CoVs like HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 (B. Chen et al., 2020; Shen et al., 2019). Sometimes CoVs that infect animals can evolve, make people sick and become a new human coronavirus. Recent examples are SARS-CoV, MERS-CoV and SARS-CoV-2 (Pillaiyar et al., 2020; Zumla et al.,

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS, Middle East respiratory syndrome; HCoV, human coronavirus; CHIKV, Chikungunya virus; DHODH, dihydroorotate dehydrogenase; HBV, hepatitis B virus; IAV, influenza A virus; HCV, hepatitis C virus; JEV, Japanese encephalitis virus; PEDV, porcine epidemic diarrhea virus; PLpro, papain-like protease; 3CLpro, 3 chymotrypsin-like proteases; RdRp, RNA-dependent RNA polymerase; SAH, S-adenosyl-l-homocysteine; RBD, receptor-binding domain; RSV, respiratory syncytial virus; ZIKV, Zika virus; IMPDH, inosine-monophosphate dehydrogenase; PPIase, peptidyl-prolyl isomerase; IMPTH, inosine-5′-monophosphate dehydrogenase; NS3, non-structural protein 3; VEGF, Vascular Endothelial Growth Factor; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; HTCC, N-(2hydroxypropyl)-3-trimethylammoniumchitosan chloride; SCV, SARS-associated coronavirus; HCMV, Human cytomegalovirus; COX, cyclooxygenase; JAK, Janus-associated kinase; NAK, Numb-associated kinase; HCMV, Human Cytomegalovirus; NS, Not studied; S protein, Spike (S) protein; E, Enveloped protein; ACE2, angiotensin-converting enzyme 2 (ACE2) blockers; TCM, traditional Chinese medicine.

* Corresponding author.
E-mail address: guoyinkai1@126.com (G. Kai).

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2016). The detail taxonomical classification of coronaviruses (according to the International Committee on Taxonomy of Viruses) illustrated in Fig. 1.

In late December 2019, several cases of unexplained pneumonia have been reported in Wuhan, China. Most of the infected or confirmed patients live near the local Huanan seafood wholesale where live animals are widely sold, where live animals are widely sold. In the early stages of pneumonia, severe acute respiratory infections occur, and some patients develop rapidly into acute respiratory distress syndrome (ARDS), acute respiratory failure and other serious complications (Huang et al., 2020). The Chinese Centers for Disease Control and Prevention identified a new type of coronavirus from a patient's throat swab sample on January 7, 2020. Subsequently, on February 7, 2020, a notice issued by the National Health Committee of China temporarily named the coronavirus-infected pneumonia a New/Novel Coronavirus Pneumonia, referred to as "New Crown Pneumonia" (NCP). On January 13, 2020, the World Health Organization temporarily referred to the coronavirus that caused the disease as 2019 new coronavirus ("2019-nCoV). On January 30, 2020, the disease caused by the virus was temporarily named "2019-nCoV acute respiratory disease" (2019 new type of coronavirus acute respiratory disease). On February 11, 2020, the World Health Organization officially named it "Coronavirus Disease 2019", abbreviated as "COVID-19". On the same day, the International Viral Classification Commission officially named the disease-causing coronavirus "severe acute respiratory syndrome coronavirus 2", abbreviated as SARS-CoV-2. According to WHO, the disease caused by Novel Coronavirus (2019-nCoV), or SARS-Cov-2 is now officially called COVID-19 (Huang et al., 2020a; Shen et al., 2019; Zhang and Liu, 2020). By February 25, 2021, more than >120000000 cases of COVID-19 have been confirmed, with an estimated mortality risk of ~3.4%, which was comparatively less than that of major viral outbreaks that occurred in past years (Table 1). So far, the infection keeps spreading and more and more exported cases were confirmed in many countries worldwide, posing great pressure on public health security.

Regarding COVID-19 treatment and its spread, it is currently unclear; current knowledge is mainly based on known similar coronaviruses. CoVs are a large series of viruses that are common in many different animal species, including camels, cows, cats, and bats. Animal coronaviruses rarely infect people and then spread from person to person, such as the respiratory system related diseases MERS, SARS, and now with SARS-CoV-2 (Pillaiyar et al., 2020; Zumla et al., 2016). The most common case is transmission between close contacts (about 6 feet). Human-to-human transmission is believed to occur mainly through respiratory droplets produced when an infected person coughs or sneezes, similar to the way influenza and other respiratory pathogens spread. These water droplets can land on the mouth or nose of nearby people, or they can be inhaled into the lungs. It is unclear whether a person can contract COVID-19 by touching a surface or object, and then touching their mouth, nose or eyes. Generally, for most respiratory viruses, when patients have the serious symptoms (most sick), they are considered most infectious. It should be noted that how easy it is for the virus to spread from person to person varies depending on the type of virus. Some viruses are highly contagious (such as measles), while others are less common (CDC, 2020; WHO, 2020). There is more to be

Table 1
Comparative detail on major outbreaks with fatality rate of epi- and pandemics.

Viral outbreaks	Year identified	Number infected cases	Number of deaths	Number of countries affected	Fatality rate (%)
Marburg	1967	466	373	11	80
Ebola***	1976	33577	13562	9	40.4
Hendra	1994	7	4	1	57
H5N1 (Bird flu)	1997	861	455	18	52.8
Nipah	1998	513	398	2	77.6
SARS-CoV	2002	8096	774	29	9.6
H1N1 (Swine flu) **	2009	> 762630000	284500	214	17.4
MERS-CoV***	2012	2494	858	28	34.4
H7N9 (Bird flu)	2013	1568	616	3	39.3
SARS-CoV-2*	2019	> 120000000	> 2600000	> 219	~3.4

*As of 25 February 2021, ** Between 2009 and 2010, ***As of November 2019 (CDC, 2020; WHO, 2020).

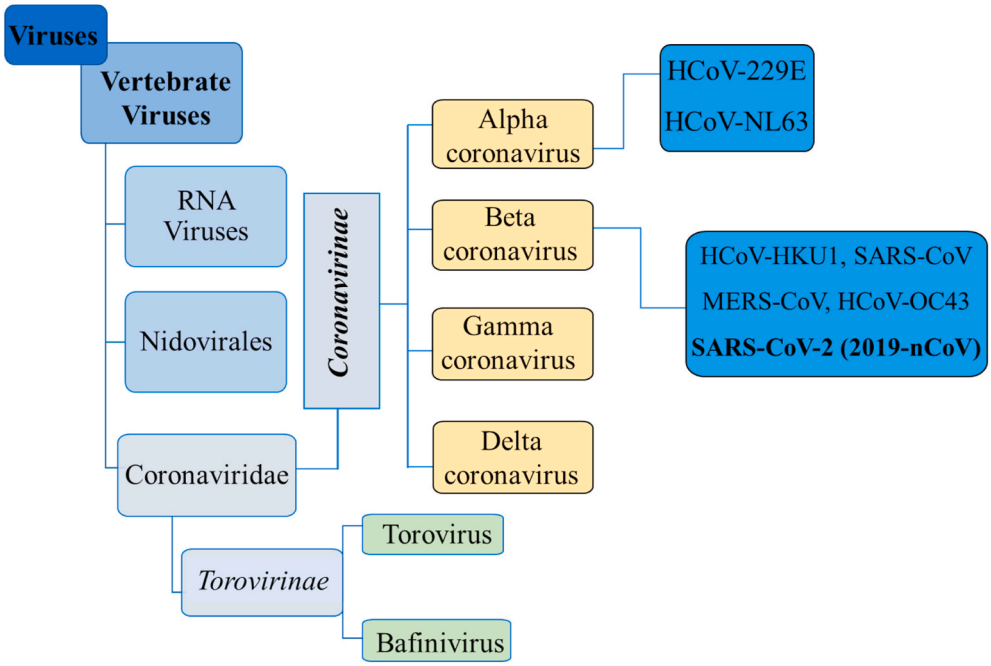

Fig. 1. Schematic taxonomical classification of coronaviruses (according to the International Committee on Taxonomy of Viruses).

understood about the transmissibility, severity and other characteristics related to SARS-CoV-2, and the investigation is ongoing.

2. Signs and symptoms

Common symptoms of COVID-19 infection include fever, cough, shortness of breath, and respiratory symptoms (Fig. 2). In more severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death. An infected person may be asymptomatic or has symptoms such as fever, cough and shortness of breath, also having diarrhea or upper respiratory symptoms, including sneezing, runny nose and sore throat (CDC, 2020; WHO, 2020). According to WHO, the estimated incubation period for development of symptom after infection ranges from 1 to 14 days, with the median incubation period being 5–6 days. A study found some rare cases with an incubation period of up to 27 days (CDC, 2020; WHO, 2020).

3. SARS-COV-2 structural details

SARS-CoV-2 (2019-nCoV) is an enveloped, single-stranded RNA, positive-sense, β-coronavirus, similar to SARS and MERS. The SARS-CoV-2 genome encodes non-structural proteins, like papain-like protease, helicase, 3-chymotrypsin-like protease, and RNA-dependent RNA polymerase, structural proteins, mainly spike glycoprotein and other accessory proteins (Fig. 3) (McKee et al., 2020). From this point of view, the Spike (S), Envelope (E) and Membrane (M) proteins, which are located on the outer surface of the particles are also identified under electron microscope (Dömling and Gao, 2020). A novel type of coronavirus called "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified as the cause of the respiratory disease outbreak that was first detected in Wuhan, China in 2019. The disease caused by this virus was named as Coronavirus Disease 2019 (COVID-19) (Nile and Kai, 2021).

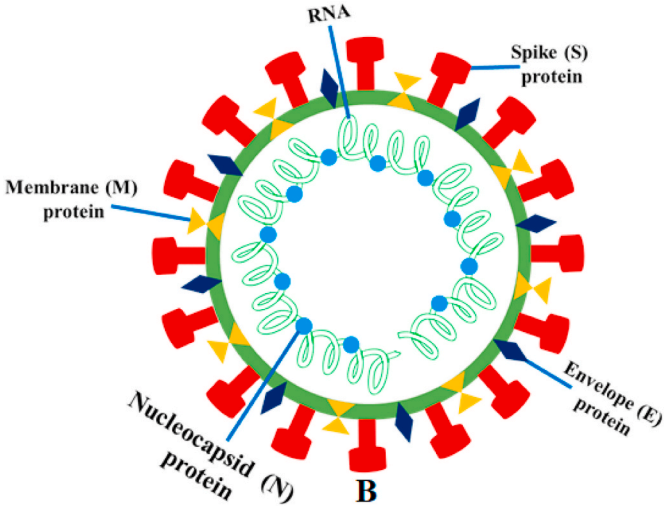

Fig. 3. The illustration is created with schematic structural details of the SARS-CoV-2 virion and its major structural proteins. Note that when observed under an electron microscope, the spikes adorned with the outer surface of the virus give rise to the corona like appearance around the virus body.

