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Review

# Human endeavor for anti-SARS-CoV-2 pharmacotherapy: A major strategy to fight the pandemic

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ABSTRACT

The global spread of COVID-19 constitutes the most dangerous pandemic to emerge during the last one hundred years. About seventy-nine million infections and more than 1.7 million death have been reported to date, along with destruction of the global economy.

With the uncertainty evolved by alarming level of genome mutations, coupled with likelihood of generating only a short lived immune response by the vaccine injections, the identification of antiviral drugs for direct therapy is the need of the hour. Strategies to inhibit virus infection and replication focus on targets such as the spike protein and non-structural proteins including the highly conserved RNA-dependent-RNA-polymerase, nucleotidyl-transferases, main protease and papain-like proteases. There is also an indirect option to target the host cell recognition systems such as angiotensin-converting enzyme 2 (ACE2), transmembrane protease, serine 2, host cell expressed CD147, and the host furin. A drug search strategy consensus in tandem with analysis of currently available information is extremely important for the rapid identification of anti-viral.

An unprecedented display of cooperation among the scientific community regarding SARS-CoV-2 research has resulted in the accumulation of an enormous amount of literature that requires curation. Drug repurposing and drug combinations have drawn tremendous attention for rapid therapeutic application, while high throughput screening and virtual searches support *de novo* drug identification. Here, we examine how certain approved drugs targeting different viruses can play a role in combating this new virus and analyze how they demonstrate efficacy under clinical assessment. Suggestions on repurposing and *de novo* strategies are proposed to facilitate the fight against the COVID-19 pandemic.

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 was reported in December 2019 [1–3]. To date, about seventy-nine million cases of infection by this novel coronavirus have been reported. More than 1.7 million people have died. This new viral disease quickly attained global spread and the number of infected people continues to increase rapidly by confirmed human-to-human transmission [4,5].

Coronaviruses are enveloped RNA viruses with a single-strand, positive-sense RNA genome of approximately 26–32 kilobases in size. Examples include severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) [6]. The latest reports show that SARS-CoV-2 is most closely related to the bat SARS-related coronaviruses found in Chinese horseshoe bats as determined by phylogenetic analysis and next-generation sequencing [4]. SARS-CoV-2 shares 88 % identity with two bat-derived SARS-like coronaviruses

*Abbreviations:* SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome (SARS) coronavirus; MERS, Middle East respiratory syndrome; MERS-CoV, Middle East respiratory syndrome (MERS) coronavirus; FDA, Food and Drug Administration; S, spike; E, envelop; M, membrane; N, nucleocapsid; NiRAN, Nucleotidyl-transferases; nsp, non-structural protein; PLpro, papain-like protease; 3CLpro, 3C-like protease; RdRp, RNA-dependent RNA polymerase; Hel, helicase; HTS, High Through-put Screening; CoVs, coronaviruses; Mpro, main protease; RBM, receptor binding motif; ACE2, Angiotensin-Converting Enzyme 2; EC50, half-maximal effective concentration; CC50, half-cytotoxic concentration; SI, selective index; IC50, half maximal inhibitory concentration; TMPRSS2, the transmembrane protease, serine 2; hrsACE2, human recombinant soluble ACE2; NK, natural killer; TCM, Traditional Chinese medicine; ADME, absorption, distribution, metabolism, and excretion.

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(bat-SL-CoVZC45 and bat-SL-CoVZXC21), approximately 79 % with SARS-CoV and 50 % with MERS-CoV [5]. Homology modeling revealed that SARS-CoV-2 has a similar receptor-binding domain structure to that of SARS-CoV [5,7].

There are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for treatment of COVID-19 [8]. However, more than 3000 studies are under clinical trial investigation [9].

Due to the considerable time required for development and global distribution of a vaccine, and the urgency for direct treatment of infected patients, the design and approval of antiviral drugs remain of critical importance. Moreover, recent report of dangerous spike protein mutations observed in the United Kingdom alarm the need of direct treatment for SARS-CoV-2 [10]. As evidenced during the AZD1222 clinical trial [11], unexpected challenges are inevitable and multiple strategies are necessary to combat this pandemic. Furthermore, reports of reinfection warn the SARS-CoV-2 may continue to circulate among the human populations despite herd immunity due to natural infection or vaccination [12].

Depending on the target, COVID-19 therapy can be divided into two categories: (1) inhibition of the enzymes central to viral replication and infection; (2) modulation of the human immune system or inhibition of the inflammatory processes that cause lung injury.[7] Herein, we discuss the drugs targeting the SARS-CoV-2 virus.

