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

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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., 2020; Zumla et al., 2016). 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.,...
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 of 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  |
| SARS-CoV             | 2002            | 8096             | 774             | 29  | 9.6 |
| H1N1 (Swine flu)**   | 2009            | > 284500         | 214             | 17.4|
| Nipah                | 1998            | 513              | 398             | 2   | 77.6|
| SARS- CoV (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).

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 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...
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 (Pillay 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). S′ 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 S′ 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 viroms 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
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; Sheereen 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
Commericially 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-arylmethoxy-5-hydroxynonohromes | Aryl diketoacids | Not available | SARS-CoV, HCV | Inhibits ATPase and helicase activities | Preclinical | Kim et al. (2011) |
| 6'-Fluorinated-Antiretroviral Analogues | Nucleoside analogs | C_{10}H_{13}N_{2}O_{5} | SARS-CoV, MERS-CoV, CHIKV, ZIKV | RdRp and host cell SAH hydrolase inhibitors | Preclinical studies | Yoon et al. (2019) |
| Abacavir | Nucleoside analogue | C_{6}H_{12}N_{2}O_{4} | HIV | Reverse transcriptase inhibitor | Approved as HIV drug | Beck et al. (2020) |
| Acyclovir | Doubly flexible synthetic nucleoside analogue | C_{6}H_{8}N_{2}S | HSV, HCoV- NL63, MERS-CoV | RNA polymerase inhibitor(RdRp) | Preclinical studies | Beck et al. (2020) |
| Alogiporin | Cyclopore A-analog | C_{6}H_{11}N_{1}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_{2}H_{14}BeN_{2}O_{3} | SARS-CoV-2 | Block viral fusion and replication | Approved for influenza. Phase 4 for 2019-nCoV, (NCT04260594) | Zhang and Liu (2020) |
| Aril diketoacids | Enolic acids | C_{10}H_{14}O_{4} | HIV, SARS-CoV, HCV | Inhibits 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) |
| Arsanaprevir (BMS-650032) | Oligopeptide | C_{6}H_{4}C_{6}N_{6}O_{6}S | HCV | NS3 protease inhibitor | Approved for HIV, Phase III clinical trials | Beck et al. (2020) |
| Atazanavir | Azido-derivative analogue | C_{6}H_{12}N_{2}O_{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_{66}H_{105}O_{71}N_{17}P_{12}S_{8} | 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_{13}F_{2}N_{3}O_{3} | SARS-CoV-2 | Inhibits TTE protease (M^{pro}) | Induce leukoencephalopathy | Jin et al. (2020) |
| Chloroquine | Aminoquinoline | C_{18}H_{14}N_{2}O_{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) | China (2020) |
| Chloroquine Phosphate | Phosphate salt of chloroquine | C_{16}H_{12}C_{12}N_{4}O_{7}P_{2} | SARS-CoV-2 | Inhibits autophagy and toll-like receptors (TLRs) | An amnialarial drug, FDA approved drug for COVID. | (Zhang and Liu, 2020; Zumba et al., 2016) |
| Hydroxychloroquine | Derivative of chloroquine | C_{18}H_{14}ClN_{2}O_{6} | SARS-CoV, MERS-CoV, SARS-CoV-2 | Antiparasitic agent | Used to treat autoimmune disease, amnialarial | Dyall et al. (2014) |
| Triflupromazine (1), Fluphenazine (2), Promethazine (3) | Phenothiazine derivative | C_{12}H_{14}F_{2}N_{3}O_{2}S (1), C_{11}H_{12}F_{2}N_{3}O_{2}S (2), C_{15}H_{14}F_{2}N_{3}O_{2}S (3) | SARS-CoV, MERS-CoV, SARS-CoV-2 | Antipsychotic that shows clathrin-mediated endocytosis | First two approved as antipsychotic agents | Li and De Clercq (2020) |
| Chlorpromazine | Phenothiazine | C_{17}H_{17}ClN_{4}S | SARS-CoV, MERS-CoV, HCV | An antipsychotic affects the assembly of clathrin-coated pits at the plasma membrane | Approved as antipsychotic agents | Zumba et al. (2016) |
| Cobicistat (GS-9350) | Monocarboxylic acid amide | C_{8}H_{17}N_{2}O_{3}S | HIV, SARS-CoV-2, MERS-CoV | Potentially inhibits Mpro and viral replication | 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}C_{4}N_{3}O_{3}S | SARS-CoV, MERS-CoV, HCV | Proteinase inhibitor, inhibits 3CLpro | Preclinical | Lee et al. (2019) |
| Cyclosporine A | Cyclic non-ribosomal peptide | C_{8}H_{11}N_{1}O_{1}S_{2} | 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 | Furufuran | C_{17}H_{21}N_{3}O_{5}S | HIV, SARS-CoV-2, MERS-CoV | Proteinase inhibitor, inhibits 3CLpro | Approved for HIV and clinical trial at phase 3 for 2019-nCoV | Li and De Clercq (2020) |
| Disulfram | Carbamoyl derivative | C_{8}H_{17}N_{2}S_{4} | SARS-CoV, MERS-CoV, HIV, SARS-CoV-2 | Papain-like protease inhibitor | Approved for treatment of chronic alcoholism | Lin et al. (2018) |
| Dolagetravir | Monocarboxylic acid amide | C_{8}H_{17}F_{2}N_{3}O_{3} | HIV, SARS-CoV-2, MERS-CoV | Second-generation integrase inhibitor | Approved for HIV and Preclinical for 2019-nCoV | Beck et al. (2020) |
| Ebselen (SPI-1005) | Organoselenium compound | C_{12}H_{12}N_{3}O_{3}Se | HCV, SARS-CoV-2 | Potentially inhibits Mpro and viral replication | Used to treat Diabetes Mellitus | Jin et al. (2020) |
