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Review Article

Current Therapeutic Drugs Treating COVID-19

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ABSTRACT

Corona virus disease 2019 (COVID-19) is a kind of viral pneumonia with an unusual outbreak in Wuhan, China, in December 2019, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the outbreak of corona virus disease 2019 (COVID-19), many researchers in the world have immediately carried out clinical research scheme of the COVID-19. Vaccines are being rapidly developed but will likely come too late to have an impact on the first wave of a potential pandemic. It highlights antiviral strategies involving small molecules and biologics targeting complex molecular interactions involved in coronavirus infection and replication. The drug-repurposing effort documented herein focuses primarily on agents known to be effective against other RNA viruses including SARS-CoV and MERS-CoV. The patent analysis of coronavirus related biologics includes therapeutic antibodies, Anti-inflammatory agents, and nucleic acid-based therapies targeting virus gene expression as well as various types of vaccines. Many patents disclose methodologies of these biologics with the potential for treating and preventing coronavirus infections, which may be applicable to COVID-19. But, there is still a lack of a review on Therapeutic Agents and Vaccines for COVID-19. Therefore, this review summarizes studies which are ongoing development of therapeutic agents and vaccines.

Keywords: COVID-19; Therapeutic drugs; Vaccines

INTRODUCTION

Novel corona virus induced pneumonia, which was named as corona virus disease 2019 (COVID-19) by the WHO on the 11th of February 2020, has rapidly increased in epidemic scale since it first appeared in Wuhan, China, in December 2019 [1]. At present, the cases of COVID-19 have been found in many countries around the world [2]. Corona Virus Disease 2019 (COVID-19), being an emerging infectious disease, is a serious threat to human health [3-5]. According to the latest data, up to March 23, 2020 the number of confirmed cases in world reached 351,083, of which 15,337 were dead, and 100,569 were cured.

To date, no clinical intervention trial has been completed and reported. Due to the urgent need for treatment prevention and control of the disease, it is necessary to develop effective intervention methods for COVID-19 to facilitate disease control. Since the outbreak of the COVID-19, many researchers in China have carried out clinical research trials, aiming to develop strategies for the treatment, prevention and diagnosis of COVID-19 [6].

Corona Viruses (CoVs) are relatively large viruses containing a single-stranded positive-sense RNA genome encapsulated within a membrane envelope. The viral membrane is studded with glycoprotein spikes that give corona viruses their crown like appearance. While corona viruses infect both humans and animals, certain types of animals such as bats that host the largest variety of corona viruses appear to be immune to corona virus-induced illness [7]. There are four classes of corona viruses designated as alpha, beta, gamma, and delta. The beta corona virus class includes Severe Acute Respiratory Syndrome (SARS) virus (SARS-CoV), Middle East Respiratory Syndrome (MERS) virus (MERS-CoV), and the COVID-19 causative agent SARS-CoV-2. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 attacks the lower respiratory system to cause viral pneumonia, but it may also affect the gastrointestinal system, heart, kidney, liver, and central nervous system leading to multiple organ failure [8,9]. Current information indicates that SARS-CoV-2 is more transmissible or contagious than SARS-CoV [10]. Patients with COVID-19 show manifestations of respiratory tract infection, such as fever, cough, pneumonia, and in severe cases, death [11,12]. The information included in this review provides a strong intellectual groundwork for the ongoing development of therapeutic agents and vaccines.

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Existing drugs with potential therapeutic applications for covid-19

Since SARS-CoV-2 is a newly discovered pathogen, no specific drugs have been identified or are currently available. An economic and efficient therapeutic strategy is to repurpose existing drugs. On the basis of genomic sequence information coupled with protein structure modeling, the scientific community has been able to rapidly respond with a suggested list of existing drugs with therapeutic potential for COVID-19 [13].

The main measure in clinical management is focused on alleviating clinical symptoms and supportive care [14].Therapeutic options that could be evaluated and used for COVID-19 include molecules binding to the virus, molecules, or inhibitors that target specific enzymes involved in viral replication and transcription, small-molecule inhibitors targeting helicase, essential proteases, or other proteins of the virus, host cell protease inhibitors, host cell endocytosis inhibitors, siRNA, anti-sense RNA and ribozyme, neutralizing antibodies, mAbs targeting host receptor or interfere with S1 RBD, antiviral peptide targeting S2, and natural products [15,16]. Barcitinib was proposed because of its anti-inflammatory effect and possible ability to reduce viral entry [17]. A fixed dose of the anti-HIV combination, lopinavir–ritonavir, is currently in clinical trials with Arbidol or Ribavirin [18]. Remdesivir, developed by Gilead Sciences Inc., was previously tested in humans with Ebola virus disease and has shown promise in animal models for MERS and SARS. The drug is currently being studied in phase III clinical trials in both China and the USA. Favipiravir, a purine nucleoside leading to inaccurate viral RNA synthesis, was originally developed by Toyama Chemical of Japan, and has recently been approved for a clinical trial as a drug to treat COVID-19 [19,20]. Chloroquine, an antimalarial drug, has proven effective in treating coronavirus in China [21]. In addition to the above-mentioned, many other antiviral drugs are also listed.