## 1. Therapeutic targets on SARS-CoV-2

The SARS-CoV-2 virus has 5 major protein regions necessary for replication or viral assembly: ORF1ab, spike (S), envelop (E), membrane (M), and nucleocapsid (N) proteins [1]. ORF1ab encodes the non-structural protein (nsp) responsible for viral replication, including the papain-like protease (PLpro), 3C-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp) and helicase (Hel). The S, E, M and N proteins encode the structural proteins of the virus. Rapidly conducted research has resulted in identification of various drug molecules that may inhibit one or more of these critical proteins. The structures of such small molecules formerly and currently under formal investigation against coronaviruses (CoVs) are listed in Fig. 1.

3CLpro, also called the main protease (Mpro), is a cysteine protease involved in precursor polyprotein maturation and cleavage to produce non-structural proteins [13–15]. The highly conserved active site of Mpro comprises 4 sites: S1, S2, S3 and S4 [16]. A combination of computational and experimental approaches has greatly accelerated the hunt for effective drug candidates that inhibit 3CLpro and drug molecules targeting 3CLpro with inhibition in the lower μM range have been reported for SARS-CoV-2 [17,18]. Availability of the crystal structure with the Michael acceptor inhibitor N3 will be of further assistance to improve inhibitor efficiency [18].