4. SARS-COV-2 genomic details

Research evidence shows that SARS-CoV, MERS-CoV and SARS-CoV-2 all originated from bats. The sequence of SARS-CoV-2 is similar to that of the β-coronavirus found in bats, and the virus is genetically different from other coronaviruses, such as severe acute respiratory syndrome-associated coronavirus (SARS), member of Beta-CoV lineage B (that is, the subspecies Sabeco virus) and the Middle East respiratory system Syndrome-associated coronavirus (MERS). The genome of CoVs is a single-stranded sense RNA (+ssRNA) (~30 kb) with a 5′-cap structure and a 3′-poly-A tail. The genome size of CoV (~30 kb) is the largest of all RNA viruses and almost twice the size of the second largest RNA virus. The maintenance of the giant genome size of CoV may be related to the

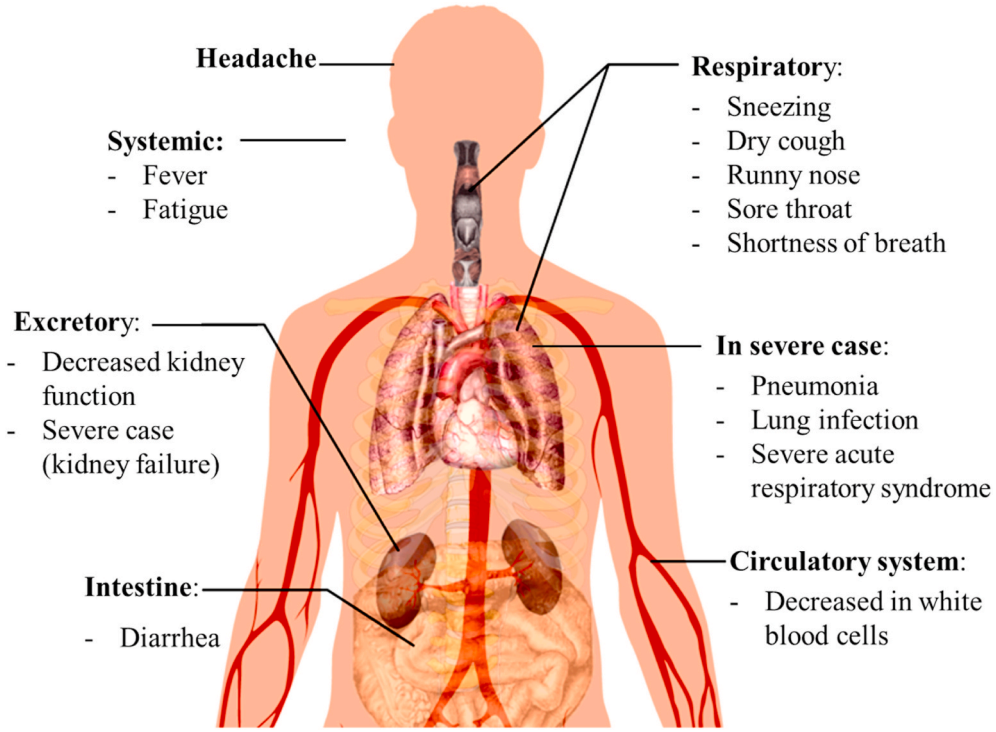

Fig. 2. Symptoms of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

special characteristics of CoV RTC, which contains several RNA processing enzymes, such as the 3′-5′ exoribonuclease enzyme of nsp14, which is unique to CoV among all RNA viruses, and has been proven to be used as a proofreading part of RTC (Chen et al., 2020). Fig. 4 shows the schematic structure of SARS-CoV-2 in the perfusion conformation. Sequence analysis shows that SARS-CoV-2 has a typical genome structure, similar to the β-coronavirus group, including bat-SL ZXC21, bat-SARS (SL)-ZC45, SARS-CoV and MERS-CoV. Based on the phylogenetic tree of CoV, SARS-CoV-2 is more closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21, and is further related to SARS-CoV (Pillaiyar et al., 2020; Zumla et al., 2016).

5. SARS-COV-2 infection and life cycle

The spike proteins present on viral outer surface act as a key that allows the virus to enter the cells of a specific host human body. The binding of viral particle to the surface of host human cells through receptors constitutes the first step in the life cycle of coronaviruses. The steps and events involved in the life cycle of SARS-Cov-2 in human cells are shown in Fig. 5. SARS-CoV-2 virion can enter human cells through endosome or plasma membrane fusion, and the spike protein of SARS-CoV-2 mediates attachment to the host cell membrane and engages angiotensin-converting enzyme 2 (ACE2) as the cellular entry receptor (Shereen et al., 2020). Once the virion enters the complete endosome, cathepsin L activates the spike protein, which is also activated by the cellular serine protease TMPRSS2 in close proximity to the ACE2 receptor, thereby initiating the fusion of the viral membrane and plasma membranes (Hoffmann et al., 2020). Plasma membrane fusion entry is unlikely to trigger host cell anti-viral immunity, so it is more effective for virus replication. Once the virus enters the cell, the gene is translated from the viral genome RNA, and the virus replicates by using viral enzymes such as RNA polymerase. These enzymes are induced by the release of virus from endosomal viral RNA. In addition, the virus hijacks the host machinery, brakes transcription, replicates, and reverse-transcribes its RNA genome for integration into host chromosome, and then reassembles, encapsulates and replicates in infected human cells (Fehr and Perlman, 2015). 5′ end two-thirds of the viral genome encode the polyproteins PP1a and PP1ab, which are cleaved by 3C-like protease (3CLPro) and papain (PLPro) into non-structural protein replicas. An important part of these nonstructural proteins is the RNA-dependent RNA polymerase (RdRp) that forms the replication complex (Fehr and Perlman, 2015; Hoffmann et al., 2020). This replication complex performs transcription of the full-length negative strand. Then, the 3′end of the virus genome encodes four structural proteins, called spike protein (S) envelope (E) protein, nucleocapsid (N) protein and matrix/membrane (M) protein, and a set of accessory proteins (Perlman and Netland, 2009). When the transcription and replication of the viral RNA genome and accessory proteins are completed, the newly synthesized viral protein is trafficked from the endoplasmic reticulum to the Golgi apparatus, and then the mature virion is assembled in the budding vesicles and finally, mature virions are released through the process of exocytosis and release viral replicas outside the host cell and infect nearby cells (Shereen et al., 2020).

6. Prevention & potential therapies

Currently, there are no any specific drugs or vaccines to prevent or treat 2019 coronavirus disease (COVID-19), as for the majority of other diseases; prevention of the infection by avoiding exposure or close contact to infected persons is the best way in the management of COVID-19. The Centers for Disease Control and Prevention recommended preventive actions to prevent the spread of COVID-19, including; avoiding close contact with infected people, touching eye, nose, mouth, and covering mouth during coughing and sneezing, staying at home in case of illness, cleaning or disinfecting objects and surfaces that are regularly touched. and CDC also recommends people with COVID-19 symptoms should use a mask to prevent the disease from spreading to others (CDC, 2020; WHO, 2020). The use of masks is also important for healthcare

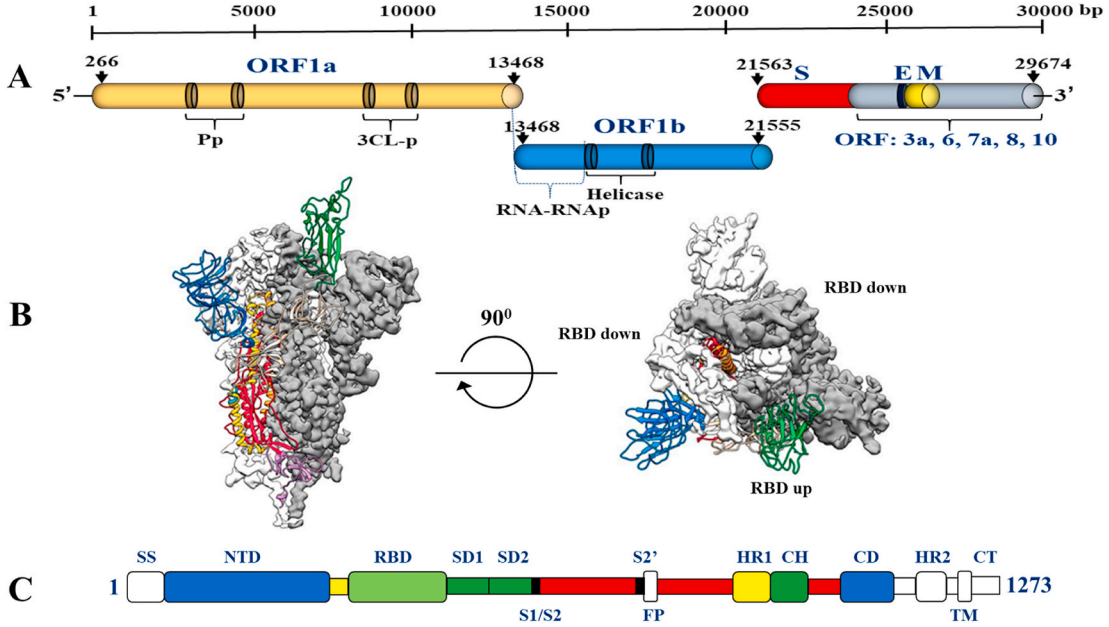

Fig. 4. Schematic structures of SARS-CoV-2 S in the prefusion conformation. (A) SARS-CoV-2 genomic structure, with the un-translated region (UTR), open reading frame regions ORF1a and ORF1b, spike (S), envelope (E), membrane (M), and nucleocapsid (N) genes. (B) Select 2D class averages of the particles that were used to calculate the SARS-CoV-2 S reconstruction (left). Side and top views of the prefusion structure of the SARS-CoV-2 S protein with a single RBD in the "up" conformation (right). The two RBD "down" protomers are shown as cryo-EM density in either white or gray and the RBD "up" protomer is shown in ribbons (C) Schematic of SARS-CoV-2 S primary structures, colored by domain. Domains that were excluded from the ectodomain expression construct or could not be visualized in the final map are colored white. SS = signal sequence, NTD= N-terminal domain, RBD = receptor-binding domain, SD1 = subdomain 1, SD2 = subdomain 2, S1/S2= S1/S2 protease cleavage site, S2′ = S2' protease cleavage site, FP = fusion peptide, HR1 = heptad repeat 1, CH = central helix, CD = connector domain, HR2 = heptad repeat 2, TM = transmembrane domain, CT = cytoplasmic tail. Arrows denote protease cleavage sites (isolate Wuhan-Hu-1, GenBank Acc MN908947).