Additionally, clinicians combined Chinese and Western medicine treatment including lopinavir/ritonavir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) and gained significant improvement in pneumonia associated symptoms in Shanghai Public Health Clinical Center, China [22]. The other antiviral drugs include nitazoxanide, favipiravir, nafamostat, and so on (Table 1).

Table 1: Neutralizing monoclonal antibodies targeting SARS-CoV and their mechanism of action.

Monoclonal antibody	Antibody mechanism of action	Authors
80R	• Binding to the conformational epitope (amino acid residues 426-492) on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 using 6 Complementary Determining Region (CDR) *in vitro* and in vivo (Mouse).	Zhang L, et al. Sui J, et al. [91,92].
CR3014	• Binding to the amino acid residues 318-510 and amino acid residue 565 with high affinity on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 *in vitro* and in vivo (Ferret).	Brink ENVD, etal. Shanmugaraj B, et al. Ter Meulen J, et al.[93-95].
CR3022	• Binding to the amino acid residues 318-510 on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 *in vitro*.	Ter Meulen J, et al. [95].
F26G18	• Binding to the linear epitope (amino acid residues 460-476) on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 *in vitro*.	Berry JD, et al. [96].
F26G19	• Binding to the conformational epitope (amino acid residues 359-362, 391-392, 424-427, and 486-492) on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 *in vitro*.	Berry JD, et al. [96].
m396	• Binding to the conformational epitope (amino acid residues 482-491) on S1 fragment of SARS-CoV. • Blocking the interaction of S subunit protein using CDR loops H1, H2, H3, and L3 with cellular receptor ACE2 *in vitro*.	Zhu Z, et al. [97].
1A9	• Binding to the Heptad repeat (HR) loops including heptad repeat 1 (HR1) and heptad repeat 1 (HR2) domain on S2 fragment of SARS-CoV. • Blocking the interaction of S2 subunit protein (amino acid residues 1111-1130) with cellular receptor *in vitro*.	Shanmugaraj B, et al. Lip KM, et al. [94,98].
201	• Binding to the amino acid residues 490-510 on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 *in vitro* and in vivo (Mouse Syrian Hamster).	Greenough TC, et al. [99].
68	• Binding to the amino acid residues 130-150 of SARS-CoV *in vitro* and in vivo (Mouse)	Greenough TC, et al. [99].
4D4	• Binding to the amino acid residues 12-261 of SARS-CoV and N-terminal of RBD • Inhibiting the post-interaction in the viral penetration *in vitro*.	Code 71 Coughlin MM, et al. Elshabrawy HA, et al. [57,100].
S230	• Binding to epitopes partially overlapping with receptor binding motifs on B domain of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 *in vitro*.	Walls AC, et al. [101].

Research and development of vaccines

With the emergence of 2019-nCoV, there are many potential vaccine candidates in the pipeline globally, in which a wide range of technology (such as messenger RNA, DNA-based, nano particle, synthetic and modified virus-like particle) was applied. The cellular receptors of SARS-CoV and MERS-CoV have been identified, and the virion spike (S) glycoprotein, was also well studied. S glycoprotein includes two subunits, S1 and S2, resulting from cleavage of the one precursor into two parts. S1 determines the virus host range and cellular tropism with the key functional domain Receptor Binding Domain (RBD), while S2 contains two tandem domains, heptad repeats 1 (HR1) and Heptad Repeats 2 (HR2), to mediate virus-cell membrane fusion. It is believed that the fusion process is similar to that of HIV-1; for example, when S1 binds to the receptor on the cell membrane, the fusion peptide at the N terminus of S2 inserts into the cell membrane, then three HR1s attach to each other in parallel as a trimer, followed by binding of three HR2s separately onto the outside of the trimer to form a 6-helix bundle, thus bringing virus and cell membranes close to each other to trigger fusion. As the major vaccine target, the S protein has been evaluated in different types of vaccines against infection by CoVs [23-27].

