Introduction

CoVs (enveloped RNA viruses, genome sizes range from 26 to 32 kb) are entrapping non-segmented, positive-sense and single-stranded ribonucleic acid (ssRNA). SARS-CoV-2 3’ terminus encodes structural proteins, containing spike (S) glycoproteins, membrane (M) glycoproteins, envelope (E) and nucleocapsid (N) proteins. Besides the genes encoding structural proteins, precise genomic regions are encoding viral proteins involved in replication [1,2]. The SARS-CoV-2 genome contains about 30,000 nucleotides; the replicate gene of SARS-CoV-2 encodes two overlapping polyproteins pp1a and pp1ab required for the replication and transcription of virus. SARS-CoV-2 entry depends on angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 (transmembrane protease serine 2), and the virus can enter host cells via ligation of its spike protein (S glycoprotein, primed by serine protease TMPRSS2) with host cell ACE2 receptor [3].

The recent emergence of SARS-CoV-2 and related COVID-19 disease have caused serious and even fatal respiratory tract infections, but there is currently no effective therapy or effective treatment to effectively resist the outbreak. This forced the world to respond via the development of new vaccines or small molecule therapies against SARS-CoV-2 [2,4,5]. Some important drugs and compounds screened for treating COVID-19 and controlling the symptoms of this viral infection are summarised in Tables 1 and 2. For the treatment of this pathogenic virus, clinical trials are underway to identify potential drugs (https://clinicaltrials.gov/). There are several drug candidates that may inhibit SARS-CoV-2 infection and replication; some of them include the inhibitors of TMPRSS2 serine protease and ACE2 [28]. Additionally, antiviral drugs that target viral RNA-dependent RNA polymerase (RdRp) and the main protease can inhibit virus replication and assembly [29]. Zhang et al., [28] suggested ACE2 receptor as a potential target, and described the potential therapeutic strategies regarding ACE2 receptor, including inhibition of TMPRSS2 activity, spike protein-based vaccine, obstructing ACE2 receptor, and delivering excessive soluble form of ACE2 (Figure 1) [28]. Blocking ACE2 (the host cell receptor for the S protein of SARS-CoV-2) and inhibiting TMPRSS2 (which is required for S protein initiation) may prevent SARS-CoV-2 from entering the cell [29].

Hydroxychloroquine and chloroquine as well as off-label antiviral drugs, such as the nucleotide analogs (remdesivir), HIV protease inhibitors (ritonavir and lopinavir), broad-spectrum antiviral drugs (such as panferivir and Arbidol) and the antiviral phytochemicals available so far may restrict/prohibit the spread of SARS-CoV-2 and reduce the morbidity/mortality of this viral infection (summarised in Figure 2) [29]. The inhibition of the main SARS-CoV-2 protease is necessary to block viral replication. For instance, the replication of SARS-CoV-2 requires viral RdRp, which is the target of the antiviral drug remdesivir. This drug has been evaluated in clinical trials for treatment of Ebola infection, and can repress the replication of SARS- and MERS-CoVs in tissue cultures and sufficiently in non-human animal models [30]. Generally, coronaviruses (CoVs) cell entry depend on the binding of the viral spike (S) protein to the cell receptor and the S protein priming by host cell proteases. Thus, clarifying which cellular factors are employed by SARS-CoV-2 to enter may provide insights into viral transmission and uncover therapeutic targets. Additionally, ACE2 has been identified as an important receptor for SARS-CoV-2 viral infection, and the inhibition of the interaction with receptor can be employed to treat patients with COVID-19; though, it is unclear whether human recombinant soluble ACE2 (hrsACE2) will prevent the growth of SARS-CoV-2. Furthermore, the functional
Table 1. Some important drug candidates analysed and screened against COVID-19.

| Potential candidates | Applications and properties | References |
|----------------------|----------------------------|------------|
| Arbidol (umifenovir)  | Antiviral drug; applied for treatment of influenza infection | [6,7] |
| Favipiravir           | Antiviral drug; approved for treatment of influenza infection | [8,9] |
| Baricitinib           | Approved for the treatment of rheumatoid arthritis | [10] |
| Darunavir             | An antiretroviral medication used to treat and prevent human immunodeficiency virus (HIV) | [7] |
| Ribavirin             | For treatment of hepatitis C virus (HCV) and respiratory syncytial virus (RSV) | [11] |
| Remdesivir            | An approved inhibitor against HIV reverse transcriptase; against Ebola | [9,12] |
| Galidesivir           | For treatment against yellow fever and HCV | [11] |
| Lopinavir/ritonavir (Kaletra) | Protease inhibitors; against HIV-1 | [11] |
| Disulfiram            | For treatment of chronic alcoholism | [11] |
| Griffithsin           | A glycoprotein isolated from red algae; Binding to oligosaccharides on the surface of viral glycoproteins (like SARS-CoV spike and HIV glycoproteins) | [11] |
| Ivermectin           | Anti-parasitic drug; broad-spectrum antiviral activity in vitro; Possible inhibitor of SARS-CoV-2, with a single addition to Vero-hSLAM cells two hours post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h | [13] |
| Pegylated interferon (IFN) Alfa 2a | Against hepatitis B virus (HBV) and HCV | [14] |
| Chloroquine/hydroxychloroquine (alone or with azithromycin) | Immune modulator; antimalarial drug | [9] |
| Nitazoxanide (alone or with azithromycin) | Orally active nitrothiazolyl-salicylamide broad-spectrum anti-parasitic and antiviral prodrg; for potentiation of IFN alfa and beta generation and in vitro activity against MERS-CoVs and other CoVs; Reduction in duration of symptoms in patients with acute uncomplicated influenza with minimal adverse effects; applied for diarrhoea treatment | [9,15–17] |
| Camostat mesylate     | Serine protease inhibitor; clinically affirmed TMPRSS2 inhibitor; effectively protect mice from death after lethal SARS-CoV infection (survival rate = 60%) | [18,19] |
| Glecaprevir and maraviroc | SARS-CoV-2 M<sup>pro</sup> inhibitors | [20] |

Table 2. Some important candidates of combination therapy (polytherapy) screened against COVID-19.

| Drugs | Description | References |
|-------|-------------|------------|
| Ritonavir, lopinavir and ribavirin | Protease inhibitors and nucleoside inhibitors | [21] |
| Tenofavir and emtricitabine | Nucleotide reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors | [22] |
| Ritonavir and lopinavir | Protease inhibitors | [11] |
| Cobicistat and darunavir | Cobicistat (for bioavailability improvement and t1/2) and antiretroviral protease inhibitors | [21] |
| Ribavirin, IFNs (α, β, IFNα2a or rIFN-α2b or IFN-β1a) | Antivirals and IFNs | [23] |
| Ribavirin, IFN and steroids | Antivirals and IFNs and steroid hormones | [24] |
| IFN alfacon-1 and corticosteroids | Synthetically developed recombinant type-I IFN and steroid hormones | [25] |
| IFN-β1α, lopinavir/ritonavir and ribavirin | Antivirals and IFNs | [26] |
| IFNs and ribavirin | Antivirals and IFNs | [27] |

The significance of chymotrypsin-like protease (3CL<sup>pro</sup>) in virus replication and maturation makes it an important target for developing operative and applicable antiviral drugs against CoVs [31]. The main protease (M<sup>pro</sup>) of SARS-CoV-2 is a key enzyme of SARS-CoV-2 and can play vital role in mediating viral replication and transcription, making it an attractive drug target for this virus [32].