| Efavirenz | Non-nucleoside | C_{6}H_{13}ClF_{3}N_{2}O_{2} | HIV, SARS-CoV-2 | Reverse transcriptase (RT) inhibitor, 3CLpro inhibitor | Approved for HIV and Preclinical for 2019-nCoV | Beck et al. (2020) |

(continued on next page)
| Name of the therapy | Chemical nature | Molecular formula | Targeted virions | Target virion mechanism | Status as drug | Ref |
|---------------------|----------------|-------------------|------------------|-------------------------|----------------|-----|
| Entecavir Guanosine nucleoside analogue | $C_{21}H_{26}N_{5}O_{6}$ | 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 | $C_{9}H_{8}F_{4}N_{2}O_{5}$ | 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 | $C_{17}H_{22}NO_{2}$ | 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) Adenine analog | $C_{11}H_{23}N_{2}O_{5}$ | SARS-CoV, MERS-CoV, SARS-CoV-2 | 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 | $C_{17}H_{20}N_{2}O_{5}$ | MERS-CoV, SARS-CoV-2 | Inhibits 3CLpro, Inhibits the replication of viruses | Preclinical studies | Kim et al. (2012) |
| GC813 Pyrrolidinone based peptide Benzamide | $C_{22}H_{25}ClN_{3}NaO_{6}$ | MERS-CoV | Inhibits 3CLpro | Preclinical studies | Pillaiyar et al. (2020) |
| Imatinib Benzamide | $C_{9}H_{8}N_{2}O$ | SARS-CoV, MERS-CoV, IAV, Ebola TGEV, FIPV and PTV, MERS-CoV, SARS-CoV | Abelson tyrosine-protein kinase 2 (Ab2) inhibitor | Approved for cancer | Coleman et al. (2016) |
| Trametinib Pyridopyrimidine | $C_{19}H_{23}F_{3}N_{2}O_{4}$ | 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 | $C_{22}H_{26}ClN_{2}O_{5}$ | MERS-CoV, SARS-CoV | BCR/ABL and Src family tyrosine kinase inhibitor | Approved for cancer treatment | Li and De Clercq (2020) |
| Selumetinib Benzimidazole | $C_{17}H_{21}BrClF_{5}N_{2}O_{3}$ | MERS-CoV, SARS-CoV | Inhibits the ERK/MAPK and PI3K/AKT/mTOR signaling pathways | Approved for cancer treatment | Li and De Clercq (2020) |
| Rapamycin Antbiotic | $C_{57}H_{77}N_{2}O_{12}$ | MERS-CoV | Inhibits the ERK/MAPK and PI3K/AKT/mTOR pathways, block early viral entry and/or post-entry | Approved as an antifungal agent | Pillaiyar et al. (2020) |
| L哈哈哈哈naminivir Octanoyl ester | $C_{13}H_{22}N_{2}O_{2}$ | Influenza virus A and B | Neuraminidase inhibitor | Approved as influenza A and B drug | Samson et al. (2014) |
| Lopinavir Phenylo-butanamide | $C_{24}H_{30}C_{2}N_{2}O_{2}$ | SARS-CoV, MERS-CoV, HCoV-229E | Inhibits viral replication. Opioid receptor binding inhibitor | Approved as an HIV protease inhibitor | Li et al. (2019) |
| Lopinavir Dicarboxylic acid amide | $C_{17}H_{46}N_{2}O_{5}$ | HIV, 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 | $C_{22}H_{26}O_{5}$ | MERS-CoV, SARS-CoV, SARSCoV-2 | Protease Inhibitor | Treat arthritis and severe allergic reactions. Randomized trial for 2019-nCoV, NCT04323592 | Huang et al., 2020; Pillaiyar et al., 2020 |
| Mucroporin-MI Scorpion venom-derived peptide | Not available | HIV, H5N1, SARS-CoV, MERS-CoV, SARS-CoV-2 | Inhibiting viral replication, Inhibits viral replication, Inhibits IMPDH and guanine monophosphate synthesis | Approved as immunosuppressant during organ transplantation | Hart et al. (2014) |
| Mycofenolic acid Antibiotic | $C_{17}H_{18}O_{6}$ | HIV, HCV | Prodrug inhibitor | Approved as an anticoagulant therapy | Li and De Clercq (2020) |
| Nafamostat Synthetic p-Guamidobenzoic acid ester | $C_{19}H_{18}N_{2}O_{2}$ | 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 | $C_{22}H_{40}N_{2}O_{6}$ | HIV, H5N1, HIV, 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 | $C_{13}H_{18}ClN_{2}O_{4}$ | SARS-CoV | ACE2 inhibitor, Inhibit replication of virus S protein and ACE2 inhibitor | Antihelminthic drug Inhibits IFV-A in A549 cells. Preclinical | Li et al. (2019) |
| Nicotianamine Metal ligand | $C_{13}H_{12}N_{2}O_{6}$ | SARS-CoV-2 | Influenza neuraminidase inhibitor | Approved for influenza, Phase 3 and 4 for 2019-nCoV, NCT04261270 | Zhang and Liu (2020) |
| Oseltamivir Ethyl ester of oseltamivir acid | $C_{16}H_{22}N_{2}O_{4}$ | SARS-CoV-2 | Influenza neuraminidase inhibitor | Approved for influenza, Phase 3 and 4 for 2019-nCoV, NCT04261270 | Lu (2020) |
| Name of the therapy               | Chemical nature                  | Molecular formula | Targeted viros                                      | Target virion mechanism                                        | Status as drug                                                                                                       | Ref                                                                 |
|----------------------------------|----------------------------------|-------------------|-----------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Peptidomimetic inhibitors        | Aldehyde derivatives             | Not available     | HCV, SARS-CoV, MERS-CoV                             | RNA polymerase inhibitor (RdRp) 3CL protease inhibitor           | Approved for HSV. Randomized trial for 2019-nCoV Preclinical                                                       | (M. Wang et al., 2020)                                               |
| Peramivir                        | Cyclopentane derivative          | C12H20N4O4        | Influenza A and B                                   | Neuraminidase inhibitor                                         | Approved as influenza A and B drug                                                                                | (De Clercq and Li, 2016; Lu, 2020)                                    |