Apart from the inactive whole virus particle, live attenuated virus with gene deletion, four more vaccines which mainly contain S protein were studied. These include a virus-like particle which incorporated S protein into hepatitis virus or influenza virus protein; virus vectors, such as Modified Vaccinia Virus Ankara (MVA) or Adenovirus carrying S protein; S protein subunit vaccine, like RBD-based protein; and DNA vaccine which encodes the full length or part of the S protein gene [28-36,27]. Most of them have been tested in mouse models and showed the ability to elicit neutralizing antibodies. The first SARS-CoV DNA vaccine was tested in humans only 19 months after the virus sequence was published, while the DNA vaccine GLS-5300, the first MERS-CoV vaccine, went to clinical trials in 2016 [37]. In addition to these conventional vaccines, Liu et al. analyzed the T cell epitopes of SARS-CoV and MERS-CoV, revealed the potential cross-reactivity of the coronaviruses, and assessed the possibility of developing universal vaccines against coronavirus infections [38].

Most CoVs share a similar viral structure, similar infection pathway, and a similar structure of the S proteins, suggesting that similar research strategies should also be applicable for the 2019-nCoV. For example, the study of MERS-CoV vaccines was accelerated by virtue of strategies that had been established for SARS-CoV [39,40]. Therefore, to predict whether vaccines developed for SARS-CoV will also be effective against 2019-nCoV infection, the full-length S protein sequences from the 2019- nCoV, a SARS-CoV, and two genetically similar bat CoV strains were selected for alignment. The results indicated more than 50% homology of the viruses. However, the most variable residues are located in S1, a critical vaccine target, implying that neutralizing antibodies thatwere so effective against SARS-CoV infection may fail to recognize the 2019-nCoV, and that multiple amino acid differences at the receptor binding motif may modify virus tropism, a possible reason for cross-species transmission. However, several bottlenecks typically delay the approval of vaccines to prevent CoVs infection. Firstly, lack of proper animal models for evaluating vaccine efficacy. Second, there are limitations from the S protein itself, such as mutations in the neutralization antibody epitopes in S protein that can cause virus escape, or non-neutralization antibody epitopes in vaccines that may elicit antibody-mediated disease enhancement (ADE) [41,42]. Third, DNA vaccines may recombine with other viruses. Fourth, pre-existing immunity may eliminate the vaccine by removing the general human virus vectors (Table 2) [43].

Table 2: Neutralizing monoclonal antibodies targeting MERS-CoV and their mechanism of action.

Monoclonal antibody	Antibody mechanism of action	Authors
MERS-4	• Binding to the C-terminal segment of the β5-β6, β6-β7 and β7-β8 loops on the receptor-binding subdomain in RBD of MERS-CoV with no overlap DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* by inducing β5-β6 shallow groove on the RBD.	Yi Y, et al. Ying T, et al. [102,103].
MERS-27	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1subunit protein with cellular receptor DPP4 *in vitro*.	Yi Y, et al. Yu X, et al. [102,104].
4C2	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and in vivo (Mouse).	Zhang S, et al. Li Y, et al. [105,106].
m336	• Binding to the C-terminal segment of the β5-β8 strands, β5-β6 loop and β6-β7 loop in RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 by mimicking the interaction between RBD and DPP4 in the similar binding angle in vitro and in vivo (Mouse and rabbit).	Doremalen NV, et al. Ying T, et al. [107,108].
G4	• Binding to the glycosylated surface on the S2 subunit protein *in vitro*.	Wang L, et al. Pallesen J,et al. [109,110].

D12	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	Wang L, et al. Pallesen J, et al. [41,110].
JC57-14	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	Wang L, et al. [41].
MERS-GD27	• Binding to the C-terminal segment of the β5-β8 strands, β5-β6 loop and β6-β7 loop in RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 by mimicking the interaction between RBD and DPP4 in the same binding angle *in vitro* and in vivo (Mice).	Niu P, et al. [111].
MERS-GD33	• Binding to the C-terminal segment of the β5-β8 strands, β5-β6 loop and β6-β7 loop in RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 mimicking the interaction between RABD and DPP4 in the same binding angle *in vitro*.	Niu P, et al. [112].
LCA60	• Binding to the C-terminal segment of the β8 strand, β6-β9 loop, and β6-β8 loop on RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	Walls AC, et al. [101].
MCA1	• Binding to RBD with 6 complementarity-determining regions • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and in vivo (Mouse).	Wit ED, et al. [113].
CDC2-C2	• Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and in vivo (Mouse).	Wang L, et al. [41].
7D10	• Binding to N-terminal domain of S protein of MERS-CoV • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and in vivo (Mouse).	Niu P, et al. [111].
G2	• Binding to N-terminal domain of S protein of MERS-CoV • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	Zhou H, et al. [114].