Due to the lack of effective treatments for COVID-19, the scientific community, began to look for new compounds that could treat this viral disease [33]. Further, based on data related to CoVs, reusing the previously identified antiviral drugs and screening available databases should be considered, a short-term strategy and economical approach to curb the SARS-CoV-2 pandemic [4,5]. In this review, we discussed about the current trends and important challenges regarding the potential inhibitors screened and evaluated by scientists against SARS-CoV-2.

**Potential inhibitors of SARS-CoV-2**

Recognisable proof of targets is remarkable for discriminating medications with elevated target explicitness or potentially revealing prevailing medications that could be repurposed to treat COVID-19 [7]. Two viral proteases, papain-like protease (PL<sup>pro</sup>) and 3C-like protease (3CL<sup>pro</sup>), are responsible for cleaving the viral peptides into functional units for virus replication and packaging inside the host cells. In this way, drugs focus on these proteases in different viruses, namely HIV drugs (such as ritonavir/lopinavir) have been screened [34]. An appealing medication focus among CoVs is the main viral protease, due to its basic role in preparation of the polyproteins translated from the viral RNA. Importantly, the lead compound was developed into an effective inhibitor of the SARS-CoV-2 M<sup>pro</sup>, and pharmacokinetic evaluations of the optimised inhibitor showed a pronounced lung tropism and aptness for inhalation approach of dispensation [35]. Additionally, RdRp is the RNA polymerase accountable for viral RNA synthesis that might be inhibited by existing antiviral medications or medication competitors (such as remdesivir) [34]. Probably, the collaboration of viral S protein with its receptor ACE2 on host cells, and ensuing viral endocytosis into the cells, may likewise be a reasonable drug objective. For instance, the broad-range antiviral medication (such as Arbidol), which works as a virus-host cell fusion inhibitor to prevent viral entry into host cells against the flu virus, has gone into a clinical trial for SARS-CoV-2 treatment [7,14].

**Tmprss4 and TMPRSS2 inhibitors (serine protease inhibitors)**

The protease TMPRSS2 delivered by the host cells assumes a significant function in proteolytic dispensation of S protein grooming to the receptor ACE2 attachment in human cells [36]. TMPRSS2 is
a serine protease that primes the spike protein of highly pathogenic human CoVs, and enables their entry into host cells [18]. It was revealed that camostat mesylate, a clinically affirmed TMPRSS2 inhibitor, had the option to block SARS-CoV-2 passage to human cells, showing promising potential as a medication for COVID-19 [7,18,36]. Previously, it was reported that camostat mesylate blocked the spread and pathogenesis of SARS-CoV in a pathogenic mouse model and showed similar effect in MERS-CoV [18]. The research results showed that the expression of TMPRSS4 and TMPRSS2 (two mucosa-specific serine proteases) can promote the virus to enter the intestinal cells and facilitate SARS-CoV-2 spike fusogenic activity [37]. Interestingly, it was revealed that the virus released into the intestinal lumen was inactivated by simulated human colonic fluid, and no infectious virus was recovered.
Camostat mesylate can be used primarily for treating postoperative reflux esophagitis and for acute exacerbations of chronic pancreatitis. This drug (over 15 years clinical experience in Japan with a very safe clinical track record) can be evaluated as suggested in vitro virus inhibition data and in vivo protective effects in a mouse model of SARS, and thus some clinical trials, such as double-blind randomised controlled clinical trial (NCT04353284) or a randomised, placebo-controlled, phase IIa trial (NCT04321096) are focused on its inhibitory effects against SARS-CoV-2 replication and the virus cellular entry blocked by this drug [18]. Furthermore, it is unclear whether compound concentrations can be achieved in the lung and are sufficient to suppress viral spread.

Other serine protease inhibitor, nafamostat mesylate, can be employed for blockade of SARS-CoV-2 entry [38]; it was revealed that nafamostat mesylate inhibited TMPRSS2-dependent host cell entry of MERS-CoV [39]. Importantly, nafamostat obstructed SARS-CoV-2 S-mediated entry into host cells with roughly 15-fold-higher efficiency than camostat mesylate, with half maximal effective concentration (EC50) in the low-nanomolar range [38]. Additionally, this drug prohibited SARS-CoV-2 infection of human lung cells with noticeably superior efficiency than camostat mesylate; though both compounds were not active against vesicular stomatitis virus infection [38]. Therefore, nafamostat mesylate can be evaluated as a potential inhibitor against SARS-CoV-2, and some clinical trials are focussed on the efficacy of this drug (such as NCT04418128, an open labelled randomised controlled clinical trial).

**Some evaluated SARS-CoV-2 main protease inhibitors**

Deep docking was employed to 1.3 billion compounds from ZINC15 library to identify top 1,000 potential ligands for SARS-CoV-2 Mpro protein; these compounds are publicly available for further characterisation and development in the scientific community [32]. In another study, to identify the potential inhibitors of the SARS-CoV-2 main protease, 33 molecules were screened, including antineutamides, natural products, antiviral, antiprotozoal, and antifungal agents. Among the screened compounds, rutin showed significant efficiency, and also ritonavir (control drug), emetine (anti-protozoal), hesperidin (a natural compound), lopinavir (control drug) and indinavir (antiviral drug) exhibited potential inhibitory effects. These molecules could bind near the crucial catalytic residues, HIS41 and CYS145 of the main protease, and the molecules were surrounded by other active site residues like MET49, GLY143, HIS163, HIS164, GLU166, PRO168, and GLN189 [40].

Mpro can play important roles in viral replication and transcription, thus Dai et al. have planned to design two inhibitors, 11a and 11b, based on analysing the structure of Mpro active site [41]. These compounds inhibited the activity of Mpro, and exhibited remarkable antiviral effects in cell culture. Furthermore, compound 11a showed better pharmacokinetic characteristics with low toxicity when analysed in mice and dogs, and it can be considered as a promising drug candidate. The X-ray crystal structures of SARS-CoV-2 Mpro in complex with these compounds were determined at a resolution of 1.5 angstroms, and following that it was revealed that the aldehyde groups of 11a and 11b were covalently bound to cysteine 145 of Mpro [41].