| Promazine                        | Phenothiazine derivative         | C17H20N5S         | SARS-CoV                                            | Blocking the interaction of S protein and ACE2 3CL protease inhibitor | Alternative for the treatment of COVID-19                                                                         | Zhang and Liu (2020)                                                 |
| Pyriothiobac derivatives (6-5)   | Benzoic acids                    | C13H11ClN2O4S     | SARS-CoV                                            |                                                                  | Preclinical                                                                                                       | Wu et al. (2019)                                                     |
| Remdesivir (GS-5734)             | Nucleoside analogue              | C27H32N6O5P       | Ebola, MERS-CoV, SARS-CoV, MERS-CoV                 | RNA polymerase inhibitor (RdRp)                                  | Randomized trials for SARS-CoV-2                                                                                 | (Shehan et al., 2020; M. Wang et al., 2020)                           |
| Ribavirin                        | Nucleoside analogue              | C5H4N2O5          | HCV, RSV, MERS-CoV                                  | Inhibits viral RNA replication and mRNA capping                 | Approved for HCV and RSV. Randomized trials for SARS and MERS-CoV                                                 | (Chan et al., 2013; Lu, 2020)                                        |
| Ritonavir                        | L-valine derivative              | C27H40N6O3S2      | HIV, MERS-CoV, SARS-CoV, MERS-CoV                   | 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       | C12H20N2O4        | SARS-CoV                                            | 3CL protease inhibitor                                           | Preclinical                                                                                                       | (Kono et al., 2017)                                                  |
| SSYA10-001                       | Triazole derivative              | C12H11N2O2S2      | MERS-CoV, MHV, MERS-CoV, MERS-CoV                   | Inhibits helicase without affecting ATPase activity             | Preclinical                                                                                                       | Adecki et al. (2014)                                                 |
| Losartan (Cozaar)                | Monopotassium salt               | C22H25CN2O       | MERS-CoV, SARS-CoV                                 | Angiotensin-receptor blocker                                    | Phase 2 for SARS-CoV-2 (NCT04312009)                                                                               | (Yan et al., 2020,)                                                  |
| Verdinexor (KPT-335)             | Synthesized chemical compound    | C18H12F3N6O       | Influenza A and B virus, Respiratory syncytiial virus (RSV) | Blocking XPO1-mediated nuclear export of viral ribonucleoprotein complexes | Inhibitor of Nuclear Export, Under clinical trial FOR Influenza (NCT02453164)                                   | Perwitasari et al. (2014)                                           |
| Zanamivir                        | Sialic acid-analogue             | C12H28N4O2        | Influenza virus                                     | Neuraminidase inhibitor                                         | Approved for influenza virus                                                                                     | Lu (2020)                                                            |
| Gemcitabine hydrochloride        | Deoxycytidine analog             | C6H20ClF3N2O4     | MERS-CoV, SARS-CoV, influenza virus                 | DNA metabolism inhibitor, inhibiting pyrimidine biosynthesis     | FDA-approved anticancer agent                                                                                        | (Li et al., 2019; Pillaiyar et al., 2020)                              |
| Amiodquine                       | Quinoline derivative             | C20H15CN3O        | 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)                           |
| Mefloquine                       | Quinoline derivative             | C17H15F2N2O       | 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)                           |
| Dihydroartemisimin               | Sesquiterpene lactone            | C12H16O5          | 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             | C17H30N2O3        | MERS-CoV, SARS-CoV                                 | Cathepsin protease inhibitor                                    | Inhibit calpain activity in intact platelets. Approved for melanoma (IFN-α2b), metastatic renal cell carcinoma (IFN-α2a), multiple sclerosis (IFN-γ), chronic granulomatous disease (IFN-γ) | Dyall et al. (2014)                                                  |
| Recombinant interferons          | Signalling proteins              | Not available     | MERS-CoV, SARS-CoV                                 | Interferon response, Inhibiting the viral protein synthesis, disables viral replication Prevent the virus from infecting and entering cells | Phase 2/3 trial for MERS endemic in Kingdom of Saudi Arabia | Beigel et al. (2018) | (Li et al., 2019; Pillaiyar et al., 2020) |