Finally, there is the problem of return on investment which may be slow and, hence, inhibit investments and slow down the clinical study. Jiang and colleagues have demonstrated that RBD in the SARS-CoV- S protein is the major target of neutralizing antibodies in SARS patients and is able to induce highly potent neutralizing antibody responses and long-term protective immunity in animal models. It contains 6 different conformational neutralizing epitopes, to which a series of mouse monoclonal antibodies (mAbs) with different neutralizing activity were generated. Interestingly, these mAbs exhibited cross-neutralizing activities against divergent SARS-CoV strains isolated from SARS patients at different stages of SARS epidemics and those from palm civets [44,45]. This group has also shown that these SARS-CoV-RBD specific neutralizing mAbs can cross-neutralize bat SL-CoVs, such as bat SL-CoV-W1V1, indicating that these antibodies may also cross-neutralize 2019-nCoV. Most importantly, RBD-based vaccine could induce neutralizing antibody responses and protection against SARS-CoV infection in the immunized animals, while it did not elicit ADE or other harmful immune responses, unlike the virus inactivated vaccines or full-length S protein-based vaccines as discussed above. Therefore, this RBD-based SARS vaccine is expected to be safer and more effective than the vaccines targeting other sites in S protein. Jiang and Du's groups have collaborated with Hotez's group at Baylor College of Medicine in Houston and Tseng's group at the University of Texas Medical Branch at Galveston, Texas, USA in development of an effective and safe vaccine at the late stage of preclinical study [46,47].

CoV fusion or entry inhibitors

Based on the previous experience in developing the HIV-1 fusion inhibitor SJ-2176, Jiang et al. [48]. discovered the first anti- SARS-CoV peptide (SC-1) from the HR2 domain of SARS-CoV S protein S2 subunit. SC-1 could bind onto the HR1 domain to form a six-helical bundle (6-HB), blocking S protein-mediated membrane fusion and inhibiting SARS-CoV infection [49]. When MERS-CoV was circulating in human populations in 2012, following similar mechanistic design, Jiang's research group developed another peptide, designated HR2P, which was derived from the virus HR2 region as well and effectively inhibited MERS-CoV infection [50]. The further modified version of HR2P, HR2P-M2, presented even better anti-MERS-CoV activity and pharmaceutical properties. Development of broad-spectrum pan-CoV fusion inhibitors would be an idealway to cope with epidemics or pandemics caused by emerging HCoVs. The conservative amino acid sequence of the HR1 region across

different CoVs has the potential to be a target domain for development of an inhibitor. Continuing to work on the HR1 and HR2 domains, Jiang's group discovered that the peptide OC43-HR2P, derived from the HR2 domain of HCoV-OC43, broadly inhibited fusion by multiple HCoVs. By optimization of this peptide, a pan-CoV fusion inhibitor, EK1, was generated. It could form a stable six-helix bundle (6-HB) structure with HR1s and showed significantly improved fusion-inhibitory activity and pharmaceutical properties [51]. The alignment of S protein exhibited 100% identity at the HR2 domains between the 2019-nCoV and SARS-CoV; however, they found 7 amino acid changes in the fusion core of the HR1, located in the EK1 binding motif. Fortunately, the substitutions were conservative replacements which would not dramatically disrupt the interactions between EK1 and HR1, meaning that EK1 would still have the potential to be an effective inhibitor for 2019-nCoV infection. The table shows selected patents associated with the aforementioned potential drugs, together with patents disclosing small molecules for treatment of SARS or MERS (Table 3).

CoV s-rbd-specific neutralizing antibodies

So far, most neutralizing antibodies recognize the RBD in the S protein S2 of CoVs. Compared with the high mutation rate in the S1 protein, S2 is much more conservative, thereby decreasing the off target risk caused by amino acid replacement, and also bypassing the special epitopes that may cause ADE [52,53]. This means that the cocktail of monoclonal antibodies binding to different epitopes of RBD would be more desirable for therapeutic purposes [54]. For treatment, the monoclonal antibodies are from a human source or are humanized antibodies, isolated or generated with various approaches. For example, wild-type mice were immunized with soluble recombinant RBD containing the S protein. Then mouse antibodies were humanized and isolated, or transgenic mice were directly immunized, to express human versions of the antibodies [55,56]. However, direct cloning of single B cells from human survivors, used in combination with the phage-display antibody library, could provide authentic human antibodies. Until now, it should be noted that many

Table 3: Selected patents associated with potential drugs (Repurposing) for COVID-19 or small molecules for treatment of SARS or MERS.