Seventeen potential SARS-CoV-2 Mpro inhibitors have been detected among the natural substances of marine origin; several classes of compounds, including flavonoids, phlorotannins, and pseudo peptides inhibited the SARS-CoV-2 Mpro, as it was revealed for the SARS-CoV-1 Mpro [42]. Additionally, Liu predicted some commercial medicines as potential inhibitors against SARS-CoV-2 Mpro including colistin (antibiotic), valrubicin (anthracycline, antitumor), icatibant (hereditary angioedema), bepotastine (rhinitis, urticaria/pruritus), epirubicin (antitumor), epoprostenol (vasodilator, platelet aggregation), vapreotide (antitumor), aprepitant (nausea, vomiting, antitumor), caspofungin (antifungal), and perphenazine (antipsychotic). Since the results of this study have been predicted in silico, more evaluations are essential for efficacy validation of these drugs [43].

A mechanism-based inhibitor (N3) by computer-aided drug was designed, and the crystal structure of SARS-CoV-2 Mpro in complex with this compound was evaluated (Figure 3) [44], via a combination of structure-based virtual and high-throughput screening, 10,000 compounds including approved drugs, drug candidates in clinical trials and other pharmacologically active...
Human recombinant soluble ACE2 (hrsACE2)

Generally, SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor approved for clinical use blocked entry and might constitute a treatment option. Additionally, it was demonstrated that the sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry [36]. Further, in another evaluation, it was revealed that clinical grade hrsACE2 reduced SARS-CoV-2 recovery from Vero cells by a factor of 1,000–5,000; though, an equivalent mouse rsACE2 showed no influences [46]. SARS-CoV-2 can precisely infect engineered human blood vessel and kidney organoids, which can be obstructed by hrsACE2; this information indicates that hrsACE2 can remarkably block early stages of SARS-CoV-2 infections [46]. In the case of human capillary organoids, they have been evaluated by qRT-PCR, and following that viral RNA existence was detected on the 3rd and 6th day after the initial SARS-CoV-2 exposure. Notably, after infection, the viral RNA was identified in vascular organoids from day 3 to day 6 after infection, which indicates active replication of this virus. Additionally, single-cell profiling of kidney organoids demonstrated the existence of cells expressing ACE2 in the proximal tubule and podocyte II cell clusters that express key marker genes of proximal tubular cells (SLC3A1 and SLC27A2) and podocytes (POXL, NPHS1, and NPHS2), respectively. Therefore, kidney organoids contain cell clusters that express ACE2 similar to those detected in the native tissue [46].

Nsp12-NSP7-NSP8 complex (as a potential target)

Nsp12-NSP7-NSP8 complex is a potential target to fight against the virus. Peng et al. [47] described the near-atomic-resolution structure of the SARS-CoV-2 polymerase complex consisting of the Nsp12 catalytic subunit and Nsp7-Nsp8 cofactors. This structure highly resembles the counterpart of SARS-CoV with conserved motifs for all viral RNA-dependent RNA polymerases and proposed a mechanism of activation by cofactors. Biochemical analysis demonstrated reduced activity of the core polymerase complex and lower thermostability of individual subunits of SARS-CoV-2 compared with SARS-CoV [47]. As for a highly active Nsp12 polymerase complex, viral cofactors Nsp7 and Nsp8 are essential, proposing that the particularly attractive compounds could disrupt the binding of Nsp7 or Nsp8 to Nsp12. In one study, potential inhibitors targeting RNA-dependent RNA polymerase activity (NSP12) were introduced. Accordingly, 44 compounds were evaluated based on virtual screening and docking scores, leading eight compounds for the calculation of binding free energy. Among them, some drugs with antiviral activity such as lonafarnib, tegobuvir, olysio, flibuvir, and cephaparine can simultaneously be employed as potential candidates against SARS-CoV-2 [48].

Nsp1 protein of SARS-CoV-2 (potential candidate for drug design)

Thoms et al. [49] indicated that Nsp1 (one of the main immune evasion factors of SARS-CoV-2) efficiently interfered with the cellular translation machinery causing shut down of host protein formation, and therefore parts of the innate immune system depending on translation of antiviral defense parameters (such as IFN-β or RIG-I) are deactivated [49]. Though, SARS-CoV-2 encodes a potential inhibitor of innate immune defense. The loss of Nsp1 function can make the virus vulnerable to immune clearance. Thus, these results may provide a starting point for rational structure-based drug design for Nsp1-ribosome interactions. Nsp1 from SARS-CoV-2 binds to the 40S ribosomal subunit, resulting in shuts down of mRNA translation both in vitro and in cells. Structural analysis by cryo-electron microscopy (cryo-EM) of in vitro reconstituted Nsp1-40S and various native Nsp1-40S and -80S complexes have demonstrated that the Nsp1 C terminus binds to the mRNA entry tunnel, and obstructs it. Thereby, Nsp1 effectively blocks RIG-I-dependent innate immune responses that would otherwise facilitate clearance of the infection. The structural representation of the inhibitory mechanism of Nsp1 can help for structure-based drug designing against SARS-CoV-2 [49].

Interferons (IFNs)

IFNs can be considered as safe and easy to upscale treatment against COVID-19 in the early stages of infection, and also in vitro analyses suggested that SARS-CoV-2 could be markedly more sensitive to IFN-I than other CoVs [50]. The inhibitory performances of the antiviral interferons of type I (IFN-α) and type III (IFN-λ)
against SARS-CoV-2 were evaluated and compared with those against SARS-CoV-1 [51]. By applying two mammalian epithelial cell lines (human Calu-3 and simian Vero E6), it was revealed that both IFNs dose-dependently inhibited SARS-CoV-2; notably, SARS-CoV-1 was limited only by IFN-β in these cell lines, and also SARS-CoV-2 exhibited a broader IFN sensitivity than SARS-CoV-1. Additionally, ruxolitinib (an inhibitor of IFN-triggered Janus kinase/signal transducer and activator of transcription signalling) increased SARS-CoV-2 replication in the IFN-competent Calu-3 cells. It was concluded that SARS-CoV-2 was sensitive to exogenously added IFNs, and type I and especially the less adverse effect-prone type III IFN can be considered as suitable candidates for managing COVID-19 [51]. In another study, the sensitivity of SARS-CoV-2 to recombinant human IFNα/β was evaluated [52]. It was detected that IFN-α and IFN-β treatment at a concentration of 50 international units (IU) per millilitre decreased the viral titres by 3.4 log or over 4 log, respectively, in Vero cells. Accordingly, the EC50 of IFN-α and IFN-β treatment was 1.35 IU/mL and 0.76 IU/mL, respectively, in Vero cells [52]. Additionally, it was reported that SARS-CoV-2 induced overt but delayed type-I IFN responses [53]. In one study, by evaluating 23 viral proteins, it was found that SARS-CoV-2 NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6 and M protein inhibited Sendai virus-induced IFN-β promoter activation, whereas NSP2 and S protein exerted opposite influences. Further evaluations revealed that ORF6 inhibited both type I IFN formation and downstream signalling, and that the C-terminus region of ORF6 was important for its antagonistic influence. Thus, IFN-β treatment can effectively block SARS-CoV-2 replication [53].