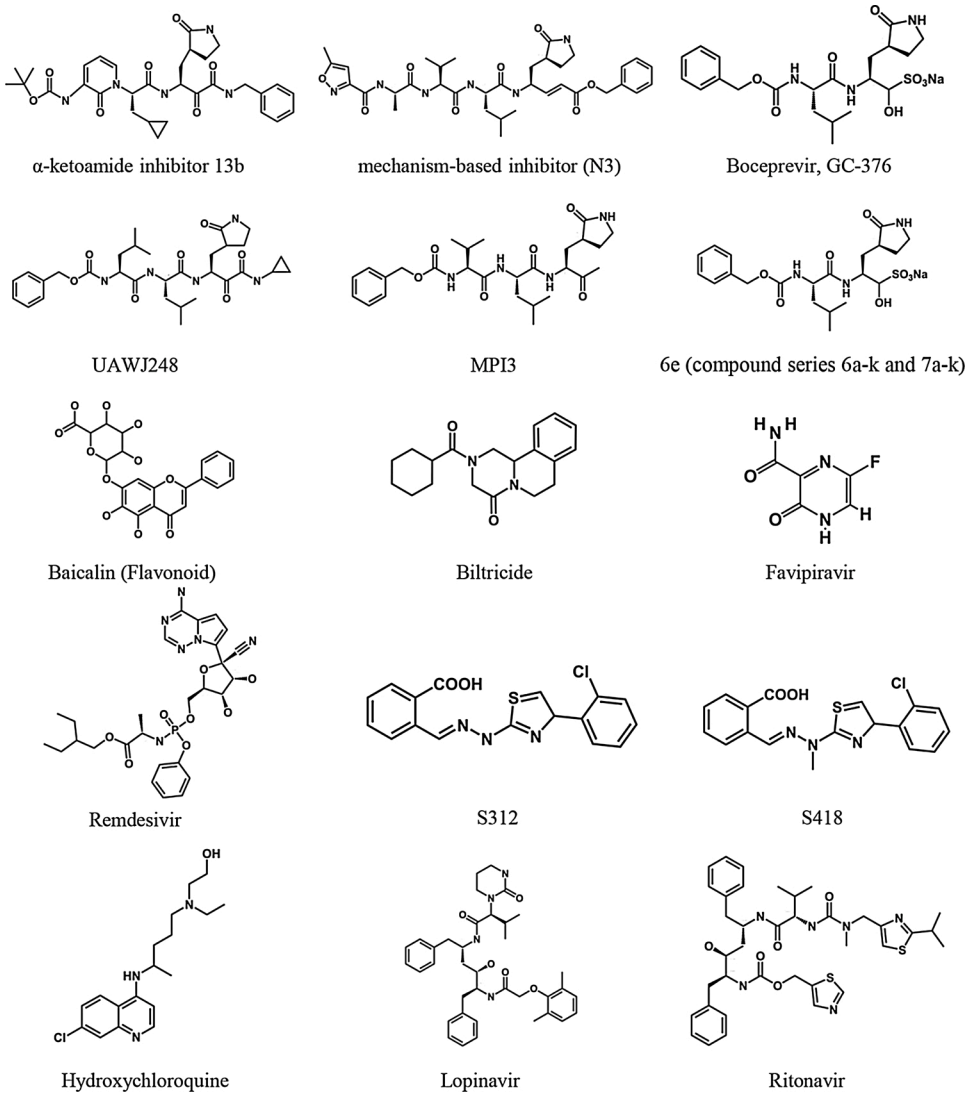


**Fig. 1.** Chemical structures of small-molecules that have shown significant antiviral activity against SARS-CoV2.

**Table 1**
$IC_{50}$ of inhibitors targeting critical CoV proteins.

| Coronavirus | SARS-CoV-1 | | MERS-CoV | | SARS-CoV-2 | |
|---|---|---|---|---|---|---|
| Protein | Inhibitor | $IC_{50}$ | Inhibitor | $IC_{50}$ | Inhibitor | $IC_{50}$ |
| Spike Protein | Peptide (P9) | 1.5 nM [36] | Peptide (P9) | 1.5 nM [36] | Peptide (P8) | 0.8 μM(VeroE6) 0.09 μM(Calu3) [89] |
| | | | m336 scFv-pep | 0.21 ± 0.06 nM [90] | Peptide (P9) | 0.3 μM(VeroE6) 0.07 μM(Calu3) [89] |
| | | | IgG1 m336 | 0.03 nM [90] | Peptide (P10) | 0.06 μM(VeroE6) 0.08 μM(Calu3) [89] |
| | | | MERS-5HB | 1 μM [91] | EK1C4 | 1.3 and 15.8 nM (PDB code 6LXT) [37] |
| 3CL protease | α-ketoamide inhibitor 13b | 0.90 ± 0.29 μM [21] | α-ketoamide inhibitor 13b | 0.58 ± 0.22 μM [21] | α-ketoamide inhibitor 13b | 0.67 ± 0.18 μM (PDB code 6Y2F, 6Y2G) [21] |
| | SARS 3CL protease inhibitors containing an aldehyde at the C terminus | 98 nM (PDB code 3ATW) [92] | | | mechanism-based inhibitor (N3) | 0.67 to 21.4 μM (PDB code 6LU7, 7BQY) [18] |
| | Herbacetin, Rhoifolin, Pectolinarin | 33.17 μM, 27.45 μM, 37.78 μM [93] | | | Boceprevir, GC-376 | 0.03 μM (PDB code 6WTT) [94] |
| | Phenylisoserine SK80 | 43 μM [95] | | | UAWJ248 | 12 nM(PDB code 6XBI) [96] |
| | 40 novel unsymmetrical aromatic disulfides | 0.516−5.954μM [97] | | | MPI3 | 8.5 nM [98] |
| | Chalcones Isolated from Angelica Keiskei | 11.4 μM [99] | | | compound series 6a-k and 7a-k | 0.17−0.82 nM [100] |
| | | | | | Flavonoid | 34.71, 53.90 and 51.64 μM [101] |
| papain-like protease | Chalcones Isolated from Angelica Keiskei | 1.2 μM [99] | 6-Mercaptopurine (6 M P) | 26.9 ± 7.5 μM [102] | Biltricide | Binding Affinity 8 nM-8 μM [103] |
| | tanshinone I | 0.7 μM [104] | 6-Thioguanine (6 TG) | 24.4 ± 4.3 μM [102] | | |
| | The isolated diarylheptanoids, hirsutenone | 4.1 μM [105] | | | | |
| | Geranylated Flavonoids tomentin A to E | 5−14.4 μM [106] | | | | |
| | No.2/No.49 | 0.46 μM/1.3 μM [107] | | | | |
| | (S)-Me inhibitor 15 h/ (R)-Me 15g | 0.56 μM/0.32 μM (PDB code 3MJ5) [108] | | | | |
| | 15 g/3k/3 j/3e/5c | 0.67 μM/ 0.15 μM/ 0.49 μM / 0.39 μM / 0.35 μM (PDB code 4OW0, 4OVZ) [109] | | | | |
| | Disulfiram with 6 TG (15 μM) with NEM (4 μM) with βME (5 mM) | 14.2 ± 0. 5μM 21.8 ± 1.0 μM | Disulfiram with 6 TG (15 μM) with MPA (150 μM) | 22.7 ± 0.5 μM 14.5 ± 0.4 μM 21.7 ± 0.4 μM | | |
| | | 18.1 ± 0.7 μM | with 6 TG (10 μM) and MPA (100 μM) | 13.7 ± 1.0 μM | | |
| | | >300 μM (PDB code 5Y3Q, 5Y3E) [110] | with 6 TG (15 μM) and MPA (150 μM) with βME (5 mM) | 4.4 ± 0.2 μM >300 μM [110] | | |
| RdRp | Favipiravir | | | | Favipiravir | 61.9 μM ($EC_{50}$) [61] |
| | Remdesivir (GS-5734) | 0.069 ± 0.036 μM [45] | Remdesivir (GS-5734) | 0.12 μM ($EC_{50}$) [47] 0.074 ± 0.023 μM ($EC_{50}$) [45] | Remdesivir (GS-5734) | 0.77 μM ($EC_{50}$); > 100 μM($CC_{50}$); SI > 129.87 [46] |
| helicase | Acyclovir fleximer analogues (Compound 2) | <10 μM ($EC_{50}$), > 100 μM [111] ($CC_{50}$) | | | | |
| | 7-ethyl-8-mercapto-3-methyl-3,7-dihydro-1H-purine-2,6-dione | 8.66 ± 0.26 μM and 41.6 ± 2.3 μM [112] | | | | |
| | 2,6-Bis-arylmethyloxy-5-hydroxychromones | 4 μM [113] | | | | |
| | SSYA10−001 | 5.7 μM [114] | | | | |
| | (E)-3-(furan-2-yl)-N-(4-sulfamoylphenyl) acrylamide | 2.09 ± 0.30 μM and 13.2 ± 0.9 μM [115] | | | | |
| DHODH | | | | | S312 | 29.2 nM [116] |
| | | | | | S416 | 7.5 nM [116] |