Patient Number	Title	Organization
WO2009114512	Preparation of azetidine and cyclobutane derivatives as JAK inhibitors	Incyte Corporation, USA
WO2014028756	Deuterated baricitinib	Concert Pharmaceuticals, Inc., USA
JP5971830	Preparation of polycyclic pyridone derivatives as cap-dependent endonuclease (CEN) inhibitors and prodrugs thereof	Shionogi and Co., Ltd., Japan
US20160122374	Preparation of nucleosides and methods for treating Filoviridae virus infections	Gilead Sciences, Inc., USA
US20170071964	Preparation of amino acid-containing nucleotides and methods for treating arenaviridae and coronaviridae virus infections	Gilead Sciences, Inc., USA
WO2007075145	Preparation of benzopyranone derivatives as anti-coronaviral agents Singapore Polytechnic,	Singapore; Shanghai Institute of Materia Medica Chinese Academy of Sciences, China
WO2005021518	Preparation of 3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid derivatives as cysLT2 receptor antagonists for treatment of respiratory diseases	Ono Pharmaceutical Co., Ltd., Japan
WO2007120160	Preparation of N-heterocyclic acetamides useful for viral inhibition	Novartis AG, USA
WO2009119167	Aniline derivative having anti-RNA viral activity	KinoPharma, Inc., Japan
WO2013049382	Broad-spectrum antivirals against 3c or 3c-like proteases of picornavirus-like supercluster: picornaviruses, caliciviruses and coronaviruses	Kansas State University Research Foundation; The Ohio State University; Wichita State University-all in USA
WO2018042343	Preparation of peptides that inhibit 3C and 3CL proteases and methods of use thereof	GlaxoSmithKline, UK
WO2007067515	Five-membered iminocyclitol derivatives as selective and potent glycosidase inhibitors: new structures for antivirals and osteoarthritis therapeutics	Academia Sinica, Taiwan

neutralizing antibodies have been successfully discovered for treatment of SARS-CoV and MERS-CoV infection.

These antibodies have all been described favorably in the literature [57]. A similar approach is known as single chain fragment variable (scFv) library screening, whereby the use of RBD as a bait protein allows some neutralizing antibodies to be screened out from non-immune humans [58,59]. Antibodies effective at inhibiting SARS-CoV infection should also have the potential for treatment of 2019-nCoV as well, as long as the binding motif in RBD shares the same sequences. The new neutralizing monoclonal antibodies would also be isolated from the patients using the established techniques. Hence the therapies for SARS-CoV can be extrapolated to use for SARS-CoV-2. The specific neutralizing monoclonal antibodies either against Receptor Binding Domain (RBD) in spike protein or specific antibody that binds to ACE2 could effectively block the virus entry.

CoV replication inhibitors

Similar to developing vaccines, drugs effective against other RNA viruses were also repurposed for CoVs. Two major types of drugs being nucleoside analogues and immunomodulators. So far, the most common therapies tried in patients with CoVs are ribavirin, lopinavir/ritonavir, IFN, or their combinations [60]. Despite the antiviral activity observed with *in vitro* studies, the clinical effect was not consistent, in that ribavirin does not prolong the survival of SARS-CoV patients, while lopinavir/ritonavir plus ribavirin seemed to improve clinical outcomes for SARS patients, but the improvement was not confirmed in MERS-CoV patients [61-63]. IFNs showed effective at inducing antiviral activity against both SARS-CoV and MRES-CoV, but without significant improvement in the outcomes for the patients [64,65]. In addition to the drug regimens used in patients, numerous drugs developed for the treatment of infection with CoVs were thoroughly discussed in the literature [66]. However, replication of an RNA virus usually generates progeny viruses with a highly diverse genome. Recombination also easily takes place between viral genomes, and these gene level changes may result in drug resistance if the mutations affect the drug target domain [67]. Development of drugs is also hampered by various evaluation methods and animal models used for testing drug activity among different labs worldwide, which could postpone selection of the best drug for clinical trials.