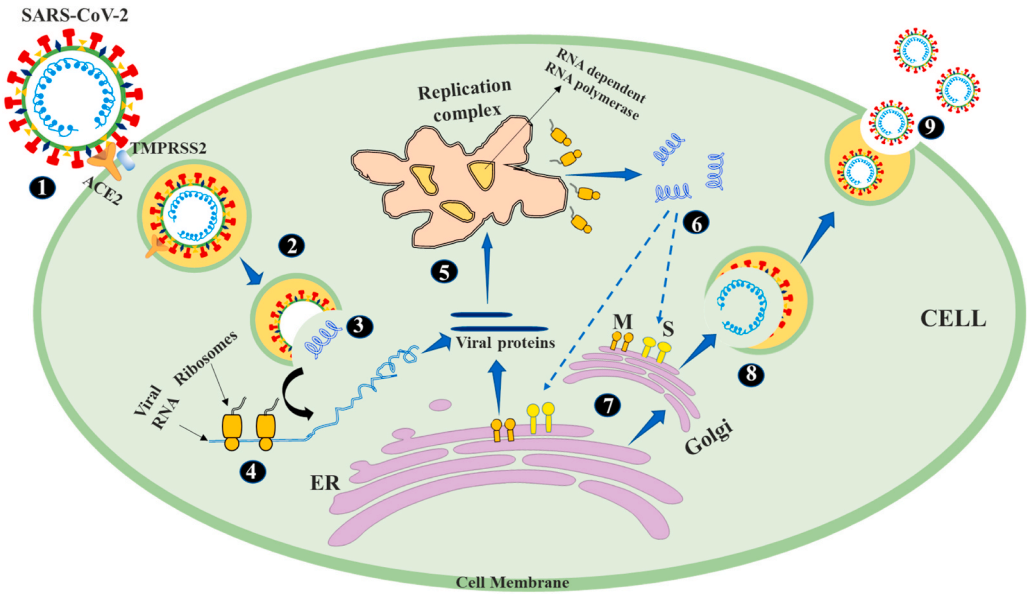

Fig. 5. Life cycle of SARS-Cov-2 in human cell (1. Binding of spike protein to ACE2, 2: TMPRSS2 helps the virion entry, 3: The virion releases its genomic RNA 4: RNA is translated into proteins by the cell's machinery 5: Proteins forms a replication complex to make more RNA 6: Translation and RNA replication 7: Proteins and RNA are assembled into a new virion in the Golgi and released 8: Packaging of RNA synthesized 9: Virion release).

professionals and those who take care of infected individuals in a closed environment (home or medical institution). Washing hands with soap and water for at least 20 s after coughing or squeezing, use at least 60% alcohol-containing hand sanitizer. In severe cases, treatment should include care that supports vital organ functions (CDC, 2020; WHO, 2020).

Researchers, clinicians and virologists have been exploring and gaining some experience since the outbreaks of SARS-2003 and MERS-2012. The study of coronaviruses such as SARS and MERS have provided us with several potentially effective drugs. Researchers are using MERS-CoV and SARS-CoV as prototypes to evaluate COVID-19 countermeasures. Broad-spectrum antiviral drugs, such as remdesivir, lopinavir/ritonavir and interferon beta, have shown promising therapeutic effects against MERS-CoV in animal models are currently being used for treatment and prevention of SARS -CoV-2 developed COVID-19 (Pillaiyar et al., 2020; Zumla et al., 2016). Based on previous studies, angiotensin-converting enzyme 2 (ACE2), trans membrane protease serine 2 (TMPRSS2), spike (S) protein, RNA-dependent RNA polymerase (RdRp), angiotensin AT2 receptor, chymotripsin-like protease (3CLpro) and papain-like protease (PLpro) are considered as major targets for development of antiviral drugs against SARS-CoV-2 and another infectious coronavirus (Zumla et al., 2016). Doctors and scientists form different countries, are trying to use different pharmacological strategies to fight COVID-19, which include currently established antiviral drugs, different modes of oxygen therapy or mechanical aeration. Development of vaccines is crucial factor to prevent and control this COVID-19 pandemic as it plays an important role in controlling replication and spread SARS-CoV-2 through production of antibodies against virus and reducing mortality. Currently about 35 vaccine candidates have been entered into a clinical trial, few of them already approved and used against covid treatment and 145 vaccines are in the preclinical phase (Kaur and Gupta, 2020; Rawat et al., 2021). The COVID-19 pandemic requires rapid development of effective treatment strategies in pursuit of three concepts being applied: (1) the first method relies on testing currently known antiviral drugs and verifying their clinical effectiveness. (2) Another model is based on molecular libraries and databases, allowing high computing power and simultaneous verification of millions of potential drugs at the same time. (3) Finally, the third strategy involves targeted treatments aimed at disrupting the genome and function of the virus (Drożdżal et al., 2020; Lu, 2020).

Scientists and physicians around the world have been carrying out an important campaign to understand this emerging disease and its epidemiology to in the context of identifying possible treatment options, finding effective therapeutic agents and developing vaccines. The development of a vaccine may take at least 12–18 months, and the typical schedule for approval of new antiviral therapies may exceed 10 years. Therefore, the reuse of known drugs currently being used for MERS and SARS can significantly accelerate the deployment of new COVID-19 therapies as described in this article. Here are some examples of synthetic (Table 2) and natural (Table 3) compounds used to treat SARS-CoV and related coronaviruses infection. Their chemical structures details provided in supplementary file (S1).

6.1. *Promising antiviral, antimalarial and anti-HIV agents*

Various antiviral, antimalarial and anti-HIV agents are currently being evaluated for use to treat or prevent COVID -19 infections. Currently, several previously available drugs such as Nafamostat, Chloroquine, Hydroxychloroquine, Lopinavir; Ritonavir, Remdesivir, Favipiravir, Lopinavir/Ritonavir, Darunavir/Umifenovir, Nitazoxanide, Ribavirin, Penciclovir, Tocilizumab, Baricitinib, Arbidol, and other antiviral, antimalarial and anti-HIV agents as discussed in Table 1, with structural details provided in supplementary file (Supplementary file S1), Some of these compounds have exhibited promising results in patients and *in-vitro* clinical studies (Costanzo et al., 2020; Shereen et al., 2020). One of the most common treatments available for SARS-CoV-2 consists of 'cocktail therapies' based on various antivirals which are mainly protease inhibitors, the binding of which to the SARS-CoV-1 protease was predicted *in silico* and *in vitro* (Costanzo et al., 2020). Various combinational therapies have been used by doctors and researchers for treatment of COVID-19. Thus, the previously approved drugs against MERS, SARS, Malaria and HIV were used as target agent against to block viral protease, clathrin-mediated endocytosis, inhibit the inflammatory cytokine surge, regulate immunity, reduce lung viral loads and improve pulmonary function (Nile et al., 2020). The anti-HIV protease inhibitory drug Kaletra, composed of ritonavir and lopinavir, showed a promising antiviral effect on SARS-CoV and SARS-CoV-2. The other anti-HIV drugs like lopinavir, ritonavir, niclosamide, promazine, and two other HIV inhibitors, PNU and UC2 were also studied as 3CLpro inhibitors of SARS-CoV, demonstrating their potential as templates for

Table 2
Commercially available remedies and drugs as possible targets for SARS-CoV-2 and related human coronavirus.

Name of the therapy	Chemical nature	Molecular formula	Targeted virions	Target virion mechanism	Status as drug	Ref
2,6-Bis-arylmethyloxy-5-hydroxychromones	Aryl diketoacids	Not available	SARS-Cov, HCV	Inhibits ATPase and helicase activities	Preclinical	Kim et al. (2011)
6′-Fluorinated-Aristeromycin Analogs	Nucleoside analogs	$C_{11}H_{15}N_5O_3$ (Aristeromycin)	SARS-CoV, MERS-CoV, CHIKV, ZIKV	RdRp and host cell SAH hydrolase inhibitors	Preclinical studies	Yoon et al. (2019)
Abacavir	Nucleoside analog	$C_{14}H_{18}N_6O$	HIV	Reverse transcriptase inhibitor	Approved as HIV drug	Beck et al. (2020)
Acyclovir	Doubly flexible synthetic nucleoside analogue	$C_8H_{11}N_5O_3$	HSV, HCoV-NL63, MERS-CoV	RNA polymerase inhibitor (RdRp)	Preclinical studies	Beck et al. (2020)
Alisporivir	Cyclosporin A-analog	$C_{63}H_{113}N_{11}O_{12}$	HCV, HIV, SARS-CoV, MERS-CoV	Non-immunosuppressive, Cyclophilin inhibitor	HCV infection in phase III clinical trial (NCT01860326)	de Wilde et al. (2017)
Umifenovir (Arbidol)	Indole derivative	$C_{22}H_{25}BrN_2O_3S$	SARS-CoV-2; SARS-CoV, Influenza virus	Block viral fusion and replication	Approved for influenza. Phase 4 for 2019-nCoV, (NCT04260594)	Zhang and Liu (2020)
Aryl diketoacids	Enoic acids	$C_{10}H_8O_4$	HIV, SARS-Cov, HCV	NTPase/helicase inhibitors, RdRp inhibitors	Inhibit HIV-1 and HCV Preclinical	Kim et al. (2011)
ASC09F	Not available	Not available	HIV, SARS-CoV-2	Inhibits 3CLpro	Phase 3 for 2019-nCoV, ASC09F/oseltamivir (NCT04261270)	Li and De Clercq (2020)
Asunaprevir (BMS-650032)	Oligopeptide	$C_{35}H_{46}ClN_5O_9S$	HCV	NS3 protease inhibitor	Approved for HCV, Phase III clinical trials	Beck et al. (2020)
Atazanavir	Aza-dipeptide analogue	$C_{38}H_{52}N_6O_7$	HIV, HBV, HCV, SARS-CoV-2	Protease inhibitor, inhibits 3CLpro	Treat infection of HIV. Preclinical for 2019-nCoV	Beck et al. (2020)
Bevacizumab (Avastin)	Immunoglobulin G 1	$C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$	SARS-CoV-2	VEGF inhibitor	Approved in clinical oncotherapy Promising drug for COVID-19. Phase 2/3 trials (NCT04275414)	Pang et al. (2021)
Carmofur	Pyrimidine analogue	$C_{11}H_{16}FN_3O_3$	SARS-CoV-2	Inhibits THE protease (M^{pro})	Induce leukoencephalopathy	Jin et al. (2020)
Chloroquine	Aminoquinoline	$C_{18}H_{26}ClN_3$	Broad spectrum: HCoV-229E HCoV-OC43, HIV, Ebola, SARS-CoV, MERS-CoV, SARS-CoV-2	S protein ACE2 inhibitor, Endosomal acidification	Approved for malaria. Open-label trial for 2019-nCoV (ChiCTR2000029609)	(Zhang and Liu, 2020; Zumla et al., 2016)
Chloroquine Phosphate	Phosphate salt of chloroquine	$C_{18}H_{32}ClN_3O_8P_2$	SARS-CoV-2	Inhibits autophagy and toll-like receptors (TLRs)	An antimalarial drug, FDA approved drug for COVID.	(Zhang and Liu, 2020; Zumla et al., 2016)
Hydroxychloroquine	Derivative of chloroquine	$C_{18}H_{26}ClN_3O$	SARS-CoV, MERS-CoV, SARS-CoV-2	Antiparasitic agent	Used to treat autoimmune disease, antimalarial	Dyall et al. (2014)
Triflupromazine (1), Fluphenazine (2), Promethazine (3)	Phenothiazine derivative	(1). $C_{18}H_{19}F_3N_2S$ (2). $C_{22}H_{26}F_3N_3OS$ (3). $C_{17}H_{20}N_2S$	SARS-CoV, MERS-CoV	Antipsychotic that shows clathrin-mediated endocytosis	First two approved as antipsychotic agents	Li and De Clercq (2020)
Chlorpromazine	Phenothiazine	$C_{17}H_{19}ClN_2S$	SARS-CoV, MERS-CoV, HCV	An antipsychotic affects the assembly of clathrin-coated pits at the plasma membrane	Approved as antipsychotic agents	Zumla et al. (2016)
Cobicistat (GS-9350)	Monocarboxylic acid amide	$C_{40}H_{53}N_7O_5S_2$	HIV, SARS-CoV-2	Protease inhibitor, inhibits 3CLpro	Approved for HIV and clinical trial at phase 3 for 2019-nCoV	Li and De Clercq (2020)
Compound 6	Pyrimidine derivative	$C_{12}H_{14}ClN_3O_3S$	MERS-CoV	Inhibits papain-like protease	Preclinical	Lee et al. (2019)
Cyclosporine A	Cyclic non-ribosomal peptide	$C_{62}H_{111}N_{11}O_{12}$	SARS-CoV, MERS-CoV, HIV, HCV	Binds to nucleocapsid protein (NP), inhibits viral replication	Approved as immunosuppressive drug in organ transplantation	Zhang and Liu (2020)
Darunavir	Furofuran	$C_{27}H_{37}N_3O_7S$	HIV, SARS-CoV-2	Protease inhibitor, inhibits 3CLpro	Approved for HIV and clinical trial at phase 3 for 2019-nCoV	Li and De Clercq (2020)
Disulfiram	Carbamoyl derivative	$C_{10}H_{20}N_2S_4$	MERS-CoV, SARS-CoV	Papain-like protease inhibitor	Approved for treat chronic alcoholism	Lin et al. (2018)
Dolutegravir	Monocarboxylic acid amide	$C_{20}H_{19}F_2N_3O_5$	HIV, SARS-CoV-2	Second-generation integrase inhibitor	Approved for HIV and Preclinical for 2019-nCoV	Beck et al. (2020)
Ebselen (SPI-1005)	Organoselenium compound	$C_{13}H_9NOSe$	HIV, SARS-CoV-2	Potently inhibits Mpro and viral replication	Used to treat Diabetes Mellitus	Jin et al. (2020)
Efavirenz	Non-nucleoside	$C_{14}H_9ClF_3NO_2$	HIV, SARS-CoV-2	Reverse transcriptase (RT) inhibitor, 3CLpro inhibitor	Approved for HIV and Preclinical for 2019-nCoV	Beck et al. (2020)