Nucleotidyl-transferases (NiRAN) have been confirmed as essential for replication of SARS-CoV and other nidoviruses and are involved in nucleic acid ligation, mRNA capping, and protein-primed RNA synthesis [7]. The NiRAN sequence of SARS-CoV-2 shares 93.2 % identity with SARS-CoV [7]. The potential for developing SARS-CoV-2 NiRAN inhibitors merits further investigation.

The SARS-CoV-2 viral genome encodes more than 20 proteins, among which are 3CLpro and PLpro (papain-like protease) that are vital to virus replication [19–23]. A recent sequence alignment study revealed that SARS-CoV-2 3CLpro clusters with SARS-CoV (96.08 %

**Table 2**
Completed clinical trials registered under United States National Library of Medicine clinical trials registry addressing the safety and efficacy of remdesivir (GS-5734™) and favipiravir as a potential therapeutic option for COVID.

| Clinical trial number | Study design | Estimated enrollment | Phase | Conditions | Intervention/ Treatment | Start Date | Completion Date |
|---|---|---|---|---|---|---|---|
| NCT04280705 | Adaptive, Randomized, Double-blind, Placebo-controlled | 1062 participants | 3 | COVID-19 | Drug: Remdesivir<br>Other: Placebo | February 21, 2020 | May 21, 2020 |
| NCT04292730 | Randomized, Parallel Assignment, Open Label | 1113 participants | 3 | COVID-19 | Drug: Remdesivir<br>Drug: Standard of Care | March 15, 2020 | June 26, 2020 |
| NCT04492501 | Non-Randomized | 600 participants | Not Applicable | COVID-19<br>Cytokine Release Syndrome Critical Illness ARDS | Procedure: Therapeutic Plasma exchange<br>Biological: Convalescent Plasma<br>Drug: Tocilizumab<br>Drug: Remdesivir<br>Biological: Mesenchymal stem cell therapy | April 1, 2020 | July 20, 2020 |
| NCT04292899 | Randomized, Parallel Assignment, Open Label | 4891 participants | 3 | COVID-19 | Drug: Remdesivir<br>Drug: Standard of Care | March 6, 2020 | June 30, 2020 |
| NCT04349241 | Randomized, Parallel Assignment, Open Label | 100 participants | 3 | COVID-19 | Drug: Favipiravir<br>Drug: Standard of care therapy | April 18, 2020 | June 20, 2020 |
| NCT04376814 | Non-Randomized, Parallel Assignment, Open Label | 40 participants | Not Applicable | COVID-19 | Drug: Favipiravir<br>Drug: Hydroxychloroquine<br>Drug: Lopinavir / Ritonavir | March 29, 2020 | May 25, 2020 |
| NCT04645433 | Observational Cohort, Retrospective | 100 participants | Not Applicable | COVID-19 | Favipiravir therapy<br>Lopinavir-ritonavir therapy | March 15, 2020 | May 15, 2020 |
| NCT04542694 | Randomized, Parallel Assignment, Open Label | 200 participants | 3 | COVID-19 | Drug: Favipiravir<br>Drug: Standard of care | May 21, 2020 | August 10, 2020 |

sequence identity) and MERS-CoV (87.00 % sequence identity) [23]. As determined by crystal structure, SARS-CoV-2 3CLpro also has a highly similar (96 % identity) ortholog in SARS-CoV [21]. SARS-CoV-2 PLpro shares 80 % sequence identity with that of SARS-CoV and 29 % with MERS-CoV [24].