Angiotensin receptor blockers

Angiotensin Receptor Blockers (ARBs) have been reported to associate with viral infection, including HCoVs [68,69]. Irbesartan, a typical ARB, was approved by the FDA for treatment of hypertension and diabetic nephropathy. Here, network proximity analysis shows a significant association between irbesartan's targets and HCoV-associated host proteins in the human interactome. Irbesartan targets SLC10A1, encoding the sodium/bile acid cotransporter (NTCP) protein that has been identified as a functional pre S1-specific receptor for the Hepatitis B Virus (HBV) and the Hepatitis Delta Virus (HDV). Irbesartan can inhibit NTCP, thus inhibiting viral entry [70,71]. SLC10A1 interacts with C11or f74, a potential transcriptional repressor that interacts with nsp-10 of SARS-CoV [72]. There are several other ARBs (such as *Eletriptan*, *Frovatriptan*, and *Zolmitriptan*) in which their targets are potentially associated with HCoV-associated host proteins in the human interactome.

Anti-inflammatory agents

Inflammatory pathways play essential roles in viral infections [73]. As a biogenic amine, melatonin (N-acetyl5-methoxytryptamine) plays a key role in various biological processes, and offers a potential strategy in the management of viral infections [74,75]. Viral infections are often associated with immune-inflammatory injury, in which the level of oxidative stress increases significantly and leaves negative effects on the function of multiple organs [76]. The antioxidant effect of melatonin makes it a putative candidate drug to relieve patients' clinical symptoms in antiviral treatment, even though melatonin cannot eradicate or even curb the viral replication or transcription [77]. In addition, the application of melatonin may prolong patients' survival time, which may provide a chance for patients' immune systems to recover and eventually eradicate the virus. Melatonin indirectly targets several HCoV cellular targets, including ACE2, BCL2L1, JUN, and IKBKB. Eplerenone, an aldosterone receptor antagonist, is reported to have a similar anti-inflammatory effect as melatonin. By inhibiting mast-cell-derived proteinases and suppressing fibrosis, eplerenone can improve survival of mice infected with encephalomyocarditis virus [78]. In summary, our network proximity analyses offer multiple candidates repurposable drugs that target diverse cellular pathways for potential prevention and treatment of 2019-nCoV/SARS-CoV-2. However, further preclinical experiments, and clinical trials are required to verify the clinical benefits of these network-predicted candidates before clinical use [21].

Toremifene plus emodin

Toremifene is among the approved first-generation nonsteroidal SERMs for the treatment of metastatic breast cancer [79]. SERMs (including toremifene) inhibited Ebola virus infection, by interacting with and destabilizing the Ebola virus glycoprotein [80,81]. *In vitro* assays have demonstrated that toremifene inhibited growth of MERSCoV, and SARA-CoV [82,83]. Emodin, an anthraquinone derivative extracted from the roots of rheum tanguticum, has been reported to have various anti-virus effects. Specifically, emdoin inhibited SARSCoV-associated 3a protein, and blocked an interaction between the SARS-CoV spike protein and ACE2 [84,85]. Altogether, network analyses and published experimental data suggested that combining toremifene and emdoin offered a potential therapeutic approach for 2019-nCoV/ SARS-CoV-2.

DISCUSSION

Mercaptopurine plus melatonin

Targets of both mercaptopurine and melatonin showed strong

network proximity with HCoV associated host proteins in the human interacttome network. Recent *in vitro* and in vivo studies identified mercaptopurine as a selective inhibitor of both SARS-CoV and MERS-CoV by targeting papain like protease [86,87]. Melatonin was reported in potential antiviral infection via its anti-inflammatory and antioxidant effects [74,77]. Melatonin indirectly regulates ACE2 expression, a key entry receptor involved in viral infection of HCoVs, including 2019-nCoV/SARS-CoV-2 [1]. Specifically, melatonin was reported to inhibit calmodulin and calmodulin interacts with ACE2 by inhibiting shedding of its ectodomain, a key infectious process of SARS-CoV [88,89]. JUN, also known as c-Jun, is a key host protein involving in HCoV infectious bronchitis virus [90-114]. Mercaptopurine and melatonin may synergistically block c-Jun signaling by targeting multiple cellular targets.

CONCLUSION

In conclusion, combination of mercaptopurine and melatonin may offer a potential combination therapy for 2019nCoV/SARS-CoV-2 by synergistically targeting papainlike protease, ACE2, c-Jun signaling, and anti-inflammatory pathways. However, further experimental observations on ACE2 pathways by melatonin in 2019-nCoV/SARS-CoV-2 are highly warranted.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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