**Ek1 (pan-CoV fusion inhibitor)**

Xia et al. [54] have demonstrated the X-ray crystal structure of six-helical bundle (6-HB) core of the HR1 and HR2 domains in the SARS-CoV-2 S protein S2 subunit, showing that several mutated amino acid residues in the HR1 domain might be related with improved interactions with the HR2 domain [54,55]. They previously established a pan-CoV fusion inhibitor, Ek1, which targeted the HR1 domain and could inhibit infection by divergent human CoVs analysed, including SARS- and MERS-CoVs [54]. Accordingly, it was reported that peptide OC43-HR2P, originated from the HR2 domain of HCoV-OC43, demonstrated wide-ranging fusion inhibitory activity against multiple human CoVs. The optimised structure of OC43-HR2P, Ek1, exhibited considerably enhanced pan-CoV fusion inhibitory activities and pharmaceutical characteristics [55]. Furthermore, they produced a series of lipopeptides derived from Ek1 and illustrated that Ek1C4 was the most potent fusion inhibitor against SARS-CoV-2 S protein-mediated membrane fusion and pseudovirus infection with half maximal inhibitory concentration (IC50) of 1.3 and 15.8 nM, about 241- and 149-fold more potent than the original Ek1 peptide, respectively. Additionally, Ek1C4 was remarkably suitable against membrane fusion and infection of other human CoV pseudoviruses analysed, such as SARS- and MERS-CoVs, and effectively obstructed the replication of 5 live human CoVs studied, including SARS-CoV-2 [54]. Importantly, intranasal application of Ek1C4 before or after challenge with HCoV-OC43 protected mice from infection, proposing that Ek1C4 could be employed for preventing and treating the viral infections occurred by CoVs, especially SARS-CoV-2 [Figure 4] [54].

**Remdesivir, lopinavir and ritonavir**

It appears that treatment with remdesivir (a nucleoside analogue prodrug) can improve the clinical conditions of patients infected by SARS-CoV-2, and a phase III clinical trial of remdesivir against this virus was launched in Wuhan (4 Feb 2020). Chakraborty et al. [56] proposed a possible mechanism: The antiviral effects of lopinavir, remdesivir, homoharringtonine (omacetaxine mepesuccinate) and emetine have been assessed against SARS-CoV-2 virus in Vero E6 cells with the estimated 50% effective concentration at 23.15 μM, 26.63 μM, 2.55 μM and 0.46 μM, respectively. Furthermore, ribavirin and favipiravir evaluated under clinical trials exhibited no inhibition at 100 μM. Synergy between remdesivir and emetine has been detected, and remdesivir (6.25 μM) in combination with emetine (0.195 μM) might obtain 64.9% inhibition in viral yield. Indeed, combination therapy can help decrease the effective concentration of the compound below the therapeutic plasma concentration and offer improved clinical values [56].

In an important study, a randomised, double-blind, placebo-controlled, multicentre trial was accomplished at ten hospitals in Hubei, China. Eligible patients were adults (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for ten days. Patients were allowed to concomitant use of lopinavir/ritonavir, IFNs, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1 = discharged to 6 = death) or discharged alive from hospital, whichever came first. It was revealed that treatment with remdesivir was not associated with a difference in time to clinical improvement. Though not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of ten days or less. Adverse events were detected in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early due to the adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early [57].

According to the reports, the cryo-electron microscopy structure of the SARS-CoV-2 RdRp is in the apo form at 2.8 Å resolution or in complex with a 50-base template-primer RNA and Remdesivir at 2.5 Å resolution [58]. Consequently, the complex structure demonstrated that the partially double-stranded RNA template was added into the central channel of the RdRp where this drug was covalently included into the primer strand at the first replicated base pair and terminated chain elongation. These structures can offer critical insights into the mechanism of viral RNA replication and a rational template for drug design to combat the viral infection [58].

It was reported that remdesivir inhibited SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures (EC50 = 0.01 μM). Weaker activity was detected in Vero E6 cells (EC50 = 1.65 μM) because of their low capacity to metabolise remdesivir. To rapidly evaluate in vitro efficacy, a chimeric SARS-CoV-2 was engineered encoding the viral target of remdesivir, the RNA-dependent RNA polymerase, of SARS-CoV-2. In mice infected with chimeric virus, therapeutic remdesivir administration reduced lung viral load and enhanced pulmonary function as compared to vehicle treated animals. Obtained data offered evidence that this...
Figure 4. (a) Some important photogenic viruses (origins). (b) Schematic illustration of SARS-CoV-2 S protein, and related S1 subunit (NTD (14–305 aa), RBD (319–541 aa) and RBM (437–508 aa), and S2 subunit (FP (788–806 aa), HR1 (912–984 aa), HR2 (1163–1213 aa), TM (1214–1237 aa) and CP (1238–1273 aa)). (c) Generation of syncytium in Huh-7 cells, 24 h after infection by SARS-CoV-2. (d) Images of SARS-CoV and SARS-CoV-2 S-mediated cell-cell fusion on 293 T/ACE2 cells at 24 h (right) and 2 h (left). (e) SARS-CoV (I-II) and SARS-CoV-2 (III-IV) S-mediated syncytium generation on 293 T/ACE2 cells at 48 h. (f) SARS-CoV (I-II) and SARS-CoV-2 (III-IV) S-mediated syncytium generation on Huh-7 cells at 48 h. Reproduced with permission from Ref [54], (CC BY 4.0).
drug can be suitable against SARS-CoV-2 in vitro and in vivo, thus supporting its additional clinical testing to treat COVID-19 [59].

Umifenovir (Arbidol)
Umifenovir (Arbidol) was proposed for treatment of COVID-19; notably, the sequence and structural similarity between the Arbidol binding site of SARS-CoV-2 spike glycoprotein and H3N2 HA seems promising, indicating that Arbidol may have efficacy for COVID-19 treatment [60]. Evaluations by applying molecular dynamics and structural analysis revealed that SARS-CoV-2 spike glycoprotein is the drug target for Arbidol, and proposed the potential drug binding mode with key interacting residues and mechanist aspects, whereby this drug can successfully block or obstruct the trimerization of SARS-CoV-2 spike glycoprotein that is vital for cell adherence and entry; additionally, blocking the trimerization of SARS-CoV-2 spike glycoprotein making the generation of naked or immature virus with minor infections. There is an urgent need for evaluation of the efficacy and safety of Arbidol against SARS-CoV-2 with clinical trials [60]. In another study, it was reported that Arbidol successfully obstructed SARS-CoV-2 infection and by blocking the virus entry, and also it showed anti-inflammatory activity that can improve its efficacy in vivo [61]. As indicated that EC50 of Arbidol against SARS-CoV-2 was 4.11 μM, which was comparable or even lower than those of influenza viruses, this drug can be considered as potentially effective candidate for treatment of COVID-19 patients. Though, the authors recommended that the current dose of Arbidol (200 mg, 3 times/day) suggested by the Chinese guidelines might not be able to obtain an ultimate therapeutic efficacy for inhibition of SARS-CoV-2 infection, and should be raised and should be established by clinical trials [61].