| SAB-301                          | Polyclonal antibody              | Not available     | MERS-CoV                                            | Prevent the virus replication in cell Interferon response in host cell | Phase 1 trial for MERS-CoV (NCT03301090) Approved for Diarrhea treatment. Phase III clinical development for Influenza virus -A and B strains | de Wit et al. (2018); Pillaiyar et al., 2020 |
| REGN3048 and REGN3051            | Monoclonal antibodies            | Not available     | MERS-CoV                                            | Prevent the virus replication in cell Interferon response in host cell | Approved for treating cancers                                                                                     | Pillaiyar et al. (2020)                                             |
| Nitazoxanide                     | Thiazolides                      | C12H14N3O2S       | Influenza viruses, HBV, HCV, HIV, SARS-CoV, MERS-CoV |                                                                  | (continued on next page)                                                                                           |                                                                       |
| Name of the therapy          | Chemical nature                   | Molecular formula        | Targeted virions            | Target virion mechanism                                                                 | Status as drug                                         | Ref                                  |
|------------------------------|-----------------------------------|--------------------------|----------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------|
| Camostat                     | Benzoic acid derivative           | C_{20}H_{28}N_{10}O_{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) |
| KI1777                       | Piperazine derivative             | C_{12}H_{13}N_{2}O_{4}S  | SARS-CoV, MERS-CoV, HCoV-229E | Cysteine protease inhibitor, targeting endosomal proteases involved in viral entry       | Preclinical                                           | Zhou et al. (2015)                  |
| Nafamostat                   | Benzoic acids derivative          | C_{10}H_{12}N_{2}O_{5}   | SARS-CoV, Influenza-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_{27}BeN_{2}O_{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_{20}H_{28}O_{5}N_{2}  | Broad-spectrum (influenza virus, HCoV, Ebola, HIV, HCV) | Inhibits peptidoglycan polymerization                                                | Effective drug against gram-positive infections       | (Li and De Clercq, 2020; Szirmai et al., 2018) |
| FA-613                       | Carboxylic acid                   | C_{18}H_{12}BeN_{2}O_{3} | SARS-CoV-2, SARS-CoV, MERS-CoV, influenza | 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, MERS-CoV, HCoV-OC43, HCoV-OC43, HCoV-NL63, MHV-A59 | Inhibits viral replication                                                           | Approved as immunosuppressant                        | Shen et al. (2019)                  |
| Mycophenolate mofetil         | Ester of mycophenolic acid        | C_{22}H_{32}NO_{2}        | SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-NL63, MHV-A59 | Inhibits viral replication                                                          | Antibacterial drug                                    | Shen et al. (2019)                  |
| Monensin sodium              | Antibiotic salt                   | C_{18}H_{9}NaO_{11}      | MERS-CoV, HCoV-OC43, HCoV-NL63, MHV-A59 | Inhibits viral replication                                                           | Urinary tract analgesic, Removed by FDA               | Shen et al. (2019)                  |
| Phenaopyridine               | Pyridine derivative               | C_{11}H_{12}N_{3}O_{5}   | MERS-CoV, HCoV-OC43, HCoV-NL63, MHV-A59 | Inhibits viral replication                                                          | -                                                     | Shen et al. (2019)                  |
| Pyrvinium pamoate             | Quinoline derivative              | C_{16}H_{22}N_{3}O_{8}   | MERS-CoV, HCoV-OC43, HCoV-NL63, MHV-A59 | Inhibits viral replication                                                          | DA-approved antihelmintic drug, inhibits WNT pathway signaling. | Shen et al. (2019)                  |
| Hexamethylene amidoridine     | Pyrazines                         | C_{12}H_{16}C_{2}N_{4}   | SARS-CoV, HCoV-OC43, HCoV-NL63, and some animal CoVs | Viroproin inhibitor that inhibits the ion channel activity of CoV E               | Preclinical                                           | Zumla et al. (2016)                 |
| Indomethacin                 | Indole derivative                 | C_{10}H_{16}C_{2}N_{4}O   | SARS-CoV, HCoV-OC43, HCoV-NL63, and some animal CoVs | Viroproin inhibitor that inhibits the ion channel activity of CoV E               | Preclinical                                           | Amici et al. (2006)                 |