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Table 2 (*continued*)

Name of the therapy	Chemical nature	Molecular formula	Targeted virions	Target virion mechanism	Status as drug	Ref
Entecavir	Guanosine nucleoside analogue	$C_{12}H_{15}N_5O_3$	HBV, SARS-CoV-2	inhibits the reverse transcriptase (RT) viral RNA-dependent HBV DNA polymerase	Approved for HBV and Preclinical for 2019-nCoV	Beck et al. (2020)
Favipiravir (T-705)	Pyrazine carboxamide	$C_5H_4FN_3O_2$	Influenza, SARS-CoV-2	RNA polymerase inhibitor (RdRp)	Approved as influenza drug in Japan. China approved for 2019-nCoV	Zhang and Liu (2020)
Fingolimod (FTY720)	Aminodiol	$C_{19}H_{33}NO_2$	2019-nCoV	Sphingosine-1-phosphate receptor agonist and a CB1 receptor antagonist	Approved for treatment of relapsing forms of multiple sclerosis. Phase 2 for 2019-nCoV, NCT04280588.	Wang (2020)
Galidesivir (BCX4430)	Adenosine analog	$C_{11}H_{15}N_5O_3$	SARS-CoV, MERS-CoV, IAV, Ebola	RNA polymerase inhibitor (RdRp)	Clinical trials as Phase 1 for yellow fever and Phase 1 for Marburg virus	Warren et al. (2014)
GC376	Bisulfite adduct	$C_{21}H_{30}N_3NaO_6S$	TGEV, FIPV and PTV, MERS-CoV, SARS-CoV	Inhibits 3CLpro, Inhibits the replication of viruses	Preclinical studies	Kim et al. (2012)
GC813	Pyrrolidinone based peptide	$C_{22}H_{31}ClN_3NaO_8S$	MERS-CoV	Inhibits 3CLpro	Preclinical studies	Pillaiyar et al. (2020)
Imatinib	Benzamide	$C_{29}H_{31}N_7O$	SARS-CoV, MERS-CoV	Abelson tyrosine-protein kinase 2 (Abl2) inhibitor	Approved for cancer	Coleman et al. (2016)
Trametinib	Pyridopyrimidine	$C_{26}H_{23}FIN_5O_4$	MERS-CoV, SARS-CoV	Inhibits the ERK/MAPK and PI3K/AKT/mTOR signalling pathways	Approved for cancer treatment	Li and De Clercq (2020)
Dasatinib	Benzimidazole	$C_{22}H_{26}ClN_7O_2S$	MERS-CoV, SARS-CoV	BCR/ABL and Src family tyrosine kinase inhibitor	Approved for cancer treatment	Li and De Clercq (2020)
Selumetinib	Benzimidazole	$C_{17}H_{15}BrClFN_4O_3$	MERS-CoV, SARS-CoV	Inhibits the ERK/MAPK and PI3K/AKT/mTOR signaling pathways	Approved for cancer treatment	Li and De Clercq (2020)
Rapamycin	Antibiotic	$C_{51}H_{79}NO_{13}$	MERS-CoV	Inhibits the ERK/MAPK and PI3K/AKT/mTOR pathways, block early viral entry and/or post-entry	Approved as antifungal agent	Pillaiyar et al. (2020)
Laninamivir	Octanoyl ester	$C_{13}H_{22}N_4O_7$	Influenza virus A and B	Neuraminidase inhibitor	Approved as influenza A and B drug	Samson et al. (2014)
Loperamide	Phenyl-butanamide	$C_{29}H_{33}ClN_2O_2$	MERS-CoV, SARS-CoV, HCoV-229E	Inhibits viral replication. Opioid receptor binding	Approved as synthetic antidiarrheal agent	de Wilde et al. (2014)
Lopinavir	Dicarboxylic acid amide	$C_{37}H_{48}N_4O_5$	HIV, HPV, HCoV-229E, MERS-CoV, SARS-CoV, SARS-CoV-2	Protease inhibitor, inhibits 3CLpro	Approved for HIV, Phase 3 for 2019-nCoV, Phase 2/3 for MERS	(Chu, 2004; Li and De Clercq, 2020)
Methylprednisolone	Corticosteroid	$C_{22}H_{30}O_5$	MERS-CoV, SARS-CoV	Protease Inhibitor	Treat arthritis and severe allergic reactions. Randomized trial for 2019-nCoV, NCT04323592	(Huang et al., 2020; Pillaiyar et al., 2020)
Mucroporin-M1	Scorpion venom-derived peptide	Not available	HBV, H5N1, SARS-CoV	Inhibiting viral replication	Drug design to target COVID-19	Zhang and Liu (2020)
Mycophenolic acid	Antibiotic	$C_{17}H_{20}O_6$	MERS-CoV, HBV, HCV	Inhibits viral replication, Inhibits IMPDH and guanine monophosphate synthesis	Approved as immunosuppressant during organ transplantation	Hart et al. (2014)
Nafamostat	Synthetic p-Guanidinobenzoic acid ester	$C_{19}H_{17}N_5O_2$	SARS-CoV-2, MERS-CoV	Serine protease inhibitor, Inhibits spike-mediated membrane fusion	Approved as an anticoagulant therapy	Li and De Clercq (2020)
Nelfinavir	Aryl sulfide	$C_{32}H_{45}N_3O_4S$	HIV, HBV, HCV, SARS-CoV	Protease inhibitor	Responsible for post-translational in HIV propeptides. Preclinical trials for 2019-nCoV	Zhang and Liu (2020)
Neuraminidase inhibitor analogs (compound 3k)	Chlorobenzoic acid derivatives	Not available	SARS-CoV, MERS-CoV	3CL protease inhibitor	Preclinical	Kumar et al. (2016)
Niclosamide	Benzamide	$C_{13}H_8Cl_2N_2O_4$	SARS-CoV	ACE2 inhibitor, Inhibit replication of virus	Antihelminthic drug Inhibits IFV-A in A549 cells.	Li et al. (2019)
Nicotianamine	Metal ligand	$C_{12}H_{21}N_3O_6$	SARS-CoV-2	S protein and ACE2 inhibitor	Preclinical	Zhang and Liu (2020)
Oseltamivir	Ethyl ester of oseltamivir acid	$C_{16}H_{28}N_2O_4$	SARS-CoV-2; Influenza virus	Influenza neuraminidase inhibitor	Approved for influenza, Phase 3 and 4 for 2019-nCoV, NCT04261270	Lu (2020)
Penciclovir	Nucleoside analogue	$C_{10}H_{15}N_5O_3$				

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Table 2 (*continued*)