The spike (S) protein mediates entry of the viral genome into human cells. The S-protein is the target of most vaccine strategies and antibody-based therapeutics [7,25]. The sequence of SARS-CoV-2 S-protein (1273 a.a.s) was aligned with those from other strains of human coronaviruses. Sequence alignments and comparisons indicated that SARS-CoV-2 spike shares 77.38 % sequence identity with SARS-CoV and 31.93 % with MERS-CoV [7]. The mutated spike D614 G of SARS-CoV-2 is particularly concerning; it was not observed in early samples submitted from China in January 2020, but has made a gradual global appearance since March 2020 [26,27]. The D614 G variant is associated with enhanced viral transmission [27]. SARS-CoV-2 VOC 202012/01, a mutant strain of SARS-CoV-2 reported in United Kingdom and South Africa is evolved to become 70 % more contagious due to it's N501Y mutation on spike protein that helps it to bind more tightly to human ACE2 (Angiotensin-Converting Enzyme 2) [10,28,29]. A mouse adapted strain with the same mutation generated in laboratory setting was reported in an earlier study [30].

The U.S. National Library of Medicine approved the world's first human safety trial with monoclonal antibody LY3819253 against COVID-19 in May 2020 [31]. The LY3819253 antibody binds to the S-protein of COVID-19 and was discovered by the pharma giant Eli Lilly [32]. A genetically engineered cocktail of mouse and human antibodies, REGN-COV2, that binds non-competitively to the S-protein is now under phase 3 clinical trial evaluation [33,34]. More recent research also demonstrates binding of this cocktail to the now prevalent D614 G variant [35].

Inhibition of the S-protein can primarily be achieved by inhibiting the receptor binding motif (RBM): such an inhibitor should have the ability to act as an interface inhibitor. There is no significant report of a small molecule that efficiently blocks the large surface involved in a protein–protein interface. However, peptide inhibitors such as lipopeptides derived from EK1 have shown inhibition of protein-mediated membrane fusion and pseudovirus infection with $IC_{50}$s of 1.3 and 15.8 nM [36,37].

APN01, a recombinant form of human ACE2 has been shown to effectively weaken the ability of SARS-CoV-2 to infect cells during the early stage of SARS-CoV-2 infection and to reduce lung injury. This peptide molecule is under a Phase II clinical trial evaluation that is expected to recruit 200 severely infected COVID-19 patients [38].

RNA-dependent RNA polymerase is the key component in SARS-CoV-2 virus replication [7,39,40]. It is a potential target for anti-SARS drugs as inhibition of this enzyme will hinder virus replication in the host [41]. Sequence alignments and comparisons indicate that SARS-CoV-2 RdRp shares a high sequence identity with SARS-CoV RdRp (98.13 %) and MERS-CoV RdRp (75.51 %) [7].

The COVID-19 pandemic has prompted a rapid effort by scientists and medical doctors to repurpose approved drugs for *off-label* use. Such drugs are primarily antivirals, whose existing detailed pharmacological and toxicological information may permit rapid clinical trials [7,42–44].

## 2. Representative repurposed drugs

Remdesivir (**GS-5734**) is a good example of anti-viral drug repurposing. It was initially developed to treat filoviruses causing Ebola disease and has proven safe in the two most recent Ebola epidemics. Remdesivir was also shown to be effective against both SARS-CoV and MERS-CoV in animal models [42].

Remdesivir is a novel nucleotide analogue prodrug under evaluation for the treatment of SARS-CoV-2. It acts as an RdRp inhibitor against a wide array of RNA viruses [45–47]. Its activity has been demonstrated against zoonotic coronaviruses SARS-CoV and MERS-CoV with a demonstrated half-maximal effective concentration ($EC_{50}$) value of 0.07 μM [46–48]. Crystal structures of RdRp from different viruses in complex with remdesivir have revealed key aspects of the structure–function of RdRps and confirmed that RdRps from coronaviruses or other viruses share a common architecture and mechanism for polymerase catalysis [49,50]. Intermolecular interaction among remdesivir, RNA and RNA-dependent RNA polymerase analyzed by Kato et al. [51] using fragment molecular orbital calculation is plotted on to the crystal

structure of the RdRp: RNA: remdesivir complex shown in Fig. 1. An understanding of such detailed interactions will accelerate the hunt for better drug candidates. As there are no RdRp homologs in humans, their inhibition is not expected to cause undesirable side effects during therapy [52]. Remdesivir showed an $EC_{50}$ of 0.77 μM for SARS-CoV-2. This was approximately 10 times weaker than for SARS-CoV and MERS-CoV, but still demonstrated significant affinity to inhibit SARS-CoV-2 RdRp. The half-cytotoxic concentration ($CC_{50}$) was higher than 100 μM and the selective index (SI) was greater than 129.87. This RdRp inhibitor of SARS-CoV-2 warrants urgent investigation (Table 1).