Favipiravir
Favipiravir triphosphate (a purine nucleoside analogue) acts as a competitive inhibitor of RNA-dependent RNA polymerase. This drug showed efficacy against influenza A and B, including activity against oseltamivir- and zanamivir-resistant influenza viruses, several agents of viral haemorrhagic fever and SARS-CoV-2 in vitro, and more elaborate studies are urgently needed [62]. For instance, clinical trial studies are focussed on safety and efficacy of this drug for COVID-19 patients such as a double-blind, placebo-controlled randomised control study (NCT04402203) or a parallel, prospective, interventional and randomised open label pilot trial involving 150 patients with COVID-19 disease (NCT04387760). Additionally, it was revealed that patients who received favipiravir showed good improvement in chest imaging compared with the control group [63].

Alisporivir
Alisporivir (Debio 025, a non-immunosuppressive analogue of cyclosporin A) has strong cyclophilin inhibition characteristics, thus can be employed to reduce SARS-CoV-2 RNA formation in a dose-dependent manner in VeroE6 cell line (EC50 = 0.46 ± 0.04 μM). This drug can obstruct a post-entry step of the SARS-CoV-2 life cycle [64]. Additionally, in a rat model, alisporivir appeared to accumulate in lung tissues (concentrations up to 37-fold higher than in plasma) [65]. Based on a human pharmacokinetic model and predicted accumulation in lung tissue, a dosing regimen of 600 mg twice per day or higher would achieve via levels of unbound alisporivir above EC90 against SARS-CoV-2 at one week of treatment in the majority of patients. Notably, alisporivir treatment should be started at rather early stages of the infection and administered for more than 14 days to pass the acute stage of clinical disease. Alisporivir obstructs all cyclophilins, including cyclophilin D, an essential component of the mitochondrial permeability transition pore. The protection of lung tissues can be obtained by alisporivir to improve the clinical course of COVID-19. More studies should be planned regarding the effect this drug on viral replication, and also the protective effect of treatment on lung disease and complications, as well as the clinical and functional improvement of patients [65].

Baricitinib
Clinical studies revealed that high concentrations of cytokines were detected in the plasma of severely infected patients with COVID-19, indicating that cytokine storm is related to the severity of this viral infection (Figure 5) [66]. In this regard, baricitinib has been suggested for treatment of cytokine storm occurred by COVID-19. It was reported that baricitinib intracellularly inhibited the pro-inflammatory signal of several cytokines by suppressing Janus kinase (JAK) JAK1/JAK2 [67]. This drug showed clinical profits (good efficacy and safety) for the patients with active systemic lupus erythematosus, atopic dermatitis, and rheumatoid arthritis. In the case of SARS-CoV-2, baricitinib could interrupt the virus entry and intracellular assembly of this virus into the target cells mediated by ACE2 receptor [67]. Interestingly, the potential use of baricitinib has been suggested against SARS-CoV-2 infection. The application of this drug may limit the cytokine-release syndrome associated with COVID-19 and it can be considered against a wide-range of cytokines. Though, findings cannot be generalised to all patients with COVID-19, and safety issues and clinical evidences should be addressed and evaluated, comprehensively [68]. In addition to the attractive opportunity to directly prevent SARS-CoV-2 from entering cells, caution should be taken when using Baricitinib in patients with pneumonia susceptibility to persistent COVID-19 infection [69]. Various clinical trials have been focussed on the efficacy and safety of baricitinib for the treatment of COVID-19 (e.g. NCT04358614), and in one study, the probable mechanisms of baricitinib actions and its efficacy on reduction of the viral entry into the target cells and cytokine storm are mentioned as well as the role of cytokine storm mediated by JAK-STAT pathway in severe COVID-19 (Figure 6) [67].

Boceprevir
By applying the fluorescence resonance energy transfer (FRET)-based enzymatic assay, some inhibitors including boceprevir, GC-376, and calpain inhibitors II, and XII were detected against SARS-CoV-2 [70]. Remarkably, these compounds inhibited SARS-CoV-2 viral replication in cell culture with EC50 values ranging from 0.49 to 3.37 μM. Boceprevir, calpain inhibitors II and XII exhibited chemotypes, which were distinct from known substrate-based peptidomimetic Mpro inhibitors. Additionally, a complex crystal structure of SARS-CoV-2 Mpro with GC-376, analysed at 2.15 Å resolution with three protoners per asymmetric unit, showed two unique binding configurations, shedding light on the molecular interactions and protein conformational flexibility underlying substrate and inhibitor binding by Mpro [70].
Figure 5. The development of cytokine storm after SARS-CoV-2 infection; the existence of this virus in the lung stimulates an uncontrolled generalised immune response. Several immune cells (such as T lymphocytes, macrophages, and dendritic cells) provide an impressive secretion of cytokines and chemokines; it can eventually cause acute respiratory distress syndrome (ARDS). Reproduced with permission from Ref [66].

Figure 6. The probable mechanistic aspects regarding baricitinib on cytokine storm happened by SARS-CoV-2. Reproduced with permission from Ref [67].
In the case of hydroxychloroquine, many clinical trial registries were found for applying this drug to reduce the length of treatment for COVID-19, and there are still flaws in the information, evidences and experiments [71]. Hydroxychloroquine is widely available to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. However, they are...
not suitable for patients with diabetes, high blood pressure and heart problems. The usage of hydroxychloroquine is less toxic than chloroquine, but sustained application of hydroxychloroquine can cause poisoning [4,5]. Wang et al. [71] evaluated the efficacy of hydroxychloroquine for inhibition of SARS-CoV-2 infection in vitro (Figure 7), and suggested this drug as potential candidate for combating this viral disease, but it should be confirmed by clinical trials. They treated Vero E6 cells with hydroxychloroquine and chloroquine (50 \mu M) for one hour, followed by virus binding (multiplicities of infection (MOI) = 10) at 4°C for one hour. After that, the unbound virions have been isolated, and the cells were additional supplemented with fresh drug-containing medium at 37°C for 90 minutes before being fixed and stained with immunofluorescence analysis (IFA) by applying anti-NP antibody for virions (red) and antibodies against early endosome antigen 1 (EEA1) for early endosomes (EEs) (green) or LAMP1 for endolysosomes (ELs) (green) (Figure 7) [71].