Name of the therapy	Chemical nature	Molecular formula	Targeted virions	Target virion mechanism	Status as drug	Ref
			HCV, SARS-CoV-2	RNA polymerase inhibitor (RdRp)	Approved for HSV. Randomized trial for 2019-nCoV	(M. Wang et al., 2020)
Peptidomimetic inhibitors (Compound 6)	Aldehyde derivatives	Not available	MERS-CoV, SARS-CoV	3CL protease inhibitor	Preclinical	Kumar et al. (2016)
Peramivir	Cyclopentane derivative	$C_{15}H_{28}N_4O_4$	Influenza A and B	Neuraminidase inhibitor	Approved as influenza A and B drug	(De Clercq and Li, 2016; Lu, 2020)
Promazine	Phenothiazine derivative	$C_{17}H_{20}N_2S$	SARS-CoV	Blocking the interaction of S protein and ACE2	Alternative for the treatment of COVID-19	Zhang and Liu (2020)
Pyrithiobac derivatives (6-5)	Benzoic acids	$C_{13}H_{11}ClN_2O_4S$ (Pyrithiobac)	SARS-CoV,	3CL protease inhibitor	Preclinical	Wu et al. (2019)
Remdesivir (GS-5734)	Nucleoside analogue	$C_{27}H_{35}N_6O_8P$	Ebola, MERS-CoV, SARS-CoV, SARS-CoV-2	RNA polymerase inhibitor (RdRp)	Randomized trials for SARS-CoV-2	(Sheahan et al., 2020a; M. Wang et al., 2020)
Ribavirin	Nucleoside analogue	$C_8H_{12}N_4O_5$	HCV, RSV, MERS-CoV, SARS-CoV, SARS-CoV-2	Inhibits viral RNA replication and mRNA capping	Approved for HCV and RSV. Randomized trials for SARS and SARS-CoV-2	(Chan et al., 2013; Lu, 2020)
Ritonavir	L-valine derivative	$C_{37}H_{48}N_6O_5S_2$	HIV, MERS-CoV, SARS-CoV-2	Protease inhibitor, inhibits 3CLpro	Approved for HIV, Phase 3 for SARS-CoV-2, Phase 2/3 for MERS	(Chu, 2004; Li and De Clercq, 2020)
SK80	Phenylisoserine derivative	$C_{31}H_{32}N_2O_4$	SARS-CoV	3CL protease inhibitor	Preclinical	Konno et al. (2017)
SSYA10-001	Triazole derivative	$C_{12}H_{12}N_4O_2S_2$	SARS-CoV, MERS-CoV, MHV	Inhibits helicase without affecting ATPase activity	Preclinical	Adedeji et al. (2014)
Losartan (Cozaar)	Monopotassium salt	$C_{22}H_{23}ClN_6O$	MERS-CoV, SARS-CoV, SARS-CoV-2	Angiotensin-receptor blocker	Phase 2 for SARS-CoV-2 (NCT04312009)	(Yan et al., 2020.)
Verdinexor (KPT-335)	Synthesized chemical compound	$C_{18}H_{12}F_6N_6O$	Influenza A and B virus, Respiratory syncytial virus (RSV)	Blocking XPO1-mediated nuclear export of viral ribonucleoprotein complexes	Inhibitor of Nuclear Export, Under clinical trial FOR Influenza (NCT02431364)	Perwitasari et al. (2014)
Zanamivir	Sialic acid-analogue	$C_{12}H_{20}N_4O_7$	Influenza virus	Neuraminidase inhibitor	Approved for influenza virus	Lu (2020)
Gemcitabine hydrochloride	Deoxycytidine analog	$C_9H_{12}ClF_2N_3O_4$	MERS-CoV, SARS-CoV nfluenza virus	DNA metabolism inhibitor, Inhibiting pyrimidine biosynthesis	FDA-approved anticancer agent	(Li et al., 2019; Pillaiyar et al., 2020)
Amodiaquine	Quinoline derivative	$C_{20}H_{22}ClN_3O$	MERS-CoV, SARS-CoV, Ebola, ZIKA virus	Targets early events of the viral replication cycle	Approved as antimalarial drug	(Dyall et al., 2014; Li and De Clercq, 2020)
Mefloquine	Quinoline derivative	$C_{17}H_{16}F_6N_2O$	MERS-CoV, SARS-CoV	Targets early events of the viral replication cycle	Approved as antimalarial drug	(Dyall et al., 2014; Li and De Clercq, 2020)
Dihydroartemisinin	Sesquiterpene lactone	$C_{15}H_{24}O_5$	HIV, HCMV, HBV, influenza virus A	Inhibits replication of virion	Used as antimalarial and anticancer agent	Krishna et al. (2008)
E-64-D (Aloxistatin)	L-leucine derivative	$C_{17}H_{30}N_2O_5$	MERS-CoV, SARS-CoV	Cathepsin protease inhibitor	Inhibit calpain activity in intact platelets.	Dyall et al. (2014)
Recombinant interferons	Signalling proteins	Not available	SARS-CoV-2; SARS-CoV; MERS-CoV	Interferon response, Inhibiting the viral protein synthesis, disables viral replication	Approved for melanoma (IFN-α2b), metastatic renal cell carcinoma (IFN-α2a), multiple sclerosis (IFN- β1a, 1b), chronic granulomatous disease (IFN-γ)	Li and De Clercq (2020)
SAB-301	Polyclonal antibody	Not available	MERS-CoV	Prevent the virus from infecting and entering cells	Phase 2/3 trial for MERS endemic in Kingdom of Saudi Arabia	Beigel et al. (2018)
REGN3048 and REGN 3051	Monoclonal antibodies	Not available	MERS-CoV	Prevent the virus replication in cell	Phase 1 trial for MERS-CoV (NCT03301090)	de Wit et al. (2018)
Nitazoxanide	Thiazolides	$C_{12}H_9N_3O_5S$	Influenza viruses, HBV, HCV, HIV, SARS-CoV, MERS-CoV, SARS-CoV-2	Interferon response in host cell	Approved for Diarrhea treatment. Phase III clinical development for Influenza virus -A and B strains	(Li et al., 2019; Pillaiyar et al., 2020)
Saracatinib	Anilinoquinazoline	$C_{27}H_{32}ClN_5O_5$	MERS-CoV	Suppression of the SFK signalling pathways, Inhibits viral replication	Approved for treating cancers	Pillaiyar et al. (2020)

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Table 2 (*continued*)

Name of the therapy	Chemical nature	Molecular formula	Targeted virions	Target virion mechanism	Status as drug	Ref
Camostat	Benzoic acid derivative	$C_{20}H_{22}N_4O_5$	SARS-CoV MERS-CoV HCoV-229E	Cysteine protease inhibitor, blocks endosomal protease mediated cleavage and the endosomal entry pathway	Preclinical	(Pillaiyar et al., 2020; Zumla et al., 2016)
K11777	Piperazine derivative	$C_{32}H_{38}N_4O_4S$	SARS-CoV MERS-CoV HCoV-229E Ebola	Cysteine protease inhibitor, targeting endosomal proteases involved in viral entry	Preclinical	Zhou et al. (2015)
Nafamostat	Benzoic acids derivative	$C_{19}H_{17}N_5O_2$	SARS-CoV Influnza-A MERS-CoV	Serine protease inhibitor	FDA-approved to treat pancreatitis, approved as an anticoagulant therapy	Li et al. (2019)
K22	Benzamide	$C_{27}H_{25}BrN_2O_3$	SARS-CoV, MERS-CoV, HCoV-229E	Inhibits membrane-bound RNA synthesis and membrane vesicle formation	Preclinical	Lundin et al. (2014)
Teicoplanin derivatives	Glycopeptide antibiotic	$C_{80}H_{81}Cl_2N_9O_{33}$	Broad-spectrum (influenza virus, HCoV, Ebola, HIV, HCV)	Inhibits peptidoglycan polymerization	Effective drug against gram-positive infections	(Li and De Clercq, 2020; Szűcs et al., 2018)
FA-613	Carboxylic acid	$C_{18}H_{14}BrNO_3$	Influenza A and B, RSV, HCoV) SARS-CoV, MERS-CoV	Inhibits DHODH, interferes intracellular pyrimidine synthesis pathways	Preclinical	(Cheung et al., 2017; Li and De Clercq, 2020)
Convalescent plasma	Immunoglobulins	Not available	SARS-CoV-2, SARS-CoV, MERS-CoV, influenza	Inhibits virus entry to the target cells	Phase 2 (NCT02190799)	(Chen et al., 2020; Li and De Clercq, 2020)
Mycophenolate mofetil	Ester of mycophenolic acid	$C_{23}H_{31}NO_7$	HCoV-OC43, HCoV-NL63, MERS-CoV MHV-A59	Inhibits viral replication	Approved as immunosuppressant	Shen et al. (2019)
Monensin sodium	Antibiotic salt	$C_{36}H_{61}NaO_{11}$	MERS-CoV, HCoV-OC43, and HCov-NL63	Inhibits viral replication	Antibacterial drug	Shen et al. (2019)
Phenazopyridine	Pyridine derivative	$C_{11}H_{12}ClN_5$	MERS-CoV, HCoV-OC43, and HCov-NL63	Inhibits viral replication	Urinary tract analgesic, Removed by FDA	Shen et al. (2019)
Pyrvinium pamoate	Quinoline derivative	$C_{49}H_{43}N_3O_6$	MERS-CoV, HCoV-OC43, and HCov-NL63	Inhibits viral replication	DA-approved antihelmintic drug, inhibits WNT pathway signaling.	Shen et al. (2019)
Hexamethylene amiloride	Pyrazines	$C_{12}H_{18}ClN_7O$	SARS-CoV, HCoV-229E, and some animal CoVs	Viroporin inhibitor that inhibits the ion channel activity of CoV E	Preclinical	Zumla et al. (2016)
Indomethacin	Indole derivative	$C_{19}H_{16}ClNO_4$	SARS-CoV	COX1 and COX2 inhibitor, Blocking viral RNA synthesis	Approved as anti-Inflammatory, used to treat gout	Amici et al. (2006)
Azithromycin	Azalide	$C_{38}H_{72}N_2O_{12}$	Zika, Ebola, SARS-CoV-2	Inhibit replication of virus	Approved as antibiotic	Gautret et al. (2020)
Tocilizumab	Monoclonal antibody	$C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$	SARS-CoV-2	Treatment of cytokine storms induced by COVID-19	Phase III clinical development for **COVID-19, NCT04361552**	Luo et al. (2020)
EIDD-2801	Prodrug of NHC	$C_{13}H_{19}N_3O_7$	SARS-CoV-2, MERS-CoV, SARS-CoV	Inhibit replication of virus	Preclinical	Sheahan et al. (2020b)
β-D-N4 hydroxycytidine (NHC, EIDD-1931)	Ribonucleoside analog	$C_9H_{13}N_3O_6$	Influenza, Ebola, SARS-CoV-2, MERS-CoV, SARS-CoV	Inhibit replication of virus	Preclinical	Sheahan et al. (2020b)
Bromhexine hydrochloride	Hydrochloride	$C_{14}H_{21}Br_2ClN_2$	Influenza, SARS-CoV-2	Inhibit transmembrane serine protease 2	Mucolytic and prophylactic drug	Habtemariam et al. (2020)
Triazavirin	Guanine nucleotide	$C_5H_4N_6O_3S$	SARS-CoV-2, H5N1, Ebola	RNA polymerase inhibitor	Antiviral drug	Shahab and Sheikhi (2020)
Carfilzomib	Epoxomicin derivate	$C_{40}H_{57}N_5O_7$	SARS-CoV-2	Protease inhibitor	Approved anticancer drug	Wang (2020)
Eravacycline	Antibiotic	$C_{27}H_{31}FN_4O_8$	SARS-CoV-2	Protease inhibitor	Broad spectrum antibacterial	Wang (2020)
Ruxolitinib	Pyrazole	$C_{17}H_{18}N_6$	SARS-CoV-2	JAK inhibitor	Anti-arthritic drugs	

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Table 2 (*continued*)