| Azithromycin                 | Azalide                           | C_{18}H_{17}N_{2}O_{12}  | ZIka, Ebola, SARS-CoV-2, SARS-CoV-2, SARS-CoV-2 | Inhibit replication of virus                                                         | Approved as antibiotic                                | Gautret et al. (2020)               |
| Tocilizumab                  | Monoclonal antibody               | C_{40}H_{35}N_{3}O_{21}  | SARS-CoV-2, MERS-CoV, SARS-CoV-2, 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_{30}H_{25}N_{3}O_{7}   | SARS-CoV-2, MERS-CoV, SARS-CoV-2, SARS-CoV-2 | Inhibit replication of virus                                                         | Preclinical                                           | Sheahan et al. (2020b)              |
| β-D-N4 hydroxycytidine (NHC, EIDD-1931) | Ribonucleoside analog           | C_{40}H_{24}N_{3}O_{6}   | Influenza, Ebola, SARS-CoV-2, MERS-CoV, SARS-CoV-2, SARS-CoV-2, SARS-CoV-2 | Inhibit replication of virus                                                         | Preclinical                                           | Sheahan et al. (2020b)              |
| Bromhexine hydrochloride     | Hydrochloride                     | C_{10}H_{16}Br_{2}C_{2}N_{2} | SARS-CoV, MERS-CoV, SARS-CoV-2, SARS-CoV-2 | Inhibit transmembrane serine protease 2, RNA polymerase inhibitor                   | Mucolytic and prophylactic drug                       | Habtemariam et al. (2020)           |
| Triazavirin                  | Guanine nucleotide                | C_{14}H_{16}N_{5}S_{8}   | SARS-CoV-2, MERS-CoV, SARS-CoV-2, SARS-CoV-2 | RNA polymerase inhibitor, blocking viral RNA synthesis                              | Antiviral drug                                        | Shahab and Sheikh (2020)            |
| Carfilzomib                  | Epoxomicin derivate               | C_{20}H_{25}N_{4}O_{4}   | SARS-CoV-2, SARS-CoV-2, SARS-CoV-2, SARS-CoV-2 | Protease inhibitor, blocking viral RNA synthesis                                   | Approved antitumor drug                               | Wang (2020)                         |
| Eravacycline                 | Antibiotic                        | C_{12}H_{16}N_{3}O_{8}   | SARS-CoV-2, SARS-CoV-2, SARS-CoV-2 | Protease inhibitor, blocking viral RNA synthesis                                   | Broad spectrum antibacterial drug                     | Wang (2020)                         |
| Ixosoltimib                  | Pyrazole                          | C_{17}H_{18}N_{6}        | SARS-CoV-2, SARS-CoV-2, SARS-CoV-2 | Protease inhibitor, blocking viral RNA synthesis                                   | Anti-arthritic drugs                                  | Wang (2020)                         |
|                            |                                   |                          |                            |                                                                                        | (continued on next page)                              |                                     |
| Name of the therapy | Chemical nature | Molecular formula | Targeted virions | Target virology mechanism | Status as drug | Ref |
|---------------------|-----------------|-------------------|------------------|---------------------------|---------------|-----|
| Fedratinib          | Anilinopyrimidine derivative | C$_{22}$H$_{36}$N$_{6}$O$_3$S | SARS-CoV-2 | JAK inhibitor | Anti-arthritic drugs | Stebbing et al. (2020) |
| Baricitinib (Olumiant) | Pyranole | C$_{10}$H$_{17}$N$_{2}$O$_3$S | SARS-CoV-2 | JAK and NAK inhibitor | Anti-arthritic drugs | Stebbing et al. (2020) |
| Pirfenidone | Pyridinedine derivative | C$_{22}$H$_{21}$N$_{3}$O$_7$ | SARS-CoV-2 | Inhibits DNA synthesis | Antifibrotic agent, phase 3 for COVID-19 NCT04282902 | (Su et al., 2020) |
| Nintedanib | Indolinedine derivative | C$_{20}$H$_{23}$N$_{3}$O$_4$ | SARS-CoV-2 | Kinase inhibitor | Antifibrotic agent, phase 2 for COVID-19 NCT04338802 | (Su et al., 2020) |
| Sofosbuvir | Nucleotide analogue | C$_{22}$H$_{22}$F$_{3}$N$_{3}$O$_9$P | Hepatitis C | RNA synthesis | Preclinical | Shah et al. (2020) |
| Tenofovir | Acyclic nucleoside analogue of adenosine | C$_{4}$H$_{8}$N$_{3}$O$_3$P | HIV, HBV, SARS-CoV-2 | Reverse transcriptase | Preclinical | Shah et al. (2020) |
| Tideglinib | Thiadiazolidinone | C$_{3}$H$_{16}$N$_{4}$O$_2$S | SARS-CoV-2 | non-ATP competitive inhibitor of glycosynthase kinase 3, inhibits Mpro | Potent anti-inflammatory and neuroprotective | Jin et al. (2020) |
| Arvudine | Cystidine analogue | C$_{9}$H$_{10}$F$_{4}$N$_{2}$O$_4$ | HIV, SARS-CoV-2 | Reverse transcriptase inhibitor | Clinical trial for COVID-19 ChCTR20000029853 | Zhai et al. (2020) |
| Danoprevir (R7227) | Macrocyclic peptidom | C$_{30}$H$_{45}$N$_{10}$O$_2$S | HCV, SARS-CoV-2 | Protease inhibitor | Antiviral agent, phase 2 for COVID-19 NCT04338802 ChCTR20000029853 | Shah et al. (2020) |
| Baloxavir marboxil | Synthesized compound | C$_{29}$H$_{35}$F$_{3}$N$_{3}$O$_5$ | Influenza | Inhibits RNA and protein synthesis | Inhibits virus replication | Li and De Clercq (2020) |
| Ciclesonide | Glucocorticoid | C$_{22}$H$_{44}$O$_7$ | SARS-CoV-2 | Protease inhibitor | Treat obstructive airway diseases, under clinical trial for COVID-19 NCT04330586 | Iwabuchi et al. (2020) |
| Paritaprevir (ABT-450) | Synthesized compound | C$_{28}$H$_{48}$O$_{5}$ | HCV, SARS-CoV-2 | Protease inhibitor | Preclinical | Shah et al. (2020) |