Remdesivir has shown significant inhibition of human and zoonotic coronaviruses *in vitro* and in a murine model of SARS-CoV [45]. Remdesivir use has been documented in the treatment of MERS-CoV infections *in vivo* [47]. In *in vitro* tests, remdesivir is recognized as highly effective against SARS-CoV-2 infection [3,46]. The first case of COVID-19 in the United States was treated with intravenous remdesivir initiated on the evening of day 7 of the illness promoting a successful outcome [53].

To date, remdesivir has been administered to hundreds of patients with severe SARS-CoV-2 infections in the United States, Europe, and Japan [54]. The clinical trial "A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults" showed that it had a significant effect on 1062 patients with advanced COVID-19 (Table 2). Preliminary results indicate that patients who received remdesivir treatment had a 31 % faster time to recovery compared with the placebo control group and a lower rate of respiratory tract infection [55]. Preliminary results were obtained from 538 patients assigned to remdesivir and 521 patients who received the placebo. The remdesivir group had a median recovery time of 11 days, compared with 15 days for the placebo group [56]. The Kaplan–Meier estimates of mortality by 14 days were 7.1 % (remdesivir group) and 11.9 % (placebo group) [56]. Serious adverse events were reported for 114 of the 541 patients in the remdesivir group and 141 of the 521 patients in the placebo group [56]. The final report of this trial was published in November 2020 and results showed that remdesivir was superior to placebo in shortening the time to recovery and lowering respiratory tract infection in COVID-19 patients [57].

Clinical trial data for remdesivir in patients under 18 years of age is expected to be available by February 2021.

Favipiravir is another well-known RdRp inhibitor originally developed against influenza and approved in Japan in 2014. It has also undergone study for drug repurposing [58]. Favipiravir has a half maximal inhibitory concentration ($IC_{50}$) value of 0.314 μM for influenza, and 67 μM for Ebola [59,60]. More recently, an $EC_{50}$ of 61.9 μM, $CC_{50} >$ 400 μM, and SI > 6.46 were demonstrated for SARS-CoV-2 [61]. The low inhibitory efficacy of favipiravir for other viruses may be indicative of the larger RdRp structural difference between influenza and other viruses. For example, the marked difference between favipiravir $IC_{50}$ for influenza and SARS-CoV-2 is in agreement with their different virus families, and the considerable genomic differences between these two viral RdRps [62]. The clinical trials ChiCTR2000029600 and ChiCTR200030254 evaluated the safety and efficacy of favipiravir for the treatment of COVID-19 [58,63]. The results from both trials support the potential of favipiravir repurposing for the treatment of this disease. Results from the ChiCTR2000029600 trial showed that the 35 patients who received favipiravir demonstrated a significantly shorter viral clearance time compared with the 45 patients of the control group (median 4 days *vs*. 11 days, respectively) [31]. X-ray examinations confirmed a higher rate of improvement in chest imaging for the favipiravir-treated group (91.43 % *vs*. 62 %)[31].

An additional two favipiravir clinical trials registered under the United States National Library of Medicine clinical trials registry have been completed (Table 2). Several favipiravir phase III clinical trials are ongoing with results expected in December 2020 [64].

Both remdesivir and favipiravir have assisted in reducing the mortality rate associated with COVID-19. However, as evident from their $EC_{50}$ values, optimization of these molecules to specifically bind to the RdRp of SARS-CoV-2 will significantly improve their potential as inhibitors of this virus. It should be remembered that neither molecule was initially developed to target SARS-CoV-2.

## 3. Drug targeting the host system

The interaction between the S-protein and human ACE2 is the major entry route of SARS-CoV-2 to human lungs. Furthermore, protein priming of the S-protein by the transmembrane protease, serine 2 (TMPRSS2) is a crucial factor in virus entry [65]. A recent mass spectroscopy-based measurement of protein–protein interaction studies has revealed 332 interactions between SARS-CoV-2 and human proteins [66]. Furthermore, sixty-nine existing drugs known to target host proteins that interact with SARS-CoV-2 were identified. Interface inhibitors for several of the interacting host proteins are underway. Angiotensin-converting enzyme 2 is the host cell receptor responsible for cellular entry of SARS-CoV-2. As such it is the prime target for most host-based drug target studies. On the other hand, results from a recent study have proposed that induction of the downstream pathway of ACE2, by activating the ACE2/Ang1-7/MAS axis will prevent the lung and cardiovascular damage initiated by SARS-CoV-2 [67]. Dr. Josef M Penninger's team reported the first course of treatment with hrsACE2 (human recombinant soluble ACE2 [APN01; Apeiron Biologics, Vienna, Austria]) in a patient with severe COVID-19. The virus was shown to rapidly disappear from the patient's serum after intravenous infusion with hrsACE2 [68].