Name of the therapy	Chemical nature	Molecular formula	Targeted virions	Target virion mechanism	Status as drug	Ref
						Stebbing et al. (2020)
Fedratinib	Anilinopyrimidine derivative	$C_{27}H_{36}N_6O_3S$	SARS-CoV-2	JAK inhibitor	Anti-arthritic drugs	Stebbing et al. (2020)
Baricitinib (Olumiant)	Pyrazole	$C_{16}H_{17}N_7O_2S$	SARS-CoV-2	JAK and NAK inhibitor	Anti-arthritic drugs	Stebbing et al. (2020)
Pirfenidone	Pyridinone derivative	$C_{12}H_{11}N_O$	SARS-CoV-2	Inhibits DNA synthesis	Antifibrotic agent, phase 3 for COVID-19 NCT04282902	(Su et al., 2020)
Nintedanib	Indolinone derivative	$C_{31}H_{33}N_5O_4$	SARS-CoV-2	Kinase inhibitor	Antifibrotic agent, phase 2 for COVID-19 NCT04338802	(Su et al., 2020)
Sofosbuvir	Nucleoside analogue	$C_{22}H_{29}FN_3O_9P$	Hepatitis C SARS-CoV-2	Bind to RdRp, Inhibits RNA synthesis	Preclinical	Shah et al. (2020)
Tenofovir	Acyclic nucleotide analogue of adenosine	$C_9H_{14}N_5O_4P$	HIV, HBV, SARS-CoV-2	Bind to RdRp, Inhibits reverse transcriptase	Preclinical	Shah et al. (2020)
Tideglusib	Thiadiazolidinone	$C_{19}H_{14}N_2O_2S$	SARS-CoV-2	non-ATP competitive inhibitor of glycogen synthase kinase 3, inhibits M^{pro}	Potent anti-inflammatory and neuroprotective	Jin et al. (2020)
Azvudine	Cystidine analogue	$C_9H_{11}FN_6O_4$	HIV, SARS-CoV-2	Reverse transcriptase inhibitor	Clinical trial for COVID ChiCTR2000029853	Zhai et al. (2020)
Danoprevir (R7227)	Macrocyclic peptidomer	$C_{35}H_{46}FN_5O_9S$	HCV, SARS-CoV-2	Protease inhibitor	Antiviral agent, phase 2 for COVID-19 NCT04338802NCT04291729	Shah et al. (2020)
Baloxavir marboxil	Synthesized compound	$C_{27}H_{23}F_2N_3O_7S$	Influenza	Inhibits mRNA and protein synthesis	ChiCTR2000029544	Li and De Clercq (2020)
Ciclesonide	Glucocorticoid	$C_{32}H_{44}O_7$	SARS-CoV-2	Inhibits virus replication	Treat obstructive airway diseases, under clinical trial for COVID -19 NCT04330586	Iwabuchi et al. (2020)
Paritaprevir (ABT-450)	Synthesized compound	$C_{40}H_{43}N_7O_7S$	HCV, SARS-CoV-2	Protease inhibitor	Preclinical	Shah et al. (2020)
Amprenavir	Derivative of hydroxyethylamine sulfonamide	$C_{25}H_{35}N_3O_6S$	HIV-1, SARS-CoV-2	Protease inhibitor	Preclinical	Wu et al. (2020)
Adefovir	Acyclic nucleotide analogue of adenosine	$C_8H_{12}N_5O_4P$	HIV, HBV, SARS- CoV	Reverse transcriptase and Protease inhibitor	Preclinical	Shah et al. (2020)
Ivermectin	Macrocyclic lactone	$C_{48}H_{74}O_{14}$	Flavivirus, HIV, dengue, influenza, SARS-CoV-2	Inhibit the non-structural 3 (NS3) helicase	FDA-approved broad-spectrum anti-parasitic drug.	Kumar et al. (2020)
Artesunate	Semi-synthetic derivative artemisinin	$C_{19}H_{28}O_8$	Hepatitis, HCMV, SARS-CoV-2	Inhibit NF-kB (Nuclear Factor kappa B)	Antimalarial drug	Uzun and Toptas (2020)
Dexamethasone	Corticosteroid	$C_{22}H_{29}FO_5$	SARS-CoV-2	Potent anti-inflammatory drug treat arthritis	Phase 6 clinical trial for COVID-19, NCT04325061	Villar et al. (2020)
Siltuximab	Monoclonal antibody	$C_{6450}H_{9932}N_{1688}O_{2016}S_{50}$	HIV, SARS-CoV-2	Interleukin-6 Inhibitors	Phase 3 clinical trial for COVID-19 NCT04330638	Saini et al. (2020)
Hydrocortisone	Corticosteroid	$C_{21}H_{30}O_5$	SARS-CoV-2	Anti-inflammatory and immunosuppressive,	Phase 3 clinical trials, NCT04348305	Saini et al. (2020)
Boceprevir	Synthetic tripeptide	$C_{27}H_{45}N_5O_5$	HCV, SARS-CoV-2	Inhibits protease and viral replication	Approved as antiviral agent	Ma et al. (2020)
GC-376	Synthetic compound	$C_{21}H_{30}N_3NaO_8S$	SARS, MERS, SARS-CoV-2	3C-like protease inhibitor	Treatment for feline infectious peritonitis	Ma et al. (2020)
Thalidomide	Synthetic derivative of glutamic acid	$C_{13}H_{10}N_2O_4$	H1N1, SARS-CoV-2	Inhibits virus replication	Phase 2 clinical trial for COVID-19, NCT04273529	Saini et al. (2020)
Lenalidomide (Revlimid)	Thalidomide analog	$C_{13}H_{13}N_3O_3$	SARS-CoV-2	Inhibits virus replication	Phase 4 clinical trial for COVID-19, NCT04361643	Saini et al. (2020)
Acalabrutinib	Synthetic compound	$C_{26}H_{23}N_7O_2$	SARS-CoV-2	Inhibitor of Bruton's tyrosine kinase (BTK), and viral replication	Phase 2 clinical trial for COVID-19, NCT03863184	Saini et al. (2020)
Duvelisib	Synthetic compound	$C_{22}H_{17}ClN_6O$	HIV, hepatitis B, and C SARS-CoV-2	Inhibitor of phosphatidylinositol 3-kinase (PI3K) and viral replication	Phase 2 clinical trial for COVID-19, NCT04372602	Saini et al. (2020)
ML188	Acetamide	$C_{26}H_{31}N_3O_3$	SARS-CoV, SARS-CoV-2	3CLpro inhibitor	Noncovalent small molecule inhibitor	(Loffredo et al., 2021)
Famotidine	Propanimidamide	$C_8H_{15}N_7O_2S_3$	SARS-CoV-2	Protease inhibitor	Histamine H2-receptor antagonist	(Loffredo et al., 2021)
Tilorone	Fluoren-9-ones	$C_{25}H_{34}N_2O_3$	MERS-CoV, Ebola	Inhibit viral replication	Broad-spectrum antiviral and immunomodulator	Ekins and Madrid (2020)

Table 3
Different types of natural compounds as possible targets for SARS-CoV-2 and related human coronavirus.

Name of the compound	Chemical nature	Molecular formula	Targeted virions	Target and inhibition mechanism	Ref
229E-HR1P 229E-HR2P	Peptide	Not available	HCoV-229E	Inhibits spike protein-mediated cell-cell fusion	Li and De Clercq (2020)
6-mercaptopurine	Thiopurine analog	$C_5H_4N_4S$	MERS-CoV, SARS-CoV	Inhibits PLpro	Li and De Clercq (2020)
6-thioguanine	Thiopurine analog	$C_5H_5N_5S$	MERS-CoV, SARS-CoV	Inhibits PLpro	Li and De Clercq (2020)
Aescin	Saponin	$C_{55}H_{86}O_{24}$	SARS-CoV	Inhibits glycoprotein	Xian et al. (2020)
Arachidonic acid	Fatty acid	$C_{20}H_{32}O_2$	SARS-CoV-2, SARS and MERS	Supress ACE2 receptor for viral cell entry	Das (2020)
Astaxanthin	Carotenoid pigment	$C_{40}H_{52}O_4$	SARS-CoV-2	Supress cathepsin L (CatL) and cytokine storm	Liu et al. (2020)
Eicosapentaenoic acid	Fatty acid	$C_{20}H_{30}O_2$	SARS-CoV-2, SARS and MERS	Supress ACE2 receptor for viral cell entry	Das (2020)
Docosahexaenoic acid	Fatty acid	$C_{22}H_{32}O_2$	SARS-CoV-2, SARS and MERS	Supress ACE2 receptor for viral cell entry	Das (2020)
Baicalin	Flavone glycoside	$C_{21}H_{18}O_{11}$	HIV-1, SARS-CoV, SARS-CoV-2	Inhibit E-protein, 3CL protease inhibitor	Su et al. (2020)
Baicalein	Trihydroxyflavone	$C_{15}H_{10}O_5$	HIV, SARS-CoV, SARS-CoV-2	3CL protease inhibitor	Su et al. (2020)
Betulinic acid	Phenolic acid	$C_{30}H_{48}O_3$	SARS-CoV	Replication, 3CLpro	(D. Zhang et al., 2020)
Celastrol	Quinone-methide triterpene	$C_{29}H_{38}O_4$	SARS-CoV	3CLpro inhibitory effect	Ryu et al. (2010)
Cepharanthine	Alkaloid	$C_{37}H_{38}N_2O_6$	HCoV-OC43, SARS-CoV, SARS-CoV-2	Protease inhibition	(Islam et al., 2020; McKee et al., 2020)
Cinanserin	Cinnamamides	$C_{20}H_{24}N_2OS$	MERS-CoV, SARS-CoV, SARS-CoV-2	Serotonin receptor antagonist, 3CL protease inhibitor	(Jin et al., 2020; Zhang and Liu, 2020)
Chrysin	Dihydroxyflavone	$C_{15}H_{10}O_4$	SARS-CoV, SARS-CoV-2	PLpro inhibitor, Inhibits interaction of SARS-CoV (S) Protein and ACE2.	(Islam et al., 2020; Wu et al., 2020)
Chlorogenic acid	Polyphenol	$C_{16}H_{18}O_9$	HCoV-NL63	Reducing the production of progeny HCoV-NL63	Weng et al. (2019)
Caffeic acid	Polyphenol	$C_9H_8O_4$	HCoV-NL63	Binds to ACE2 receptor, Inhibits viral replication	Weng et al. (2019)
Curcumin	Polylphenol	$C_{27}H_{28}O_{12}$	SARS-CoV	GSK-3 Inhibitor, Suppress viral replication	Kandeel and Al-Nazawi (2020) [99]
Ginkgolide A	Terpenoids	$C_{20}H_{24}O_9$	SARS-CoV-2	Protease inhibitor	
Gallic acid	Phenolic acid	$C_7H_6O_5$	HCoV-NL63	Inhibits the viral replication	Weng et al. (2019)
Cyanidin-3-sambubioside	Flavonoid	$C_{26}H_{29}O_{15}^{+}$	Influenza A and B	Neuraminidase inhibitor	Porter and Bode (2017)
Dieckol	Phlorotannin	$C_{36}H_{22}O_{18}$	SARS-CoV	3CLpro inhibitor	Park et al. (2013)
Dihydrotanshinone I	Lipophilic diterpenes	$C_{18}H_{14}O_3$	MERS-CoV	3CLpro and PLpro protease inhibitors	Kim et al. (2018)
Emetine	Alkaloid	$C_{29}H_{40}N_2O_4$	MERS-CoV	Inhibits RNA synthesis	Shen et al. (2019)
Emodin	Anthraquinone	$C_{15}H_{10}O_5$	SARS-CoV HCoV-OC43 SARS-CoV-2	S protein and ACE2 inhibitor	(Ho et al., 2007; Zhang and Liu, 2020)
Ginsenoside Rb1	Steroid glycosides	$C_{42}H_{72}O_{14}$	HIV, SARS-CoV	Prevent viral entry	Li et al. (2005)
Glycyrrhetinic acid	Triterpenoids	$C_{30}H_{46}O_4$	Herpes, HIV, Hepatitis, SARS-CoV	Inhibits viral replication	Wang et al. (2015)
Glycyrrhizin	Saponin	$C_{42}H_{62}O_{16}$	Herpes, HIV, Hepatitis, SARS-CoV	Inhibits viral replication	Wang et al. (2015)
Griffithsin	Algal lectin	Not available	SARS-CoV, MERS-CoV, HCoV-229E, HCoV-OC43, HIV, HCV and Ebola virus	Binds to Spike glycoprotein, inhibiting virus–host cell binding	(Lusvarghi and Bewley, 2016; Zumla et al., 2016)
Helichrysetin	Flavonoid	$C_{16}H_{14}O_5$	SARS-CoV-2, MERS-CoV,	3CL protease	Zhang and Liu (2020)
Herbacetin	Flavonoid	$C_{15}H_{10}O_7$	SARS-CoV, SARS-CoV-2, MERS-CoV,	3CL protease	(Jo et al., 2020; Zhang and Liu, 2020)
Heparin	Sulfur-rich glycosaminoglycan	$C_{26}H_{42}N_2O_{37}S_5$	SARS-CoV-2	Anticoagulant, Supress cathepsin L (CatL)	Liu et al. (2020)
Homoharringtonine	Alkaloid	$C_{29}H_{39}NO_9$	SARS-CoV-2	Inhibits viral replication	Choy et al. (2020)
Hesperidin	Dihydroxyflavanone	$C_{28}H_{34}O_{15}$	SARS-CoV-2	ACE2 inhibitor	Wu et al. (2020)
Neohesperidin	Flavanone glycoside	$C_{28}H_{34}O_{15}$	SARS-CoV-2	ACE2 inhibitor	Wu et al. (2020)
Hesperetin	Trihydroxyflavanone	$C_{16}H_{14}O_6$	SARS-CoV-2	Inhibits ACE2 and 3C-like protease	Utomo et al. (2020)
HR1P, HR1M, HR1L, HR2L, HR2P, HR2L HR2P-M1, HR2P-M2	Peptides	Not available	MERS-CoV SARS-CoV-2	Inhibits replication and spike protein-mediated cell-cell fusion	(Li and De Clercq, 2020; Lu et al., 2014)
Iguesterin	Triterpene	$C_{28}H_{36}O_2$	SARS-CoV	Inhibits 3CLpro	Xian et al. (2020)
Kaempferol	Flavonol	$C_{15}H_{10}O_6$	SARS-CoV, SARS-CoV-2	PLpro and 3CLpro inhibitor	(D. Zhang et al., 2020)
Lignan	Phytonutrients	$C_{25}H_{30}O_8$	SARS-CoV, SARS-CoV-2	Inhibition of replication, 3CLpro	(D. Zhang et al., 2020)