| Amprenavir | Derivative of hydroxyethylamine sulfonamide | C$_{38}$H$_{38}$N$_{3}$O$_6$S | HIV-1, SARS-CoV-2 | Protease inhibitor | Preclinical | Wu et al. (2020) |
| Adefovir | Acyclic nucleoside analogue of adenosine | C$_{12}$H$_{30}$N$_{3}$O$_5$P | HIV, HBV, SARS-CoV-2 | Reverse transcriptase | FDA-approved broad-spectrum anti-parasitic drug. | Kumar et al. (2020) |
| Ivermectin | Macroyclic lactone | C$_{40}$H$_{92}$O$_{14}$ | Flavivirus, HIV, dengue, influenza, SARS-CoV-2 | Inhibit the non-structural 3 (NS3) helicase | Phase 6 clinical trial for COVID-19, NCT04325061 | Muller et al. (2020) |
| Atesunate | Semi-synthetic derivative artemisinin | C$_{16}$H$_{18}$O$_{3}$ | Hepatitis, HCMV, SARS-CoV-2 | Inhibit NF-kB (Nuclear Factor kappa B) | Antimalarial drug | Uzun and Toptas (2020) |
| Dexamethasone | Corticosteroid | C$_{22}$H$_{28}$F$_{3}$O$_{3}$ | SARS-CoV-2 | Potent anti-inflammatory drug treat arthritis | Phase 3 clinical trial for COVID-19, NCT04330638 | Saini et al. (2020) |
| Silvuximab | Monoclonal antibody | C$_{43}$H$_{44}$N$_{4}$O$_{7}$S$_{10}$ | HIV, SARS-CoV-2 | Interleukin-6 Inhibitors | Phase 3 clinical trial for COVID-19, NCT04330638 | Saini et al. (2020) |
| Hydrocortisone | Corticosteroid | C$_{22}$H$_{28}$O$_{3}$ | SARS-CoV-2 | Anti-inflammatory and immunosuppressive, Inhibits protease and viral replication | Phase 3 clinical trials, NCT04348305 | Approved as antiviral agent | Ma et al. (2019) |
| Boceprevir | Synthetic tripeptide | C$_{24}$H$_{46}$N$_{4}$O$_{3}$S | HCV, SARS-CoV-2 | 3C-like protease inhibitor | Treatment for feline infectious peritonitis | Ma et al. (2019) |
| GC-376 | Synthetic compound | C$_{32}$H$_{52}$N$_{2}$O$_{3}$S | SARS, MERS, SARS-CoV-2 | Inhibits virus replication | Phase 2 clinical trial for COVID-19, NCT04273529 | Saini et al. (2020) |
| Thalidomide | Synthetic derivative of glutamic acid Tetracyclic | C$_{13}$H$_{21}$N$_{4}$O$_{3}$ | H1N1, SARS-CoV-2 | Inhibits virus replication | Phase 4 clinical trial for COVID-19, NCT04561643 | Saini et al. (2020) |
| Lenalidomide (Revlimid) | Thalidomide analog | C$_{13}$H$_{21}$N$_{4}$O$_{3}$S | SARS-CoV-2 | Inhibitors of Bruton’s tyrosine kinase (BTK), and viral replication | Phase 2 clinical trial for COVID-19, NCT03863184 | Saini et al. (2020) |
| Acalabrutinib | Synthetic compound | C$_{29}$H$_{28}$N$_{2}$O$_{2}$S | SARS-CoV-2 | Inhibitor of phosphatidylinositol 3-kinase (PI3K) and viral replication | Phase 2 clinical trial for COVID-19, NCT04372602 | Saini et al. (2020) |
| Duvelisib | Synthetic compound | C$_{22}$H$_{23}$N$_{6}$O$_{3}$ | HIV, hepatitis B, and C; SARS-CoV-2 | Phosphoinositide 3-kinase (PI3K) and viral replication | Phase 2 clinical trial for COVID-19, NCT03863184 | Saini et al. (2020) |
| ML188 | Acetamide | C$_{14}$H$_{36}$N$_{4}$O$_{7}$S | SARS-CoV, SARS-CoV-2 | 3CLpro inhibitor | Noncovalent small molecule inhibitor | (Loffredo et al., 2021) |
| Famotidine | Propanidimamide | C$_{19}$H$_{38}$N$_{2}$O$_{3}$S$_{3}$ | SARS-CoV, SARS-CoV-2 | Protease inhibitor | Histamine H2-receptor antagonist | (Loffredo et al., 2021) |
| Tilorone | Fluoren-9-ones | C$_{27}$H$_{30}$N$_{4}$O$_{3}$ | 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     | Thio purine analog | C$_4$H$_8$N$_6$S | MERS-CoV, SARS-CoV | Inhibits PLpro                   | Li and De Clercq (2020) |
| 6-thioguanine        | Thio purine analog | C$_4$H$_8$N$_6$S | MERS-CoV, SARS-CoV | Inhibits PLpro                   | Li and De Clercq (2020) |
| Aescin               | Saponin        | C$_6$H$_6$O$_3$   | SARS-CoV          | Inhibits glycoprotein            | Xian et al. (2020) |
| Arachidonic acid     | Fatty acid      | C$_6$H$_6$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$_{14}$ | SARS-CoV-2       | Supress cathepsin L (CatL) and cytokine storm | Liu et al. (2020) |
| Eicosapentenoic acid | Fatty acid      | C$_{20}$H$_{40}$  | SARS-CoV-2, SARS and MERS | Supress ACE2 receptor for viral cell entry | Das (2020) |
| Doconahexaenoic 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$_{20}$H$_{30}$O$_1$ | HIV-1, SARS-CoV, SARS-CoV-2 | Inhibit E-protein, 3CL protease inhibitor | Su et al. (2020) |
| Baicalein            | Trihydroxyflavone | C$_{15}$H$_{20}$O$_5$ | HIV, SARS-CoV, SARS-CoV-2 | 3CL protease inhibitor           | Su et al. (2020) |
| Betulinic acid       | Phenolic acid   | C$_{26}$H$_{40}$O$_2$ | SARS-CoV          | Replication, 3CLpro              | (D. Zhang et al., 2020) |
| Celastrol            | Quinone-methide triterpene | C$_{22}$H$_{34}$O$_4$ | SARS-CoV          | 3CLpro inhibitory effect         | Ryu et al. (2010) |
| Cepharantheine       | Alkaloid        | C$_{20}$H$_{32}$N$_6$O$_6$ | HCoV-OC43, SARS-CoV, SARS-CoV-2 | Protease inhibition             | Islam et al. (2020), Mckee et al. (2020) |
| Cinanserin           | Cinnamamides    | C$_{20}$H$_{30}$N$_6$OS | 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$_{20}$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$_{12}$H$_{12}$O$_3$ | HCoV-NL63         | Reducing the production of progeny HCoV-NL63 | Weng et al. (2019) |
| Caffeic acid         | Polyphenol      | C$_{10}$H$_{14}$O$_3$ | HCoV-NL63         | Binds to ACE2 receptor, Inhibits viral replication | Weng et al. (2019) |
| Curcumin             | Polyphenol      | C$_{27}$H$_{36}$O$_{12}$ | SARS-CoV          | GSK3 Inhibitor, Suppress viral replication | Kandeel and Al-Nazawi (2020) |