Cleavage of the S1 protein is achieved by acid-dependent proteolysis by one or several host proteases including TMPRSS2. A clinically approved TMPRSS2 inhibitor, Nafamostat mesylate has been proposed as a treatment option [65,69] and is ready for clinical trial evaluation (ClinicalTrials.gov Identifier: NCT04435015). Despite *in vitro* studies showing an $EC_{50}$ of 10 nM it is unclear whether a sufficient ligand concentration can be attained in the lungs to block viral spread. However, administration of Nafamostat mesylate with favipiravir has shown a promising clinical outcome [70]. Inhibition of TMPRSS2 by the serine protease inhibitor Camostat has been demonstrated in an *in vitro* model of SARS-CoV [71]. Camostat significantly reduced SARS-CoV-2 infection of Calu-3 lung cells [65], and has entered into a Phase II clinical trial (MUHC_CAMOSTAT MESILATE (Control #240313)).

A novel route of entry for SARS-CoV-2 into the host *via* spike protein CD147 has been reported [72]. Host-cell-expressed CD147 could bind the spike protein of SARS-CoV-2 and facilitate host cell invasion. Meplazumab, a humanized anti-CD147 antibody has efficiently improved the recovery of patients with SARS-CoV-2 pneumonia. Though a small scale clinical trial has been reported, large scale recruitment is necessary to validate the final outcome [73].

The furin-based polybasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells [74]. While many furin inhibitors have been reported from *in vitro* and *in vivo* studies, most also inhibit other proprotein convertases recognising the same or similar polybasic cleavage sites. Although the host system provides additional routes for drug targeting, increased toxicity is of concern. However, treatment with a more recent drug, RLF-100, that binds to the susceptible type 2 cells in the lungs that are directly attacked by the coronavirus, leads to rapid recovery from respiratory failure and inhibition of coronavirus replication in human lung cells [75].

It is evident that multiple therapeutic strategies are necessary to mitigate the mortality rate and prepare for the potential emergence of drug resistance by the virus. A recent report identified twenty-one clinically-approved drug molecules, including remdesivir, which were confirmed to possess dose/activity relationships, with thirteen of these compounds demonstrating $EC_{50}$ values < 500 nM *in vitro* [43]. These include drugs targeting the virus in addition to the host biological system.

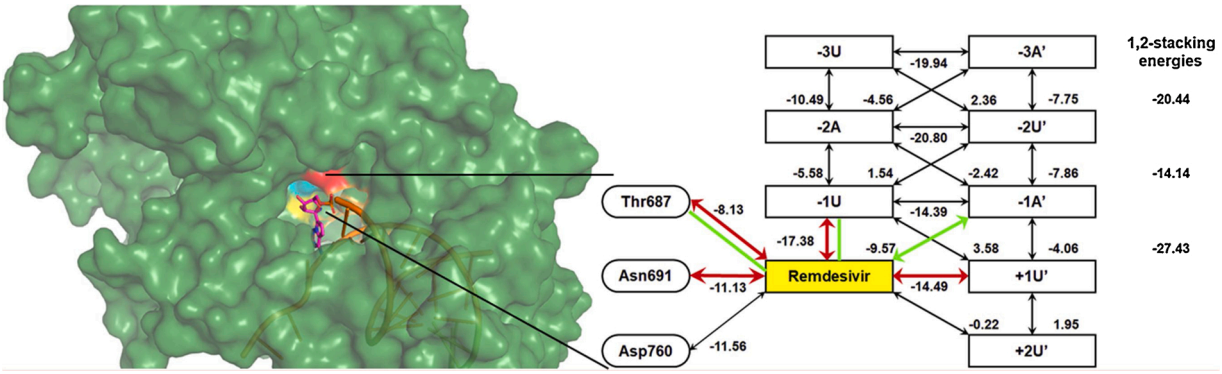


**Fig. 2.** Interactions established by remdesivir on, RdRp based on the remdesivir crystal structure. RdRp is shown as a surface view and colored in green. Remdesivir is shown as a stick model and colored magenta. RNA is shown as a cartoon and colored orange. Thr687 (yellow), Asn691 (cyan), and Asp760 (red) are the amino acids interacting with remdesivir. For clear visibility, 20 % transparency is allowed in the surface view and Lys551 is deleted. Inset figure (right): A diagram of interaction energies between remdesivir, nearby residues, and bases. The square frames represent RNA bases, and the rounded frames signify RdRp residues. The value beside each arrow represents an interaction energy value, with the unit of kcal/mol. The red lines specifically indicate stabilization by hydrogen bonding. The green lines indicate stabilization by π–π stacking interaction between -1U and -1A′ and stabilization by OH/π interaction with Thr687. (For details on the inset figure: see reference [51]) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