**Natural inhibitors**

The latest research results indicate that garlic essential oil may be a valuable natural antiviral drug. Although more research is needed, it can provide a preventive effect for coronavirus attacks on the human body [72]. Molecular docking methods have confirmed the inhibitory effect of organic sulphur compounds present in garlic essential oil on the human host receptor ACE2 protein. The 17 organosulfur compounds containing 99.4% constituents of garlic essential oil have significant interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV-2. Allyl disulphide and allyl trisulphide, the main components in garlic essential oil, showed significant anti-coronavirus effects (51.3%). The docking assessment indicated that there was a synergistic effect between these seventeen components, which has a good inhibitory effect on PDB6LU7 and ACE2 proteins [72]. Additionally, glycyrrhizin can downregulate the pro-inflammatory cytokines, combine with ACE2, block the intracellular reactive oxygen species (ROS) accumulation, inhibit thrombin, provoke the endogenous IFNs and obstruct the extra formation of airway secretions. This triterpene saponin can be considered as a potential candidate against COVID-19 [73]; though, clinical assessments and analytical studies should be carefully planned.

Andrographolide compound from *Andrographis paniculata* was screened as a potential inhibitor of SARS-CoV-2 M\textsuperscript{pro} through *in silico* evaluations, including target analysis, toxicity prediction, molecular docking, and ADMET prediction (absorption, distribution, metabolism, excretion and toxicity prediction). It was revealed that this molecule had good pharmacodynamics properties, target accuracy, and solubility [74]. Additionally, active hexose correlated compound (AHCC) is \(\alpha\)-glucan-based standardised mushroom extract which was mostly analysed as an immunostimulant for herpes, West Nile, hepatitis C, flu, avian flu, papillomavirus, hepatitis B and HIV by improving a controlled and defensive
immune response [75]. AHCC can be evaluated for its possible therapeutic role in patients infected with SARS-CoV-2; the activity of AHCC for improving a defensive reaction to a wide scope of viral infections can bolster its utilisation against COVID-19 [75]. By evaluation of Moroccan medicinal plants and using molecular docking to uncover the interaction between the molecules analysed and the receptor of COVID-19, Aanouz et al., [76] proposed three molecules including crocin, digitoxigenin, and β-Eudesmol as potential inhibitors against the coronavirus based on the energy types of interaction between these molecules and evaluated protein. In another study, the results of virtual screening of ten Aloe vera compounds based on the docking scores, hydrogen bonding interactions and the Lipinski’s rule of five proposed that three molecules were potential inhibitors of the protease 3CL\textsuperscript{Pro}, an enzyme that plays a key role in post-translational protein regulation, particularly the cleavage of viral polyprotein into functional protein units [77]. Additionally, it was revealed that the nine phytochemicals (such as Tenufolin and Pavetannin C1) of Cinnamon were against the main protease enzyme of SARS-CoV-2, and thus can be further evaluated against COVID-19 [78]. Interestingly, after analysis of microbial natural products, several compounds were proposed to possess remarkable potentials as anti-SARS-CoV-2 candidates (Figure 8) [79].

Alkaloids from Cryptolepis sanguinolenta have been investigated for their ability to inhibit two of the main proteins in SARS-CoV-2, the main protease and the RNA-dependent RNA polymerase, using in silico techniques [76]. Molecular docking was employed for assessment of the binding potential of alkaloids to the viral proteins whereas molecular dynamics was employed for evaluation of the stability of binding event. It was indicated that all 13 alkaloids could bind strongly to the main protease and RNA-dependent RNA polymerase; particularly, cryptomisrine, cryptospirolepine, cryptoquindoline, and biscryptolepine exhibited significant inhibitory potentials towards both proteins [76]. In another study, the antiviral activity of some flavonoids against was evaluated against SARS-CoV 3CL\textsuperscript{Pro} [80]. As a result, herbacetin, rhoifolin and pectolidin-narin were detected to successfully block the enzymatic activity of SARS-CoV 3CL\textsuperscript{Pro}, and can be suggested for designing functionally improved inhibitors. An induced-fit docking evaluation showed that S1, S2 and S3’ sites were involved in binding with these flavonoids [80].

Lianhuaqingwen with broad-spectrum antiviral effects pathogenic viruses and immune regulatory effects can be considered as a potential natural candidate against SARS-CoV-2 [81]. The antiviral activity of lianhuaqingwen against SARS-CoV-2 was evaluated in Vero E6 cells using microscopic cytopathic effect (CPE) and plaque reduction assay. Interestingly, the influence of lianhuaqingwen on virion morphology was visualised under transmission electron microscope (TEM) (Figure 9). It was demonstrated that lianhuaqingwen remarkably inhibited SARS-CoV-2 replication in Vero E6 cells and evidently decreased the pro-inflammatory cytokines (TNF-\textgreek{a}, IL-6, CCL-2/MCP-1 and CXCL-10/IP-10) formation at the mRNA levels; additionally, lianhuaqingwen treatment could result in abnormal particle morphology of virion in cells. This strategy can be employed against SARS-CoV-2, by inhibiting the viral replication, affecting the virus morphology and producing anti-inflammatory effects, in vitro [81].

\textbf{Nanomaterials against SARS-CoV-2}

Indeed, nanomaterials and nanotechnology-based approaches can be employed to combat against COVID-19 and other future viral infectious diseases [82]. Nano-based approaches can help in this new pandemic by designing innovative drugs (especially antivirals for targeted therapy/drug delivery and inactivation of SARS-CoV-2) and vaccines. In this regard, the detection of pathogenic viruses with highly sensitive and selective evaluation techniques and the production of superfine filters (especially for face masks or blood filtering) and innovative surface coatings or surfaces (for inactivation and capture of viruses or resistant to viral adhesion) are important field of research. As an example, two-dimensional carbides and nitrides, MXenes, which are specifically suitable for developing coatings can be employed for inactivating and capturing viruses, and also can be applied on face masks and other personal protective equipment (Figure 10) [82,83]. Balagna et al. [84] reported the antiviral performance of silver nanocluster/silica composite (less than 200 nm) sputtered coating, which specifically has been utilised on FFP3 masks against SARS-CoV-2. Consequently,
this coating can be utilised to reduce the titre of the virus to zero, but it appears that more evaluations regarding the toxicity issues and efficacy are still needed [84].