| Ginkgoide A          | Terpenoids      | C$_{20}$H$_{34}$O$_2$ | SARS-CoV-2        | Protease inhibitor               | (Islam et al. (2020), Mckee et al. (2020) |
| Gallic acid          | Phenolic acid   | C$_{10}$H$_{14}$O$_3$ | HCoV-NL63         | Inhibits the viral replication   | Weng et al. (2019) |
| Cyanidin-3-sambubioside | Flavonoid  | C$_{20}$H$_{20}$O$_15$ | Influenza A and B | Neuraminidase inhibitor           | Porter and Bode (2017) |
| Dieckol              | Phlorotannin    | C$_{20}$H$_{24}$O$_{14}$ | SARS-CoV          | 3CLpro inhibitor                 | Park et al. (2013) |
| Dihydrorasthinone I  | Lipophilic diterpenes | C$_{14}$H$_{12}$O$_2$ | MERS-CoV          | 3CLpro and PLpro protease inhibitors | Kim et al. (2018) |
| Emetine              | Alkaloid        | C$_{20}$H$_{24}$N$_{10}$O$_4$ | MERS-CoV          | Inhibits RNA synthesis           | Shen et al. (2019) |
| Emolin               | Anthraquinone   | C$_{20}$H$_{24}$O$_{15}$ | SARS-CoV-HCoV-OC43 | S protein and ACE2 inhibitor      | Ho et al. (2007), Zhang and Liu (2020) |
| Ginsenoside Rh1      | Steroid glycosides | C$_{26}$H$_{44}$O$_{14}$ | HIV, SARS-CoV     | Prevent viral entry              | Li et al. (2005) |
| Glycyrrhetinic acid  | Triterpenoids   | C$_{22}$H$_{34}$O$_{14}$ | Herpes, HIV, Hepatitis, SARS-CoV | Inhibits viral replication       | Wang et al. (2015) |
| Glycyrrhizin         | Saponin         | C$_{22}$H$_{42}$O$_{16}$ | Herpes, HIV, Hepatitis, SARS-CoV | Inhibits viral replication       | Wang et al. (2015) |
| Griffithsin          | Algal lectin    | Not available     | SARS-CoV, MERS-CoV, HIV-229E, HCoV-OC43, HIV, HCV and Ebola virus | Binds to Spike glycoprotein, inhibiting virus-host cell binding | Luzvarghi and Bewley, 2016; Zumla et al., 2016 |
| Helichrysetin        | Flavonoid       | C$_{15}$H$_{14}$O$_2$ | SARS-CoV-2, MERS-CoV, | 3CL protease                     | Zhang and Liu (2020) |
| Herbacetin           | Flavonoid       | C$_{15}$H$_{20}$O$_7$ | SARS-CoV, SARS-CoV-2, MERS-CoV, | 3CL protease                     | Jo et al., 2020; Zhang and Liu, 2020 |
| Heparin              | Sulfur-rich glycosaminoglycan | C$_{20}$H$_{26}$N$_{12}$O$_{27}$S$_{6}$ | SARS-CoV-2 | Anticoagulant, Supress cathepsin L (CatL) | Liu et al. (2020) |
| Homoharringtonine    | Alkaloid        | C$_{20}$H$_{32}$O$_{16}$ | SARS-CoV-2        | Inhibits viral replication       | Choy et al. (2020) |
| Hesperidin           | Dihydroxyflavone | C$_{20}$H$_{34}$O$_{15}$ | SARS-CoV-2        | ACE2 inhibitor                   | Wu et al. (2020) |
| Neohesperidin        | Flavonane glycoside | C$_{20}$H$_{34}$O$_{15}$ | SARS-CoV-2        | ACE2 inhibitor                   | Wu et al. (2020) |
| Hesperetin           | Trihydroxyflavone | C$_{10}$H$_{12}$O$_2$ | SARS-CoV-2        | Inhibits ACE2 and 3C-like protease | Utomo et al. (2020) |
|                   | Peptides        | Not available     | MERS-CoV          | Inhibits replication and spike protein-mediated cell-cell fusion | Li and De Clercq (2020), Lu et al., 2014 |
| Quercetin            | Triterpene      | C$_{20}$H$_{30}$O$_6$ | SARS-CoV          | Inhibits 3CLpro                  | Xian et al. (2020) |
| Kaempferol           | Flavonol        | C$_{10}$H$_{14}$O$_6$ | SARS-CoV, SARS-CoV-2 | PLpro and 3CLpro inhibitor       | (D. Zhang et al., 2020) |
| Lignan               | Phyto nutrients | C$_{20}$H$_{26}$O$_8$ | SARS-CoV, SARS-CoV-2 | Inhibition of replication, 3CLpro | (D. Zhang et al., 2020) |

(continued on next page)
| Name of the compound | Chemical nature | Molecular formula | Targeted virions | Target and inhibition mechanism | Ref |
|----------------------|----------------|------------------|-----------------|---------------------------------|-----|
| Luteolin             | Flavonoid      | C_{16}H_{14}O_{6} | SARS-CoV         | Activation of the NLRP3 inflammatory and modulate inflammatory response | McKee et al. (2020) |
| Lycorine             | Alkaloid        | C_{17}H_{17}NO_{4} | HCoV-OC43, HCoV-NL63, MERS-CoV, MHV-AS9 | Protein synthesis inhibitor | Li et al. (2005) |
| Apigenin             | Flavonoid      | C_{15}H_{12}O_{5} | SARS-CoV         | Activation of the NLRP3 inflammatory and modulate inflammatory response | McKee et al. (2020) |
| Melatonin            | Hormone        | C_{18}H_{22}N_{2}O_{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_{16}H_{17}N_{4}O_{3} | SARS-CoV-2 | PI3K inhibitor | (D. Zhang et al., 2020) |
| Myricetin            | Flavonoid      | C_{15}H_{12}O_{9} | SARS-CoV         | Activation of the NLRP3 inflammatory | McKee et al. (2020) |
| Myricitrin           | Glycosylflavone | C_{15}H_{24}O_{13} | SARS-CoV-2 | Protein kinase inhibitor, 3CLpro receptor inhibitor | Tahir ul Qamar et al. (2020) |
| Methyl rosmarinate   | Phenylpropanoids | C_{18}H_{22}O_{9} | SARS-CoV-2 | 3CLpro receptor inhibitor | Tahir ul Qamar et al. (2020) |
| N-cis-feruloyltyramine| Hydroxycinnamic | C_{18}H_{17}O_{6} | SARS-CoV-2 | PI3K and 3CLpro inhibitor | (D. Zhang et al., 2020) |
| OC43-HR2P (most promising EKI) | Peptide | Not available | SARS-CoV and MERS-CoV | Spike glycoprotein, inhibits pan-CoV fusion targeting the HR1 domain. | Xia et al. (2019) |
| Oleoylthanolamide     | Lipid amide    | C_{29}H_{32}O_{12} | SARS-CoV-2 | Binds with high affinity to PPAR-a receptors | Ghaifari et al. (2020) |