(*continued on next page*)

Table 3 (*continued*)

Name of the compound	Chemical nature	Molecular formula	Targeted virions	Target and inhibition mechanism	Ref
Luteolin	Flavonoid	$C_{15}H_{10}O_6$	SARS-CoV	Activation of the NLRP3 inflammasome and modulate inflammatory response	McKee et al. (2020)
Lycorine	Alkaloid	$C_{16}H_{17}NO_4$	HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-A59	Protein synthesis inhibitor	Li et al. (2005)
Apigenin	Flavonoid	$C_{15}H_{10}O_5$	SARS-CoV	Activation of the NLRP3 inflammasome and modulate inflammatory response to SARS	McKee et al. (2020)
Melatonin	Hormone	$C_{13}H_{16}N_2O_2$	SARS-CoV-2	Regulates ACE2 expression, target papain like protease	(R. Zhang et al., 2020)
MERS-5HB	Peptide	Not available	MERS-CoV	Inhibits pseudo typed entry and S protein mediated syncytial formation	Sun et al. (2017)
Moupinamide	Alkaloid	$C_{18}H_{19}NO_4$	SARS-CoV-2	PLpro inhibitor	(D. Zhang et al., 2020)
Myricetin	Flavonoid	$C_{15}H_{10}O_8$	SARS-CoV	Activation of the NLRP3 inflammasome	McKee et al. (2020)
Myricitrin	Glycosyloxyflavone	$C_{21}H_{20}O_{12}$	SARS-CoV-2	Protein kinase inhibitor, $3CL^{pro}$ receptor inhibitor	Tahir ul Qamar et al. (2020)
Methyl rosmarinate	Phenylpropanoids	$C_{19}H_{18}O_8$	SARS-CoV-2	3CLpro receptor inhibitor	Tahir ul Qamar et al. (2020)
N-cis-feruloyltyramine	Hydroxycinnamic acid	$C_{18}H_{19}NO_4$	SARS-CoV-2	PLpro and 3CLpro inhibitor	(D. Zhang et al., 2020)
OC43-HR2P (most promising EK1)	Peptide	Not available	SARS-CoV and MERS-CoV	Spike glycoprotein, inhibits pan-CoV fusion targeting the HR1 domain.	Xia et al. (2019)
Oleoylethanolamide	Lipid amide	$C_{20}H_{39}NO_2$	SARS-CoV-2	Binds with high affinity to PPAR-a receptors	Ghaffari et al. (2020)
Ouabain	ATP1A1-binding cardiotonic steroid	$C_{29}H_{44}O_{12}$	MERS-CoV	Inhibit clathrin-mediated endocytosis	Zumla et al. (2016)
Oxymatrine	Alkaloid	$C_{15}H_{24}N_2O_2$	HBV	Inhibition of replication	Wang et al. (2011)
P21S10	Peptide	Not available	MERS-CoV	Inhibits spike protein-mediated cell−cell fusion	Li and De Clercq (2020)
Pectolinarin	Flavonol	$C_{29}H_{34}O_{15}$	SARS-CoV	3CL protease	Jo et al. (2020)
Peptide (P9)	β-defensin derivative	Not available	Broad-spectrum antiviral, SARS-CoV, MERS-CoV, influenza	Inhibits spike protein-mediated cell-cell entry or fusion	Zhao et al. (2016)
Pristimerin	Quinone-methide triterpene	$C_{30}H_{40}O_4$	SARS-CoV	3CLpro inhibitory effect	Ryu et al. (2010)
Quercetin	Flavonoid	$C_{15}H_{10}O_7$	SARS-CoV	Inhibits 3CLpro and viral replication	Chen et al. (2006)
Quercetin-3-β-galactoside	Flavonoid	$C_{21}H_{20}O_{12}$	SARS-CoV	3C-like protease (3CLpro) inhibitor	Chen et al. (2006)
Bavachinin	Flavonoid	$C_{21}H_{22}O_4$	SARS-CoV	Inhibitors of papain-like protease (PLpro).	Islam et al. (2020)
Betulonic acid	Pentacyclic triterpenic	$C_{30}H_{46}O_3$	SARS-CoV	Inhibition of 3CL protease	Islam et al. (2020)
Cepharanthine	Alkaloid	$C_{37}H_{38}N_2O_6$	SARS-CoV, HCoV-OC43, SARS-CoV-2	ACE inhibitor	Xia et al. (2019)
Diplacone	Flavonoid	$C_{25}H_{28}O_6$	SARS-CoV	Inhibition of papain-like protease	Islam et al. (2020)
Ferruginol	Diterpenoid	$C_{20}H_{30}O$	SARS-CoV	Inhibition of viral replication	Islam et al. (2020)
Hinokinin	Lignan	$C_{20}H_{18}O_6$	SARS-CoV	Inhibition of 3CL protease.	Islam et al. (2020)
Hirsutenone	Diarylheptanoid	$C_{19}H_{20}O_5$	SARS-CoV	Inhibits PLpro activity	Xian et al. (2020)
Indigo	Organic compound	$C_{16}H_{10}N_2O_2$	SARS-CoV	3CL protease inhibition.	Islam et al. (2020)
Isobavachalcone	Chalcone	$C_{20}H_{20}O_4$	SARS-CoV	Papain-like protease (PLpro) inhibition	Islam et al. (2020)
Juglanin	Cyclic ketone	$C_{20}H_{18}O_{10}$	SARS-CoV	Blocks the 3a channel.	Islam et al. (2020)
Reserpine	Alkaloid	$C_{33}H_{40}N_2O_9$	SARS-CoV	Inhibits glycoprotein activity	Xian et al. (2020)
Rhein	Dihydroxyanthraquinone	$C_{15}H_8O_6$	SARS-CoV	Inhibited interaction (S) protein and ACE2	Islam et al. (2020)
Resveratrol	Polyphenol	$C_{14}H_{12}O_3$	MERS-CoV	Inhibits viral replication	Lin et al. (2017)
Selamectin	Avermectin	$C_{43}H_{63}NO_{11}$	SARS-CoV-2	Inhibits ACE_2 receptor entry	McKee et al. (2020)
Rhoifolin	Apigenin derivative	$C_{27}H_{30}O_{14}$	SARS-CoV	3CLpro inhibitor	Jo et al. (2020)
Scutellarein	Flavone	$C_{15}H_{10}O6$	SARS-CoV-2	Binds to ACE2 receptor	Chen and Du (2020)
Shikonin	Hydroxynaphthoquinones	$C_{16}H_{16}O_5$	SARS-CoV-2	Inhibits M^{pro}	Jin et al. (2020)
Silvestrol	Rocaglate derivative	$C_{34}H_{38}O_{13}$	MERS-CoV, HCoV-229E, EBOV	Inhibits the DEAD-box RNA helicase eIF4A to affect virus translation	Müller et al. (2018)
Sugiol	Diterpenoid	$C_{20}H_{28}O_2$	SARS-CoV, SARS- CoV-2	Replication, 3CLpro	(D. Zhang et al., 2020)
Tanshinone I	Diterpenoid	$C_{18}H_{12}O_3$	SARS–CoV	Inhibits PLpro activity	Xian et al. (2020)
Tanshinone IIa	Diterpenoid	$C_{19}H_{18}O_3$	SARS-CoV, SARS- CoV-2	PLpro and 3CLpro	(D. Zhang et al., 2020)
Tingenone	Quinone-methide triterpene	$C_{28}H_{36}O_3$	SARS-CoV	3CLpro inhibitory effect	Ryu et al. (2010)
Theaflavin	Flavonoid	$C_{29}H_{24}O_{12}$	SARS-CoV-2	Inhibits RdRp activity	Xian et al. (2020)
Vitamin C (Ascorbic acid)	Vitamin	$C_6H_8O_6$	SARS- CoV-2	Antioxidant and immunomodulator agent	Boretti and Banik (2020)
β-sitosterol	Phytosterol	$C_{29}H_{50}O$	SARS-CoV	Inhibition of 3CLpro	Mani et al. (2020)
Sinigrin	Glucosinolate	$C_{10}H_{17}NO_9S_2$	SARS-CoV	Inhibition of 3CLpro	Mani et al. (2020)
α-Helical lipopeptides (e.g. LLS, FFS, IIS, IIK)	Proteins	Not available	MERS-CoV, IAV	Inhibit s protein-mediated cell-cell entry	Wang et al. (2018)