Interestingly, quantum dots (QDs) can be employed as potential candidates for targeting and inhibiting SARS-CoV-2 (60–140 nm) [85–87]. Indeed, the positive surface charge of carbon-based QDs could be applied to disable or sequester the S protein of SARS-CoV-2 [88]. Additionally, cationic surface charges showed by QDs can interact with the negative RNA strand of SARS-CoV-2, making the formation of ROS within this pathogenic virus [89]. Furthermore, nanomaterials for imaging and biosensing purposes (as imaging probes) are introduced in prognosis/diagnosis procedures; notably, therapeutic molecules can be employed for surface functionalization and/or coating of nanomaterials and nanostructures for improving the drug release profiles or developing the targeted drug delivery systems against SARS-CoV-2 [87]. For instance, nanoparticle targeting of autophagy at the sites of interest should be studied by researchers for combating against COVID-19 without common adverse side effects occurred by off-target accumulation and release [90]. Importantly, multidrug nanoparticles with remarkable biocompatibility and drug loading properties should be studied for the mitigation of uncontrolled inflammation, especially for COVID-19. As an example, the selective delivery of adenosine and antioxidants together can serve as promising approach for acute inflammation treatment with low-side effects and remarkable therapeutic efficacy, especially for cytokine storm caused by COVID-19 [91].

**Conclusion**

Currently, there are no officially licenced or approved targeted therapeutic agents for treating the viral infection caused by SARS-CoV-2, or drugs against this virus. The effective treatment strategies are still very limited and the current standard of care is supportive treatment. Ideal antiviral drugs should target essential proteins involved in the SARS-CoV life cycle. At present, antiviral drugs (such as remdesivir, favipiravir and lopinavir/ritonavir) have been proposed for the treatment of COVID-19, but their effectiveness has not been fully proven, and also toxicity issues should be evaluated and addressed systematically and comprehensively. Small-molecule compounds approved for other human ailments may control the virus-host interaction of new CoVs, but much more scientific effort is needed to introduce certain anti-CoV agents for prophylactic and therapeutic procedures, and related molecular mechanisms regarding viral infections.

Drug candidates are mostly focussed on main protease inhibitors, ACE2 inhibitors, viral RNA polymerase, and potential drug candidates to obstruct the trimerization of SARS-CoV-2 spike glycoprotein. Additionally, the combinational therapy may needed and have profound efficacy against SARS-CoV-2. Currently, scientists and researchers try to find the potential drug targets and related mechanistic aspects, which can help in the development of innovative therapeutics for this infectious virus; several preclinical investigations have suggested different FDA-approved drugs for clinical trials, and importantly the administration of these drugs can be related to severe adverse side effects due to their off-target accumulation and release. In this regard, innovative targeted drug delivery systems (multifunctionalization for specific tissue/organ targeting), nano-based structures, metal-grafted graphene oxide, nanocomposites, nano-phytotherapeutics, biodegradable nanocarriers, carbon nanotubes, and multidrug nanoparticles can help the fight against SARS-CoV-2 and other pathogenic viruses, but it appears that more elaborative academic studies are still needed, and there is an urgent need to find new targets for developing anti-SARS-CoV-2 agents. Some critical future perspectives should be noted:

1. The identification of innovative formulations with antiviral activity and new delivery systems with enhanced efficacy and low toxicity.
2. Further research on antiviral agents and drugs to find the relationship between the structure and related bioactivities.
3. Understanding the effect and mechanism implicated in antiviral effects of the identified compounds, and more academic studies on cytotoxicity, safety and biocompatibility of them. Notably, the structure-activity relationship analyses and mechanisms involved in anti-CoVs activity of these identified compounds can provide insights on future research direction;
clinical trials regarding the application of potential antiviral agents against SARS-CoV-2 should be comprehensively performed. Additionally, modern and innovative strategies and technologies for effective extraction/isolation of the active ingredients from natural resources against SARS-CoV-2 should be noted.