| Ouabain              | ATP1A1-binding | C_{24}H_{40}O_{12} | MERS-CoV | Inhibit clathrin-mediated endocytosis | Zulma et al. (2016) |
| Oxymatrine           | Peptide        | C_{12}H_{16}N_{2}O_{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_{12}H_{16}O_{5} | SARS-CoV         | 3CL protease | Jo et al. (2020) |
| Peptide (P9)         | β-defensin derivative | C_{12}H_{16}O_{5} | Not available | Broad-spectrum antiviral, SARS-CoV, MERS-CoV, influenza | Zhao et al. (2016) |
| Pritzinerin          | Quinone-methide | C_{12}H_{16}O_{4} | SARS-CoV         | 3CLpro inhibitory effect | Ryu et al. (2010) |
| Quercetin            | Flavonoid      | C_{12}H_{16}O_{4} | SARS-CoV         | Inhibits 3CLpro and viral replication | Chen et al. (2006) |
| Quercetin-3-β-galactoside | Flavonoid | C_{12}H_{16}O_{12} | SARS-CoV-2 | 3C-like protease (3CLpro) inhibitor | Chen et al. (2006) |
| Isobavachalcone      | Flavonol       | C_{12}H_{16}O_{2} | SARS-CoV         | Inhibitors of papain-like protease (PPlpro). | Islam et al. (2020) |
| Betulonic acid       | Pentacyclic triterpene | C_{20}H_{24}O_{6} | SARS-CoV | Inhibition of 3CL protease | Islam et al. (2020) |
| Cephapenthine        | Alkaloid        | C_{17}H_{23}N_{6}O_{6} | SARS-CoV, HCoV-OC43, SARS-CoV-2 | ACE inhibitor | Xia et al. (2019) |
| Diplacene            | Flavonoid      | C_{16}H_{22}O_{4} | SARS-CoV         | Inhibition of papain-like protease | Islam et al. (2020) |
| Ferruginol           | Diterpenoid    | C_{18}H_{22}O_{4} | SARS-CoV         | Inhibition of viral replication | Islam et al. (2020) |
| Hinokinin            | Lignan         | C_{12}H_{16}O_{6} | SARS-CoV         | Inhibition of 3CL protease. | Islam et al. (2020) |
| Hirutunone           | Diarylheptanoid | C_{12}H_{16}O_{6} | SARS-CoV         | Inhibits PLpro activity | Xian et al. (2020) |
| Indigo               | Organic compound | C_{12}H_{16}N_{2}O_{2} | SARS-CoV | 3CL protease inhibition. | Islam et al. (2020) |
| Isobavachalcone      | Chalcone       | C_{12}H_{16}O_{4} | SARS-CoV         | Papain-like protease (PPlpro). | Islam et al. (2020) |
| Juglans              | Cyclic ketone  | C_{20}H_{16}O_{10} | SARS-CoV | Inhibition of 3CL protease | Islam et al. (2020) |
| Reserpine            | Alkaloid        | C_{16}H_{16}N_{3}O_{9} | SARS-CoV | Inhibits glycoprotein activity | Xian et al. (2020) |
| Rhein                | Dihydroxyanthraquinone | C_{12}H_{16}O_{6} | SARS-CoV | Inhibited interaction (3) protein and ACE2 | Islam et al. (2020) |
| Resveratrol          | Polyphenol     | C_{16}H_{20}O_{5} | MERS-CoV         | Inhibits viral replication | Lin et al. (2017) |
| Selamectin           | Avermectin     | C_{12}H_{18}N_{11}O_{2} | SARS-CoV-2 | Inhibits ACE2 receptor entry | McKee et al. (2020) |
| Rhofolin             | Apigenin derivative | C_{15}H_{22}O_{4} | SARS-CoV | 3CLpro inhibitor | Jo et al. (2020) |
| Scutellarin          | Flavone        | C_{13}H_{16}O_{6} | SARS-CoV-2 | Binds to ACE2 receptor | Chen and Du (2020) |
| Shikonin             | Hydroxynaphthoquinones | C_{12}H_{16}O_{8} | SARS-CoV-2 | Inhibits Mpro | Jin et al. (2020) |
| Silvestrol           | Rocaglate derivative | C_{14}H_{18}O_{3} | MERS-CoV, HCoV-229E, EBOV | Inhibits the DEAD-box RNA helicase eIF4A to affect virus translation | Müller et al. (2018) |
| Sugiol               | Diterpenoid    | C_{12}H_{20}O_{2} | SARS-CoV, SARS-CoV-2 | Replication, 3CLpro | (D. Zhang et al., 2020) |
| Tanshinone-1         | Diterpenoid    | C_{12}H_{18}O_{2} | SARS-CoV | Inhibits PLpro activity | Xian et al. (2020) |
| Tanshinone-lla       | Diterpenoid    | C_{12}H_{18}O_{2} | SARS-CoV, SARS-CoV-2 | PLpro and 3CLpro | Xian et al. (2020) |
| Tingenon              | Flavonoid      | C_{12}H_{16}O_{3} | SARS-CoV         | 3CLpro inhibitory effect | Ryu et al. (2010) |
| Theobavin            | Flavonoid      | C_{12}H_{16}O_{12} | SARS-CoV-2 | Inhibits RdRp activity | Xian et al. (2020) |
| Vitamin C             | Vitamin        | C_{10}H_{8}O_{6} | SARS-CoV-2 | Antioxidant and immunomodulator agent | Boere and Bank (2020) |
| β-sitosterol          | Phytosterol   | C_{19}H_{32}O_{6} | SARS-CoV | Inhibition of 3CLpro | Mani et al. (2020) |
| Sinigrin              | Glucosinolate  | C_{12}H_{16}N_{2}O_{5} | SARS-CoV | Inhibition of 3CLpro | Mani et al. (2020) |
| α-Helical lipopeptides (e.g. LLS, PFS, ILS, IK) | Peptide | Not available | MERS-CoV, IAV | Inhibit s protein-mediated cell-cell entry | Wang et al. (2018) |

(continued on next page)
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 remdesivre, 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 (Domingl 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 include 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, antiarrheal, antidiabetic, anticancer, antifungal, antibacterial, anticoagulant, and antihelmithic agents have been suggested as potential targets preventive or therapeutic 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, tizanavir, hydroxychloroquine, ASC09F, baloxavir marboxil, azudine, 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: collected data, Writing – original draft, Writing – review & editing. Arti Nile: collected information on this topic and provided all chemical structural details. Shvikumar 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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