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Table 3 (*continued*)

Name of the compound	Chemical nature	Molecular formula	Targeted virions	Target and inhibition mechanism	Ref
Psoralidin	Coumestans	$C_{20}H_{16}O_5$	SARS-CoV	Inhibits PLpro activity	Mani et al. (2020)
Tryptanthrin	Alkaloid	$C_{15}H_8N_2O_2$	SARS-CoV	Inhibits PLpro activity	Mani et al. (2020)
Amentoflavone	Biflavonoid	$C_{30}H_{18}O_{10}$	SARS-CoV	3CLpro inhibitory effect	Islam et al. (2020)
(−)-Catechin gallate	Polyphenol	$C_{22}H_{18}O_{10}$	SARS-CoV	Inhibition RNA oligonucleotide	Islam et al. (2020)
Savinin	Lignan	$C_{20}H_{16}O_6$	SARS-CoV	Inhibition of 3CL protease	Islam et al. (2020)
Tylophorine	Pentacyclic compound	$C_{24}H_{27}NO_4$	SARS-CoV	Protease inhibition	Islam et al. (2020)

designing promising drug against SARS-CoV replication (Ghosh et al., 2020).

Although there have been some preliminary positive reports on use of preexisting antiviral, antimalarial and anti-HIV drugs against treatment of COVID-19 infection, well-designed randomized, controlled clinical trials for evaluating their safety and efficacy will be necessary for the proper treatment of patients diagnosed with COVID-19 in comparison with controls who did not receive the same treatment (Costanzo et al., 2020). The details on potential therapeutic remedies against COVID-19 and related human coronavirus were discussed and presented in Tables 1 and 2, with structural details provided as supplementary file (S1).

6.2. Nucleoside and nucleotide analogs (NAs)

Nucleoside and nucleotide analogs (NAs) are chemically synthesized of purines and pyrimidines analogs having a heterocyclic ring or a sugar moiety. NAs are essential building blocks for nucleic acid biosynthesis and represents as the largest class of anti-inflammatory and antiviral drugs for the treatment of cancer and different viral infections (Pruijssers and Denison, 2019). Some NAs, including amivudine, sofosbuvir, adefovir, telbivudine, entecavir, and tenofovir (Supplementary file S1), have strong antiviral activity and have been used for the treatment of immunodeficiency virus type 1 (HIV-1), hepatitis C (HCV) and hepatitis B (HBV) infection provided proof that these class of compounds used as strong antiviral agents (Fung et al., 2011; Jordheim et al., 2013). Over twenty NAs were approved by US FDA as antiviral drugs for use against various viral infections like; immunodeficiency virus type 1 (HIV-1), hepatitis C (HCV) and hepatitis B (HBV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), varicella zoster virus (VZV)(Mahmoud et al., 2018). These NAs are used to treat both acute and chronic viral infections are delivered as nucleoside and nucleotide precursors or pro-drugs, which are metabolized by host or viral kinases to their active triphosphate once inside the cell and inhibits the viral replication by non-mutually exclusive mechanisms (Pruijssers and Denison, 2019). In this review we summarized the antiviral effects of NAs, mainly remdesivir, lamivudine, amivudine, sofosbuvir, adefovir, entecavir, telbivudine, ribavirin, velpatasvir, and tenofovir against SARS-CoV-2 and related coronaviruses (Table 1, the drug structural details provided as supplementary file (S1).

6.3. Protein (enzyme) inhibitors

The SARS-CoV-2 containing positive-strand RNA causes severe respiratory syndrome in humans and responsible for COVID-19. This virus contains four structural proteins: Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) protein (Fig. 3). S protein plays a role in viral attachment to host cell, E and M proteins are involved in viral assembly, and N protein is needed for RNA synthesis (Dömling and Gao, 2020). Angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), spike (S) protein, RNA-dependent RNA polymerase (RdRp), angiotensin AT2 receptor, chymotripsin-like protease (3CLpro) and papain-like protease (PLpro) are considered as major targets for antiviral drugs against SARS-CoV-2 and another infectious coronavirus (McKee et al., 2020; Zumla et al., 2016). We summarized all the synthetic and natural protein (enzyme) inhibitors used to treat SARS-CoV and related coronaviruses infection in Tables 1 and 2, respectively. The structural details of these synthetic and natural protein (enzyme) inhibitors were provided as supplementary file (S1).

6.4. Corticosteroids

Corticosteroids are a class of drugs used to treat illnesses that result from inflammation and reduces immune system activity by mounting an exaggerated response to something or attacks its own cells (Singh et al., 2020). The study reported by RECOVERY Collaborative Group showed the benefit of dexamethasone for patients with COVID-19 who were receiving mechanical ventilation at the time of randomization. Corticosteroids might be effective in preventing acute respiratory distress syndrome and death for patients having shortness of breath or requires oxygen therapy (The RECOVERY Collaborative Group, 2020). Also, World Health Organization has confirmed that the corticosteroids as a potentially effective for the treatment of COVID-19, and patients' survival rates were improved significantly through the application of dexamethasone and other corticosteroids (Table 1). Interestingly, most of earlier studies conducted on SARS-CoV and MERS-CoV showed adverse outcomes for use of corticosteroid in treatment (Singh et al., 2020). Indeed, the Lancet study also reported that corticosteroids should be avoided for the treatment of COVID19. However, such warnings are mainly based on the experiences in a similar viral illness but not on COVID-19 specifically (Russell et al., 2020). Debates are continuing on potential use of corticosteroids as therapy for the treatment of acute respiratory distress syndrome (ARDS) and COVID -19. Indeed, corticosteroids have been speculated to be used as a potential therapy for ARDS as they have ability to reduce inflammation and fibrosis (Reddy et al., 2020). The various corticosteroids which are used as potential drug candidates were discussed in Table 1 and structural formulas provided as supplementary file (S1).

6.5. Natural products and traditional medicines

Plant based natural products and various traditional medicines have been used as an excellent source for discovery of natural/herbal drugs, as they display great diversity among their chemical structures and wide range of biological activities (Wang et al., 2020). Many natural compounds are widely used as antiviral drugs shown to possess promising antiviral effects against influenza viruses, coronaviruses, herpes simplex virus, human immunodeficiency virus, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and hepatitis B and C viruses (Mani et al., 2020; Xian et al., 2020). Numerous natural compounds have been screened *in silico* targeting various viral proteins; main protease (3CLpro, also named 3-chymotrypsin-like protease), papain like protease (PLpro), helicase, RNA-dependent RNA polymerase (RdRp), and spike protein(Mani et al., 2020; Wu et al., 2020). Various traditional medications based on indigenous theories and experiences are currently being used in the prevention and treatment various microbial diseases, these medicines mainly includes traditional Chinese medicine (TCM), Indian ayurvedic medicine, ancient Iranian medicine, traditional African medicine and Islamic medicine (Wang et al., 2020). Naturally occurring agents that have potential for prevention of COVID-19 include various alkaloids, anthraquinones, terpenoids, fatty acids, flavonoids, glucosinolates, lignans, peptides, phenolics, proteins,

saponins, and vitamins (Wang et al., 2020; Zhang and Liu, 2020). (Table 3 and Supplementary file S1), details about these natural products provided in Table 2 and structural details provided as supplementary file (S1). This comprehensive review provides details insights on some active natural products which are being proposed for COVID-19 drug development and prevention.

6.6. Convalescent plasma

Convalescent (immune) plasma therapy refers to use of antibodies obtained from individual who has been recently recovered from particular resolution of infection and disease (Bloch et al., 2020). Convalescent plasma therapy is a passive immunization used to prevent and manage of infectious diseases and considered to be an emergency intervention in controlling several pandemics like SARS-CoV, West Nile virus, Spanish flu, Ebola virus, and recently emerged COVID-19 (Chen et al., 2020). Food and Drug Administration has recently suggested that administration and study of investigational convalescent plasma therapy may provide effective clinical treatment against COVID-19 (Rajendran et al., 2020). Hence, convalescent plasma transfusion therapy has been the subject of increasing attention, especially in the wake of large-scale epidemics like COVID-19.

7. Conclusions

To date, there is no any approved therapy for prevention or treatment of COVID-19, thus many scientists working on possible drug repurposing by using available different Therefore, therapies preexisting drugs including antivirals, antimalarial, immunosuppressive, antipsychotic, antidiarrheal, antidiabetic, anticancer, antifungal, antibacterial, anticoagulant, and antihelminthic agents have been suggested as potential targets preventives or therapeutics against COVID-19. However, the factors like small sample size, poor quality of drug and long completion period are not allowing obtaining reliable and there is paucity of clinical evidence for the therapeutic efficacy as well as safety of aforementioned agents for COVID-19 treatments. Development of effective therapeutic agents is subordinated to the understanding of molecular mechanisms underlying SARS-CoV-2 replication, pathogenesis and virus-host interaction.

The current available knowledge on the safety and efficacy on various therapies needs proper research, like *in vitro* studies, animal studies and clinical trials for use as potential drug against COVID-19. Several drugs currently being used and which are under clinical trials are remdesivir, umifenovir, oseltamivir, favipiravir, lopinavir/ritonavir, danoprevir/ritonavir, darunavir/cobicistat, triazavirin, hydroxychloroquine, ASC09F, baloxavir marboxil, azvudine, sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, and emtricitabine/tenofovir (Table 1 2). Also, clinical trials are undergoing for various natural compounds like heparin and vitamin C as therapeutic agents or immune boosters in against COVID-19 infection (Table 2 3). Thus, application of the existing potential candidate therapies may represent an effective strategy for the identification of new pathways and targets for intervention of SARS-CoV-2 infection and pathogenesis. In order to effectively deal with the current strategies, needs further exploration to determine the effective agent/therapies for modifying research conduct for this COVID -19. The safety and efficacy of various suggested COVID-19 therapies needs proper systematic research, coordinated by both preclinical studies and clinical trials.

CRediT authorship contribution statement

Shivraj Hariram Nile: colleted data, Writing – original draft, Writing – review & editing. **Arti Nile:** collected information on this topic and provided all chemical structural details. **Shivkumar Jalde:** collected information on this topic and provided all chemical structural details. **Guoyin Kai:** Writing – review & editing, All authors read and approved the final version of this manuscript.

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Declaration of competing interest

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

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Appendix A. Supplementary data

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