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References
[1] Florindo HF, Kleiner R, Vaskovich-Koubi D, et al. Immune-mediated approaches against COVID-19. Nat Nanotechnol. 2020;15(8):630–645.
[2] Ali I, Alharbi OML. COVID-19: disease, management, treatment, and social impact. Sci Total Environ. 2020;728:138861.
[3] Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273.
[4] Jamalipour Soufi G, Hekmatnia A, Nasrollahzadeh M, et al. SARS-CoV-2 (COVID-19): new discoveries and current challenges. Applied Sciences. 2020;10(10):3641.
[5] Nasrollahzadeh M, Sajjadi M, Jamalipour Soufi G, et al. Nanomaterials and nanotechnology-associated innovations against viral infections with a focus on Coronavirus. Nanomaterials. 2020;10(6):1072.
[6] Caron J, Reddy LH, Lepèbre-Mouelhi S, et al. Squalenoyl nucleoside monophosphate nanoscale assemblies: new produg strategy for the delivery of nucleotide analogues. Bioorg Med Chem Lett. 2010;20(9):2761–2764.
[7] Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained lopinavir–combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. Int J Infect Dis. 2020;95:183–191.
[8] Clercq ED. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem Asian J. 2019;14(22):3962–3968.
[9] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–271.
[10] Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30–e31.
[11] Zumla A, Chan JF, Azhar EI, et al. Coronavirus – drug discovery and therapeudic options. Nat Rev Drug Discov. 2016;15(5):327–347.
[12] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–936.
[13] Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787.
[14] Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19(3):149–150.
[15] Kelleni MT. Nitazoxanide/azithromycin combination for COVID-19: a suggested new protocol for early management. Pharmacol Res. 2020;157:104874.
[16] Rossignol J-F. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome Coronavirus. J Infect Public Health. 2016;9(3):227–230.
[17] Haffizulla J, Hartman A, Hoppers M, et al. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. Lancet Infect Dis. 2014;14(7):609–618.
[18] Uno Y. Camostat mesilate therapy for COVID-19. Intern Emerg Med. 2020;15(8):1572–1577.
[19] Zhou Y, Vedantham P, Lu K, et al. Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res. 2015;116:76–84.
[20] Shamsi A, Mohammad T, Anwar S, et al. Glecaprevir and Maraviroc are high-affinity inhibitors of SARS-CoV-2 main protease: possible implication in COVID-19 therapy. Biosci Rep. 2020;40:BSR20201256.
[21] Chau T-N, Lee K-C, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology. 2004;39(2):302–310.
[22] Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787–1799.
[23] Coleman CM, Sisk JM, Mingo RM, et al. Abelson kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and middle east respiratory syndrome coronavirus fusion. J Virol. 2016;90(19):8924–8933.
[24] Al Ghamdi M, Alghamdi KM, Ghoora Y, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. BMC Infect Dis. 2016;16:174–177.
[25] Chan JF-W, Yao Y, Yeung M-L, et al. Treatment with lopinavir–ritonavir or interferon–β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis. 2015;212(12):1904–1913.
[26] Hung IF-N, Lung K-C, Tso EY-K, et al. Triple combination of interferon beta-1a, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1913–1919.
[27] Zhang H, Penninger JM, Li Y, et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46(4):586–590.
[28] Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother. 2020;64(5):e00399-20.
[29] Khan SA, Zia K, Ashraf S, et al. Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach. J Biomol Struct Dyn. 2020;1–10.
Thoms M, Buschauer R, Ameismeier M, et al. Structural Ruan Z, Liu C, Guo Y, et al. SARS-CoV-2 and SARS-CoV: viral Tal- AT, Gentile F, Hsing M, et al. Rapid identification of potential SARS-CoV-2 main protease by deep docking of 1.3 Billion compounds. Mol Inform. 2020;39:1–7. Tu Y-F, Chien C-S, Yarmishyn AA, et al. A review of SARS-CoV-2 and the ongoing clinical trials. Int J Mol Sci. 2020;21(7):2657. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat. Commun. 2020;11(1):222. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science. 2020;368(6489):409–412. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2): 271–280.e8. Zang R, Castro MFG, McCune BT, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol. 2020;5(47):eabc3582. Hoffmann M, Schroeder S, Kleine-Weber H, et al. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrob Agents Chemother. 2020;64(6):e00754–00720. Yamamoto M, Matsuyama S, Li X, et al. Identification of nafamostat as a potent inhibitor of Middle East respiratory syndrome coronavirus S protein-mediated membrane fusion using the split-protein-based cell-cell fusion assay. Antimicrob Agents Chemother. 2016;60(11):6532–6539. Das S, Samrah S, Lyndem S, et al. An investigation into the identification of potential inhibitors of SARS-CoV-2 main protease using molecular docking study. J Biomol Struct Dyn. 2020;1–11. Dai W, Zhang B, Su H, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science. 2020;368(6497):eabb4489. Gentile D, Patamia V, Scala A, et al. Putative inhibitors of SARS-CoV-2 main protease from a library of marine natural products: a virtual screening and molecular modeling study. Mar Drugs. 2020;18(4):225. Liu X, Wang X-J. Potential inhibitors against 2019-nCoV Coronavirus M protease from clinically approved medicines. J Genet Genomics. 2020;47(2):119–121. Jin Z, Du X, Xu Y, et al. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature. 2020;582(7811):289–293. Lang P, Tian S-H, Meng Z-H, et al. Anti-HIV drug repurposing against SARS-CoV-2. RSC Adv. 2020;10(27):15775–15783. Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020;181(4):905–913. Peng Q, Peng R, Yuan B, et al. Structural and biochemical characterization of the nsp12-nsp7-nsp8 core polymerase complex from SARS-CoV-2. Cell Rep. 2020;31(11):107774. Ruan Z, Liu C, Guo Y, et al. SARS-CoV-2 and SARS-CoV: virtual screening of potential inhibitors targeting RNA-dependent RNA polymerase activity (NSP12). J Med Virol. 2020. DOI:10.1002/jmv.26222. Thoms M, Buschauer R, Ameismeier M, et al. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. Science. 2020;369: eabc8665. Sallard E, Lescure F-X, Yazdanpanah Y, et al. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020;178:104791. Felgenhauer U, Schoen A, Gad HH, et al. Inhibition of SARS-CoV-2 by type I and type III interferons. J Biol Chem. 2020;295(41):13958–13964. Mantlo E, Bukreyeva N, Maruyama J, et al. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Res. 2020;179:104811. Lei X, Dong X, Ma R, et al. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat Commun. 2020;11(1):3810. Xia S, Liu M, Wang C, et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res. 2020;30(4):343–355. Xia S, Yan L, Xu W, et al. A pan-coronavirus fusion inhibitor targeting the N1R1 domain of human coronavirus spike. Sci Adv. 2019;5(4):eaav4580. Choy K-T, Wong AY-L, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication In vitro. Antiviral Res. 2020;178:104786. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–1578. Yin W, Mao C, Luan X, et al. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by Remdesivir. Science. 2020;368(6498):1499–1504. Pruijssers AJ, George AS, Schäfer A, et al. Remdesivir potently inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. Cell Rep. 2020;32(3):107940. Vankadari N. Arbidol: a potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. Int J Antimicrob Agents. 2020;56(2):105998. Wang X, Cao R, Zhang H, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discov. 2020:6:28. Coomeds EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? J Antimicrob Chemother. 2020;dkaa171. Cai Q, Yang M, Liu D, et al. Experimental treatment with Favipiravir for COVID-19: an open-label control study. Engineering. 2020. Sofic L, Brillet R, Berry F, et al. Inhibition of SARS-CoV-2 Infection by the Cyclphilin Inhibitor Alisporivir (Debio 025). Antimicrob Agents Chemother. 2020;64(7): AAC.00876–00820. Pawlotsky J-M. COVID-19 pandemic: time to revive the cyclophilin inhibitor alisporivir (Debio 025). Antimicrob Agents Chemother. 2020;64(7): AAC.00876–00820. Coperchini F, Chiovato L, Croce L, et al. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25–32. Zhang X, Zhang Y, Qiao W, et al. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol. 2020;86:106749. Cantini F, Niccoli L, Matrarrese D, et al. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. J Infect. 2020;81(2):318–356.
Favalli EG, Biggioggero M, Maioli G, et al. Baricitinib for COVID-19: a suitable treatment? Lancet Infect Dis. 2020; 20(9):1012–1013.

Ma C, Sacco MD, Hurst B, et al. Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. Cell Res. 2020;30(8): 678–692.

Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

Thuy BTP, My TTA, Hai NTT, et al. Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. ACS Omega. 2020;5(14):8312–8320. https://dx.doi.org/10.1021/acsomega.0c00772.

Luo P, Liu D, Li J. Pharmacologic perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. Int J Antimicrob Agents. 2020;55(6):105995.

Enmozi SK, Raja K, Sebastine I, et al. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. J Biomol Struct Dyn. 2020;1–7.

Pierro FD, Bertuccioli A, Cavecchia I. Possible therapeutic role of a highly standardized mixture of active compounds derived from cultured Lentinula edodes mycelia (AHCC) in patients infected with 2019 novel coronavirus. Minerva Gastroenterol Dietol. 2020;66(2):172–176.

Aanouz I, Belhassan A, El-Khatabi K, et al. Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: computational investigations. J Biomol Struct Dyn. 2020;1–9.

Mpiana PT, Ngbolua K-t-N, Tshibangu DST, et al. Identification of potential inhibitors of SARS-CoV-2 main protease from Aloe vera compounds: a molecular docking study. Chem Phys Lett. 2020;754:137751.

Prasanth DSNBK, Murahari M, Chandramohan V, et al. In silico identification of potential inhibitors from Cinnamon against main protease and spike glycoprotein of SARS CoV-2. J Biomol Struct Dyn. 2020.

Sayed AM, Alhadrami HA, El-Gendy AO, et al. Microbial natural products as potential inhibitors of SARS-CoV-2 main protease (Mpro). Microorganisms. 2020;8(7):970.