## 4. Other treatment options for COVID-19

### 4.1. Natural killer cells

The FDA recently cleared an investigational new drug application for the use of Celularity's drug candidate CYNK-001 in adults with COVID-19. CYNK-001 is an infusion of natural killer (NK) cells, a type of white blood cell that may kill cells infected by the virus and address the resulting inflammation caused by the immune system [76,77]. This trial will include approximately one hundred patients with COVID-19 infection that has resulted in pneumonia and has an estimated primary completion on January 3, 2022.

### 4.2. Treatments combined with traditional oriental medicine

Traditional Oriental medicine, also known as Traditional Chinese medicine (TCM), has been proven to have a compelling beneficial effect in the treatment of SARS [78]. The fatality rate of SARS in Beijing was dramatically reduced from more than 52 % before May 5, to 4%–1% after May 20, 2003, using TCM as a supplement to conventional therapy [79].

Based on the fact that natural compounds have been biologically confirmed against SARS-CoV or MERS-CoV, rational screening of oriental herbal medicines can help in the selection of suitable drugs to directly inhibit SARS-CoV-2 [80]. Thirteen natural compounds in use in TCM have shown potential with anti-SARS-CoV-2 activity [81]. Confirmed COVID-19 cases (60107) have been treated by TCM since early this year[67]. In 102 COVID-19 patients with mild symptoms treated with TCM, the clinical cure rate was increased by 33 %; common to severe cases were reduced by 27.4 % and patients' lymphocytes were increased by 70 % [82]. Qing-fei-pai-du decoction showed over a 90 % effective cure rate against COVID-19 among 701 patients [82,83].

In traditional TCM treatments are formulated on symptom-based diagnoses [2]. From existing reports, COVID-19 patients mainly presented with fever, fatigue, dry cough, upper airway congestion, sputum production, dyspnoea, myalgia/arthralgia, diarrhoea, thick greasy fur on tongue and slippery pulse [2,53,84,85]. The huo-xiang-zheng-qi capsule was used for patients presenting with fatigue and gastrointestinal disorder [2,78]. Jin-hua-qing-gan granules, lian-hua-qing-wen capsules, or shu-feng-jie-du capsules were recommended for patients with fatigue and fever [2,78,86].

TCM medicine not only inhibits the virus, but may also block infection, regulate the immune response, cut off the inflammatory storm, and promote repair of the body [78,79,81,87]. Clinical results showed that TCM plays a significant role in the treatment of COVID-19.

## 5. Conclusion

Despite rigorous effort and impressive collaborations, no drugs have yet been shown to exert a remarkable inhibitory effect against SARS-CoV-2. Many drugs such as oseltamivir, paramivir, neuraminidase, zanamivir, baloxavir marboxil, hydroxychloroquine, lopinavir *etc*., which were initially believed to have positive effects, have now been discontinued from most clinical use. Effective drugs against COVID-19 are in increasing demand as an alternative strategy to contain the pandemic during vaccine development. Moreover, dangerous mutations on SARS-CoV-2 genome is an alarm to search for alternative approaches for inhibiting the spread of this virus. The efficacies of particular drugs against various viruses shown in Table 1 correlate well with the similarity of their corresponding targets. Despite eight months of diligent repurposing trials, a significant therapy against SARS-CoV-2 has not been achieved. Furthermore, many of the ongoing repurposing efforts suffer from the lack of central coordination and a high probability of redundancy for molecules under test by different laboratories. Thus, we propose the implementation of novel strategies such as optimizing moderately inhibitory drug molecules such as remdesivir and favipiravir to promote binding to the specific binding pocket of SARS-CoV-2. Moreover, modifying chemical structures to improve absorption, distribution, metabolism, and excretion (ADME) may modulate the toxicity of exceptionally performing *in vitro* inhibitors such as Ivermectin to provide another feasible approach [88]. The structural and intermolecular interaction information shown in Fig. 1 will aid the scientific community in efficiently modifying a particular molecule and improving its $IC_{50}$ and ADME. In conclusion, in addition to repurposing drug efforts, optimization of lead molecules is an immediate approach that we propose to the scientific community (Fig. 2).

## Author contributions

RX. W, P.S, and Y.T are co-first authors contributing to the present review. W.-F. Z participated in the writing of the original draft and prepared the figures. S.-X. Lin supervised the work, contributed in the writing, and finalized the manuscript.

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## Declaration of Competing Interest

The authors declare there is no conflict of interests.

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